The Use of Contrast Agents in Interventional Pain Procedures: A Multispecialty and Multisociety Practice Advisory on Nephrogenic Systemic Fibrosis, Gadolinium Deposition in the Brain, Encephalopathy After Unintentional Intrathecal Gadolinium Injection, and Hypersensitivity Reactions

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This Practice Advisory presents a comprehensive and evidence-based set of position statements and recommendations for the use of contrast media in interventional pain procedures. The advisory was established by an international panel of experts under the auspices of 11 multinational and multispecialty organizations based on a comprehensive review of the literature up to December 31, 2019. The advisory discusses the risks of using gadolinium-based contrast agents. These include nephrogenic systemic fibrosis, gadolinium brain deposition/retention, and encephalopathy and death after an unintentional intrathecal gadolinium injection. The advisory provides recommendations on the selection of a specific gadolinium-based contrast agent in patients with renal insufficiency, those who had multiple gadolinium-enhanced magnetic resonance imaging examinations, and in cases of paraspinal injections. Additionally, recommendations are made for patients who have a history of mild, moderate, or severe hypersensitivity reactions to contrast medium. (Anesth Analg XXX;XXX:00–00)

WHY WAS THIS GUIDELINE DEVELOPED?

Interventional pain physicians often switch to a gadolinium-based contrast agent when a patient reports a previous hypersensitivity reaction to iodinated contrast medium. However, there are risks associated with the use of gadolinium: nephrogenic systemic fibrosis is an established risk; gadolinium brain deposition/retention is a trending risk; and, encephalopathy/death after an unintentional intrathecal gadolinium injection is a newly reported but catastrophic risk. Additionally, recent publications showed a low risk of hypersensitivity reaction when contrast medium is injected extravascularly, which is the intended target of pain interventions. As these issues impact the use of contrast agents in interventional pain procedures, 11 multisociety, multispecialty organizations developed a Practice Advisory on this topic.

WHAT OTHER GUIDELINES ARE AVAILABLE ON THIS TOPIC?

None.

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Contrast agents are obligatory in interventional pain procedures to ensure delivery of the diagnostic and/or therapeutic agent to the target tissue or anatomic space, and to exclude off-target delivery (intravascular, subarachnoid), which may incur patient risk or diminish the efficacy or specificity of the procedure. The primary contrast agents used for this purpose have historically been iodinated contrast medium (ICM) due to their long history in medicine and ability to delineate vascular and tissue structures under fluoroscopic observation. Patients may describe a hypersensitivity reaction (HR) during prior administration of ICM, ranging from hives to laryngeal edema or even cardiovascular collapse. In these circumstances, the physician must choose either to not perform the procedure, proceed without injecting a contrast agent, premedicate the patient to lessen the likelihood of a serious adverse event, or use an alternative contrast agent, most commonly a gadolinium-based contrast agent (GBCA). Although these latter agents were developed for intravascular enhancement during magnetic resonance imaging (MRI) studies, they also exhibit radiopacity (although to a lesser degree than ICM) and can be used to document on-target delivery and exclude off-target delivery. They do not appear to exhibit hypersensitivity cross-reactivity with ICM.

GBCAs represent a significant advancement in clinical medicine. Their use allows the detection of lesions in the brain on MRI, led to contrast-enhanced MR angiography, and enables the assessment of tissue perfusion. Early clinical reports of the use of GBCAs appeared in 1984, and their clinical use was approved by the Food and Drug Administration (FDA) in 1988. The GBCAs differ in their structure and ionicity (Table 1). GBCAs have since been used in >300 million patients worldwide.

Three recent developments impact the continued use of GBCAs as an alternative to ICM during interventional pain procedures. These include nephrogenic systemic fibrosis (NSF) in patients with preexisting renal disease, and gadolinium deposition/retention in the brain from repeated administration of GBCAs, and encephalopathy from unintentional intrathecal (IT) injection of GBCA. Appearance of these new reports of previously unrecognized adverse events resulted in calls for caution in the continued use of GBCA, an informed discussion with the patient, and the creation of a guideline.

NATURE OF INTERVENTIONAL PAIN PROCEDURES
Contrast medium is used to document on-target tissue delivery and to exclude flow to off-target tissue in procedures including but not limited to epidural, paravertebral, intravertebral (kyphoplasty), joint (eg, facet, sacroiliac, hip, and knee), sympathetic nerve or ganglia (stellate ganglion, lumbar sympathetic plexus, and visceral sympathetic blocks), and deep muscle (piriformis) injections. These procedures are performed frequently; approximately 2 million epidural injections were performed annually in the US Medicare population alone from 2008 to 2014.
In most instances, the volume of contrast injected is between 1.5 and 3 mL and may be repeated. These injection procedures are distinct from diagnostic radiologic studies such as computed tomography (CT) or MRI in which large volumes of contrast are injected intravascularly. Most patients seen in a pain clinic are referred, and their medical issues have been identified and treated. Injections are usually not performed on an emergency basis as the patient’s pain can be partially controlled with medications and other nonpharmacologic alternatives until a procedure can be scheduled. Although injections for pain may be repeated, it is typically after a 2–4 weeks observation of the patient’s response.

Our statements and recommendations pertain to interventional pain procedures where fractionated doses totaling ≤10 mL of contrast medium are injected in the extravascular space unless the needle tip is unintentionally positioned in an intravascular compartment.

**Method**

Eleven multispecialty organizations were involved in the formulation of this PA. These include the American Academy of Pain Medicine, the American Society of Neuroradiology, the American Society of Regional Anesthesia and Pain Medicine, the British Pain Society, the Canadian Pain Society, the European Pain Federation (EFIC), the Korean Pain Society, the Society for Interventional Radiology, the Spine Intervention Society, the World Allergy Organization, and the World Institute of Pain. Representatives of each society are listed in the Appendix. Conflicts of interest were noted for each participant. In addition, experts who have published on the topic were invited as thought leaders.

