Prevention of Gadolinium-Induced Toxicity in Adults

Gadolinium-based contrast (GBC) agents are safe, and toxicity is exceedingly rare. This guideline outlines pregnancy risks; reviews two issues that can be encountered with gadolinium (allergies and nephrogenic systemic fibrosis [NSF]); and describes agent-specific indications for gadolinium. This guideline was developed primarily for non-emergent imaging studies. Emergency study indications may fall outside of this guideline; therefore, further communication between the requestor and the radiology attending is indicated.

**Pregnancy Testing**

- GBC agents are not currently recommended for use during pregnancy.
- GBC is regarded as a category C substance for use in pregnancy (there is evidence of growth retardation in the fetus from animal models, but human data are lacking).
  - It should be avoided unless benefit outweighs potential (although unknown) risks. Advice should be sought from the Radiologist as to whether the exposure is justified if part of an emergency procedure.

**Determine Pregnancy Prior to Diagnostic Imaging Procedure:** Refer to Imaging Pregnancy Policy PC-54

- **Breastfeeding:** Evidence suggests that only a small proportion (< 0.04%) of the maternal dose of gadolinium passes into the breast milk, and only a minute proportion is systemically absorbed from the infant gut. Consequently, the American College of Radiology Manual on Drugs and Contrast Media: Version 9; 2013 and the European Society of Urogenital Radiology (ESUR) Guideline both consider it unnecessary to stop breastfeeding following gadolinium contrast agents.

**Gadolinium Allergies**

- Acute adverse reactions to gadolinium are rare. The rate seems to be higher in women with abdominal MRI, with history of prior allergic reactions, and with use of gadobenate dimeglumine and gadoteridol. The reactions may be fewer with use of nonionic linear GBC agents.
- With a history of prior reaction to a GBC contrast agent, every effort should be made to identify the specific GBC agent so that a different GBC agent can be used if it is required again.

**Pre-Treatment for Previous Allergies to Gadolinium**

- Assess allergies and medications and provide relevant education to all patients (by technologist/nurse).
- Define previous known allergy-like symptoms (0.004- 0.7%) as mild, moderate, or severe (see classifications of severity and manifestations of adverse reactions below).

For safe practice, pre-medication is recommended in all patients with a prior history of immediate (within an hour of exposure) moderate to severe allergy to gadolinium or iodinated contrast media.

- There are rare patients with allergic reactions to iodinated contrast media who also react to gadolinium, despite pre-medication.
  - All patients with moderate/severe reactions to gadolinium should have the study scheduled in a hospital setting (East or Main).

**Routine Procedures (Patients with a Suspected Moderate / Severe Gadolinium Allergy)**

- Prednisone 50 mg PO at 12 hours, 6 hours, and 1 hour pre-test in adults.
- Diphenhydramine (Benadryl®) 50 mg PO/IV 1 hour pre-test in adults.
- If previous mild reaction such as tissue reaction (hives), switch to different gadolinium contrast agent and give oral or sublingual Benadryl 50 mg prior to the contrast administration.

**Emergent Procedures (Patients with a Suspected Moderate / Severe Gadolinium Allergy)**

- Hydrocortisone 200 mg IV, immediately and every 4 hours until completion of the procedures in adults
- Diphenhydramine (Benadryl®) 50 mg PO/IV or IM) 1 hour pre-test in adults

**Allergy Symptoms Developed During a Gadolinium Contrast Study**

*(In patients with no previous history gadolinium allergy)*

**Mild:** Signs and symptoms appear self-limited without evidence of progression (e.g., limited urticaria with mild pruritus, transient nausea, one episode of emesis), and include:

- Nausea, vomiting
- Cough
- Warmth
- Headache
- Dizziness
- Shaking
- Altered taste

- Itching
- Pallor
- Flushing
- Chills, sweats
- Rash, hives, nasal stuffiness
- Swelling (eyes, face)
- Anxiety

**Treatment:** Requires observation (60 min) to confirm resolution and/or lack of progression, but usually no treatment.
Moderate / Severe: Signs and symptoms are more pronounced. Moderate degree of clinically evident focal or systemic signs or symptoms that could be life-threatening, including:

- Tachycardia / bradycardia
- Hypertension
- Generalized or diffuse erythema
- Dyspnea
- Bronchospasm, wheezing
- Laryngeal edema
- Mild hypotension

**Treatment:** Requires prompt recognition and aggressive treatment; manifestations and treatment frequently require hospitalization. Use of emergency response kit is indicated.

**IMAGING EMERGENCY RESPONSE KIT**

**Note:** The above classifications (mild, moderate, severe) do not attempt to distinguish between allergic-like and non-allergic-like reactions.

**Nephrogenic Systemic Fibrosis (NSF)**

- Exposure to GBC agents may facilitate the development of nephrogenic systemic fibrosis (NSF), a multi-system disease reported almost exclusively in patients suffering from acute renal failure or chronic severe renal insufficiency with markedly reduced estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m²;

- The predominant clinical manifestation is a progressive, painful, sclerosing, dermopathy leading to functional disability. A skin biopsy is necessary to confirm the diagnosis. Patients may also develop widespread fibrosis involving many organs, which can be fatal.

