American College of Radiology™

ACR® Manual on Contrast Media

ACR Committee on Drugs and Contrast Media

ACR Manual on Contrast Media

2025

ACR Committee on Drugs and Contrast Media

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PREFACE

This edition of the *ACR Manual on Contrast Media* replaces all earlier editions. It is being published as a web-based document only so it can be updated as frequently as needed.

This manual was developed by the ACR Committee on Drugs and Contrast Media of the ACR Commission on Quality and Safety as a guide for radiologists to enhance the safe and effective use of contrast media. The Committee offers this document to practicing radiologists as a consensus of scientific evidence and clinical experience concerning the use of contrast media. Suggestions for patient screening, premedication, recognition of adverse reactions, and emergency treatment of such reactions are emphasized. Its major purpose is to provide useful information regarding contrast media used in daily practice.

The editorial staff sincerely thanks all who have contributed their knowledge and valuable time to this publication.

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Finally, the committee wishes to recognize the efforts of supporting members of the ACR staff.

VERSION HISTORY
2025

Version 2025 of the ACR Manual on Contrast Media was published as a web-based product. Content changes may take place as a result of changes in technology, clinical treatment, or other evidence-based decisions from the contrast committee.

The following changes have been made:

Last Updated	Chapter	Change
2010	Introduction	Updated
2013	Chapter 7 – Allergic-like and Physiologic Reactions to Intravascular Iodinated Contrast Media	Updated
2013	Chapter 8 – Contrast Media in Children	Updated
2013	Chapter 12 – Gastrointestinal (GI) Contrast Media in Adults: indications and Guidelines	Updated
2013	Chapter 19 - Administration of Contrast Media to Women Who Are Breast-Feeding	Updated
2014	Chapter 11- Contrast Media in Children	Updated
2014	Appendix A	Updated
2015	Preface	Updated
2016	Chapter 13– ACR-ASNR Position Statement on the Use of Gadolinium Contrast Agents	A collaborative statement on gadolinium deposition was added to the manual
2016	Table 1 – Indications for Use of Iodinated Contrast Media	Deleted
2016	Table 2 – Organ and System-Specific Adverse Effects from the Administration of Iodine-Based or Gadolinium-Based Contrast Agents	Deleted
2016	Chapter 9 – Metformin	Updated footnote based on new FDA advisory
2016	Chapter 14 – Injection of Contrast Media	New section on intra-osseous injection
2016	Chapter 13 – ACR-ASNR Position Statement on the Use of Gadolinium Contrast Agents	New Chapter added
2017	Chapter 15 – Nephrogenic Systemic Fibrosis	Updated
2017	Chapter 4 – Patient Selection and Preparation Strategies	Updated
2017	Chapter 17 – Ultrasound Contrast Media	New chapter added
2017	Chapter 19 – Administration of Contrast Media to Pregnant or Potentially Pregnant Patients	Updated
2018	Chapter 5 – Injection of Contrast Media	Updated
2018	Chapter 6 – Extravasation of Contrast Media	Updated
2020	Chapter 18 – Treatment of Contrast Reactions	Updated
2020	Table 4 – Equipment for Contrast Reaction Kits in Radiology	Updated

2020	Appendix (Approved Contrast Media Agents)	Updated
2021	Chapter 5 - Fasting Prior to Intravascular Contrast Media Administration	New added chapter
2021	Chapter 10 - Post-Contrast Acute Kidney Injury and Contrast-Induced Nephropathy in Adults	ACR-NKF Consensus language harmonization update with chapter title change
2021	Chapter 16 - Nephrogenic Systemic Fibrosis (NSF)	ACR-NKF Consensus language harmonization update
2022	Chapter 7 – Extravasation of Contrast Media	Evidence based update with recommendations and strength of evidence
2022	Chapter 15 - Adverse Reactions To Gadolinium-Based Contrast Media	New Gadolinium Pregnancy Screening Statement
2023	Chapter 16 - Nephrogenic Systemic Fibrosis (NSF)	Updated Calculating eGFR for Adults
2023	TABLE 1. ACR Manual Classification of Gadolinium-Based Agents Relative to Nephrogenic Systemic Fibrosis	Gadopiclenol Update
2023	Appendix A – Contrast Media Specifications	Gadopiclenol Update
2024	TABLE 1. ACR Manual Classification of Gadolinium-Based Agents Relative to Nephrogenic Systemic Fibrosis	Eovist Update
2024	Chapter 12 – Contrast Media in Children	Update and New Ferumoxytol addition
2024	Chapter 13 - Gastrointestinal (GI) Contrast Media in Adults: indications and Guidelines	Updated
2024	Chapter 20 - Administration of Contrast Media to Women Who are Breast-Feeding	Evidence based update with recommendations and strength of evidence
2025	Chapter 16 - Nephrogenic Systemic Fibrosis (NSF)	Clarification on gadolinium-based contrast agent groups

INTRODUCTION

Various forms of contrast media have been used to improve medical imaging. Their value has long been recognized, as attested to by their common daily use in imaging departments worldwide. Like all other pharmaceuticals, however, these agents are not completely devoid of risk. The major purpose of this manual is to assist radiologists in recognizing and managing the small but real risks inherent in the use of contrast media.

Adverse side effects from the administration of contrast media vary from minor physiological disturbances to rare severe life-threatening situations. Preparation for prompt treatment of contrast media reactions must include preparation for the entire spectrum of potential adverse events and include prearranged response planning with availability of appropriately trained personnel, equipment, and medications. Therefore, such preparation is best accomplished prior to approving and performing these examinations. Additionally, an ongoing quality assurance and quality improvement program for all radiologists and technologists and the requisite equipment are recommended. Thorough familiarity with the presentation and emergency treatment of contrast media reactions must be part of the environment in which all intravascular contrast media are administered.

Millions of radiological examinations assisted by intravascular contrast media are conducted each year in North America. Although adverse side effects are infrequent, a detailed knowledge of the variety of side effects, their likelihood in relationship to pre-existing conditions, and their treatment is required to insure optimal patient care.

As would be appropriate with any diagnostic procedure, preliminary considerations for the referring physician and the radiologist include:

1. Assessment of patient risk versus potential benefit of the contrast-assisted examination.
2. Imaging alternatives that would provide the same or better diagnostic information.
3. Assurance of a valid clinical indication for each contrast medium administration.

Because of the documented low incidence of adverse events, intravenous injection of contrast media may be exempted from the need for informed consent, but this decision should be based on state law, institutional policy, and departmental policy.

Usage Note: In this manual, the term “low-osmolality” in reference to radiographic iodinated contrast media is intended to encompass both low-osmolality and iso-osmolality media, the former having osmolality approximately twice that of human serum, and the latter having osmolality approximately that of human serum at conventionally used iodine concentrations for vascular injection. Also, unless otherwise obvious in context, this manual focuses on issues concerning radiographic iodinated contrast media.

PATIENT SELECTION AND PREPARATION STRATEGIES BEFORE CONTRAST MEDIUM ADMINISTRATION

General Considerations

The approach to patients about to undergo a contrast-enhanced examination has four general goals:

1) Ensure that the administration of contrast is appropriate for the patient and the indication
2) Balance the likelihood of an adverse event with the benefit of the examination
3) Promote efficient and accurate diagnosis and treatment
4) Be prepared to treat a reaction should one occur (see Tables 2, and 3)

Achieving these aims depends on obtaining an appropriate and adequate history for each patient, considering the risks and benefit of using or avoiding contrast medium, preparing the patient appropriately for the examination, having equipment available to treat reactions, and ensuring that personnel with sufficient expertise are available to treat severe reactions.

The history obtained should focus on identification of factors that may indicate either a contraindication to contrast media use or an increased likelihood of an adverse event. Screening questions should include historical elements that will affect decision-making in the patient selection and preparation period.