These practice recommendations followed due process for development of practice advisories including identification of the literature on specific clinical questions, selection and grading of the available evidence, use of the Delphi process to reach consensus on the PA, and development and grading of the strength of the recommendations. Each of the 4 topics was appointed a leader and 2–3 additional members, inclusive of at least 1 pain medicine physician, either an anesthesiologist, radiologist, or a physical medicine and rehabilitation specialist. Additionally, an allergist was part of the group that drafted the initial statements and recommendations on HRs to contrast media. Each group searched the literature (PubMed; EMBASE; Cochrane Central Register of Controlled Trials; relevant references from articles, reviews, and book chapters) based on key terms and concepts from the development group and the Writing Committee. Medical subject heading (MeSH) terms included “nephrogenic systemic fibrosis,” “brain deposition/retenion from gadolinium,” “encephalopathy from IT gadolinium,” and “HRs to contrast media.” The modified Delphi process was followed in the formulation of the PA. We used a modified version of the US Preventive Services Task Force (USPSTF) classification when grading the statements and recommendations (Supplemental Digital Content, Table, http://links.lww.com/AA/D406). The initial statements and recommendations were defined by each section and discussed with the PA co-leaders (H.T.B. and T.P.M.), then sent to participants for voting. For the statements receiving negative votes, a discussion

### Table 1. Gadolinium-Based Contrast Agents

<table>
<thead>
<tr>
<th>Gadolinium-based contrast agent</th>
<th>Type, stability</th>
<th>Concentration mmol/mL*</th>
<th>Usual MRI dose mmol/kg (mL dose in 70-kg person)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadodiamide (Omniscan)</td>
<td>Nonionic linear, low</td>
<td>0.5</td>
<td>0.1 (14)</td>
</tr>
<tr>
<td>Gadoversetamide (Optimark)</td>
<td>Nonionic linear, low</td>
<td>0.5</td>
<td>0.1 (14)</td>
</tr>
<tr>
<td>Gadobenate dimeglumine (MultiHance)</td>
<td>Ionic linear</td>
<td>0.5</td>
<td>0.1 (14)</td>
</tr>
<tr>
<td>Gadopentetate dimeglumine (Magnevist)</td>
<td>Ionic linear</td>
<td>0.5</td>
<td>0.1 (14)</td>
</tr>
<tr>
<td>Gadofosveset trisodium (Ablavir, Vasovist)</td>
<td>Ionic linear</td>
<td>0.25</td>
<td>0.03 (8.4)</td>
</tr>
<tr>
<td>Gadotreotide disodium (Eovist, Primovist)*</td>
<td>Ionic linear</td>
<td>0.25</td>
<td>0.025 (7)</td>
</tr>
<tr>
<td>Gadoteridol (ProHance)</td>
<td>Nonionic macrocyclic</td>
<td>0.5</td>
<td>0.1 (14)</td>
</tr>
<tr>
<td>Gadobutrol (Gadavist)</td>
<td>Nonionic macrocyclic</td>
<td>1</td>
<td>0.1 (7)</td>
</tr>
<tr>
<td>Gadoterate meglumine (Dotarem)</td>
<td>Ionic macrocyclic</td>
<td>0.5</td>
<td>0.1 (14)</td>
</tr>
</tbody>
</table>

*Usual radiology dose for MRI of the brain or body parts.

*bUsed for liver MRI imaging.

Abbreviation: MRI, magnetic resonance imaging.
ensued with the dissenters, the result of which was either reversal of the dissenting vote or revision of the statement in question with subsequent revote by all the participants. All of the participants voted on all statements except for the representatives of the World Allergy Organization who voted only on the statements and recommendations relevant to HRs to contrast media. One organization, the American Society of Neuroradiology, joined after the statements were approved. Their representatives vetted the statements on gadolinium brain deposition/retention and their Board of Directors (BOD) approved the statements and recommendations on that topic.

Randomized clinical trials are considered the gold standard in judging whether an intervention does more good than harm. Clinicians and developers of guidelines have considered randomized trials and meta-analyses as primary sources on which they base their levels of evidence and strength of their recommendation. However, as early as 1996, Sackett et al18 recommended the integration of individual clinical expertise with the best available external evidence found on a systematic search of the literature, in making decisions. By individual clinical experience, they meant the competence and judgment clinicians acquire through their clinical practice and clinical experience. Recently, the evidence-based medicine (EBM) group refined their definition of “evidence-based” to “best available evidence.” They concluded that best available evidence includes the use of observational studies, case reports, and clinician experience in making recommendations consistent with “the circumstances and their values.”19 They noted that

### Table 2. Statements and Recommendations in Relation to Nephrogenic Systemic Fibrosis

<table>
<thead>
<tr>
<th>Statements</th>
<th>Level of certainty</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The risk factors for compromised renal function include age &gt;60 y, hypertension, diabetes, single kidney, kidney surgery, history of kidney malignancy, and kidney transplant.</td>
<td>High</td>
<td>Moderate</td>
</tr>
<tr>
<td>2. The development of NSF after GBCA-enhanced intravenous MRI is higher with the least stable linear nonionic GBCAs gadodiamide and gadoversetamide and the linear/ionic GBCA gadopentetate dimeglumine.</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>3. Patients with mild renal impairment (CKD stage 2; eGFR between 60 and 89 mL/min/1.73 m²) are NOT at an increased risk of NSF after a GBCA-enhanced interventional pain procedure.</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>4. The risk of developing NSF after a GBCA-enhanced interventional pain procedure in patients with moderate renal impairment (CKD stage 3; eGFR between 30 and 59 mL/min/1.73 m²) is very low.</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>5. In CKD stages 4 (eGFR between 15 and 29 mL/min/1.73 m²) and 5 (eGFR &lt;15 mL/min/1.73 m²), AKI or dialysis, intravenous use of linear nonionic GBCAs gadodiamide and gadoversetamide and the linear ionic GBCA gadopentetate carry risk for development of NSF; the risk with GBCA-enhanced interventional pain procedures is not known.</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patients at risk of developing NSF should be identified before administering a GBCA. Patients with CKD stage 4 or kidney failure (CKD stage 5), AKI and patients on dialysis should be noted.</td>
<td>A</td>
</tr>
<tr>
<td>2. In interventional pain procedures, whenever GBCA is necessary, it’s indication should be stated and the gadolinium formulation and total dose adequately registered.</td>
<td>A</td>
</tr>
<tr>
<td>3. In interventional pain procedures, screening for renal function may not be necessary with the stable macrocyclic GBCAs (gadobutrol, gadoteridol, and gadoterate) and the linear ionic GBCA gadobenate dimeglumine.</td>
<td>A</td>
</tr>
<tr>
<td>4. The lowest possible dose of GBCA to obtain necessary clinical information should be administered.</td>
<td>A</td>
</tr>
<tr>
<td>5. In interventional pain procedures, the low-risk macrocyclic (gadoteridol, gadobutrol, and gadoterate) and medium-risk linear/ionic (gadoxetate and gadobenate dimeglumine) GBCAs can be administered in patients with moderately reduced kidney function (CKD 3, eGFR between 30 and 59 mL/min/1.73 m²).</td>
<td>B</td>
</tr>
<tr>
<td>6. In interventional pain procedures, when GBCA is necessary, the low-risk macrocyclic (gadoteridol, gadobutrol, and gadoterate) and medium-risk linear/ionic (gadoxetate and gadobenate dimeglumine) GBCAs may be used with caution in patients with severely reduced kidney function (CKD 4, eGFR 15–29 mL/min/1.73 m²; CKD 5, eGFR &lt;15 mL/min/1.73 m²) and those on dialysis.</td>
<td>B</td>
</tr>
<tr>
<td>7. In interventional pain procedures, GBCAs in the high-risk category (gadodiamide, gadoversetamide, and gadopentetate dimeglumine) are contraindicated in patients with CKD 4 or 5, patients with end-stage renal disease on chronic hemodialysis, and in patients with AKI.</td>
<td>A</td>
</tr>
<tr>
<td>8. In an anuric patient with no renal function, GBCA should be avoided. Instead, iodinated contrast media should be considered if the use of contrast is essential. In this instance, the smallest amount should be used.</td>
<td>A</td>
</tr>
</tbody>
</table>

Interventional pain procedures involve the extravascular injection of small doses (< 3 mL) of contrast medium.

