

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

Honorio T. Benzon, MD,* Timothy P. Maus, MD,† Hye-Ryun Kang, MD,‡ David A. Provenzano, MD,§ Anuj Bhatia, MD,|| Felix Diehn, MD,† Ariana Nelson, MD,¶ Zachary L. McCormick, MD,# Benjamin P. Liu, MD,** Javier de Andres Ares, MD,†† Magdalena Anitescu, MD,‡‡ Kristine Blackham, MD,§§ Arun Bhaskar, MD,|||| Silviu Brill, MD,¶¶ Jeremy Collins, MD,† Ashish Gulve, MD,## Robert W. Hurley, MD,*** Young Hoon Jeon, MD,††† Jee Youn Moon, MD,‡‡‡ Richard L. Rauck, MD,§§§ Meghan Rodes, MD,* Ryan K. Lee, MD,||||| Vinil Shah, MD,¶¶¶ Harsha Shanthanna, MD,### Jan van Zundert, MD, PhD,**** Marc Huntoon, MD,†††† James P. Rathmell, MD,‡‡‡‡ Mario Sanchez Borges, MD,§§§§ Steven P. Cohen, MD,|||||| and Paul A. Greenberger, MD,¶¶¶¶

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 2021;133:535–52)

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.

From the *Department of Anesthesiology, Northwestern University Feinberg School of Medicine, Chicago, Illinois; †Department of Radiology, Mayo Clinic, Rochester, Minnesota; ‡Department of Medicine (Allergy and Immunology), Seoul National University, Seoul, South Korea; §Pain Diagnostics and Interventional Care, Pittsburgh, Pennsylvania; || Department of Anesthesiology, University of Toronto, Toronto, Ontario, Canada; ¶Department of Anesthesiology, University of California at Irvine, Irvine, California; #Department of Physical Medicine and Rehabilitation, University of Utah, Salt Lake City, Utah; **Department of Radiology, Northwestern University Feinberg School of Medicine, Chicago, Illinois; ††Department of Anesthesiology-Pain Unit, Hospital Universitario La Paz, Madrid; ‡‡Department of Anesthesiology, University of Chicago, Chicago, Illinois; §§Department of Radiology,

University Hospital, Basel, Basel, Switzerland; ||||Imperial College Healthcare NHS Trust, London, United Kingdom; ¶¶Institute of Pain Medicine, Tel Aviv Medical Centre, Tel Aviv, Israel; ##Department of Pain Management, James Cook University Hospital, Middlesbrough, United Kingdom; ***Department of Anesthesiology, Wake Forest School of Medicine, Winston-Salem, North Carolina; †††Anesthesiology and Pain Medicine, School of Dentistry, Kyungpook National University, Daegu, South Korea; ‡‡‡Department of Anesthesiology, Seoul National University, Seoul, South Korea; §§§Carolina Pain Institute, Winston-Salem, North Carolina; ||||Department of Radiology, Sydney Kimmel Medical College at Thomas Jefferson University, Philadelphia, Pennsylvania; ¶¶¶Department of Radiology, University of California at San Francisco, San Francisco, California; ###Department of Anesthesiology, McMaster University, Hamilton, Ontario, Canada; ****Anesthesiology and Pain Medicine, Maastricht University Medical Center, Maastricht, the Netherlands; ††††Department of Anesthesiology, Virginia Commonwealth

Copyright © 2021 International Anesthesia Research Society

DOI: 10.1213/ANE.0000000000005443

GLOSSARY

AAPM = American Academy of Pain Medicine; **ACR** = American College of Radiology; **AKI** = acute kidney injury; **ASNR** = American Society of Neuroradiology; **ASRA** = American Society of Regional Anesthesia and Pain Medicine; **BOD** = Board of Directors; **BPS** = British Pain Society; **CAR** = Canadian Association of Radiologists; **CI** = confidence interval; **CKD** = chronic kidney disease; **CM** = contrast medium; **CPS** = Canadian Pain Society; **CSF** = cerebrospinal fluid; **CT** = computed tomography; **EBM** = evidence-based medicine; **EFIC** = European Pain Federation; **eGFR** = estimated glomerular filtration rate; **ESUR** = European Society of Urogenital Radiology; **FDA** = Food and Drug Administration; **GBCA** = gadolinium-based contrast agent; **HR** = hypersensitivity reaction; **ICM** = iodinated contrast medium; **IgE** = immunoglobulin E; **IL** = interleukin; **IT** = intrathecal; **KPS** = Korean Pain Society; **LD₅₀** = median lethal dose; **MeSH** = Medical subject heading; **MRI** = magnetic resonance imaging; **NSF** = nephrogenic systemic fibrosis; **PA** = Practice Advisory; **SIS** = Spine Intervention Society; **TGF** = transforming growth factor; **USPSTF** = US Preventive Services Task Force; **WAO** = World Allergy Organization; **WIP** = World Institute of Pain

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.¹ 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.²

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,^{3,4} gadolinium deposition/retention in the brain from repeated administration of GBCAs,⁵⁻⁷ and encephalopathy from unintentional intrathecal (IT) injection of GBCA.⁸⁻¹⁰ Appearance of these new reports of previously unrecognized adverse events resulted in calls for caution in the continued use of GBCA,⁹⁻¹¹ an informed discussion with the patient,¹² and the creation of a guideline.¹³ These developments, together with the recent finding of rare breakthrough HRs (HR after exposure to the culprit contrast medium) in interventional pain procedures,¹⁴ prompted a group of concerned investigators and organizations to develop a Practice Advisory (PA) on contrast agents.

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 2014.¹⁵

University, Medical College of Virginia, Richmond, Virginia; ####Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Boston, Massachusetts; §§§§Department of Allergy and Clinical Immunology, Centro Medico Docente La Trinidad, Caracas, Venezuela; |||||Department of Anesthesiology and Critical Care Medicine, Pain Medicine Division, Department of Physical Medicine and Rehabilitation, and Department of Neurology, and Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine, Baltimore, Maryland; and ¶¶¶¶Department of Medicine, Division of Allergy and Immunology, Northwestern University Feinberg School of Medicine, Chicago, Illinois.

Accepted for publication January 7, 2021.

Funding: None.

Conflicts of Interest: See Disclosures at the end of the article.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.anesthesia-analgesia.org).

Reprints will not be available from the authors.