Risk Factors for Adverse Reactions to Intravenous Contrast Media Primary Considerations

Allergic-like reactions to modern iodinated and gadolinium-based contrast medium are uncommon (iodinated: 0.6% aggregate [1], 0.04% severe [2]; gadolinium-based: 0.01-0.22% aggregate [2], 0.008% severe) [3]. Risk factors exist that increase the risk of a contrast reaction. These generally increase the likelihood of a reaction by less than one order of magnitude, effectively increasing the risk that an uncommon event will occur, but not guaranteeing a reaction will take place. The following are some examples:

Allergy: Patients who have had a prior allergic-like reaction or unknown-type reaction (i.e., a reaction of unknown manifestation) to contrast medium have an approximately 5-fold increased risk of developing a future allergic-like reaction if exposed to the same class of contrast medium again [2]. A prior allergic-like or unknown type reaction to the same class of contrast medium is considered the greatest risk factor for predicting future adverse events.

In general, patients with unrelated allergies are at a 2- to 3-fold increased risk of an allergic-like contrast reaction, but due to the modest increased risk, restricting contrast medium use or premedicating solely on the basis of unrelated allergies is not recommended. Patients with shellfish or povidone-iodine (e.g., Betadine®) allergies are at no greater risk from iodinated contrast medium than are patients with other allergies (i.e., neither is a significant risk factor) [4,5].

There is no cross-reactivity between different classes of contrast medium. For example, a prior reaction to gadolinium-based contrast medium does not predict a future reaction to iodinated contrast medium, or vice versa, more than any other unrelated allergy.

Asthma: A history of asthma increases the likelihood of an allergic-like contrast reaction [2,6].

Patients with asthma may be more prone to develop bronchospasm. Due to the modest increased risk, restricting contrast medium use or premedicating solely on the basis of a history of asthma is not recommended.

Renal Insufficiency: Screening and selection strategies to mitigate the possible risks of the non-allergic adverse events of contrast-induced nephrotoxicity (CIN) and nephrogenic systemic fibrosis (NSF) can be found in the Chapters on Post-Contrast Acute Kidney Injury and Contrast Induced Nephropathy in Adults and Nephrogenic Systemic Fibrosis.

Cardiac Status: Patients with severe cardiac disease may be at increased risk of a non-allergic cardiac event if an allergic-like or non-allergic contrast reaction occurs. These include symptomatic patients (e.g., patients with angina or congestive heart failure symptoms with minimal exertion) and also patients with severe aortic stenosis, cardiac arrhythmias, primary pulmonary

hypertension, or severe but compensated cardiomyopathy. Due to the modest increased risk, restricting contrast medium use or premedicating solely on the basis of a patient's cardiac status is not recommended.

Anxiety: There is some evidence that contrast reactions are more common in anxious patients [7]. Reassuring an anxious patient before contrast medium injection may mitigate the likelihood of a mild contrast reaction.

Other Historical and Pre-Procedure Considerations

Age and Gender: Infants, neonates, children, and the elderly have lower reaction rates than middle-aged patients [1,8]. Male patients have lower reaction rates than female patients. Due to the modest increased risk, restricting contrast medium use or premedicating solely on the basis of patient age or gender is not recommended.

Beta-Blockers: Some have suggested that use of beta-blockers lowers the threshold for contrast reactions, increases the severity of contrast reactions, and reduces the responsiveness of treatment with epinephrine [9]. Due to the modest increased risk, restricting contrast medium use or premedicating solely on the basis of beta-blocker use is not recommended. Patients on beta-blocker therapy do not need to discontinue their medication(s) prior to contrast medium administration.

Sickle-Cell Trait/Disease: Some have suggested that contrast medium exposure to patients with sickle cell trait or sickle cell disease might increase the risk of an acute sickle crisis; however, there is no evidence this occurs with modern iodinated or gadolinium-based contrast medium [10]. Therefore, restricting contrast medium use or premedicating solely on the basis of sickle cell trait or sickle cell disease is not recommended.

Pheochromocytoma: There is no evidence that IV administration of modern iodinated or gadolinium-based contrast medium increases the risk of hypertensive crisis in patients with pheochromocytoma [11]. Therefore, restricting contrast medium use or premedicating solely on the basis of a history of pheochromocytoma is not recommended. Direct injection of any type of contrast medium into the adrenal or renal arteries in a patient with pheochromocytoma has not been adequately studied and is of unknown risk.

Myasthenia Gravis: There is a questionable relationship between IV iodinated contrast medium and exacerbations of myasthenic symptoms in patients with myasthenia gravis. While one retrospective study showed no immediate increase in myasthenic symptoms following the administration of iodinated or gadolinium-based contrast medium [12], another that searched for myasthenic exacerbations occurring up to 45 days after a CT scan found that IV non-ionic iodinated contrast medium was associated with an acute (within 1 day of contrast administration) myasthenic exacerbation in approximately 6% of patients (compared to a 1% acute exacerbation rate in patients who had undergone non-contrast CT, $p=0.01$) [13]. However, that study was retrospective, and the number of events was small. Premedication is not recommended solely on the basis of a history of myasthenia gravis. It is controversial whether iodinated contrast medium should be considered a relative contraindication in patients with myasthenia gravis.

Hyperthyroidism: Patients with a history of hyperthyroidism can develop thyrotoxicosis after exposure to iodinated contrast medium, but this complication is rare [14]. Therefore, restricting contrast medium use or premedicating solely on the basis of a history of hyperthyroidism is not recommended. However, two special situations may affect this:

1. In patients with acute thyroid storm, iodinated contrast medium exposure can potentiate thyrotoxicosis; in such patients, iodinated contrast medium should be avoided. Corticosteroid premedication in this setting is unlikely to be helpful.

2. In patients considering radioactive iodine therapy or in patients undergoing radioactive iodine imaging of the thyroid gland, administration of iodinated contrast medium can interfere with uptake of the treatment and diagnostic dose. If iodinated contrast medium was administered, a washout period is suggested to minimize this interaction. The washout period is ideally 3-4 weeks for patients with hyperthyroidism, and 6 weeks for patients with hypothyroidism [15,16].

Normal Thyroid Function: Iodinated contrast medium does not affect thyroid function test results in patients with a normally functioning thyroid gland [14]. Multiple studies have shown that a single dose of iodinated contrast medium administered to a pregnant mother has no effect on neonatal thyroid function.

Angiography: Iso-osmolality contrast media (IOCM) are associated with the least amount of vasospasm and the least peripheral discomfort for peripheral angiograms [17]. Concomitant use of iodinated contrast medium with certain intra-arterial medications (e.g., papaverine) may lead to precipitation of contrast medium and crystal or thrombus formation. Decisions about the use and timing of such medication are outside the scope of this document.

Pretesting

Intradermal skin testing with contrast media to predict the likelihood of adverse reactions has not been shown to be useful in minimizing reaction risk [18-20].

Corticosteroid Premedication

The purpose of corticosteroid premedication is to mitigate the likelihood of an allergic-like reaction in high- risk patients.

Etiology of Hypersensitivity Contrast Reactions: The etiological mechanism of most immediate hypersensitivity contrast reactions is incompletely understood [21]. It is known, however, that approximately 90% of such adverse reactions are associated with direct release of histamine and other mediators from circulating basophils and eosinophils. It is also generally accepted that most adverse allergic-like reactions are not associated with the presence of increased IgE, and therefore are unlikely to be typical IgE-mediated hypersensitivity reactions. However, some studies show evidence of IgE mediation [18]. No antibodies to IV contrast media have been consistently identified, and according to skin testing and basophil activation, IgE-mediated allergy is uncommon, for example occurring in 4% of patients having anaphylaxis symptoms [19]. This likely explains why patients who have never been exposed to contrast media can experience a severe hypersensitivity reaction on first exposure. Prior sensitization is not required for a contrast reaction to occur.

Pathophysiologic explanations for allergic-like hypersensitivity reactions include activation of mast cells and basophils releasing histamine, activation of the contact and complement systems, conversion of L-arginine into nitric oxide, activation of the XII clotting system leading to production of bradykinin [10], and development of "pseudoantigens" [22].