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GBCA, gadolinium-based contrast agent; MRI, magnetic resonance imaging; NSF, nephrogenic systemic fibrosis.
deliberate interpretations are essential regardless of the type of evidence and that optimal decisions balance benefits and harms, rather than to only grade the quality of available evidence.19 For this reason, we used “best available evidence” in providing levels of certainty in some of our recommendations when randomized clinical trials or meta-analyses did not exist, but the evidence suggested obvious and significant clinical benefit.

RESULTS
The statements and recommendations for NSF, gadolinium brain deposition/retention, and encephalopathy after unintentional IT injection of gadolinium were approved after 1 revision while the HRs to contrast media required 3 revisions (Tables 2–5). The final statements and recommendations for all 4 topics were unanimously approved by all participants. The BODs or Executive Committee of each organization approved the final recommendations.

DISCUSSION

Nephrogenic Systemic Fibrosis

Dissociation of Linear and Macroyclic GBCAs. Free gadolinium ion (Gd³⁺) is toxic and must be bound to chelating agents before safe use in humans. GBCAs are either linear or macrocyclic in structure based on how the chelating agent contains the gadolinium ion.20 Linear GBCAs have an open-chain chemical structure in which the chelating agent is wrapped around the gadolinium ion. This is in contrast to macrocyclic agents in which the gadolinium ion is caged in the center of a chelating agent.21,22 Macro cyclic agents are more stable and are less likely to dissociate from their chelating agent. Among linear GBCAs, ionic GBCAs are more thermodynamically stable than nonionic GBCAs and therefore release less free gadolinium than nonionic agents (Table 1). The risk of gadolinium toxicity differs among available formulations based on structural classifications and dissociation, thermodynamic, and kinetic stability constants. As such, it is important to note that volume recommendations regarding safety cannot be assumed to apply to all formulations of GBCAs.

NSF: Pathophysiology. NSF is a systemic inflammatory condition accompanied by cutaneous and systemic symptoms resulting from gadolinium administration. Preexisting renal insufficiency is the principal risk factor. The pathophyslogic mechanisms of NSF include the release of free gadolinium into the tissues, internalization of the gadolinium into the phagosome, which then ruptures, releasing the gadolinium into the cytosol, and production of profibrotic cytokines (e.g., transforming growth factor [TGF]-beta, interleukin [IL]-4, IL-6, and IL-13), resulting in fibroblast formation.23 Gadolinium is a lanthanide...
element; the fibrogenic effect of lanthanides has been recognized since 1983. Lanthanides also enhance the polymerization of skin collagen in vitro and may be involved in fibril formation. The early symptoms of NSF include leg pain, pruritus, swelling, and erythema. Later symptoms include thickened skin and subcutaneous tissue resulting in stiffness and contractures with difficulty in ambulation. Fibrosis of internal organs (heart, liver, lungs, muscle, and diaphragm) can occur resulting in cachexia and contractures with difficulty in ambulation. NSF has been recognized since 1983. Lanthanides also enhance the polymerization of skin collagen in vitro and may be involved in fibril formation. The early symptoms of NSF include leg pain, pruritus, swelling, and erythema. Later symptoms include thickened skin and subcutaneous tissue resulting in stiffness and contractures with difficulty in ambulation.

Thomsen et al categorized GBCAs according to the risk of development of NSF. GBCAs with the highest risk, because of the greatest potential for dissociation from their chelating agent, include the linear nonionic GBCAs gadodiamide (Omniscan, GE Healthcare, Marlborough, MA) and gadoversetamide (Optimark, Liebel-Flarsheim Company LLC, Raleigh, NC) and the linear ionic gadopentetate (Magnevist, Bayer HealthCare Pharmaceuticals Inc, Whippany, NJ) (see Table 1). The intermediate risk group consists of the linear ionic agents gadobenate (MultiHance, Bracco Diagnostics Inc, Princeton, NJ), gadoxetate (Eovist [Bayer HealthCare Pharmaceuticals Inc, Whippany, NJ] and Primovist [Bayer Schering AG, Berlin-Wedding, Germany]), and gadofesetetam (Vasovist, Lantheus Medical Imaging, North Billerica, MA). The lowest risk group, that is, the GBCAs with the lowest likelihood of dissociation, includes the macrocyclic agents gadoteridol (ProHance, Bracco Diagnostics Inc, Princeton, NJ), gadobutrol (Gadavist, Bayer HealthCare Pharmaceuticals Inc, Whippany, NJ) and gadoterate (Dotarem, Guerbet, Raleigh, NC). The American College of Radiology (ACR) classified GBCAs according to their association with NSF: group I (agents with greatest number of NSF cases): gadodiamide and gadopentetate dimeglumine; group II (few, if any, unconfounded cases): gadobenate dimeglumine; group III (most likely to dissociate): gadobutrol; group IV (least likely to dissociate): gadoteridol.
Table 5. Statements and Recommendations in Relation to Hypersensitivity Reactions From Iodinated Contrast Medium

<table>
<thead>
<tr>
<th>Statements</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Nonimmunologic anaphylaxis, also previously termed anaphylactoid reaction or idiosyncratic/nonallergic hypersensitivity reaction, comprise at least 80% of HRs to ICM.</td>
<td>Strength of recommendation: A</td>
</tr>
<tr>
<td>2. HRs to GBCA are less common than HRs to ICM.</td>
<td>Level of certainty: Moderate</td>
</tr>
<tr>
<td>3. The greatest risk factor for HR to CM is history of HR. Other risk factors include multiple allergies, atopic tendencies including asthma, female sex, severe cardiovascular disease, repeated exposure to contrast media, and intravascular compared to extravascular (oral, gastrointestinal, genitourinary, abdominal cavity, and subarachnoid) exposure to radiocontrast media. Seafood intolerance is not a risk factor.</td>
<td>Level of certainty: High</td>
</tr>
<tr>
<td>4. Reexposure to CM in a patient with a history of HR may result in recurrent HR, especially with intravascular administration of large volumes.</td>
<td>Level of certainty: High</td>
</tr>
<tr>
<td>5. Most HRs occur within 1 h, usually within 20 min, of intravenous ICM administration. Immediate HR is more common with ionic than nonionic ICM. The reaction intensity may be mild, moderate, severe, or life-threatening.</td>
<td>Level of certainty: Low</td>
</tr>
<tr>
<td>6. Late HRs may occur 1 h to 1 wk after CM administration. Most of the delayed HRs are usually mild and cutaneous in nature. However, some HRs which occur 1–6 h after CM administration can be severe or life-threatening as immediate HRs.</td>
<td>Level of certainty: High</td>
</tr>
<tr>
<td>7. Premedication with corticosteroids and antihistamines is highly, but not completely effective in preventing HR in all patients.</td>
<td>Level of certainty: Moderate</td>
</tr>
<tr>
<td>8. Premedication with corticosteroids and antihistamines does not increase the risk of HR to CM after an interventional pain procedure, even in patients with a history of HR.</td>
<td>Level of certainty: Low</td>
</tr>
<tr>
<td>9. Beta-blocker use does not increase the risk of HR to CM after an interventional pain procedure that involves the extravascular injection of less than 10 mL of CM in patients with a history of prior HR after an intravenous ICM-enhanced radiologic examination is low.</td>
<td>Level of certainty: Moderate</td>
</tr>
<tr>
<td>10. HRs to nonionic linear GBCAs are less common than HRs to ionic linear GBCAs.</td>
<td>Strength of recommendation: A</td>
</tr>
</tbody>
</table>