Address correspondence to Honorio T. Benzon, MD, Department of Anesthesiology, Northwestern University Feinberg School of Medicine, Chicago, IL 60611. Address e-mail to h-benzon@northwestern.edu.

Table 1. Gadolinium-Based Contrast Agents

Gadolinium-based contrast agent	Type, stability	Concentration mmol/mL ^a	Usual MRI dose mmol/kg (mL dose in 70-kg person)
Gododiamide (Omniscan)	Nonionic linear, low	0.5	0.1 (14)
Gadoversetamide (Optimark)	Nonionic linear, low	0.5	0.1 (14)
Gadobenate dimeglumine (MultiHance)	Ionic linear Intermediate	0.5	0.1 (14)
Gadopentetate dimeglumine (Magnevist)	Ionic linear Intermediate	0.5	0.1 (14)
Gadofesveset trisodium (Ablavar, Vasovist)	Ionic linear Intermediate	0.25	0.03 (8.4)
Gadoxetate disodium (Eovist, Primovist) ^b	Ionic linear Intermediate	0.25	0.025 (7)
Gadoteridol (ProHance)	Nonionic macrocyclic High	0.5	0.1 (14)
Gadobutrol (Gadavist)	Nonionic macrocyclic High	1	0.1 (7)
Gadoterate meglumine (Dotarem)	Ionic macrocyclic High	0.5	0.1 (14)

^aUsual radiology dose for MRI of the brain or body parts.

^bUsed for liver MRI imaging.

Abbreviation: MRI, magnetic resonance imaging.

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.¹⁶ 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/retention from gadolinium,” “encephalopathy from IT gadolinium,” and “HRs to contrast media.” The modified Delphi process was followed in the formulation of the PA.¹⁶ 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>).¹⁷ 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

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

Statements

1. The risk factors for compromised renal function include age >60 y, hypertension, diabetes, single kidney, kidney surgery, history of kidney malignancy, and kidney transplant.

Level of certainty: High

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.

Level of certainty: High

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.

Level of certainty: Moderate

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.

Level of certainty: Moderate

5. In CKD stages 4 (eGFR between 15 and 29 mL/min/1.73 m²) and 5 (eGFR <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.

Level of certainty: Moderate

Recommendations

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.

Strength of recommendation: A

2. In interventional pain procedures, whenever GBCA is necessary, its indication should be stated and the gadolinium formulation and total dose adequately registered.

Strength of recommendation: A

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.

Strength of recommendation: A

4. The lowest possible dose of GBCA to obtain necessary clinical information should be administered.

Strength of recommendation: A

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).

Strength of recommendation: B

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 <15 mL/min/1.73 m²) and those on dialysis.

Strength of recommendation: A

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.

Strength of recommendation: A

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.

Strength of recommendation: A

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.

Table 3. Statements and Recommendations in Relation to Gadolinium Deposition/Retention in the Brain**Statements**

1. After intravenous injection, gadolinium deposition occurs essentially in all tissues, including but not limited to the brain, and may remain in the body months to years.
Level of certainty: Moderate
2. Gadolinium deposition in the brain can occur after intrathecal injection of gadolinium.
Level of certainty: Low
3. A single GBCA-enhanced MRI can cause gadolinium retention visible on subsequent MRI.
Level of certainty: Moderate
4. Gadolinium deposition in the brain may be dose dependent and can occur in patients with no clinical evidence of kidney or liver disease.
Level of certainty: Moderate
5. Brain deposition is higher with the linear GBCAs than with the macrocyclic GBCAs and washout occurs to a greater/faster degree with macrocyclic GBCAs than linear GBCAs, but brain deposition occurs with agents in both classes.
Level of certainty: Moderate
6. The available evidence suggests that the clinical relevance of gadolinium deposition in the brain is low; no adverse sequela has been reported.
Level of certainty: Moderate

Recommendations

1. The interventional pain physician should be aware of patients who have incurred a gadolinium administration burden from multiple gadolinium-enhanced MRI examinations.
Strength of recommendation: B
2. Gadolinium is a drug that should be used with caution in interventional pain procedures. It should be administered only when necessary.
Strength of recommendation: A
3. It is prudent to consider the clinical benefit of the interventional pain treatment against the unknown potential risk of gadolinium deposition in the brain for each individual patient.
Strength of recommendation: B
4. Several factors need to be considered when selecting a GBCA, including diagnostic efficacy, rate of adverse reactions, dosing/concentration, radiopacity, and propensity to deposit in organs such as the brain.
Strength of recommendation: B
5. Ongoing research and emerging evidence need to be monitored and relevant information incorporated into clinical practice as this field of inquiry evolves.
Strength of recommendation: A

Abbreviations: GBCA, gadolinium-based contrast agent; MRI, magnetic resonance imaging.

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 Macrocyclic GBCAs. Free gadolinium ion (Gd^{3+}) 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} Macrocyclic 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 pathophysiologic 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 (eg, transforming growth factor [TGF]-beta, interleukin [IL]-4, IL-6, and IL-13), resulting in fibroblast formation.²³ Gadolinium is a lanthanide

Table 4. Statements and Recommendations in Relation to Gadolinium Encephalopathy From Intrathecal Injection**Statements**

1. In interventional pain procedures, gadolinium-induced encephalopathy can occur after unintentional and intentional subarachnoid (intrathecal) GBCA administration.

Level of certainty: High

2. The pharmacological properties of gadolinium, including its molar concentration and structural classification influence the risk of acute neurotoxicity and encephalopathy.

Level of certainty: Moderate

3. Case reports have shown that volumes as low as 1.5 mL of intrathecal GBCA resulted in signs and symptoms of encephalopathy.

Level of certainty: Low

Recommendations

1. The use of GBCAs is contraindicated in intrathecal interventional pain injections.

Strength of recommendation: A

2. Patients in whom there is increased risk of intrathecal injection should be identified including those with spinal stenosis, previous spine surgery, or kyphoscoliosis.

Strength of recommendation: B

3. In view of the likelihood of unintentional intrathecal spread of the gadolinium, a GBCA is not recommended in epidural injections via an interlaminar approach, including epidurograms.

Strength of recommendation: A

4. In view of the likelihood of unintentional intrathecal spread of the gadolinium, a GBCA is not recommended in transforaminal epidural injections. In circumstances of previously well-documented severe HR to current generation ICM, a shared decision-making process is reasonable to balance the relative risks of using ICM, gadolinium, or alternative interventional procedures not requiring a contrast agent.