The osmolality of the contrast medium as well as the size and complexity of the molecule has potential influence on the likelihood of contrast reactions. Hyperosmolality is associated with stimulation of histamine release from basophils and mast cells. Increase in the size and complexity of the contrast molecule may potentiate the release of histamine [23,24]. There is some evidence to suggest that low-osmolality nonionic monomers produce lower levels of histamine release from basophils compared with high-osmolality ionic monomers, low-osmolality ionic dimers and iso-osmolality nonionic dimers [24]. Low-osmolality monomeric contrast media also are associated with a reduced likelihood of physiologic reactions following intravenous administration (i.e., non-allergic-like; e.g., nausea and vomiting). In general, non-ionic iodinated contrast media are associated with less adverse events than ionic contrast media (iodinated and gadolinium- based) [2,25].

Benefits of Premedication: A randomized trial showed that premedication of average-risk patients prior to high- osmolality iodinated contrast medium administration reduces the likelihood of immediate adverse events of all severity [21]. However, high-osmolality contrast medium is no longer used for intravascular purposes.

Another randomized trial showed that premedication of average-risk patients prior to modern low- osmolality iodinated contrast medium administration reduce the likelihood of mild and aggregate immediate adverse events, but the trial was underpowered to evaluate the effect on moderate and severe reactions [26].

Both of these randomized trials of premedication did not study the effect of premedication in high-risk patients who are usually premedicated today, and neither study was sufficiently powered to evaluate the efficacy of premedication in the prevention of moderate or severe reactions [21,26].

Nonetheless, many experts believe that premedication does reduce the likelihood of a reaction in high- risk patients receiving low-osmolality iodinated contrast medium [26], although the number needed to treat to prevent a reaction is high [27,28]. One study estimated that the number needed to premedicate to prevent one reaction in high-risk patients was 69 for a reaction of any severity and 569 for a severe reaction [27]. Another study estimated the number needed to treat to prevent a lethal reaction in high-risk patients to be 50,000 [28].

There are no studies evaluating the efficacy of premedication prior to oral contrast medium administration or gadolinium-

based contrast medium administration in high-risk patients. Premedication strategies in these patients are based on extrapolated data from patients receiving intravascular iodinated media.

Risks of Premedication: The direct risks of premedication are small [29] and include transient leukocytosis, transient (24-48h) and usually asymptomatic hyperglycemia (non-diabetics: +20-80 mg/dL, diabetics: +100-150 mg/dL) [30,31], and a questionable infection risk, among other things. Diphenhydramine may cause drowsiness and should not be taken shortly before operating a vehicle. Some patients have experienced allergies to the individual medications used in premedication.

The largest risk of premedication is indirect and related to the delay in diagnosis imparted by the multi- hour duration of premedication [30]. In one retrospective cohort study of 2829 subjects, 13-hour oral premedication of high-risk inpatients was associated with increased hospital length of stay (median:
+25h), increased time to CT (median: +25h), increased hospital-acquired infection risk, and increased costs compared to non-premedicated controls [30]. The indirect harms of premedication likely overshadow the benefits of premedication in some vulnerable populations.

Breakthrough Contrast Reactions: Premedication does not prevent all contrast reactions [27,32,33]. Allergic- like contrast reactions that occur despite premedication are called "breakthrough reactions" [32]. Physiologic reactions are not mitigated by premedication and are not considered "breakthrough reactions," even if they occur following premedication.

Patients premedicated for a prior contrast reaction have a breakthrough reaction rate (2.1%) that is 3-4 times the ordinary reaction rate in the general population, while patients premedicated for other indications have a breakthrough reaction rate close to 0% [27]. In most cases (~81%), breakthrough reaction severity is similar to index reaction severity [32,33]. Patients with a mild index reaction have a very low risk (<1%) of developing a severe breakthrough reaction [27].

The majority (~88%) of contrast injections in premedicated patients with a prior breakthrough reaction will not result in a repeat breakthrough reaction [32,33]. Repeat breakthrough reactions, if they occur, usually are of similar severity to prior breakthrough reactions. Therefore, patients who have had a prior moderate or severe breakthrough reaction are at the highest risk for developing a future moderate or severe breakthrough reaction [32,33].

Premedication Strategies: Oral premedication is preferable to IV premedication in most settings due to lower cost, more convenience, and greater evidentiary support in the literature [21,26]. The randomized trials of premedication in average-risk patients were conducted with oral methylprednisolone [21,26]. Uncontrolled studies in high-risk patients were conducted with oral prednisone [34,35].

Supplemental administration of a non-selective antihistamine (e.g., diphenhydramine) orally or intravenously 1 hour prior to contrast medium administration may reduce the frequency of urticaria, angioedema, and respiratory symptoms. Use of selective anti-histamines (i.e., selective H2 blockers) has not been well studied [34].

The minimum duration of premedication necessary for efficacy is unknown. Lasser et al [26] showed that one dose of 32 mg oral methylprednisolone 2 hours prior to IV high-osmolality iodinated contrast medium administration in average-risk patients was not effective, while two doses administered at 2- and 12-hours before contrast medium administration were effective [26].

A dose-response study of single-dose IV methylprednisolone (1 mg/kg) [36] in 11 volunteers showed a reduction in circulating basophils and eosinophils by the end of the first post-injection hour, reaching statistical significance compared with controls by the end of the second hour and a concomitant reduction in histamine in sedimented leukocytes by 4 hours. Most of these effects reached their peak at 8 hours.

There is no evidence to support a premedication duration of 2 hours or less (oral or IV; corticosteroid- or antihistamine-based).

An IV corticosteroid regimen with a minimum duration of 4-5 hours may be efficacious [10,26,29,36].

Indications for Premedication

Given that premedication does not prevent all reactions, has not been confirmed to reduce the incidence of moderate or severe reactions or reaction-related deaths, has limited supporting efficacy in high-risk patients, and is accompanied by direct and indirect harms, the utility of premedication in high- risk patients is uncertain. Given the tradeoffs between what is known and not known with respect to the benefits and harms of premedication, premedication may be considered in the following settings and scenarios:

12- or 13-hour oral premedication may be considered in the following settings:

1. Outpatient with a prior allergic-like or unknown-type contrast reaction to the same class of contrast medium (e.g., iodinated – iodinated).

2. Emergency department patient or inpatient with a prior allergic-like or unknown-type contrast reaction to the same class of contrast medium (e.g., iodinated – iodinated) in whom the use of premedication is not anticipated to adversely delay care decisions or treatment.

Accelerated IV premedication may be considered in the following settings:

1. Outpatient with a prior allergic-like or unknown-type contrast reaction to the same class of contrast medium (e.g., iodinated – iodinated) who has arrived for a contrast-enhanced examination but has not been premedicated and whose examination cannot be easily rescheduled.

2. Emergency department patient or inpatient with a prior allergic-like or unknown-type contrast reaction to the same class of contrast medium (e.g., iodinated – iodinated) in whom the use of 12- or 13-hour premedication is anticipated to adversely delay care decisions or treatment.

In rare clinical situations, the urgency of a contrast-enhanced examination may outweigh the benefits of prophylaxis, regardless of duration, necessitating that contrast medium be administered to a high-risk patient in the absence of premedication. This determination is best made jointly by the radiology team, the referring service, and potentially the patient (if feasible). In such cases, a team of individuals skilled in resuscitation should be available during the injection to monitor for and appropriately manage any developing reaction.

Regardless of patient status, history of a prior severe contrast reaction is considered a relative contraindication to receiving the same class of contrast medium in the future. If the same class of contrast medium is necessary and there are no alternatives, premedication should be considered, if feasible.

Routine premedication or avoidance of contrast medium for other indications, such as allergic reactions to other substances (including shellfish or contrast media from another class [e.g., gadolinium-based – iodinated]), asthma, seasonal allergies, or multiple drug and food allergies is not recommended.

Specific Recommended Premedication Regimens

Elective Premedication (12- or 13-hour oral premedication)

1. Prednisone-based: 50 mg prednisone by mouth at 13 hours, 7 hours, and 1 hour before contrast medium administration, plus 50 mg diphenhydramine intravenously, intramuscularly, or by mouth 1 hour before contrast medium administration [21].

Or

2. Methylprednisolone-based: 32 mg methylprednisolone by mouth 12 hours and 2 hours before contrast medium administration. 50 mg diphenhydramine may be added as in option 1 [37].