Recommenations

1. When a HR occurs, the interventional physician should document the incident. In the report, the physician should note the name and volume of the CM that was injected. | Strength of recommendation: A |
| 2. The physician should be notified immediately if a patient scheduled for procedure with contrast injection has a history of HR to CM. The specific type, dose, route of CM used and severity of reaction, symptom management, sequelae and results of laboratory investigations should be documented contemporaneously in the medical record. | Strength of recommendation: A |
| 3. Patients with a history of mild HR to CM may receive appropriate pretreatment and receive a different low-osmolar nonionic ICM if culprit ICM is known. Patients with relative contraindications to steroid administration should receive pretreatment only if benefits outweigh the risks and should be counseled as to expected adverse effects. | Strength of recommendation: A |
| 4. Patients with history of moderate or severe HR to ICM should be pretreated and injected with a different low-osmolar nonionic ICM, if culprit ICM is known, and if alternative contrast choices such as GBCM or air are contraindicated. These patients may be considered for referral to an allergist for evaluation, explanation of HRs, and optimization before elective procedures using CM. | Strength of recommendation: B |
| 5. Prophylaxis for late reactions, in the absence of an immediate reaction, is not recommended and treatment should be exclusively symptomatic. | Strength of recommendation: A |
| 6. Patients with a history of true IgE-mediated allergic HR, and a positive skin test (done within 6 mo of HR) should receive a premedication of steroid and H1 antihistamine medication. | Strength of recommendation: A |
| 7. Patients with a history of true IgE-mediated allergic HR should be injected with a different ICM that is skin-test negative. | Strength of recommendation: B |
| 8. If CM must be administered within 4–12 h to a patient qualifying for premedication, the patient should receive 40 mg methylprednisolone or 200 mg hydrocortisone intravenously every 4 h and 50 mg diphenhydramine intravenously 1 h before receiving CM. | Strength of recommendation: A |
| 9. In patients who report allergy to methylprednisolone or hydrocortisone, intravenous dexamethasone 7.5 mg or betamethasone 6 mg may be substituted. | Strength of recommendation: A |
| 10. Recommendations for duration of monitoring in patients with history of HR to CM | Duration of monitoring for HR following CM administration |
| Clinical setting | Premedicated patients with history of mild HR and no symptoms following exposure to CM | 30 min |
| | Nonmedicated patients with history of mild HR and no symptoms following exposure to the same CM | 30 min–1 h |
| | Patients with a history of moderate/severe HR but no reaction in the first 15 min (irrespective of premedication status) | 30 min |
| | 11. Acute HR should be managed symptomatically | Strength of recommendation: A |
| | 12. For the staff associated with interventional pain procedures, there should be an annual review of the following: (a) grading system of the severity of hypersensitivity reactions (mild, moderate, severe, or life-threatening); (b) components of documentation for witnessed or historical HRs; (c) emergency preparedness of the staff (who calls for rapid response); and (d) steps involved in cardiopulmonary resuscitation. | Strength of recommendation: A |
| | 13. Emergency equipment, including airway supplies, defibrillator, and cardiovascular support medications should be immediately available during interventional procedures involving administration of CM, especially in patients with history of HR to CM. Manufacturer and/or institutional protocols should be followed regarding maintenance and care of emergency resuscitation equipment and medications. | Strength of recommendation: A |

*The recommended durations pertain to monitoring for possibility of a HR, in patients who had no sedation. Note that at least 15 min usually elapse from the time the CM is injected to the time the patient is in the recovery room. For patients who have sedation, additional time is usually observed as per institution’s protocol.

*Patients should be cautioned of the possibility of late HR. Immediate life-threatening CM HRs usually occurs within 1 h but severe life-threatening HRs can occur even after 6 hours. The duration of monitoring should be individually determined by the previous nature of CM HRs.

Abbreviations: CM, contrast medium; GBCA, gadolinium-based contrast agent; HR, hypersensitivity reaction; ICM, iodinated contrast medium; IgE, immunoglobulin E.
gadobenate dimeglumine, gadobutrol, gadoterate acid, and gadoteridol; and group III (data are limited; few, if any, confounded cases have been reported): gadoxetate disodium. Per a recent systematic review and meta-analysis, gadoteric acid is similar in its safety profile to ACR group 2 GBCAs with regard to NSF (and HR) but contains a lower potential for risk because of the smaller number of administrations in patients with severe renal disease.28 The European Society of Urogenital Radiology (ESUR), the Canadian Association of Radiologists (CAR), and the ACR have published guidelines on the use of GBCAs in relation to NSF. However, all relate to the use of GBCAs in radiologic diagnostic procedures involving intravascular administration, rather than use during interventional pain procedures.2,26,28,29

**STATEMENTS AND RECOMMENDATIONS**

The ACR, the CAR, and the ESUR guidelines stated that measurement of kidney function is not obligatory for the lowest risk GBCAs.2,29 We did not discuss routine screening of renal function in our PA as most patients evaluated in pain clinics are referred and patients with impaired kidney function will already have been identified. The risk factors are considered in detail (see Table 2), and interventional pain physicians should now be aware of situations that require further preprocedural evaluation. We also did not examine the readministration of the GBCAs since most injections for pain indications are repeated only after 2–4 weeks of observation. Regarding patients on hemodialysis, pain injections are very rarely emergencies, and these can usually be timed appropriately after discussion with the patient’s managing nephrologist.

Our statements note that after a GBCA-enhanced interventional pain procedure, patients with mild renal failure are not at risk for development of NSF and that patients with moderate renal impairment are at very low risk for development of NSF (Table 2). The ACR considered and the ESUR implied that the lowest risk GBCAs (group II agents: gadobenate dimeglumine, gadoteridol, gadoterate meglumine, and gadobutrol) present very low, if any, risk of development of NSF.2 Our statements regarding patients with mild and moderate renal failure are the same as the CAR guidelines; additional assurance is provided by the small volume and mostly extravascular location of injections for pain indications.