Strength of recommendation: B

5. If it is deemed that gadolinium is necessary for an interventional pain procedure where there is a low risk of possible unintentional intrathecal administration (eg, lumbar sympathetic blocks, facet joint injections, and medial branch blocks), then the low risk of intrathecal gadolinium administration should be adequately explained to the patient.

Strength of recommendation: A

6. If gadolinium is considered essential to the pain procedure and is to be injected near the epidural/subarachnoid space, measures should be observed to avoid advancement of the needle tip into the subarachnoid space. These measures include multiple radiographic images, stabilizing the needle and repeated aspirations to detect the undesired presence of CSF. The lowest possible volume of the GBCA should be utilized and if possible, a GBCA with low molar concentration of gadolinium.

Strength of recommendation: A

7. If gadolinium is used, digital subtraction imaging guidance may be considered as this increases the detection of intrathecal spread and allow the safer use of a lower molar concentration of GBCA.

Strength of recommendation: B

8. If there is a concern for unintentional intrathecal or subdural administration of a GBCA, appropriate radiographic imaging, such as MRI and CT, should be considered to investigate the occurrence of intrathecal or subdural administration.

Strength of recommendation: A

9. If gadolinium-induced encephalopathy occurs or is considered, immediate supportive measures should be instituted.

Strength of recommendation: A

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; GBCA, gadolinium-based contrast agent; HR, hypersensitivity reaction; ICM, iodinated contrast medium; MRI, magnetic resonance imaging.

element; the fibrogenic effect of lanthanides has been recognized since 1983.²⁴ Lanthanides also enhance the polymerization of skin collagen *in vitro* and may be involved in fibril formation.²⁵ 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.^{26,27} Fibrosis of internal organs (heart, liver, lungs, muscle, and diaphragm) can occur resulting in cachexia and potentially death.

Thomsen et al²⁶ 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 gadofesveset (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 NSF²: group I (agents with greatest number of NSF cases): gadodiamide and gadopentetate dimeglumine; group II (few, if any, unconfounded cases):

Table 5. Statements and Recommendations in Relation to Hypersensitivity Reactions From Iodinated Contrast Medium**Statements**

1. Nonimmunologic anaphylaxis, also previously termed anaphylactoid reaction or idiosyncratic/nonallergic hypersensitivity reaction, comprise at least 80% of HRs to ICM.

Level of certainty: Moderate

2. HRs to GBCA are less common than HRs to ICM.

Level of certainty: High

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 radiopaque media. Seafood intolerance is not a risk factor.

Level of certainty: High

4. Reexposure to ICM in a patient with a history of HR may result in recurrent HR, especially with intravascular administration of large volumes.

Level of certainty: High

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.

Level of certainty: High

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.

Level of certainty: High

7. The incidence of HR 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.

Level of certainty: Low

8. Premedication with corticosteroids and antihistamines is highly, but not completely effective in preventing HR in all patients.

Level of certainty: High

9. Beta-blocker use does not increase the risk of HR to CM after an interventional pain procedure, even in patients with a history of HR.

Level of certainty: Moderate

10. HRs to nonionic linear GBCAs are less common than HRs to ionic linear GBCAs.

Level of certainty: Moderate

Recommendations

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 CM 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: B

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

Clinical setting

Premedicated patients with history of mild HR and no symptoms following exposure to CM

Nonpremedicated patients with history of mild HR and no symptoms following exposure to the same CM

Patients with a history of moderate/severe HR but no reaction in the first 15 min (irrespective of premedication status)

Strength of recommendation: B

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

^aThe 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.

^bPatients 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.

Duration of monitoring for HR^a
following CM administration
30 min
30 min
30 min–1 h^b

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, gadoxetic 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.^{2,28,29} 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.^{36–38} Interestingly, some investigators detected higher gadolinium levels in bone compared to the brain.³⁶

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.³⁹ Their warning was updated on September 20, 2018.⁴⁰

No definite clinical consequences of GBCA retention in the brain have been proven.⁴¹ 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.⁴² However, these symptoms overlap with those of NSF, and the acute occurrence (66% of the responders 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%).⁴³ 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.⁴⁴ 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 brain⁴⁵ and also reviewed guidelines from 9 different national organizations and regulatory agencies. Most of the recommendations pertain to diagnostic radiologic procedures involving intravascular 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 exposure⁴⁵ (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 IT injection of gadopentetate dimeglumine, probably via the glymphatic pathway,⁴⁶ 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 sequela 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.^{9–11,47,48} 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.⁹ Another patient developed pain and spasms in her lower extremities after she was injected with 2-mL gadobutrol during an IT catheter contrast study.⁴⁸ 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.”⁴⁷ One patient developed seizures, apnea, and pulseless tachycardia after a 5-mL gadoteridol injection during a minimally invasive lumbar decompression procedure.¹⁰ The patient died 14 days after the procedure. All 3 patients who had unintentional IT injection showed gadolinium in their subarachnoid space on MRI.^{9,10,47}

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 dimeglumine followed by an intentional IT injection of iotrolan.⁴⁹ 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.⁵⁰ A

third patient, who had CT myelography, exhibited visual disturbances 1 month after being injected with 6-mL gadopentetate.⁵¹ 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.⁵²

Gadolinium has been shown to accumulate in the cerebrospinal fluid (CSF) after intravenous injection in humans.^{53,54} 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.⁵³ 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.⁵³ Similar findings were noted in a retrospective study on gadoterate meglumine.⁵⁴ 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 glymphatic pathway.^{55–57} Gadopentetate dimeglumine, 0.5 mL diluted in 4-mL saline, was injected intrathecally in 19 patients without adverse events.⁵⁵ 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.⁵⁶ In a prospective safety and feasibility study of 100 patients, 0.5-mL gadobutrol (Gadovist, 1.0 mmol/mL) and 3-mL iodixanol (Visipaque, 270 mg I/mL) were injected intrathecally.⁵⁷ 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.⁵⁷ 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.⁵⁸

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.¹⁰ 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.⁵⁹ 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 80.⁵⁹

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.”¹⁹ 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 transforaminal access (0.2% vs 0.04% incidence, respectively).⁶⁰ 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.⁶¹ 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).¹⁰ 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.¹⁰ 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.⁶² Gadobutrol has the highest radiographic conspicuity (pixel value difference with respect to the background) allowing for better visualization.⁶² 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.⁶³ Most HRs to contrast media are anaphylactoid in nature; previously termed anaphylactoid reaction or idiosyncratic/nonallergic HR, these are presently called nonimmunologic anaphylaxis.^{64,65}