   Although never formally compared, both regimens are considered similarly effective. The presence of diphenhydramine in regimen 1 and not in regimen 2 is historical and not evidence-based. Therefore, diphenhydramine may be considered optional.

If a patient is unable to take oral medication, option 1 may be used substituting 200 mg hydrocortisone IV for each dose of oral prednisone [38]. If a patient is allergic to diphenhydramine in a situation where diphenhydramine would otherwise be considered, an alternate anti-histamine without cross-reactivity may be considered, or the anti-histamine portion of the regimen may be dropped.

Accelerated IV Premedication (in decreasing order of desirability)

1. Methylprednisolone sodium succinate (e.g., Solu-Medrol®) 40 mg IV or hydrocortisone sodium succinate (e.g., Solu-Cortef®) 200 mg IV immediately, and then every 4 hours until contrast medium administration, plus diphenhydramine 50 mg IV 1 hour before contrast medium administration. This regimen usually is 4-5 hours in duration.

2. Dexamethasone sodium sulfate (e.g., Decadron®) 7.5 mg IV immediately, and then every 4 hours until contrast medium administration, plus diphenhydramine 50 mg IV 1 hour before contrast medium administration. This regimen may be useful in patients with an allergy to methylprednisolone and is also usually 4-5 hours in duration.

3. Methylprednisolone sodium succinate (e.g., Solu-Medrol®) 40 mg IV or hydrocortisone sodium succinate (e.g., Solu-Cortef®) 200 mg IV, plus diphenhydramine 50 mg IV, each 1 hour before contrast medium administration. This regimen, and all other regimens with a duration less than 4-5 hours, has no evidence of efficacy. It may be considered in emergent situations when there are no alternatives.

   Note: Premedication regimens less than 4-5 hours in duration (oral or IV) have not been shown to be effective. The accelerated 4-5-hour regimen listed as Accelerated IV option 1 is supported by a case series and by a retrospective cohort study with 828 subjects [38].

Missing One or More Doses of Premedication

Sometimes, patients undergoing premedication present for a contrast-enhanced scan without completing their premedication regimen. In such cases, there is no evidence base to guide decision-making, so management should be individualized. Generally speaking, if premedication is being used, a guiding principle is to have a minimum of 4-5 hours of corticosteroid therapy prior to contrast medium exposure, with repeat doses every 4-8 hours. Diphenhydramine administration is optional.

Premedication in Patients Undergoing Chronic Corticosteroid Therapy

In patients who have had a prior allergic-like reaction to contrast medium and who are also on chronic corticosteroid therapy, premedication dosing may be modified. In this circumstance, there is no evidence base to guide decision-making, so management should be individualized. Generally speaking, if corticosteroid premedication is being used, a guiding principle is to reduce the dose of the chosen premedication dose regimen by an amount equivalent to the patient's chronic therapeutic corticosteroid dose. If the patient is on simple replacement (not therapeutic) corticosteroids, the premedication dosing regimen may not need to be adjusted.

Changing Contrast Media Within the Same Class

In patients with a prior allergic-like or unknown-type contrast reaction to a known contrast medium, changing contrast media within the same class (e.g., one iodinated medium for another) may help reduce the likelihood of a subsequent contrast reaction [39,40]. Some studies have shown that the effect size of switching contrast media actually may be greater than that of premedication alone, but combining premedication with a change in agent seems to have the greatest effect [39,40]. Unfortunately, many patients do not know which specific agent they have reacted to in the past; they simply remember they had a reaction. In the future, through improved electronic medical records, routine linking of reactions to specific contrast media is likely to add value. In the current state, investigating which agent was responsible for one or more prior reactions often is not possible.

Premedication Is Not a Panacea

No premedication strategy is a substitute for pre-administration preparedness. Contrast reactions occur despite premedication [32], and radiology teams must be prepared to treat breakthrough reactions when they occur. Patients should receive

information concerning their risk of a reaction according to local policy and practice.

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Fasting Prior to Intravascular Contrast Media Administration

To decrease the likelihood of vomiting and aspiration, some practices request that patients fast prior to administration on intravenous contrast media [1]. However, currently used low- and iso-osmolality nonionic iodinated contrast media used for CT, and gadolinium-based contrast media (GBCM) used for MRI, have much lower risk of vomiting compared to the previously used ionic high-osmolality iodinated contrast media [2-9]. Furthermore, pre-procedure fasting may have negative effects including scheduling limitations, hypoglycemic risk in patients with diabetes mellitus, and general discomfort.

A 2012 meta-analysis of 13 studies and 2,001 patients exposed to intravascular iodinated contrast media found that, despite heterogeneous fasting practices (including many with no restrictions), there were no cases of aspiration pneumonia attributable to iodinated contrast media [1]. A 2009 study of 158,439 injections of GBCM demonstrated that only 0.03% resulted in mild adverse events including nausea, vomiting, or mild rash [10]. No assessment of the risk aspiration pneumonia attributable to GBCM has been performed. Data indicate there is no preventive effect of fasting prior to modern iodinated and gadolinium-based intravascular contrast media administration on risk of nausea, vomiting, or aspiration [11].

Given the potential for negative consequences due to fasting and a lack of evidence that supports the need for fasting, fasting is not required prior to routine intravascular contrast material administration. However, for patients receiving conscious sedation, anesthesia guidelines should be consulted (e.g., the American Society of Anesthesiology [ASA] Practice Guidelines for Preoperative Fasting in Health Patients Undergoing Elective Procedures) [12].

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SAFE INJECTION OF CONTRAST MEDIA

General Considerations

Injection methods vary depending on vascular access, differential diagnosis, and imaging examination type. The mode and method of delivery, either by hand or by power injector, also vary by procedure. Subject to the requirements of state law, a radiologist, radiologic technologist, or nurse may administer contrast media. Stable intravenous (IV) access is necessary. For current American College of Radiology (ACR) recommendations regarding injection of contrast media (including radiopharmaceuticals), see the ACR–SPR Practice Parameter for the Use of Intravascular Contrast Media.

Referring to FDA package inserts may be appropriate in determining contrast media doses and concentrations (see Appendix A – Contrast Media Specifications). It is important to avoid prolonged admixture of blood and contrast media in syringes and catheters whenever possible due to the risk of clot formation. In general, unless known to be safe, the admixture of contrast media and any medication should be avoided. However, heparin may be combined with contrast media.

Mechanical Injection of Intravenous Contrast Media

Bolus or power injection of IV contrast material is superior to drip infusion for enhancing normal and abnormal structures during body computed tomography (CT). Radiology personnel must recognize the need for proper technique to avoid the potentially serious complications of contrast media extravasation and air embolism. (See the Chapter on Extravasation of Contrast Media). When proper technique is used, contrast medium can be safely administered intravenously by power injector in the vast majority of patients, even at high-flow rates.

Technique

To avoid potential complications, the patient's cooperation should be obtained whenever possible. Communicating with the patient before the examination and during the injection may reduce the risk of contrast medium extravasation. If the patient reports pain or the sensation of swelling at the injection site, injection should be discontinued.

Intravenous contrast media should be administered by power injector through a flexible plastic cannula. Use of metal needles for power injection should be avoided whenever possible. In addition, the flow rate should be appropriate for the gauge of the catheter used. Although 22-gauge catheters may be able to tolerate flow rates up to 5 ml/sec, a 20-gauge or larger catheter is preferable for flow rates of 3 ml/sec or greater. An antecubital or large forearm vein is the preferred venous access site for power injection. If a more peripheral (e.g., hand or wrist) venipuncture site must be used, flow rates should be reduced if feasible (e.g., 1-2 mL/sec).

Careful preparation of the power injection apparatus is essential to minimize the risk of contrast medium extravasation or air embolism. Standard procedures should be used to clear the syringe and pressure tubing of air, after which the syringe should be reoriented with the tubing directed downward. Several maneuvers can be performed to confirm the proper intravenous location of an inserted catheter. The catheter to be used can be checked for backflow of blood into the tubing, although backflow is not always noted, even in an appropriately positioned intravenous line. A saline test flush can be performed by hand or once the tubing is connected to a power injector. Direct monitoring of the site during injection can be performed if feasible, but direct monitoring often is not feasible, particularly when CT arteriography is performed or when automatic triggering programs are employed. If the venipuncture site is found to be tender or infiltrated during any of these maneuvers, an alternative site should be sought. In all instances, the power injector and its tubing should be positioned to allow adequate table movement without tension on the intravenous line.

