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Updated Clinical Practice Guideline on Use of Gadolinium-Based Contrast Agents in Kidney Disease Issued by the Canadian Association of Radiologists

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Abstract

In 2017, the Canadian Association of Radiologists issued a clinical practice guideline (CPG) regarding the use of gadolinium-based contrast agents (GBCAs) in patients with acute kidney injury (AKI), chronic kidney disease (CKD), or on dialysis due to mounting evidence indicating that nephrogenic systemic fibrosis (NSF) occurs with extreme rarity or not at all when using Group II GBCAs or the Group III GBCA gadoxetic acid (compared to first generation Group I linear GBCAs). One of the goals of the work group was to re-evaluate the CPG after 24 months to determine the effect of more liberal use of GBCA on reported cases of NSF in patients with AKI, CKD Stage 4 or 5 (estimated glomerular filtration rate [eGFR] $<$ 30 mL/min/1.73 m^2), or those that are dialysis-dependent. A comprehensive review of the literature was conducted by a subcommittee of the initial CPG panel between the dates of January 1, 2017-December 31, 2018 to identify new unconfounded cases of NSF linked to Group II or Group III GBCAs and an updated CPG developed. To our knowledge, when using a Group II or Group III GBCA between 2017-2018, only a single unconfounded case report of a fibrosing dermopathy has been reported in a patient who received gadobenate dimeglumine with Stage 2 CKD. No other unconfounded cases of NSF have been reported with Group II or III agents in during this timeframe. The subcommittee concluded that the main recommendations from the 2017 CPG should remain unaltered, but agreed that screening for renal disease in the outpatient setting is no longer justifiable, cost-effective or recommended. Patients on hemodialysis (HD) should, however, be identified prior to GBCA administration to arrange timely HD to optimize gadolinium clearance, although there remains no evidence that HD reduces the risk of NSF. When administering Group II or III GBCAs to patients with AKI, on dialysis or with severe CKD, informed consent relating to NSF is also no longer explicitly recommended.

Résumé

En 2017, l'Association canadienne des radiologistes a publié des lignes directrices de pratique clinique (LDPC) sur l'utilisation de produits de contraste à base de gadolinium (PCBG) chez des patients atteints d'insuffisance rénale aiguë (IRA), de néphropathie chronique ou sous dialyse, en raison de l'accumulation de données démontrant que la fibrose systémique néphrogénique (FSN) se manifeste avec une rareté extrême, voire pas du tout, lors de l'emploi de PCBG du groupe II ou d'acide gadoxétique-PCBG du groupe III (par rapport aux PCBG linéaires du groupe I de première génération). L'un des objectifs du groupe de travail était de réévaluer les LDPC après 24 mois pour déterminer l'effet d'une utilisation plus générale de PCBG sur des cas signalés de FSN chez des patients atteints d'IRA ou de néphropathie chronique de stade 4 ou 5 (débit de filtration glomérulaire estimé [DFGe] $<$ 30 mL/min/1,73 m^2), ou dialysés. Une revue approfondie des publications a été conduite par un sous-comité composé du groupe d'experts d'origine sur les LDPC entre le 1er janvier 2017 et le 31 décembre 2018 pour identifier de nouveaux cas non confondus de FSN associés aux PCNG du groupe II ou du groupe III, permettant ainsi une mise à jour des LDPC. À notre connaissance, dans le cadre de l'utilisation de PCBG du groupe II ou du groupe III entre 2017 et 2018, un seul rapport de cas non confondu de dermopathie fibrosante a été déclaré chez un patient atteint de néphropathie chronique de stade 2 et ayant reçu une injection de gadobénate de diméglumine. Aucun cas additionnel non confondu de FSN n'a été signalé avec des produits du groupe II

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ou du groupe III pendant cet intervalle de temps. Le sous-comité a conclu que les principales recommandations émanant des LDPC de 2017 doivent demeurer inchangées, mais a convenu que le dépistage des néphropathies en ambulatoire n'est plus justifié, rentable ou préconisé. Néanmoins, les patients sous hémodialyse (HD) devraient être identifiés avant l'injection de PCBG pour planifier le traitement par HD en conséquence afin de maximiser l'élimination du gadolilium, malgré l'absence de preuve de réduction des risques de FSN par l'HD. Lors de l'injection de PCBG du groupe II ou du groupe III à des patients atteints d'IRA ou de néphropathie chronique grave, ou sous dialyse, l'obtention du consentement éclairé dédié à la FSN n'est plus explicitement recommandée.