We recommend that the low-risk macrocyclic and medium-risk linear ionic agents can be administered in patients with chronic kidney disease (CKD) stage 3, and that they can be used with caution in patients with CKD stages 4 and 5 as well as those on dialysis; this is consistent with the CAR, ACR, and ESUR guidelines. A recent review and meta-analysis showed that the rate of NSF in patients with CKD stages 4 and 5 from group II GBCAs (gadobenate, gadobutrol, gadoterate, and gadoteridol) was 0 of 4093 (0%; upper bound of 95% confidence interval [CI], 0.07%).30 The authors concluded that the harms of withholding group II GBCAs for an indicated examination may outweigh the risk of NSF in these patients. For patients with severe renal disease and those on dialysis, the CAR guidelines recommend that the use of a GBCA be applied on a case-by-case basis.28 The risk of NSF after interventional pain procedures in these patients is not known because of a lack of data. For patients with no discernible renal function, we recommend that ICM be used in the smallest dose possible. This reflects the recent guideline published by the ACR and the National Kidney Foundation on the use of intravenous ICM in patients with kidney disease.31 Although the group commented that the risk of contrast-induced acute kidney injury is lower than previously thought, the lowest possible doses should still be administered in patients at higher risk for contrast-induced acute kidney injury.

**Gadolinium Deposition/Retention in the Brain**

The occurrence of high signal intensity in the dentate nucleus and globus pallidus in the brains of patients exposed to linear GBCAs was first reported by Kanda et al.32 In their study, 19 patients who had at least 6 contrast-enhanced MRI examinations using linear GBCAs showed increased signal intensity compared to 16 patients who had at least 6 unenhanced examinations. They noted that the dentate nucleus-to-pons and globus pallidus-to-thalamus signal intensity ratios in patients who had undergone contrast-enhanced examinations were significantly greater than those of patients who had undergone unenhanced examinations. In another study, Kanda et al33 evaluated autopsied brains of 5 patients exposed to linear GBCAs and detected gadolinium in all specimens. Although they also noted gadolinium in 5 subjects who had no history of GBCA administration, the gadolinium concentration was significantly higher in the GBCA group. Kanda et al34 also showed the strong association of linear GBCAs, in contrast to macrocyclic GBCAs, with brain deposition/retention similar to NSF and the lack of an association between gadolinium brain deposition and kidney function.33 McDonald et al35 confirmed the dose-response relationship between signal intensity and gadolinium exposure in decedents who had at least 4 gadolinium-enhanced brain MR examinations. Additionally, they noted undetectable levels of gadolinium in neuronal tissues from the dentate nucleus, pons, globus pallidus, and thalamus in patients who had not received GBCA.35 Other investigators confirmed the presence of gadolinium deposits in the brain and bone after a single-agent exposure with the more stable nongroup
I GBCAs gadobutrol, gadoteridol, gadobenate, and gadoxetate in patients with normal renal function. Interestingly, some investigators detected higher gadolinium levels in bone compared to the brain. The US FDA issued an initial warning, on December 21, 2017, that GBCAs are retained in the body, including the brain for months to years after receiving these drugs. Their warning was updated on September 20, 2018.

No definite clinical consequences of GBCA retention in the brain have been proven. A survey of patients in whom gadolinium had been administered reported bone/joint pain, headache, vision/ hearing change, flu-like symptoms, skin changes, digestive and chest symptoms within 6 weeks of exposure. However, these symptoms overlap with those of NSF, and the acute occurrence (66% of the respondents had symptoms immediately) suggests the lack of relationship between these symptoms and retention of gadolinium in the brain. A large population-based study (246,557 patients; 99,739 received gadolinium) demonstrated the incidence of Parkinsonism to be the same in patients who received at least 1 gadolinium dose (1.16%) compared to patients who had noncontrast enhanced MRI (1.17%). As knowledge on this area is incomplete and evolving, the National Institutes of Health convened an international meeting in 2018 to identify knowledge gaps and create a research roadmap on this topic. The experts concluded that the greatest priorities were to investigate whether gadolinium retention adversely affects the function of human tissues; if retention is causally associated with short- or long-term clinical manifestations of disease; and, whether vulnerable populations, including children, are at increased risk for experiencing clinical disease.

The CAR issued policy statements in relation to gadolinium deposition in the brain and also reviewed guidelines from 9 different national organizations and regulatory agencies. Most of the recommendations pertain to diagnostic radiologic procedures involving extravascular injections. Statements from these guidelines that are relevant to interventional pain medicine include restricting the use of GBCAs to only medically necessary procedures, not exceeding recommended dosages, avoiding repeated GBCA administrations, and monitoring the literature for developments. Some of the guidelines recommend that linear agents should not be withheld if there is a history of an adverse reaction to a macrocyclic GBCA or when macrocyclic agents are not available.

**Statements and Recommendations.** Our statements reflect the conclusions of published guidelines on gadolinium brain deposition/retention after intravenous gadolinium exposure (Table 3). We were unable to identify any published case reports of lesions with a high T1 signal intensity after an interventional pain procedure involving the use of gadolinium. A causal relationship may be difficult to establish since many patients presenting to pain clinics will have previous exposure to GBCA during diagnostic MRIs. The occurrence of signal hyperintensity in the globus pallidus and dentate nucleus in 5 of 6 patients after 0.5–1 mL injection of gadopentetate dimegline, probably via the glymphatic pathway, should serve as a cautionary note for interventional pain physicians performing injections around the vertebrae. However, any possibility of risk associated with brain deposition/retention of gadolinium pales in comparison to the severity of sequel from unintentional IT gadolinium injection (see section on encephalopathy). Overall, our recommendations balance the need for contrast injection with the low risk of gadolinium brain deposition from small extravascular injections and the lack of clinical significance of these brain depositions.

**Encephalopathy From Unintentional IT Gadolinium Injection**

Cases of encephalopathy after unintentional IT injection of gadolinium have been reported after interventional pain procedures. In one report, seizures, impaired consciousness, and intubation for 1 day resulted from 1.5-mL gadobutrol unintentionally injected into the IT space before an epidural steroid injection. Another patient developed pain and spasms in her lower extremities after she was injected with 2-mL gadobutrol during an IT catheter contrast study. Both patients fully recovered. Other reports involved administration of larger volumes. Mental status changes, seizures, and respiratory distress requiring intubation occurred in a patient after 4 mL of gadodiamide was injected twice into the epidural space in the presence of a “wet tap.” One patient developed seizures, apnea, and pulseless tachycardia after a 5-mL gadoteridol injection during a minimally invasive lumbar decompression procedure. The patient died 14 days after the procedure. All 3 patients who had unintentional IT injection showed gadolinium in their subarachnoid space on MRI.