The ACR classified adverse reactions into allergic-like and physiologic in nature, and the severity of reactions as mild, moderate, or severe.² 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.⁶⁶⁻⁶⁸

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.^{69,70} 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.^{71,72} For patients on beta-blockers, recent studies showed that the intake of these medications does not increase the risk of HR to ICM.⁷³

Clinical trials demonstrate an overall allergic-like reaction rate to low osmolar ICM to be 0.6%.^{66,74,75} 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.⁷⁰ 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.⁷⁶ Similar to ICMs, HRs to GBCAs are mostly mild in nature. The most frequent allergic-like symptoms are urticaria and respiratory or throat symptoms.^{77,78} The risk factors are similar to those for ICM (previous HR, female sex, patients with asthma, or other allergies), but there are some factors specific to GBCAs including number of exposures, admission status (greater for inpatients), and imaging location (abdomen and/or pelvis).⁷⁸ HRs are more common with the macrocyclic GBCAs compared to the linear GBCAs, partly because of their higher osmolality.^{63,79} 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 with ionic linear chelates that do not undergo extensive protein binding (gadopentetate).⁷⁶ Macrocyclic 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 patients' care for the rest of their life; thus, the veracity of a HR must be carefully documented. Measures to reduce HR in patients with a previous history of HR include premedication, usually antihistamine and steroid (glucocorticoid)⁸⁰ or steroid alone⁸¹; using a different ICM; and, switching to a GBCA. Radiologists who do interventional pain procedures may also use air, instead of contrast, under CT guidance.

Risk factors for recurrent reactions, termed "breakthrough reactions," include greater severity of the initial ("index") reaction, diabetes, urticaria, drug allergies, and a history of chronic oral corticosteroid intake.⁸² The nature of the breakthrough reaction usually duplicates the severity of the index reaction.⁸³

The efficacy of premedication and changing the ICM was shown in several studies. In patients who

had a mild HR, premedication with an antihistamine 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) premedication. 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 osmolar ICM, the premedication consisted of antihistamine only or antihistamine and steroid.⁸² The overall recurrence 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 regardless 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 premedication. 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.⁸³ In contrast to their previous study,⁸² the group noted an association between the effectiveness 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 moderate 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 subsequent reactions, and does not prevent all types of reactions.^{69,87–89} However, it should be noted that premedication with prednisone and diphenhydramine is also not 100% effective in preventing all allergic reactions.⁹⁰

There is a lack of data regarding prior ICM hypersensitivity 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 factors such as a history of general “allergies.” There is unlikely any direct immunological cross-reactivity 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 corticosteroids 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 injections 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, genitourinary, 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 extravascular space. In a small case series, 6 patients who had a history of previous HR to intravenous ICM for diagnostic procedures did not have a breakthrough reaction 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) volumes injected, slow absorption into the intravascular compartment from the epidural space, and concurrent administration of steroid.

The incidence of HRs after interventional pain procedures was shown in 3 publications. In an earlier 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” of 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.⁹⁸

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 bronchospasm; epinephrine for hypotension, moderate or severe bronchospasm 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.⁷⁹ 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 paraspinal 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. ■■

ACKNOWLEDGMENTS

Robert J. McDonald, MD, provided us with reference #59. Carolyn L. Wang, MD, reviewed the statements on NSF, gadolinium brain deposition/retention, and hypersensitivity reactions to contrast media.

DISCLOSURES

Name: Honorio T. Benzon, MD.

Contribution: This author helped with the conception, design, and writing of the manuscript.

Conflicts of Interest: H. T. Benzon is a member of Advisory Board, Sandoz International.

Name: Timothy P. Maus, MD.

Contribution: This author helped with the conception, design, and writing of the manuscript.

Conflicts of Interest: T. P. Maus received travel support from Spine Intervention Society, American Academy of Pain Medicine, American Academy of Neurology, International Musculoskeletal Society; and research support from National Institutes of Health and Mayo/University of Minnesota.

Name: Hye-Ryun Kang, MD.

Contribution: This author helped with the conception, design, and writing of the manuscript.

Conflicts of Interest: None.

Name: David A. Provenzano, MD.

Contribution: This author helped with the conception, design, and writing of the manuscript.

Conflicts of Interest: D. A. Provenzano received consulting fees from Avanos, Boston Scientific, Medtronic, Nevro, and Esteve and also research support from Avanos, Medtronic, Nevro, Stimpson, and Abbott.

Name: Anuj Bhatia, MD.

Contribution: This author helped with the conception, design, and writing of the manuscript.

Conflicts of Interest: None.

Name: Felix Diehn, MD.

Contribution: This author helped with the conception, design, and writing of the manuscript.

Conflicts of Interest: None.

Name: Ariana Nelson, MD.

Contribution: This author helped with the conception, design, and writing of the manuscript.

Conflicts of Interest: None.

Name: Zachary L. McCormick, MD.

Contribution: This author helped with the conception, design, and writing of the manuscript.

Conflicts of Interest: None.

Name: Benjamin P. Liu, MD.

Contribution: This author helped with the conception, design, and writing of the manuscript.

Conflicts of Interest: B. P. Liu is a member of Advisory Board, Guerbet and received research support from Guerbet, Bayer AG.

Name: Javier de Andres Ares, MD.

Contribution: This author helped with the conception, design, and writing of the manuscript.

Conflicts of Interest: None.

Name: Magdalena Anitescu, MD.

Contribution: This author helped with the conception, design, and writing of the manuscript.

Conflicts of Interest: M. Anitescu received consulting fee from Medtronic, Boston Scientific and fellowship grant from Medtronic, Abbott.

Name: Kristine Blackham, MD.

Contribution: This author helped with the conception, design, and writing of the manuscript.

Conflicts of Interest: None.

Name: Arun Bhaskar, MD.

Contribution: This author helped with the conception, design, and writing of the manuscript.

Conflicts of Interest: None.

Name: Silviu Brill, MD.

Contribution: This author helped with the conception, design, and writing of the manuscript.

Conflicts of Interest: None.

Name: Jeremy Collins, MD.

Contribution: This author helped with the conception, design, and writing of the manuscript.

Conflicts of Interest: J. Collins received research support from Siemens Healthineers; Advisory Board, Guerbet; Stock ownership, CETA, Inc.

Name: Ashish Gulve, MD.