Key Words: Gadolinium based contrast agents; Magnetic resonance imaging; Nephrogrenic systemic fibrosis; Kidney

In 2017, the Canadian Association of Radiologists (CAR) issued a clinical practice guideline (CPG) through an expert panel of assembled radiologists and nephrologists studying the use of gadolinium-based contrast agents (GBCAs) in patients with acute kidney injury (AKI), severe chronic kidney disease (CKD) or on dialysis [1,2]. The rationale for the initial CPG was to acknowledge the mounting evidence indicating that nephrogenic systemic fibrosis (NSF), a debilitating and feared systemic sclerosing condition with no known effective treatment and linked to the use of GBCA in patients with renal impairment, was exceedingly rare or not reported when using macrocyclic GBCA and newer linear GBCA products (eg, gadobenate dimeglumine and gadoxetic acid).

The CPG primary objective was to potentially achieve improved access for patients with AKI, severe CKD, or those on dialysis to GBCA-enhanced examinations when medically indicated and when using a macrocyclic agent, gadobenate dimegluimine, or gadoxetic acid. Secondary objectives of the CPG were to provide recommendations on the use of dialysis and need for consent in patients with renal impairment receiving GBCA for medically indicated exams and to update CAR recommendations for outpatient screening of renal function prior to GBCA administration. The CPG cautiously suggested that outpatient screening for renal function should continue, albeit with far less stringent regulation than what was change presently to previously recommended at the time by the CAR for 2 main reasons: (1) to prevent a deluge of requests for enhanced cross-sectional imaging studies to transit from computed tomography to magnetic resonance imaging (MRI) in patients with renal impairment due to persistent fears over post contrast acute kidney injury and a perceived far less significant or non-existent risk for NSF, and (2) because of evidence suggesting that gadolinium deposition (now preferably referred to as retention [3]) in the brain occurs to a greater extent in patients with renal impairment [4], since guidelines pertaining to gadolinium deposition at the time suggested restricting use of GBCA only when medically necessary in vulnerable populations [5,6]. This recommendation was concordant with the European Society of Urogenital Radiology guidelines available at the time [7]; however, differed from the American College of Radiology (ACR) manual (version 10.3) on contrast media which suggested that outpatient screening for renal function when using a Group II (macrocyclic agents + gadobenate dimeglumine) GBCA was no longer recommended [8]. The CPG also recommended informed consent for at-risk patients receiving a GBCA, which was not recommended by the ACR but this was deferred to local practice [8]. The CPG work-group intended to review their recommendations after a 2-year period to evaluate for new reported cases of NSF using Group II agents and gadoxetic acid in an era of more liberal use of GBCA in patients with renal impairment.

A subcommittee of the initial CPG work-group was assembled and a comprehensive review of the literature for reports of unconfounded cases of NSF associated with the use of a Group II and III GBCA, namely: macrocyclic GBCAs, gadobenate dimeglumine and gadoxetic acid, was performed. Results are summarized in Table 1. For the macrocyclic agents (gadobutrol, gadoteridol, and gadoterate) and linear agent gadoxetic acid there were no unconfounded case reports of NSF from 2017-2018. For the linear agent gadobenate dimeglumine, there was a single unconfirmed case report published in 2017 of a patient diagnosed with fibrosing dermopathy in the lower extremities with no systemic involvement. The authors of this case report described this as being compatible with NSF, though unverified, due to a temporal relation to administration of gadobenate dimeglumine when the patient's eGFR was 64 mL/min/1.73 m^2 [9]. The results of our audit of the past 2 years of data further confirm the safe practice of using a Group II or Group III GBCA in patients with AKI, severe CKD, or on dialysis when the examination is considered medically necessary. It should be noted that during the updated time period of our audit, 51 cases in 2017 and 22 cases in 2018 of NSF were reported to the Food and Drug Administration Adverse Events Reporting System [10]. However, these reported cases have not been formally published, or adjudicated as cases of NSF using histopathological analysis, nor is there any formal documentation of which GBCAs is implicated, the timing of the dose and first occurrence of symptoms, and whether cases are contaminated by multiple agents or unconfounded. It can also be argued that our review, which encompasses only the past 2 years of data, does not account for delayed presentations of NSF which can occur up to 8 years after GBCA administration [11]; however, our audit of the past 2 years of data builds upon the initial review we conducted in 2017 when the first CPG was published. The results of our audit support the recommendations of the ACR (version 10.3), namely that outpatient screening for renal

Table 1
GBCA and number of new unconfounded reports of nephrogenic systemic fibrosis from 2017-2018[a]