There have been reports of encephalopathy after IT gadolinium injection in nonpain settings. A patient, scheduled for a CT-myelogram, became unresponsive after she was accidentally injected with 20-mL gadopentetate dimegline followed by an intentional IT injection of iotrolan. The patient reportedly recovered 56 days after the procedure but had residual concentration difficulties and mild ataxia. Another patient showed no sequela 60 days after IT injection of 15-mL gadopentetate for an MRI examination.
third patient, who had CT myelography, exhibited visual disturbances 1 month after being injected with 6-mL gadopentetate. Finally, a patient required 2 months in an intensive care unit after 10-mL gadopentetate was injected into the side port of a ventriculostomy catheter.

Gadolinium has been shown to accumulate in the cerebrospinal fluid (CSF) after intravenous injection in humans. In a prospective observational cohort study performed in 82 patients with normal renal function and an intact blood brain barrier (68 had gadobutrol, 14 patients had lumbar puncture without MRI), 9 mL (range, 7–10 mL) of gadolinium was injected in adults and 4 mL (2.6–6.5 mL) in pediatric patients. In the patients given gadobutrol, lumbar puncture was performed within 30 days of the MRI. Gadolinium was detected in the CSF in all 68 patients who had GBCA-enhanced MRI (95% CI, 94.7%; range, 0.2–1494 ng/mL) compared to none in the control group (0 ng/mL; interquartile range, 0–0 ng/mL). The authors detected gadolinium not only in the CSF but also in the serum of patients for up to 24 days after the intravenous administration of gadobutrol. Similar findings were noted in a retrospective study on gadoterate meglumine. The investigators reported that patients who had 1 gadolinium-enhanced MRI showed gadolinium in their CSF, while those who had MRI without contrast showed none. Gadolinium concentrations decreased after 8 hours and were almost completely gone after 48 hours.

Interestingly, gadolinium has been intentionally injected into the IT space by radiologists in their evaluation of dural leaks, hydrocephalus and other CSF disorders (arachnoid cyst communications, aqueductal stenosis, obstruction of the fourth ventricle), and during investigation of the sympathetic pathway. Gadopentetate dimeglumine, 0.5 mL diluted in 4-mL saline, was injected intrathecally in 19 patients without adverse events. In a review of 100 patients, 0.5-mL gadopentetate dimeglumine, diluted in 1-mL CSF, was injected into the IT space without complications other than a headache. In a prospective safety and feasibility study of 100 patients, 0.5-mL gadobutrol (Gadovist, 1.0 mmol/mL) and 3-mL ioxagol (Visipaque, 270 mg I/mL) were injected intrathecally. Serious adverse events included anaphylaxis in a patient who was known to be allergic to ICM. The nonserious events included severe headache (28%) and severe nausea (34%). By 4 weeks, all adverse reactions had resolved. The authors concluded that IT injection of 0.5-mL gadobutrol was safe. It is worth noting that the investigators diluted the GBCA with either 4-mL saline or 1-mL CSF before injection. Another investigator commented that in his practice, he mixed 0.5-mL gadopentetate dimeglumine with 5-mL iohexol and slowly injected the mixture over a 3-minute period, with no adverse sequelae.

The proposed mechanisms of gadolinium neurotoxicity and cell death include impairment of mitochondrial function, endoplasmic reticulum alterations in signal transduction, alterations in cell signal processes, inhibition of cellular calcium hemostasis, and modulation of unfolded protein responses. The median lethal dose (LD₅₀) of several gadolinium formulations after intracisternal application in rats has been investigated. The LD₅₀ (µmol per kg) was noted to be lower for the macrocyclic GBCAs gadoteridol, gadoterate meglumine, and gadobutrol compared to the linear agents gadodiamide and gadopentetate. In spite of their findings, the authors concluded that the margin of safety between a diagnostic dose and LD₅₀ would still be very high, with a safety factor of 80.

**Statements and Recommendations.** Encephalopathy after unintentional IT gadolinium was identified only recently, and, as such, controlled studies are lacking. Our statements and recommendations (Table 4) reflect “best available evidence and clinician experience and judgment consistent with circumstances and values.” In this topic, practical and ethical considerations prevent studies aimed at determining the effectiveness of preventive measures for life-threatening complications. Our recommendations emphasize that pain physicians should observe every precaution to prevent unintentional IT injections of gadolinium.

Unintentional injection into the IT space is more likely with interlaminar compared to transforminal access (0.2% vs 0.04% incidence, respectively). Use of a GBCA for interlaminar epidural access is not recommended. The choice of approach should be rationally based after weighing the likelihood of on-target delivery of medication and side effects, with every effort expended to reduce the likelihood of unintentional IT contrast injection. The procedure should be aborted if IT injection of GBCA is observed or even suggested.

The molar concentration of each gadolinium preparation (mol/L) should be considered when evaluating the risk of gadolinium-induced encephalopathy (mol/L). A volume recommendation should be based on the individual GBCAs molar concentration of gadolinium (see Table 1). Based on the review of case reports, toxicity in humans has occurred at doses that result in brain concentrations as low as 1 µmol/g. If physicians want to remain <1 µmol/g of brain tissue, then depending on the molar concentration of gadolinium within the GBCA, a volume of injection ranging between 1.4 mL (molar concentration of gadolinium of 1 mol/L in the GBCA, eg, gadobutrol) and 5.6 mL (molar concentration of gadolinium...
0.25 mol/L of gadolinium in the GBCA, eg, gadofosveset trisodium and gadoxetate disodium) would be acceptable. In addition, it must be noted that the ability to visualize a GBCA under fluoroscopy decreases as the molar concentration of gadolinium in the agent decreases. Gadobutrol has the highest radiographic conspicuity (pixel value difference with respect to the background) allowing for better visualization. However, it contains the highest molar concentration increasing the risk of encephalopathy after unintentional IT injection.

Among ICM compounds, iohexol and iopamidol are FDA-approved for IT use and are therefore the most appropriate for spine interventional pain procedures. In the absence of HRs to ICM, these agents should be utilized when there is a risk of IT injection. If a GBCA is selected after a shared decision-making process with the patient, the use of digital subtraction imaging or CT as the guidance modality may limit the risk of unintentional IT injection by improving the interventional pain physician’s ability to detect IT spread. Additionally, these techniques enable the use of lower volumes and/or lower molar concentrations of GBCA, reducing the risk of encephalopathy should subtle or partial IT injection escape detection.

**HRs to Contrast Agents**

Immediate contrast reactions are either non–IgE-mediated or immunoglobulin E (IgE) mediated. The pathways of non–IgE-mediated reaction include a direct membrane effect on the basophil or mast cell, complement activation, or bradykinin generation. Most HRs to contrast media are anaphylactoid in nature; previously termed anaphylactoid reaction or idiosyncratic/nonallergic HR, these are presently called nonimmunologic anaphylaxis.