A means of easy communication between the technologist and the patient is required at all times prior to, during, and following a contrast media injection. This initially can occur via direct contact and then by use of an intercom or television system. When feasible, the patient should be notified of the presence of such a system and instructed to notify the technologist for any changes in sensation, including increasing pain or swelling at the injection site.

It should not be assumed that power injection can be performed in all central venous catheters. However, power injection of contrast media through some central venous catheters can be performed safely provided that certain precautions are followed. Before connecting the catheter to the injector system tubing, the catheter tip position should be tested for venous backflow. Occasionally backflow will not be obtained because the catheter tip is positioned against the wall of the vein in which it is located. If saline can be injected through the catheter without abnormal resistance, contrast media can be administered through the catheter safely. If abnormal resistance or discomfort is encountered, an alternative venous access site should be sought. Injection with large-bore (9.5-F to 10-F) central venous catheters using flow rates of up to 2.5 ml/ sec has been shown to

generate pressures below manufacturers' specified limits. For power injection of contrast media through some central venous catheters, the radiologist should consult manufacturers' recommendations. Contrast media should not be administered by power injector through small-bore, peripheral (e.g., arm) access central venous catheters unless permitted by the manufacturer's specifications because of the risk of catheter breakage. Such catheters will usually have a specific rating that indicates they can be used for power injection up to a specified flow rate.

Air Embolism

Clinically significant large-volume venous air embolism is a potentially fatal but rare complication of IV contrast media injection. However, small-volume clinically insignificant venous air embolism commonly occurs. Using care when using power injection for contrast-enhanced CT minimizes the risk of clinically significant air embolism. On CT, venous air embolism is most commonly identified as air bubbles or air-fluid levels in the intrathoracic veins, main pulmonary artery, or right ventricle, although it can conceivably be visualized in any vessel downstream of the injection (e.g, intracranial veins).

Inadvertent injection of large amounts of air into the venous system may result in air hunger, dyspnea, cough, chest pain, pulmonary edema, tachycardia, hypotension, and expiratory wheezing. Neurologic deficits may result from stroke due to decreased cardiac output or paradoxical air embolism. Patients with right-to-left intracardiac shunts or pulmonary arteriovenous malformations are at a higher risk of having a neurological deficit develop from small volumes of air embolism.

Treatment of venous air embolism includes administration of 100% oxygen and placing the patient in the left lateral decubitus position (i.e., left side down). Hyperbaric oxygen has been recommended to reduce the size of air bubbles and to restore circulation and oxygenation. If cardio-pulmonary arrest occurs, closed-chest cardiopulmonary resuscitation should be initiated immediately.

Intra-osseous Injection

Intra-osseous (IO) catheters allow rapid intravascular access for the administration of fluids and medications in critically ill patients without intravenous access. Over the last two decades, there have been improvements in product design and speed of line placement that have translated into a low reported complication rate [1-3]. Three common devices on the market in the United States include: The Bone Insertion Gun (BIG) (WaisMed, Israel); the First Access in Shock and Trauma (FAST1) (Pyng Medical Corporation, Richmond, Canada); and the EZ-IO (Vidacare, San Antonio, USA), which uses a battery-powered driver (similar to a hand-held drill) to place the specially designed needle [1,2]. Humeral placement is now the preferred site of access secondary to quick line placement and higher achievable flow rates compared to tibial access [1,4,5]. High pressures are needed to infuse through IO lines because of high intramedullary compartmental pressures. Power injection is possible for CT and MRI; however, the rates for injection and pressure settings are not well studied in humans. While no large studies looking at IO access for administration of contrast media exist, several case reports document successful acquisition of contrast-enhanced CT with no reported complications using injection rates up to 5 ml/sec (max PSI of 300) [4,6-9]. Intra-osseous injection of gadolinium-based contrast media has not been studied, but there is no reason to believe it would behave differently.

A local anesthetic is needed in non-sedated patients prior to infusion of any substance through IO access. A few small studies have looked at different lidocaine algorithms to minimize the pain of infusion [1,5,10]. One suggested pretreatment reported from a single institution with the EZ-IO device is 40 mg 2% (2 ml) of epinephrine-free lidocaine slowly infused over 2 minutes after the line is primed with 1 ml lidocaine. The medication was allowed to dwell for one minute, and then the line was flushed with 5-10 ml of saline followed by another 20 mg (1 ml) of lidocaine infused over one minute. For pediatric patients the same algorithm would be used, with 0.5 mg/kg as the initial dose (not to exceed 40 mg), followed by a 2-5 ml saline flush and a second 0.25 mg/kg lidocaine dose [4]. If a radiology practice is not familiar with IO infusions, consult the local trauma team for advice on how and whether to prime the line with anesthetic using local protocols.

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Suggested Reading (Articles that the Committee recommends for further reading on this topic are provided here).

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Extravasation Bullet Points and Recommendations with Associated Strength of Evidence

Below is a summary of the recommendations related to contrast extravasation and the associated strength of evidence for those recommendations using the ACR Appropriateness Criteria® Methodology.

Frequency

- **0.1-1.2% of CT injections result in extravasations [1-9].**
- **Most extravasations resolve without complication [6, 7, 11, 13, 14]; severe extravasation injuries, including compartment syndrome (most common [11]) and skin ulceration / necrosis, are very rare (<<1% of extravasations) [7, 8, 11].**

Risks

- Extravasations and severe extravasation injuries are more common in patients who 1) are uncommunicative, 2) have altered circulation in the injected extremity, 3) have had radiation of the injected extremity, or 4) are injected in the hand, foot, or ankle [1, 32].
- Extravasations are also more common in patients injected with more viscous contrast material [6, 8, 35].
- The risk of extravasation can be minimized by 1) using angiocatheters rather than butterfly needles, 2) performing meticulous intravenous catheter insertion technique (confirming intravenous location by aspirating blood through an inserted catheter and flushing the inserted catheter with a test injection), 3) and carefully securing an inserted catheter [41].

Evaluation and treatment

- **A health care provider should examine any patient in whom a contrast-media extravasation occurs; physical examination should include assessment of tenderness, swelling, erythema, paresthesia, active and passive range of finger motion, and perfusion [22].**
- **There is no known effective treatment for contrast medium extravasation, although initial steps should include elevation of the affected extremity above the level or the heart [22, 24], and use of cold or warm compresses [22-25]. No medical interventions have been deemed helpful [15, 22, 28, 29].**
- **Since severe extravasation injuries can develop slowly (up to hours after an extravasation), all discharged outpatients should be given clear instructions concerning where and when to seek additional medical care (including for worsening pain, development of paresthesia, diminished range of motion, and new skin ulceration or blistering) [22].**
- **Surgical consultation should be obtained whenever there is concern for a severe extravasation injury [11, 22]; this can be suspected if the patient develops severe pain, progressive swelling or pain, decreased capillary refill, change in sensation, worsening active or passive range of motion in the elbow, wrist, or fingers, or skin ulceration or blistering [17]; reliance on an extravasation volume threshold to trigger surgical consultation is not recommended [11, 13, 18].**

Power-injection through central venous catheters and peripherally inserted central catheters (PICCs)

- **Contrast material can only be power-injected into central venous catheters [38] or PICCs [39] if these catheters have been certified for such use, with the flow-rate limit provided. All manufacturer recommendations should be followed.**

Gadolinium-based contrast media

- Extravasation injuries after injection of gadolinium-based contrast media are much less common than those seen after injection of iodinated contrast material [20], likely due, in part, to less toxicity [21] and the low volumes of gadolinium-based contrast media that are injected.

Summary Questions and Answers
(Study Quality = SQ)

Question 1. What actions can be performed to minimize the likelihood of an extravasation?