Contribution: This author helped with the conception, design, and writing of the manuscript.

Conflicts of Interest: None.

Name: Robert W. Hurley, MD.

Contribution: This author helped with the conception, design, and writing of the manuscript.

Conflicts of Interest: R. W. Hurley received research support from Avanos and Robert Wood Johnson Foundation, National Institutes of Health.

Name: Young Hoon Jeon, MD.

Contribution: This author helped with the conception, design, and writing of the manuscript.

Conflicts of Interest: None.

Name: Jee Youn Moon, MD.

Contribution: This author helped with the conception, design, and writing of the manuscript.

Conflicts of Interest: None.

Name: Richard L. Rauck, MD.

Contribution: This author helped with the conception, design, and writing of the manuscript.

Conflicts of Interest: R. L. Rauck received research support from Mainstay, Saluda, Stimgenics, Biogen, Medtronic, Boston Scientific, Tekada. R. L. Rauck is a consultant for BioDelivery Sciences International (BDSI), Boston Scientific, Mainstay, Salix.

Name: Meghan Rhodes, MD.

Contribution: This author helped with the conception, design, and writing of the manuscript.

Conflicts of Interest: None.

Name: Ryan K. Lee, MD.

Contribution: This author helped with the conception, design, and writing of the manuscript.

Conflicts of Interest: R. K. Lee is a member of Advisory Board, Bracco COVID-19; and a consultant for Philips, Bayer.

Name: Vinil Shah, MD.

Contribution: This author helped with the conception, design, and writing of the manuscript.

Conflicts of Interest: None.

Name: Harsha Shanthanna, MD.

Contribution: This author helped with the conception, design, and writing of the manuscript.

Conflicts of Interest: None.

Name: Jan van Zundert, MD, PhD.

Contribution: This author helped with the conception, design, and writing of the manuscript.

Conflicts of Interest: None.

Name: Marc Huntoon, MD.

Contribution: This author helped with the conception, design, and writing of the manuscript.

Conflicts of Interest: M. Huntoon is a consultant for SPR (Sprint PNS System) Therapeutics, Saluda, Mainstay Medical.

Name: James P. Rathmell, MD.

Contribution: This author helped with the conception, design, and writing of the manuscript.

Conflicts of Interest: J. P. Rathmell is the Chair, Clinical Events Committee for ReActiv8 B Clinical Trial, Mainstay Medical LLC.

Name: Mario Sanchez Borges, MD.

Contribution: This author helped with the conception, design, and writing of the manuscript.

Conflicts of Interest: None.

Name: Steven P. Cohen, MD.

Contribution: This author helped with the conception, design, and writing of the manuscript.

Conflicts of Interest: S. P. Cohen is a consultant for Scilex, Avanos, Medtronic, SPR Therapeutics, Persica.

Name: Paul A. Greenberger, MD.

Contribution: This author helped with the conception, design, and writing of the manuscript.

Conflicts of Interest: P. A. Greenberger is a member of FDA Allergenic Products Advisory Committee and member of FDA Pulmonary Allergy Drugs Advisory Committee.

This manuscript was handled by: Jianren Mao, MD, PhD.

REFERENCES

1. Runge VM, Ai T, Hao D, Hu X. The developmental history of the gadolinium chelates as intravenous contrast media for magnetic resonance. *Invest Radiol.* 2011;46:807–816.
2. ACR Committee on Drugs and Contrast Media. ACR manual on contrast media, version 10.3. 2018. Accessed May 20, 2020. <https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast-Media.pdf>.
3. Edward M, Quinn JA, Burden AD, Newton BB, Jardine AG. Effect of different classes of gadolinium-based contrast agents on control and nephrogenic systemic fibrosis-derived fibroblast proliferation. *Radiology.* 2010;256:735–743.
4. Thomsen HS. Nephrogenic systemic fibrosis: a serious adverse reaction to gadolinium - 1997-2006-2016. Part 1. *Acta Radiol.* 2016;57:515–520.
5. Kanda T, Oba H, Toyoda K, Kitajima K, Furui S. Brain gadolinium deposition after administration of gadolinium-based contrast agents. *Jpn J Radiol.* 2016;34:3–9.
6. Olchowy C, Cebulski K, Łasecki M, et al. The presence of the gadolinium-based contrast agent depositions in the brain and symptoms of gadolinium neurotoxicity - a systematic review. *PLoS One.* 2017;12:e0171704.
7. Radbruch A, Weberling LD, Kieslich PJ, et al. Gadolinium retention in the dentate nucleus and globus pallidus is dependent on the class of contrast agent. *Radiology.* 2015;275:783–791.
8. Arlt S, Cepek L, Rustenbeck HH, Prange H, Reimers CD. Gadolinium encephalopathy due to accidental intrathecal administration of gadopentetate dimeglumine. *J Neurol.* 2007;256:810–812.
9. Popescu A, Patel J, McCormick ZL, et al; on behalf of the Patient safety Committee of the Spine Intervention Society. FactFinders for patient safety: are gadolinium-based contrast media safe alternatives to iodinated contrast agents for the safe performance of spinal injection procedures? *Pain Med.* 2018;19:2089–2090.
10. Provenzano D, Pellis Z, DeRiggi L. Fatal gadolinium-induced encephalopathy following accidental intrathecal administration: a case report and a comprehensive evidence-based review. *Reg Anesth Pain Med.* 2019;44:721–729.
11. Benzon HT, Liu BP, Patel AS, Benzon HA. Caution in using gadolinium-based contrast agents in interventional pain procedures. *Anesth Analg.* 2018;127:1452–1456.
12. Durbhakula S, Cohen SP. Gadolinium use for interventional procedures: where we are and where are we heading. *Reg Anesth Pain Med.* 2019;44:118–121.
13. Maus T. Intrathecal gadolinium: a fatal flaw. *Reg Anesth Pain Med.* 2019;44:687–688.
14. Benzon HT, Schecthman J, Zheng S, et al. Patients with a history of adverse reaction to iodinated contrast medium and given iodinated contrast during an interventional procedure. *Reg Anesth Pain Med.* 2019;44:118–121.
15. Manchikanti L, Pampati V, Hirsh J. Retrospective cohort study of usage patterns of epidural injections for spinal pain in the US fee-for-service Medicare population from 2000 to 2014. *BMJ Open.* 2016;6:e013042.