The ACR classified adverse reactions into allergic-like and physiologic in nature, and the severity of reactions as mild, moderate, or severe. Mild reactions are self-limited and do not progress while moderate and severe reactions require medical management. Another approach to classifying HRs to contrast agents is based on the timing of presentation. Acute reactions generally occur within 20 minutes of contrast administration, while late reactions materialize between 1 hour and 1 week after administration.

The greatest risk factor for a HR is a history of a previous HR, while other determinants include asthma, atopy, severe cardiovascular disease, female sex, and drug allergies. Patients with seafood allergies do not represent an increased risk compared to patients with various types of atopy such as other food allergies or asthma. For patients on beta-blockers, recent studies showed that the intake of these medications does not increase the risk of HR to ICM.

Clinical trials demonstrate an overall allergic-like reaction rate to low osmolar ICM to be 0.6%. A recent clinical study conducted in 196,081 patients found the incidence rates of overall HRs and severe HRs to be 0.73% and 0.01%, respectively. In terms of severity, 83.2% were mild, 15.6% were moderate, and 1% were severe.

The incidence of HRs is less with GBCAs compared to ICM. A review and meta-analysis of 9 trials (716 patients, 978 administrations) showed the overall and severe rates of allergic-like reactions to be 9.2 (0.092%) and 0.52 (0.0053%) per 10,000 administrations, respectively. Similar to ICMs, HRs to GBCAs are mostly mild in nature. The most frequent allergic-like symptoms are urticaria and respiratory or throat symptoms. The risk factors are similar to those for ICM (previous HR, female sex, patients with asthma, or asthma). However, the rate of HRs is also influenced by protein binding and ionicity, as ionic agents become less stable after entering the blood stream. Among the GBCAs, immediate reactions are less frequent with nonionic linear GBCAs compared to ionic linear and nonionic macrocyclic GBCAs (see Table 1). The ionic linear GBCAs with high protein binding capacity (gadofosveset, gadobenate, and gadoxetate) have higher rates of immediate allergic-like reactions compared to nonionic linear chelates that do not undergo extensive protein binding (gadopentetate).

Macro cyclic GBCAs do not bind to serum proteins. A history of a previous HR to contrast media should be rigorously verified, as the implications for current care are significant and measures to prevent recurrence should be strictly followed. Notation of a HR to contrast media in the medical record may alter current care significantly and measures to prevent recurrence should be strictly followed. Notation of a HR to contrast media in the medical record may alter current care.
had a mild HR, premedication with an antihista-
mine and changing the ICM were shown to reduce
the recurrence rate for breakthrough reaction: 31%
recurrence rate without premedication, 12% when
the ICM was changed without premedication and
8% using antihistamine premedication and changing
the ICM.84 Other studies confirmed these findings. In
a retrospective study, the same ICM that previously
caused the adverse reaction was administered in
patients with and without (control group) premedica-
tion. The other groups received a different ICM, with
and without premedication.85 The investigators noted
that repeat reactions occurred in 28% of the control
group compared to 17% in the premedication alone
group. In the group in whom the ICM was changed,
the incidence was 5% without premedication; this
was reduced to 2.7% with additional premedication.
The authors concluded that while premedication is
protective, changing the ICM is more effective.85 In
another retrospective study conducted in patients
with a history of moderate to severe HR to low osmo-
lar ICM, the premedication consisted of antihistamine
only or antihistamine and steroid.82 The overall recur-
rence rate was 19%; broken down by severity of the
initial reaction, recurrence rate was observed in 19%
and 24% of patients who had moderate and severe
reactions, respectively. Changing the ICM resulted in
a lower incidence of HRs compared to using the same
ICM (13% vs 27%). Premedication with steroid did
not decrease the incidence in patients regardless of
whether the same ICM was used or not, and regard-
less of the dose (<40 mg of prednisolone or ≥40 mg).82

Another study by the same group of investigators
showed the inconsistent effect of steroid premedica-
tion. In one of their studies, 3% of high-risk patients
and 14% of patients who had a previous severe reaction
experienced a recurrence despite corticosteroid
premedication.86 In contrast to their previous study,82
the group noted an association between the effective-
ness of prevention and dose of the steroid. The group
concluded that steroids may be effective in preventing
HRs in patients with history of mild and moder-
ate HRs, but not in patients who experienced severe
HRs. A more recent study of the group, however
showed no additional effect of steroids in patients
with a history of mild HR.86

Other authors showed that steroid premedication
by itself has only a weak salutary effect on allergic-
like reactions, is unlikely to affect the severity of sub-
sequent reactions, and does not prevent all types of
reactions.69-71 However, it should be noted that pre-
medication with prednisone and diphenhydramine
is also not 100% effective in preventing all allergic
reactions.90

There is a lack of data regarding prior ICM hyper-
sensitivity as a risk factor for GBCA reactions over
and above the risk posed by the GBCA, but the risk
may be increased by shared underlying risk fac-
tors such as a history of general “allergies.” There
is unlikely any direct immunological cross-react-
tivity between ICM and GBCAs; however, similar
to ionic ICMs, ionic GBCAs are hyperosmolar and
may directly activate mast cells.91 Case series attest
to the safe use of GBCAs in some individuals with
a history of ICM allergy, but an instance of severe
anaphylaxis to a GBCA on first exposure occurred in
a patient who had recently suffered anaphylaxis to
ICM.92 There is no substantive evidence to support
the use of premedication when a GBCA is utilized in
patients with a history of mild or moderate/severe
HRs to ICM.

Premedication with antihistamines and cortico-
steroids has not been systematically studied in a
large number of patients with a history of GBCA
reactions, though it has not been effective in a small
cohort of patients.77 In 1 study, 4 of 11 patients who
were premedicated had recurrent immediate HR.77
Breakthrough reactions despite premedication have
also been documented in another small study.93

To our knowledge, nonimmediate HRs to GBCA
have not been described. Although rare, IgE-mediated
reactions to gadolinium derivatives have been
reported with an incidence of 0.07% in adults.77 The
most common clinical manifestation is urticaria (50%–
90% of cases). Anaphylactic reactions with GBCA are
rare, with an incidence of 0.004%–0.01%.77

Moderate to severe HRs after extravascular injec-
tions of ICM are rare. This lower incidence was shown
in a study of 257 patients who had previous acute
allergic-like reactions to ICM.94 Twenty patients had
45 extravascular injections (gastrointestinal, genito-
urinary, pancreaticobiliary tract, abdominal cavity,
and CSF). The recurrence rate was 19% in the patients
who had an intravascular injection compared to 0% in
patients who were given the ICM in the extravascul-
rar space. In a small case series, 6 patients who had a
history of previous HR to intravenous ICM for diag-
nostic procedures did not have a breakthrough reac-
tion when ICM was injected into the epidural space
without pretreatment.95 The authors ascribed the lack
of breakthrough reactions to the small (1–3 mL) vol-
umes injected, slow absorption into the intravascular
compartment from the epidural space, and concur-
rent administration of steroid.