- The onset of disease following exposure to GBC agents is highly variable, ranging from 6-1990 days. While GBC agents used for magnetic resonance are clearly linked with NSF, the pathogenic mechanisms are unknown. It has recently been reported that circulating gadolinium can be identified months to years following GBC agent exposure. Gadolinium complexes have also been found in skin biopsies of affected individuals.

**Risk factors for NSF include the following:**

- Hepatorenal syndrome
- Liver transplant – perioperatively
- Acute renal failure
- Chronic kidney disease (CKD) (GFR < 30 ml/min)
- Iron overload conditions

**Note:** Among patients with gadolinium exposure, NSF onset could be delayed to as long as 18 months.

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**Patients with Decreased Kidney Function, Cr Cl < 30, or High Risk for NSF**

Due to the temporal lag between serum creatinine values and actual glomerular filtration rates, it is not possible to determine whether a given patient is in acute kidney injury based on a single eGFR determination. Accordingly, caution should be exercised in use of gadolinium in patients with known or suspected acute kidney injury regardless of measured serum creatinine or calculated eGFR.

If possible, scan without contrast or with another modality without contrast.

If NOT possible, consider macrocyclic agent (see chart).

- Consultation with referring physician and Nephrologist.
- Document medical necessity and informed consent by radiologist and/or requesting physician.

**Dialysis Considerations**

Hemodialysis immediately after gadolinium exposure is effective in removing the free -- but not tissue-bound -- gadolinium. Hence, it is not clear if immediate hemodialysis lowers the risk or severity of NSF.

Nephrologist will determine dialysis and length of treatment. Coordination of dialysis treatment and contrast administration will be planned prior to examination.

- Patients already on dialysis should receive hemodialysis
- GFR < 30 ml/min/1.73m²:
  - **With functioning vascular access,** patients should receive hemodialysis within 3 hours of contrast exposure.
  - **Without functioning vascular access** – assess risk/ benefit of hemodialysis vs. risk of NSF.

Every effort should be made to postpone the gadolinium imaging study in patients with acute kidney injury.

**General Dialysis Guidelines for High-Risk NSF Patients**

- No IV iron during dialysis.
- Perform two dialysis sessions within 24 hours of receiving contrast.
- Recommend a third dialysis session if clinically safe.
- Three consecutive dialysis sessions have been shown to remove 99% of gadolinium.
- Hemodialysis for a minimal duration of 4 hours for each session.

**Note:** Options vary with regard to whether multiple dialysis sessions are more beneficial than a single session in reducing the risk of NSF. The OSUWMC Nephrology Department recommends the above.
# MR Contrast Agent Selection

<table>
<thead>
<tr>
<th>MR Contrast Agent</th>
<th>Clinical Use</th>
<th>Safety Indications</th>
<th>Dose</th>
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</table>
| Dotarem*           | General use agent | Chronic kidney disease with eGFR <30**  
| (gadoterate meglumine) |  
| (Macrocyclic / Ionic / Extra-cellular) | Acute renal failure** | 0.1 mmol/kg |
| Gadavist           | Angiography | Allergies to other MRI contrast agents | 0.1 mmol/kg |
| (gadobutrol) |  
| (Macrocyclic / Non-Ionic / Extra-cellular) |  |
| MultiHance         | Clinical trials requiring MultiHance  
| (Gd-BOPTA) |  
| (Linear / Ionic / Extra-cellular) | Special indications as requested  
|  | Allergies to other MRI contrast agents | 0.1 mmol/kg |
| Eovist             | Hepatobiliary imaging  
| (Gadoxetate Disodium) |  
| (Linear / Ionic / Extra-cellular) | Special indications as requested | 0.025 mmol/kg |

*Default general use agent  
**Agent may be considered in patients at high risk for NSF (chronic kidney disease with eGFR < 30, acute renal failure) if diagnostic information is essential and not available with non-contrasted MRI or other modality.

**CAUTION:**

- If using higher than recommended dose:  
  - Documentation of medical necessity and informed consent from the patient / guardian must be completed

- If repeat gadolinium dosing within 24 hours  
  - Discuss with Radiology or Cardiology Department as appropriate.  
  - eGFR should be obtained. If normal, proceed per routine.  
  - If GFR < 30 ml/min, documentation of medical necessity and informed consent from the patient / guardian must be completed

**Repeated use of gadolinium-based contrast agents**

The FDA is investigating the risk of brain deposits following repeated use of gadolinium-based contrast agents. This has been observed in as little as four contrasted MRI scans with GBCAs. It is currently unknown whether these gadolinium deposits are harmful or have any adverse health effects.
References


Quality Measures

- Cases of NSF (nephrogenic systemic fibrosis)
- Adverse events or allergic reactions associated with gadolinium based contrast administration:
  - Hypersensitivity reactions (% of total injections: mild, moderate, severe)
  - Extravasation and injection site reactions (% of total injections)

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Disclaimer: Clinical practice guidelines and algorithms at The Ohio State University Wexner Medical Center (OSUWMC) are standards that are intended to provide general guidance to clinicians. Patient choice and clinician judgment must remain central to the selection of diagnostic tests and therapy. OSUWMC’s guidelines and algorithms are reviewed periodically for consistency with new evidence; however, new developments may not be represented.

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Associated Tool

- Adult eGFR calculator