Agent	Structure	Number of unconfounded cases of NSF	ACR classification[b]
Gadobenate dimeglumine (Multihance; Bracco Pharmaceuticals, Toronto, ON)	Linear ionic	1[c]	II
Gadoxetic acid (Primovist; Bayer Pharmaceutical, Toronto, ON)	Linear non-ionic	0	III
Gadoteridol (Prohance; Bracco Pharmaceuticals, Toronto, ON)	Macrocyclic non-ionic	0	II
Gadobutrol (Gadovist; Bayer Pharmaceuticals, Toronto, ON)	Macrocyclic non-ionic	0	II
Gadoteric acid (Dotarem; Guerbet Group, Toronto, ON)	Macrocyclic ionic	0	II

ACR = American College of Radiology; CKD = chronic kidney disease; GBCA = gadolinium-based contrast agents; NSF = nephrogenic systemic fibrosis.
[a] Based upon a comprehensive literature review of reported cases of NSF from January 1, 2017-December 31, 2018.
[b] American College of Radiology.
[c] A single case report of a patient with Stage 2 CKD who received gadobenate dimeglumine with a subsequent diagnosis of a fibrosing dermopathy in the lower extremities only was published in 2017 [9].

function to prevent instances of NSF when using Group II agents is unnecessary given the exceedingly low or non-existent risk of causing NSF when using Group II agents. It is the opinion of the CPG that this conclusion can also be applied to the Group III agent gadoxetic acid, albeit the CPG acknowledges there is far less data regarding gadoxetic acid compared to the more commonly used Group II agents.

In accordance with the results of our audit, an update of the initial CPG is presented in Appendix 1. Highlights of important changes between the 2017 and updated CPG are presented in Figure 1. The CAR no longer recommends outpatient screening (in the form of questionnaires or serum creatinine) for renal function prior to administration of a Group II GBCA or gadoxetic acid, with the exception of continued identification of patients on hemodialysis to arrange for prompt hemodialysis following Group II GBCA administration. For patients with AKI, Stage 4 or 5 CKD or on dialysis, GBCA enhanced MRI should only be performed when considered medically necessary, when there is no suitable alternative test, and should only be performed using a Group II or III agent. The CAR no longer recommends obtaining informed consent from at-risk patients (specifically discussing risks of causing NSF) when administering a Group II GBCA or gadoxetic acid. The rationale for the changes is supported by the updated evidence which clearly indicates the risk of causing NSF, even in the most at-risk patients, when administering a Group II GBCA or gadoxetic acid is exceedingly small or non-existent. The costs associated with outpatient screening for renal function, complexity incurred by organizations pertaining to screening, as well as the inconvenience and morbidity imposed on the patient are no longer justifiable. In a recent study by Shankar et al, the elimination of outpatient screening for renal function prior to Group II GBCA administration would have resulted in a substantial cost savings [12]. With respect to gadolinium retention, while those patients with impaired renal function may be at heightened risk for retention of gadolinium in the brain, there remains no substantiated cases of any deleterious effects associated with this phenomenon and 2 well-designed population-based studies indicated no clinical symptoms related to gadolinium administration [13,14]. The reader may refer to the 2018 position statement on gadolinium deposition issued by the CAR for further information on gadolinium retention [15].

Figure 1. Important updates to Canadian Association of Radiologists clinical practice guideline regarding the use of gadolinium-based contrast agents in renal dysfunction. This figure is available in colour online at http://carjonline.org/.

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Appendix 1. Updated CAR Clinical Practice Guidelines 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 m^2

- 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 m^2)

- 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 m^2 generally occurred in patients with AKI [16,17].
  - One study reported 3 cases of NSF in patients with eGFR above 30 mL/min/1.73 m^2; however, these patients were grouped in together 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 [18]. The authors did not reply to a request for this additional information.
  - In 1 case report, a single patient with eGFR above 30 mL/min/1.73 m^2 reportedly developed NSF. The eGFR in this case report varied; however, ranged between 34.4 and 31.8 mL/min/1.73 m^2 during the course of the patients' follow-up, which consisted of 7 MRI examinations [19].
  - Given the paucity of reported cases of NSF in patients with moderate CKD, the panel suggested that no special precautions are required in this patient population. Institutions which use gadopentetate dimeglumine, gadodiamide, and gadoversetaminde may optionally consider a macrocyclic or newer linear GBCA when renal function approaches 30 mL/min/1.73 m^2.
  - Regular vendor suggested dosing is recommended, half- or quarter-dosing is not considered necessary and double or triple dosing is not recommended.