The incidence of HRs after interventional pain
procedures was shown in 3 publications. In an ear-
lier study, 16 of 200 patients (8%) who presented to
a pain clinic reported a previous “allergic reaction.”
However, their symptoms included generalized
pain, sneezing, cough, and glossitis.96 In another
study, there were 10 cases out of “allergic reactions”
26,061 (0.038%) interventional pain procedures.97
In this investigation, the number of interventions in which contrast were used and the specific contrast used were not stated. Another recent study showed the absence of HR after 6781 iohexol-enhanced epidural injections.68

**Statements and Recommendations.** Our PA does not comment on the role of skin testing since there are several recommendations on this subject from different national and international allergy society guidelines.69,99,100 Neither did we discuss intravenous provocation testing, to identify alternative ICM, since this topic is under the purview of allergists.69

Our Statements affirm the established relationship of HR to contrast media (Table 5). Most applicable to interventional pain procedures is the rare occurrence of HRs after extravascular injection of contrast media. Our recommended duration of observation following administration of the contrast media represents the minimum waiting period, especially in patients with previous history of HRs. For patients with a history of moderate/severe HR but no reaction in the first 15 minutes (irrespective of premedication status), a 30-minute to 1-hour observation time is recommended. In these cases, a 1-hour time may be ideal. Provisions should be made for the patient to contact the pain clinic in case of an emergency. The patients should be cautioned on the possibility of a late HR, and symptoms to watch out for. Prophylaxis for late reactions, in the absence of an immediate reaction, is not recommended and treatment should be exclusively symptomatic. Rescue medicines such as antihistamines or short-term corticosteroids can be prescribed prophylactically should symptoms occur. Equally important is education of clinic staff. Our recommendations on the availability of emergency equipment in the clinical environment where contrast media is administered are the same as the ACR’s and reflects Bridenbaugh’s101 call for adequate training of physician and nonphysician providers and the adequacy of resuscitative equipment.

Our recommendations in patients with a history of mild or moderate/severe HR (recommendations 3 and 4) reflect the varied approaches of interventional pain physicians to these patients, dependent on their training background/comfort level. For patients with a history of mild reactions, the pain physician alone may decide whether pretreatment is necessary (recommendation 3, see Table 5). Our suggestion on the use of a different ICM, if culprit is known, reflects the effectiveness of this measure in reducing the recurrence of HR. For patients with a history of mild HRs, changing the ICM and antihistamine prophylaxis is likely to be sufficient.84 The use of steroid premedication in patients with mild HR should be discussed with patients who have diabetes since steroid prophylaxis can cause hyperglycemia (increase of 40–150 mg/dL) for 24–48 hours.90 For diabetic patients with a history of moderate to severe HRs, premedication including a steroid may be appropriate. Our recommendation number 4 assumes that the decision to administer ICM is made because GBCA use is contraindicated (ie, interlaminar epidural injection). A referral to an allergist in patients with a history of moderate and severe HRs should be considered not only for evaluation for the upcoming procedure, but also for educational purposes and optimization of the patient’s future encounters regarding the requirements for all forms of contrast administration.

The treatments of acute reactions include diphenhydramine for hives; a beta-2 agonist inhaler for bronchospass; epinephrine for hypotension, moderate or severe bronchospass and laryngeal edema (patients on beta-blockers may not respond to epinephrine); and cardiopulmonary resuscitation for unresponsiveness and pulselessness. Treatment protocols are available in the ACR manual on contrast media and should be readily accessible in the procedure suite.2

**Concluding Comments, Choosing the Ideal GBCA.**
Experts from 11 appropriate multispecialty societies participated in the development of our PA. Almost all pain societies in the United States participated in this PA to avoid redundant or conflicting advisories.102,103 Our experts examined 4 clinically important topics associated with contrast medium (CM), specifically GBCAs, such that all adverse reactions were compiled into a PA. A criticism against some practice guidelines and advisories is that its focus is too narrow.102 Additionally, limiting a PA to isolated issues related to contrast medium may result in a recommendation (eg, macrocyclic GBCAs are better in patients with renal insufficiency or in patients suspected of having gadolinium brain deposition/retention from several gadolinium-enhanced MRIs) that is in conflict with another advisory confined to the other topics (eg, linear GBCAs are better because of lower incidence of HRs and higher LD50 when injected intrathecally). Some of our grades are stronger than the evidence supporting them, partly reflecting the recommendation that the best available evidence takes into consideration physician judgment and experience, and unique patient factors.18,19 In the case of encephalopathy after IT gadolinium injection, prospective controlled clinical studies are not ethically advisable.104

In patients with a well-documented history of moderate/severe HR to ICM, available options include changing the ICM and pretreatment. However, premedication, especially with steroids, is not consistently effective in preventing breakthrough HRs. There are also concerns with steroid-related side
effects in patients with diabetes. Breakthrough reactions appear to be less frequent with extravascular administration, the intended target in nearly all interventional pain procedures. Additional mitigating factors in pain management include the small volumes typically injected, injecting areas with slow rates of absorption, and the frequent concomitant administration of steroid as part of treatment. The relative lack of CT availability renders the alternative use of air as a contrast agent moot but changing to a GBCA remains a viable alternative. However, GBCA use is now more problematic given identification of NSF, brain deposition/retention and encephalopathy after unintentional IT injection.

There is no ideal GBCA. NSF and gadolinium brain deposition/retention are less problematic in interventional pain procedures since low volumes of contrast are injected extravascularly. However, encephalopathy after unintentional gadolinium injection is of grave concern to the interventional pain physician, especially since a majority of pain procedures involve the neuraxis with proximity to the thecal sac. For nonspine injections, macrocyclic GBCAs may be used in patients with a concern for NSF or at high-risk for gadolinium brain deposition. For injections in the spine, linear GBCAs with the lowest molar concentration of gadolinium that balances safety risks while optimizing visibility (ie, radiopacity) may be an option. For paraspinous injections, it should be noted that gadobutrol is not only a macrocyclic GBCA, it also has the highest molar concentration which is a significant risk factor in the development encephalopathy after unintentional IT injection. It is imperative that the physician understand the significant risks associated with unintentional IT administration and weigh them against the potential benefits in a shared decision model with the patient. The use of GBCAs in the IT and epidural spaces is not FDA-approved and if it is determined that a GBCA is needed based on a benefit/risk analysis, then the lowest volume and molar concentration of gadolinium should be utilized. Regardless of which gadolinium product is used, every precaution should be observed to avoid unintentional injection of the gadolinium into the IT space.

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APPENDIX. PARTICIPATING SOCIETIES AND ITS REPRESENTATIVES

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