Recommendation 1: Extravasation risk is minimized by 1) using angiocatheters over butterflies, 2) performing meticulous intravenous insertion technique (confirming intravenous location by aspirating blood through an inserted catheter and flushing the inserted catheter with a test injection), 3) and carefully securing an inserted catheter.

Strength of evidence: Limited 1

Reference #	Original SQ	Reassessed SQ	Final SQ
41	2	-	2

Question 2: What risk factors should clinicians take into consideration in determining the likelihood of a contrast extravasation?

Recommendation 1: Clinicians should consider patient related factors such as history of altered circulation in the injected extremity, prior radiation to the injected extremity, or uncommunicative patients.

Strength of evidence: Limited 1

Reference #	Original SQ	Reassessed SQ	Final SQ
1	2	-	2
32	4	-	4

Recommendation 2: Clinicians should consider contrast and injection parameters such as viscosity of contrast material and location of injection other than non-antecubital fossa regions (such as hand, foot, and ankle more at risk)

Strength of evidence: Viscosity = Strong 3

Reference #	Original SQ	Reassessed SQ	Final SQ
6	2	-	2
8	2	-	2
35	2	-	2

Strength of evidence: Location of injection = Strong 3

Reference #	Original SQ	Reassessed SQ	Final SQ
1	2	-	2
20	4	-	4
36	2	-	2

Question 3: How should clinicians evaluate patients for potential contrast extravasation?

Recommendation 1: Clinicians should do a physical exam of the affected extremity to evaluate for tenderness, swelling, erythema, paresthesia, active and passive range of finger motion, and perfusion.

Strength of evidence: Limited 3

Reference #	Original SQ	Reassessed SQ	Final SQ
22	4	-	4

Question 4: How should contrast extravasations be treated?

Recommendation 1: Elevation of the affected extremity above the heart.

Strength of evidence: Limited 3

Reference #	Original SQ	Reassessed SQ	Final SQ
22	4	-	4
24	4	-	4

Recommendation 2: Cold compresses or ice packs should initially be applied to the extravasation site (rather than warm compresses)

Strength of evidence: Limited 1

Reference #	Original SQ	Reassessed SQ	Final SQ
22	4	-	4
23	Inadequate	-	Inadequate
24	4	-	4
25	1	-	1

Recommendation 3: Routine use of hyaluronidase or corticosteroid injections or aspiration of the affected limb is not recommended.

Strength of evidence: Limited 1

Reference #	Original SQ	Reassessed SQ	Final SQ
15	4	4	4
22	4	-	4
28	4	-	4
29	2	-	2

Recommendation 4: All discharged outpatients should be given clear instructions concerning where and when to seek additional medical care (including for worsening pain, development of paresthesia, diminished range of motion, and new skin ulceration or blistering) as severe extravasation could develop several hours later.

Strength of evidence: Limited 3

Reference #	Original SQ	Reassessed SQ	Final SQ
11	4	3	3
22	4	-	4

Question 5: When should surgical consultation be placed?

Recommendation 1: Surgical consultation should not be routinely requested based on volume alone.

Strength of evidence: Strong 3

Reference #	Original SQ	Reassessed SQ	Final SQ
11	4	3	3
13	4	4	4
18	1	-	1
14	2	-	2

Recommendation 2: Surgical consultation should be requested whenever there is concern for a severe extravasation injury; this can be suspected if the patient develops severe pain, progressive swelling or pain, decreased capillary refill, change in sensation, worsening active or passive range of motion in the elbow, wrist, or fingers, or skin ulceration or blistering.

Strength of evidence: Limited 3

Reference #	Original SQ	Reassessed SQ	Final SQ
11	4	3	3
22	4	-	4

Question 6: Can automated (power) injectors be utilized for injections in central venous or PICC lines?

Recommendation 1: Use central venous catheter to power inject contrast or PICCs if the catheters have been certified for such use, with the flow-rate limit provided. All manufacturer recommendations should be followed.

Strength of evidence: Limited 1

Reference #	Original SQ	Reassessed SQ	Final SQ
38	2	-	2
39	4	-	4

Question 7: What is the extravasation risk from injection of gadolinium-based contrast media?

Recommendation 1: Extravasation injuries are extremely unlikely during gadolinium-based contrast media injection, likely due to lower toxicity than iodinated contrast agents and lower total volumes of injected contrast media.

Strength of evidence: Limited 3

Reference #	Original SQ	Reassessed SQ	Final SQ
20	4	-	4
21	4	-	4

EXTRAVASATION OF CONTRAST MEDIA

Frequency

The reported incidence of intravenous (IV) contrast media extravasation in adults and children related to power injection for CT has ranged from 0.1% to 1.2% [41-49] (1/1,000 patients to 1/83 patients). Extravasation can also occur during hand injections. Extravasations may occur at both low and high flow rates [50]. Extravasation occurring with dynamic bolus CT may involve large volumes of contrast media [51].

Initial Signs and Symptoms

Most extravasations are limited to the immediately adjacent soft tissues (typically the skin and subcutaneous tissues).

Although most patients complain of initial swelling or tightness, and/or stinging or burning pain at the site of extravasation, some experience little or no discomfort [51,52]. On physical examination, the extravasation site may be edematous, erythematous, and tender [51].

Extravasation of Iodinated Contrast Material

In most patients, initial swelling and tenderness resolves within hours to days after the extravasation. The vast majority of patients in whom extravasations occur recover without clinically important sequelae [46,47,51,53,54]. However, in some patients, extravasated iodinated contrast media can result in injury to surrounding tissues, particularly the skin, producing an acute local inflammatory response that peaks at 24 to 48 hours [55]. Most of the time there are no lasting complications. Only rarely will a low-osmolality contrast media (LOCM) extravasation injury proceed to a severe adverse event [51]. Acute tissue injury resulting from extravasation of iodinated contrast media is probably related at least in part to its hyperosmolality [56,57].

Several large series have illustrated the infrequency of severe injuries after LOCM extravasation. In one single institutional study, all 321 extravasation injuries were mild [48]. In another single institutional study [51], only one of 442 adult LOCM extravasations resulted in a severe injury (a compartment syndrome). Three other patients developed blisters or ulcerations that were successfully treated locally. In a third study, utilizing a practice quality improvement database established by the American College of Radiology [47] only six of 1,085 reported extravasations resulted in severe injuries, and only one patient required surgical intervention.

The most commonly reported severe injury after LOCM extravasation is compartment syndrome [51]. Compartment syndrome results from mechanical compression and is probably more likely to occur after extravasation of larger volumes of contrast media; however, it also has been observed after extravasation of small volumes, especially when these occur in less capacious areas (such as over the ventral or dorsal surfaces of the wrist) [51]. Compartment syndrome may develop soon after an extravasation [51] or result from swelling that sometimes occurs hours after the extravasation [58].

Less commonly encountered severe injuries include skin ulceration and tissue necrosis [59]. These can occur within hours or days of the extravasation event.

Extravasation of Gadolinium Based Contrast Media

Extravasation of gadolinium-based contrast media is less common (i.e., approximately one-sixth as often) than iodinated contrast media [60]. The difference is likely the due to much lower volumes of administered gadolinium-based contrast media for most clinical indications. Additionally, on a cc to cc basis, gadolinium-based contrast media may also have less toxicity than iodinated contrast agents [61].

Evaluation of Patients in Whom Extravasations Occur

A responsible health care provider should be summoned to examine any patient in whom an extravasation of contrast material has occurred. The patient should be asked about symptoms of pain and paresthesias. A brief examination should be performed and should include assessment of extremity tenderness, swelling, erythema, paresthesia, active and passive range of motion of the fingers, and perfusion [62].

Treatment

Studies evaluating potential treatments of extravasation injuries are generally of low quality [63]. Given the absence of any studies demonstrating definite efficacy of any specific treatment regimen, the optimum treatment of extravasation events has

not been determined. Our limited guidance is to suggest treatments that have a low risk of harm, but that might have some efficacy.