16. Benzon HT, Joshi G, Gan TJ, Vetter T. Development, reporting and evaluation of clinical practice guidelines. *Anesth Analg*. 2019;129:1771–1777.
17. US Preventive Services Task Force Grade Definitions after July 2012. Levels of certainty Regarding Net Benefit. Accessed January 5, 2020. <https://www.uspreventiveservicestaskforce.org/Page/Name/grade-definitions>.
18. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what is s and what it isn't. *BMJ*. 1996;312:71–72.
19. Djulbegovic B, Guyatt G. Evidence vs consensus in clinical practice guidelines. *JAMA*. Published online July 19, 2019. doi: 10.1001/jama.2019.9751.
20. Schieda N, Maralani PJ, Hurrell C, Tsampalieros AK, Hiremath S. Updated clinical practice guideline on use of gadolinium-based contrast agents in kidney disease issued by the Canadian Association of Radiologists. *Can Assoc Radiol J*. 2019;70:226–232.
21. Malayeri AA, Brooks KM, Bryant LH, et al. National Institutes of Health perspective on reports of gadolinium deposition in the brain. *J Am Coll Radiol*. 2016;13:237–241.
22. Gulani V, Calamante F, Shellock FG, et al. Gadolinium deposition in the brain: summary of evidence and recommendations. *Lancet Neurol*. 2017;16:564–570.
23. Todd DJ, Kay J. Gadolinium-induced fibrosis. *Annu Rev Med*. 2016;67:273–291.
24. Evans CH, Drouven BJ. The promotion of collagen polymerization by lanthanide and calcium ions. *Biochem J*. 1983;213:751–758.
25. Brouven BJ, Evans CH, Evans CH. Collagen fibrillogenesis in the presence of lanthanides. *J Biol Chim*. 1986;261:11792–11797.
26. Thomsen HS, Morcos SK, Almen T, et al. Nephrogenic systemic fibrosis and gadolinium-based contrast media: updated ESUR Contrast Medium Safety Committee guidelines. *Eur Radiol*. 2013;23:307–318.
27. Girardi M, Kay J, Elston DM, et al. Nephrogenic systemic fibrosis: clinicopathological definition and workup recommendations. *J Am Acad Dermatol*. 2011;65:1095–1106.
28. Schieda N, van der Pol CB, Walker D, et al. Adverse events to the gadolinium-based contrast agent gadoteric acid: systematic review and meta-analysis. *Radiology*. 2020;297:565–572.
29. European Society of Urogenital Radiology. ESUR guidelines on contrastagents, version 10.0. 2018. Accessed May 20, 2020. <http://www.esur-cm.org/index.php/a-general-adverse-reactions-2>.
30. Woolen SA, Shankar PR, Gagnier JJ, et al. Risk of nephrogenic systemic fibrosis in patients with stage 4 or 5 chronic kidney disease receiving a group II gadolinium-based contrast agent: a systematic review and meta-analysis. *JAMA Intern Med*. 2020;180:223–230.
31. Davenport MS, Perazella MA, Yee J, et al. Use of intravenous iodinated contrast media in patients with kidney disease: consensus statements from the American College of Radiology and the National Kidney Foundation. *Radiology*. 2020;294:660–668.
32. Kanda T, Ishii K, Kawaguchi H, Kitajima K, Takenada D. High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material. *Radiology*. 2014;270:834–841.
33. Kanda T, Fukusato T, Matsuda M, et al. Gadolinium-based contrast agent accumulates in the brain even in subjects without severe renal dysfunction: Evaluation of autopsy brain specimens with inductively coupled plasma mass spectroscopy. *Radiology*. 2015;276:228–232.
34. Kanda T, Osawa M, Oba H, et al. High signal intensity in dentate nucleus on unenhanced T1-weighted MR images: association with linear versus macrocyclic gadolinium chelate administration. *Radiology*. 2015;275:803–809.
35. McDonald RJ, McDonald JS, Kallmes DF, et al. Intracranial gadolinium deposition after contrast-enhanced MR imaging. *Radiology*. 2015;275:772–782.
36. Murata M, Gonzalez-Cuyar LF, Murata K, et al. Macrocyclic and other non-group 1 gadolinium contrast agents deposit low levels of gadolinium in brain and bone tissue: preliminary results from patients with normal renal function. *Invest Radiol*. 2016;51:447–453.
37. Murata M, Murata K, Gonzalez-Cuyar LF, Maravilla KR. Gadolinium tissue deposition in brain and bone. *Magn Reson Imaging*. 2016;34:1359–1365.
38. Roberts DR, Lindhorst SM, Welsh CT, et al. High levels of gadolinium deposition in the skin of a patient with normal renal function. *Invest Radiol*. 2016;51:280–289.
39. FDA Drug Safety Podcast: FDA warns that gadolinium-based contrast agents (GBCAs) are retained in the body; requires new class warnings. Accessed October 1, 2020. <https://www.fda.gov/drugs/fda-drug-safety-podcasts/fda-drug-safety-podcast-fda-warns-gadolinium-based-contrast-agents-gbcas-are-retained-body-requires#:~:text=On%20December%2019%2C%202017%2C%20FDA,years%20after%20receiving%20these%20drugs>.
40. Update on FDA approach to safety issue of gadolinium retention after administration of gadolinium-based contrast agents. Accessed October 1, 2020. <https://www.fda.gov/media/116492/download>.
41. Levine D, McDonald RJ, Kressel HY. Gadolinium retention after contrast-enhanced MRI. *JAMA*. 2018;320:1853–1854.
42. Burke LM, Ramalho M, AlObaidy M, Chang E, Jay M, Semelka RC. Self-reported gadolinium toxicity: a survey of patients with chronic symptoms. *Magn Reson Imaging*. 2016;34:1078–1080.
43. Welk B, McArthur E, Morrow SA, et al. Association between gadolinium contrast exposure and the risk of parkinsonism. *JAMA*. 2016;316:96–98.
44. McDonald RJ, Levine D, Weinred J, et al. Gadolinium retention: a research roadmap from the 2018 NIH/ACR/RSNA workshop on gadolinium chelates. *Radiology*. 2018;289:517–534.
45. Costa AF, van der Pol CV, Maralani PJ, et al. Gadolinium deposition in the brain: a systematic review of existing guidelines and policy statement issued by the Canadian Association of Radiologists. *Can Assoc Radiol J*. 2018;69:373–82.
46. Oner AY, Barutcu B, Aykoll S, Talli ET. Intrathecal contrast-enhanced magnetic resonance imaging-related brain signal changes: residual gadolinium deposition? *Invest Radiol*. 2017;52:195–197.
47. Kapoor R, Liu J, Devasenapathy A, Gordin V. Gadolinium encephalopathy after intrathecal gadolinium injection. *Pain Physician*. 2010;13:E321–E326.
48. Reeves C, Galang E, Padalia R, Tran N, Padalia D. Intrathecal injection of gadobutrol: a tale of caution. *J Pain Palliat Care Pharmacother*. 2017;31:139–143.
49. Arlt S, Cepek L, Rustenbeck HH, Prange H, Reimers CF. Gadolinium encephalopathy due to accidental intrathecal administration of gadopentetate dimeglumine. *J Neurol*. 2007;254:810–812.
50. Li L, Gao FQ, Zhang B, et al. Overdosage of intrathecal gadolinium and neurological response. *Clin Radiol*. 2008;63:1063–1068.