3. Use of Gadolinium-Based Contrast Agents in Patients With Severe CKD (eGFR $<$ 30 mL/min/1.73 m^2) or Dialysis-Dependent Patients

- For patients with known severely reduced kidney function and those on dialysis, examinations should be considered on a case by case basis. Alternative diagnostic tests (eg, unenhanced MRI, computed tomography, ultrasound, biopsy, scintigraphic examinations, etc) should be considered before GBCA are prescribed. When MRI is considered necessary for patient care then gadolinium enhanced examinations using Group II GBCAs (namely macrocyclic GBCA and gadobenate dimeglumine) or the Group III agent gadoxetic acid may be performed without any patient informed consent.
- Qualifying statements:
  - Gadopentetate dimeglumine, gadodiamide, and gadoversetaminde are considered absolutely contraindicated [20–22]. The risk of NSF when one of these agents is used in AKI or severe renal impairment is estimated to be between 1%-7% [8]; 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.
  - 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) [23,24]; however, there are cases of NSF reported when patients have received standard vendor recommended dosing [25]. The panel felt there is insufficient evidence to support the notion that reducing the dose of GBCA beyond standard vendor suggested dosing further minimizes the risk of NSF and studies evaluating the minimum required dose of GBCA to maintain diagnostic accuracy of MRI are lacking.
  - Patients should not receive multiple doses of GBCA until sufficient time has passed to allow for excretion. Clearance of GBCA is partly agent specific and the panel suggests institutional review of the literature to estimate a safe interval between repeated injections. When repeat studies are anticipated, a macrocyclic or newer linear agent remain a requirement.
  - Informed consent is no longer recommended when administering Group II GBCA or the Group III agent gadoxetic acid when GBCA enhanced MRI is considered medically necessary with no alternative test available for patients with AKI, severe CKD or on dialysis.
  - Patients should be monitored for signs and symptoms of NSF when they have received a GBCA with known 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 2-year period following the administration of GBCA; however, a case of NSF occurring up to 9 years after administration of GBCA has been reported [26]. 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 compared to macrocyclic non-ionic GBCA or macrocyclic GBCA versus gadobenate dimeglumine or gadoxetic acid 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 gadoxetic acid remain 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 2-3 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 1 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 [27,28].
  - 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 [29–32].
  - Multiple frequent dialysis sessions have been previously advocated to promote gadolinium clearance [33,34]; however, there are no formal studies showing that these practices reduce the incidence of NSF [28]. 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 [29,35]. 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 [36]. Patients on PD also have residual kidney function, which can provide additional GBCA clearance. Thus, though increasing the number of exchanges (eg, 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 [31,37–39]. 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 [29], 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 m^2 who are deemed to require GBCA; however, in patients who are dialysis dependent the dialysis service should be contacted to coordinate anticipated changes in HD scheduling and for patients on PD to consider potential alterations in PD prescription.

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

5. Acute Kidney Injury

- Patients with AKI should be managed similar to those with eGFR < 30 mL/min/1.73 m^2 (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.
  - Cases of NSF with eGFR >30 mL/min/1.73 m^2 in patients with AKI have been documented [16,17], and patients with AKI risk level for NSF should be considered separately from absolute reference to eGFR.

6. Pediatric Patients

- Pediatric patients with severely reduced kidney function (eGFR < 30 mL/min/1.73 m^2), 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 [38,40]. There is no convincing evidence that

pediatric patients have an increased risk compared to adults.
  - When eGFR is calculated, it should be calculated using the bedside Schwartz equation [41,42].
  - eGFR during the neonatal period is lower especially in preterm infants and serum creatinine is not a reliable marker [43–45].

7. Outpatient Screening for Renal Function Prior to GBCA Administration

- Screening for renal function in outpatients with patient questionnaires at time of ordering GBCA enhanced MRI, scheduling of GBCA enhanced MRI or at the time of GBCA enhanced MRI to identify patients with possible renal dysfunction is no longer recommended when using Group II GBCAs or the Group III agent gadoxetic acid.
- Qualifying Statements:
  - The lack of any new unconfounded cases of NSF attributed to Group II GBCAs or the Group III agent gadoxetic acid in 2017-2018 despite more liberal use of GBCAs in at risk patients makes screening for renal function an unnecessary time consuming, costly process which presents a potential barrier to timely patient access to MRI and imposes unnecessary complexity on health care systems and morbidity on patients.
  - Screening for patients on hemodialysis is recommended at time of MRI ordering, scheduling, and at time of MRI to ensure that timely hemodialysis has been arranged following GBCA enhanced MRI (see Guideline 4).
  - In outpatients with serum creatinine results already available (with the exception of those with AKI) at time of ordering GBCA-enhanced MRI, scheduling of GBCA-enhanced MRI or at time of GBCA-enhanced MRI (regardless of date of results), calculation of eGFR is no longer necessary or recommended when using Group II GBCAs or the Group III agent gadoxetic acid prior to GBCA administration.