Extravasations that resolve rapidly probably need no treatment other than brief observation and discharge instructions (see section entitled Discharging Patients in Whom Extravasations Occur, below). More symptomatic extravasations may be treated with extremity elevation above the level of the heart (to decrease capillary hydrostatic pressure and thereby promote resorption of extravasated fluid [22, 24]) and either warm or cold compresses that an outpatient may continue intermittently at home until symptoms resolve, along with discharge instructions, or may be continued on the wards for inpatients. Controlled studies demonstrating the efficacy of these interventions are lacking, however [25]. There is no clear evidence favoring the use of warm over cold compresses or vice versa [64]. Some surgeons empirically recommend initial use of cold compresses to promote vasoconstriction and diminish inflowing blood and swelling [62,65].

Severe cases in which there is concern for neurologic or vascular compromise or skin ulceration and necrosis require surgical consultation to assess the need for operative management (see next section).

There is no consistent evidence that the effects of an extravasation can be mitigated by trying to aspirate the extravasated contrast medium through an inserted needle or angiocatheter [62,66]. When such attempts are made, usually little or no extravasated contrast material can be successfully aspirated. Therefore, aspiration is not recommended.

Some have suggested that the extravasation site can be treated by performing multiple punctures around the extravasation site and then manually squeezing the site [67,68]; however, the effectiveness of this approach has not been validated and it is not recommended.

Topical application of silver sulfadiazine ointment and steroid cream three to four times daily has been recommended by some as an approach to soothe irritated skin, reduce inflammation, and to prevent infection should any blistering occur, although the efficacy of this treatment is unknown [52].

There is no consistent evidence that local injection of potentially therapeutic agents, such as corticosteroids or hyalurinidase is beneficial [55,69,70]. Hyaluronidase has been used in the management of extravasation events for medications unrelated to contrast media, and there are a few case reports in which it was attempted following a contrast material extravasation event [71-73]. However, no adequate studies confirm efficacy of hyaluronidase after contrast media extravasation [68]. Therefore, use of hyaluronidase for the management of contrast material extravasation is not recommended [62].

Surgical Consultation

Urgent surgical consultation should be obtained whenever there is concern for a severe extravasation injury [11,22]. Although consultation can prolong length of stay (eg, by 2.5 hours in one ED population [14]), it should be obtained for any patient in whom one or more of the following extravasation-related signs or symptoms develops: severe pain; progressive swelling or pain; altered tissue perfusion as evidenced by decreased capillary refill; change in sensation in the affected limb; worsening passive or active range of motion; and skin ulceration or blistering [17].

Reliance on an extravasation volume threshold (such as estimated volumes exceeding 100 or 150 mL) to indicate the need for surgical consultation has been recommended by some [51,53]. Although a severe injury is probably more likely when larger volumes are involved, most patients with large volume extravasation do not develop severe complications, even when distal to the elbow [53]. Because of this, surgical consultation should be based on signs and symptoms rather than an absolute volume threshold. If the patient is asymptomatic or has only mild symptoms, appropriate evaluation and clinical follow-ups are usually sufficient.

Discharging Patients in Whom Extravasations Occur

Outpatients who have suffered contrast media extravasation should be released from the radiology department only after an initial period of observation, provided the radiologist is satisfied that any signs and symptoms that were present initially have improved or that new symptoms have not developed during the observation period. Clear instructions should be given to the patient to seek additional medical care for severe pain, progressive pain, numbness or tingling, diminished range of motion (active or passive), skin ulceration, or other neurologic or circulatory symptoms [62]. This is because initial symptoms of a serious compartment syndrome may be absent or relatively mild (such as limited to the development of focal paresthesia) [58].

Other Considerations

Patients at Increased Risk for Extravasations

Extravasations are more common in patients who cannot communicate effectively (e.g., the elderly, infants and children, and patients with altered consciousness), severely ill or debilitated patients, and patients with abnormal circulation in the limb to be injected [74]. Patients with altered circulation include those with atherosclerotic peripheral vascular disease, diabetic vascular disease, Raynaud's disease, venous thrombosis or insufficiency, or prior radiation therapy or extensive surgery (e.g., axillary lymph node dissection or saphenous vein graft harvesting) in the limb to be injected. Women may have a mild increased risk of extravasation [63]. Some of these conditions are systemic and cannot be avoided by choosing a different injection site.

Certain intravenous access sites (e.g., hand, wrist, foot, and ankle) are more likely to result in extravasation and should be avoided, when possible [41]. However, use of these alternate injection sites may be necessary due to lack of availability of the more traditional locations.

In some studies, extravasations were more common in patients injected through small-bore (22 gauge) catheters compared to larger-bore catheters (2.2% versus 1.0-1.1%) [41].

While some reviews have found that injection at higher flow rates likely increases the risk of extravasation [48], in others, no such difference has been detected [41,75]. In fact, it has been shown that flow rates of up to 3 and 5 mL/sec can be safely achieved through 22 gauge and 20 gauge intravenous catheters, respectively, in the vast majority of patients, provided that there is no increased resistance or pain during a rapid test injection [75].

Patients injected with more viscous contrast material may be more likely to have extravasations than are patients injected with less viscous contrast material [46,48,76]. This effect may be mitigated for viscous media by extrinsic warming to human body temperature prior to injection [76].

The risk of extravasation also appears to be increased in patients in whom deep brachial intravenous access is achieved under ultrasound guidance, a practice used more often in Emergency Departments for patients in whom IV access is otherwise difficult [77]. In one series, contrast media extravasation occurred during CT in 0.3% of all patients, but in 3.6% of patients who were injected through ultrasound-guided peripheral intravenous catheters [78]. That difference is likely in part due to selection bias (patients requiring ultrasound-guided access likely have more difficult venous access).

Extravasation Risk of Injection through Indwelling Central Venous Catheters

All central venous catheter port sites can be utilized for venous access if gentle hand injections are performed; however, only certain central venous catheter port sites are certified for use with mechanical injectors. Prior to using a central venous line for power injection, it is important to ensure that the port site is certified as power-injectable, and the flow limit should be noted. If this process is followed, it can be safe. In one report of 142 injections through certified power port sites (11 at high rates up to 5 mL/second), there were no extravasations [79].

Mechanical injections can also be performed through some pressure-injectable peripherally inserted central catheters (PICCs). Manufacturer recommendations should be followed. There have been isolated reports of PICC tip migrations following pressure injections through these catheters [80].

Patients at Increased Risk for a Severe Extravasation Injury Once an Extravasation Occurs

A severe extravasation injury may be more likely to result from an extravasation in certain patients, such as those with arterial insufficiency or compromised venous or lymphatic drainage in the affected extremity. In addition, extravasations involving larger volumes of contrast media and those occurring in the dorsum of the hand, foot, or ankle are more likely to result in severe injury [22, 32].

Preventing Extravasation Injuries

Methods for reducing the risk of extravasation include: meticulous intravenous line insertion technique, using angiocatheters instead of butterfly catheters, confirming position by aspirating blood (although failure to aspirate blood does not exclude the possibility of proper catheter location), flushing an inserted catheter with a test injection of saline to ensure proper flow into the accessed vein, and carefully securing the inserted catheter [81].

Low-risk intravenous line insertion sites are preferred when feasible. If not feasible, higher risk sites may be considered depending on the risks and benefits of administrating contrast media for the examination indication. Use of a preliminary

saline flush to assess injection pressure prior to contrast media administration has been advocated by a few investigators [82]; however, this has not been adopted by most institutions. Some have recommended use of a hand-held alarm, which the patient can press should any new symptoms develop [52]. Interestingly, the practice quality improvement project created by the ACR to assist practices in identifying improvements that could be made to reduce the frequency of extravasations did not find that any significant improvement could be achieved, even when risk factors for extravasations were identified and attempts were made to reduce the extravasation risk in advance [47].

Documentation

All extravasation events and their treatment should be documented in the medical record. In addition, the referring provider should be notified following any symptomatic extravasation.