51. Park K-W, Im S-B, Kim B-T, et al. Neurotoxic manifestations of an overdose intrathecal injection of gadopentetate dimeglumine. *J Korean Med Sci.* 2010;25:505–508.
52. Nayak NB, Huang JC, Hathout GM, et al. Complex imaging features of accidental cerebral intraventricular gadolinium administration. *J Neurosurg.* 2013;118:1130–1134.
53. Nehra AK, McDonald RJ, Bluhm AM, et al. Accumulation of gadolinium in human cerebrospinal fluid after gadobutrol-enhanced MR imaging: a prospective observational cohort study. *Radiology.* 2018;288:416–423.
54. Berger F, Kubik-Huch RA, Niemann T, et al. Gadolinium-distribution in cerebrospinal fluid after administration of a gadolinium-based MR contrast agent in humans. *Radiology.* 2018;288:703–709.
55. Albayram S, Kilic F, Ozer H, et al. Gadolinium-enhanced MR cisternography to evaluate dural leaks in intracranial hypotension syndrome. *AJNR Am J Neuroradiol.* 2008;29:116–121.
56. Algin O, Turkbey B. Intrathecal gadolinium-enhanced MR cisternography: a comprehensive review. *AJNR Am J Neuroradiol.* 2013;34:14–22.
57. Edeklev CS, Halvorsen M, Lovland G, et al. Intrathecal use of gadobutrol for glymphatic MR imaging: prospective safety study of 100 patients. *AJNR Am J Neuroradiol.* 2019;40:1257–1264.
58. Dillon WP. Intrathecal gadolinium: its time has come? *AJNR Am J Neuroradiol.* 2008;29:3–4.
59. Vogler H, Platzek J, Schuhmann-Giamperi G, et al. Pre-clinical evaluation of gadobutrol: a new, neutral, extracellular contrast agent for magnetic resonance imaging. *Eur J Radiol.* 1995;21:1–10.
60. El-Yahouchi CA, Plastaras CT, Maus TP, et al. Adverse event rates associated with transforaminal and interlaminar epidurals injections: a multi-institutional study. *Pain Med.* 2016;17: 239–249.
61. Popescu A, McCormick ZL, Smith CC; Spine Intervention Society's Patient Safety Committee. Strategies to minimize risk in lumbar transforaminal injections: Imaging and injectate. *Pain Med.* 2019;20:1449–1450.
62. Maus TP, Schueler BA, Magnuson DJ, Magnuson D. Relative conspicuity of gadolinium-based contrast agents in interventional pain procedures. *Pain Med.* 2017;18:651–654.
63. Costello JR, Kalb B, Martin DR. Incidence and risk factors for gadolinium-based contrast agent immediate reactions. *Top Magn Reson Imaging.* 2016;25:257–263.
64. Kim MH, Lee SY, Lee SE, et al. Anaphylaxis to iodinated contrast media: clinical characteristics related with development of anaphylactic shock. *PLoS One.* 2014;9:e100154.
65. Morzycki A, Bhatia A, Murphy K. Adverse reactions to contrast material: a Canadian update. *Can Assn Radiol J.* 2017;68:187–193.
66. Masch WR, Wangl CL, Davenport MS. Severe allergic-like contrast reactions: epidemiology and appropriate treatment. *Abd Radiol.* 2016;41:1632–1639.
67. Bohm I, Morelli J, Nairz K, et al. Myths and misconceptions concerning contrast media-induced anaphylaxis: a narrative review. *Postgrad Med.* 2017;129:259–266.
68. Mayorga C, Fernandez TD, Montañez MI, Moreno E, Torres MJ. Recent developments and highlights in drug hypersensitivity. *Allergy.* 2019;74:2368–2381.
69. Sánchez-Borges M, Aberer W, Brockow K, et al. Controversies in drug allergy: radiographic contrast media. *J Allergy Clin Immunol Pract.* 2019;7:61–65.
70. Cha MJ, Kang DY, Lee W, et al. Hypersensitivity reactions to iodinated contrast media: a multicenter study of 196 081 patients. *Radiology.* 2019;293:117–124.
71. Schabelman E, Witting M. The relationship of radiocontrast, iodine, and seafood allergies: a medical myth exposed. *J Emerg Med.* 2010;39:701–707.
72. Long B, Chassee T, Jones JS. BET 2: is there an association between iodine, shellfish and contrast agent allergies? *Emerg Med J.* 2019;36:698–699.
73. Smith MA, Newton LP, Barcena Blanch MA, et al. Risk for anaphylactic reaction from cardiac catheterization in patients receiving β -adrenergic blockers or angiotensin converting enzyme-inhibitors. *J Allergy Clin Immunol Pract.* 2020;8:1900–1905.
74. Wang CL, Cohan CH, Ellis JH, Caoili EM, Wang G, Francis JR. Frequency, outcome, and appropriateness of treatment of nonionic iodinated contrast media reactions. *AJR Am J Roentgenol.* 2008;191:409–415.
75. Mortelet KJ, Oliva MR, Ondategui S, Ros PR, Silverman SG. Universal use of nonionic iodinated contrast medium for CT: evaluation of safety in a large urban teaching hospital. *AJR Am J Roentgenol.* 2005;185:31–34.
76. Behzadi AH, Zhao Y, Farooq Z, Prince MR. Immediate allergic reactions to gadolinium-based contrast agents: a systematic review and meta-analysis. *Radiology.* 2018;286: 471–482.
77. Jung JW, Kang HR, Kim MH, et al. Immediate hypersensitivity reaction to gadolinium-based MR contrast media. *Radiology.* 2012;264:414–422.
78. McDonald JS, Hunt CH, Kolbe AB, et al. Acute adverse events following gadolinium-based contrast agent administration: a single-center retrospective study of 281945 injections. *Radiology.* 2019;292:620–627.
79. Davenport MS. Choosing the safest gadolinium-based contrast medium for MR imaging: not so simple after all. *Radiology.* 2018;286:483–485.
80. Greenberger PA, Patterson R. The prevention of immediate generalized reactions to radiocontrast media in high-risk patients. *J Allergy Clin Immunol.* 1991;87:867–872.
81. Lasser EC, Berry CC, Talner LB, et al. Pretreatment with corticosteroids to alleviate reactions to intravenous contrast material. *N Engl J Med.* 1987;317:845–849.
82. Park HJ, Park JW, Yang MS, et al. Re-exposure to low osmolar iodinated contrast media in patients with prior moderate-to-severe hypersensitivity reactions: A multicenter retrospective cohort study. *Eur Radiol.* 2017;27:2886–2893.
83. Jung JW, Choi YH, Park CM, et al. Outcomes of corticosteroid prophylaxis for hypersensitivity reactions to low osmolar contrast media in high-risk patients. *Ann Allergy Asthma Immunol.* 2016;117:304–309.
84. Park SJ, Kang DY, Sohn KH, et al. Immediate mild reactions to CT with iodinated contrast media: strategy of contrast media readministration without corticosteroids. *Radiology.* 2018;288:710–716.
85. Abe S, Fukuda H, Tobe K, Ibukuro K. Protective effect against repeat adverse reactions to iodinated contrast medium: premedication vs. changing the contrast medium. *Eur Radiol.* 2016;26:2148–2154.
86. Park SJ, Lee SY, Yoon SH, Choi YH, Kang HR. Corticosteroid prophylaxis may be not required for patients with mild hypersensitivity reaction to low-osmolar contrast media. *Eur J Radiol.* 2020;130:109152.
87. Tramer MR, von Elm E, Loubeyre P, Hauser C. Pharmacological prevention of serious anaphylactic reactions due to iodinated contrast media: systematic review. *BMJ.* 2006;333:675–681.
88. Freed KS, Leder RA, Alexander C, DeLong DM, Kliever MA. Breakthrough adverse reactions to low-osmolar contrast media after steroid premedication. *AJR Am J Roentgenol.* 2001;176:1389–1392.
89. Davenport MS, Cohn RH, Caoili EM, Ellis JH. Repeat contrast medium reactions in premedicated patients: frequency and severity. *Radiology.* 2009;253:372–379.

90. Davenport MS, Cohan RH. The evidence for and against corticosteroid prophylaxis in at-risk patients. *Radiol Clin North Am.* 2017;55:413–421.
91. Fok JS, Smith WB. Hypersensitivity reactions to gadolinium-based contrast agents. *Curr Opin Allergy Clin Immunol.* 2017;17:241–246.
92. Tardy B, Guy C, Barral G, et al. Anaphylactic shock induced by intravenous gadopentetate dimeglumine. *Lancet.* 1992;339:494.
93. Dillman JR, Ellis JH, Cohan RH, et al. Allergic-like breakthrough reactions to gadolinium contrast agents after corticosteroid and antihistamine premedication. *Am J Roentgenol.* 2008;190:187.
94. Kim YS, Choi YH, Cho YJ, et al. Incidence of breakthrough reaction in patients with prior acute allergic-like reactions to iodinated contrast media according to the administration route. *Korean J Radiol.* 2018;19:352–357.
95. Benzon HT, Schechman J, Zheng S, et al. Patients with a history of adverse reaction to iodinated contrast medium and given iodinated contrast during an interventional procedure. *Reg Anesth Pain Med.* 2019;44:118–121.
96. Mishra RK, Heavner JE, Day M. Prevalence of adverse reactions to radiopaque contrast reported by patients presenting for interventional pain procedure. *Pain Pract.* 2012;13:182–190.
97. Carr CM, Plastaras CT, Pingree MJ, et al. Immediate adverse events in interventional pain procedures: a multi-institutional study. *Pain Med.* 2016;17:2155–2161.
98. Kalangara J, Lanier K, Beckworth W, Kuruvilla M. Absence of iodinated contrast hypersensitivity and characterization of gadolinium utilization in an interventional pain population. *Pain Pract.* 2021;21:184–189.
99. Brockow K, Romano A, Aberer W, et al. Skin testing in patients with hypersensitivity reactions to iodinated contrast media - a European multicenter study. *Allergy.* 2009;64:234–241.
100. Greenberger P. Hypersensitivity reactions to iodinated radiocontrast media: to skin test or not to skin test. *J Allergy Clin Immunol Pract.* 2018;6:1255–1256.
101. Bridenbaugh PO. Office-based anesthesia: requirements for patient safety. *Anesth Prog.* 2005;52:86–90.
102. Shanefelt TM, Centor RM. Reassessment of clinical practice guidelines: go gently into that good night. *JAMA.* 2009;301:868–869.
103. Kahn R, Gale EA. Gridlocked guidelines for diabetes. *Lancet.* 2010;375:2203–2204.
104. Smith GC, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. *BMJ.* 2003;327:1459–1461.

APPENDIX. PARTICIPATING SOCIETIES AND ITS REPRESENTATIVES

American Academy of Pain Medicine (AAPM): R. W. Hurley, MD and Z. L. McCormick, MD; American Society of Neuroradiology (ASNR): R. K. Lee, MD and K. Blackham, MD; American Society of Regional Anesthesia and Pain Medicine (ASRA): S. P. Cohen, MD and D. A. Provenzano, MD; British Pain Society (BPS): A. Bhaskar, MD and A. Gulve, MD; Canadian

Pain Society (CPS): A. Bhatia, MD and H. Shanthanna, MD; European Pain Federation (EFIC): S. Brill, MD; Korean Pain Society (KPS): J. Youn Moon, MD and Y. H. Jeon, MD; Society for Interventional Radiology: J. Collins, MD; Spine Intervention Society (SIS): T. P. Maus, MD and F. Diehn, MD; World Allergy Organization (WAO): M. S. Borges, MD and H.R. Kang, MD; World Institute of Pain (WIP): R. L. Rauck, MD and J. van Zundert, MD.