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ALLERGIC-LIKE AND PHYSIOLOGIC REACTIONS TO INTRAVASCULAR IODINATED CONTRAST MEDIA

The frequency of allergic-like and physiologic adverse events related to the intravascular administration of iodinated contrast media (ICM) is low and has decreased considerably with changes in usage from ionic high- osmolality contrast media (HOCM) to nonionic low-osmolality contrast media (LOCM) [1-11]. The majority of adverse side effects to LOCM are mild non-life-threatening events that usually require only observation, reassurance, and/or supportive measures [3,12,13]. Severe and potentially life-threatening adverse events continue to occur rarely and unpredictably. Nearly all life-threatening contrast reactions occur within the first 20 minutes after contrast medium injection.

All personnel who inject intravascular contrast media should be prepared to: 1) recognize the variety of adverse events that may occur following ICM administration and 2) institute appropriate measures to manage the reaction. These measures include notifying the supervising radiologist (or his/her designee), monitoring the patient, administering certain medications, and/or calling for additional assistance (emergency service providers, "code team", etc.).

Acute Adverse Events

Classification of Acute Adverse Events

Acute adverse events can be categorized as either allergic-like or physiologic and organized into three general categories of severity (mild, moderate, or severe). A suggested classification system (which can be utilized for both ICM and gadolinium-based contrast media [GBCM]), stratifying adverse events by severity and type, is presented in Table 1.

A standardized classification system is important to minimize variation between published reports. It is of particular importance to avoid contaminating the reported incidence of allergic-like reactions with that of physiologic reactions, because the management of patients experiencing these reaction types is different (e.g., patients who experience allergic-like reactions may require future premedication prior to ICM- enhanced studies, while patients who experience physiologic reactions would not).

Allergic-Like Reactions

Allergic-like reactions to ICM manifest similarly to true allergic reactions seen with other drugs and allergens, but because an antigen-antibody response cannot be always identified, allergic-like contrast reactions are classified as "anaphylactoid", "allergic-like", or "idiosyncratic" [2,3,12,13]. Treatment of an allergic-like contrast reaction is identical to that of an equivalent allergic reaction. Allergic-like contrast reactions are likely independent of dose and concentration above a certain unknown threshold [3].

The pathogenesis of most allergic-like reactions is unclear. There are multiple possible mechanisms that result in activation of immunologic effectors [14]. It is believed that some allergic-like contrast reactions may involve activation, deactivation, or inhibition of a variety of vasoactive substances or mediators (such as histamine, complement, and the kinin system) [3,12-15]. ICM are known to directly cause histamine release from basophils and mast cells [9]. Histamine release must have occurred when patients develop urticaria, but the precise cause and pathway of histamine release are not known [3,12,13]. Skin and intradermal testing are positive in a minority of individuals, indicating that an allergic IgE-mediated etiology may be responsible for some reactions [16], but this is the minority of cases.

Additives or contaminants, such as calcium-chelating substances or substances eluted from rubber stoppers in bottles or syringes, have been suggested as contributory in some allergic-like contrast reactions [12,13].

Physiologic Reactions

Physiologic reactions to ICM likely relate to specific molecular attributes that lead to direct chemotoxicity [3,12,13], osmotoxicity (adverse effects due to hyperosmolality) [14], or molecular binding to certain activators [9]. Physiologic reactions are frequently dose and concentration dependent [3].

Cardiac arrhythmias, depressed myocardial contractility, cardiogenic pulmonary edema, and seizures are very rare, potentially serious physiologic reactions to ICM [3,9,12,13]. These phenomena are likely related to either contrast media-related hyperosmolality and/or calcium binding leading to functional hypocalcemia [3,9,12,13]. Cardiac adverse events are much more common during angiocardiography than intravenous ICM administration.

Cardiovascular effects are more frequent and significant in patients with underlying cardiac disease. For example, patients with left heart failure are less able to compensate for the osmotic load and minor negative chronotropic effects of ICM. As a result, there is an increased risk of developing acute pulmonary edema. Noncardiogenic pulmonary edema can also very rarely occur following intravascular ICM administration [16], although it is unclear whether this represents a physiologic or allergic-like reaction.

Vasovagal reactions are relatively common and characterized by hypotension with bradycardia. While the exact pathogenesis is unknown, this particular response is thought to be the result of increased vagal tone arising from the central nervous system. The effects of increased vagal tone include depressed sinoatrial and atrioventricular nodal activity, inhibition of atrioventricular conduction, and peripheral vasodilatation [3]. Vasovagal reactions may be related to anxiety and can occur while informed consent is being obtained, during placement of a needle or catheter for contrast medium injection, or during intravascular administration of contrast media. Such reactions commonly present with a feeling of apprehension and accompanying diaphoresis [3].

While most vagal reactions are mild and self-limited, close patient observation is recommended until symptoms resolve fully. Severe hypotension may very rarely cause loss of consciousness, cardiovascular collapse, angina, or seizures [3].

Patient anxiety may also contribute to or exacerbate nonvagal adverse events. Similar to allergic-like reactions, some additives and contaminants have been associated with physiologic reactions [12,13].

For a discussion of renal failure, please see the separate chapter on Contrast-Induced Nephrotoxicity.

Frequency of Acute Adverse Events

The frequency of acute adverse events after the administration of intravascular ICM is difficult to determine with precision because similar signs and symptoms may arise from concomitant medical conditions, medications, anxiety, etc. Underreporting and variation in the classification of acute adverse reactions have affected the reported incidence of these events.

Historically, acute adverse events occurred in 5% to 15% of all patients who received HOCM. Many patients receiving intravascular HOCM experienced physiologic disturbances (e.g., generalized warmth, nausea, or emesis), and this was often documented as a contrast reaction. HOCM are now rarely or never used for intravascular purposes because of their greater adverse event profile compared to LOCM.

LOCM are associated with a very low incidence of acute adverse events, and the bulk of these are not life- threatening. Cochran et al [17] reported an overall acute adverse reaction rate (allergic-like + physiologic) of 0.2% for nonionic LOCM administered at a single institution. A slightly higher overall frequency of 0.7% (allergic-like + physiologic) was reported from another institution upon review of 29,508 patients given iopromide over a 2-year period [18]. Wang et al [19] reported an overall acute allergic-like reaction frequency of 0.6% in 84,928 adult patients who received iohexol, iopromide, or iodixanol.

A single institutional study of pediatric patients receiving intravenous LOCM by Dillman et al [20] demonstrated a frequency of acute allergic-like reactions of 0.18%. Another single institutional study in children by Callahan et al [21] demonstrated an overall acute adverse reaction rate of 0.46% (allergic-like + physiologic).

Serious acute reactions to IV LOCM are rare, with an historical rate of approximately four in 10,000 (0.04%) [6].

The mortality incidence related to intravascular ICM is unknown. In a large Japanese study by Katayama et al [6], no fatal reactions were attributed to LOCM despite greater than 170,000 injections. The conservative estimate of 1 fatality per 170,000 contrast media administrations is thus often quoted. Fatal reactions to LOCM have been reported [4,17,18,22,23]. A meta-analysis performed by Caro et al [4] documented a fatality rate of 0.9 per 100,000 injections of LOCM. A review of U.S. FDA and drug manufacturer data from 1990 to 1994 demonstrated 2.1 fatalities per 1 million contrast-enhanced studies using LOCM [7].

Common Risk Factors for Acute Contrast Reactions

Although it is clear that certain patients are at increased risk of experiencing an adverse event to intravascular ICM, contrast reactions remain sporadic and unpredictable.

A prior allergic-like reaction to ICM is the most substantial risk factor for a recurrent allergic-like adverse event [1,2,6,18,24]. Such a history is not an absolute predictor, and the incidence of recurrent allergic-like reactions in high-risk nonpremedicated patients is unknown. It is estimated to range from 10 to 35% [6,25,26]. The estimated risk in high-risk premedicated patients is estimated to be approximately 10% [26,27]. Atopic individuals (particularly those with multiple severe allergies) and asthmatics are also at increased risk for allergic-like contrast reactions, although probably not to as great an extent [3,6,9,12,13,24,25,28]. Those with a history of prior allergic-like reaction to GBCM are at no greater risk for allergic-like reaction to ICM than other patients with a similar number of allergies and other risk factors (e.g., asthma). A prospective study by Kopp et al [24] of over 74,000 patients who received iopromide demonstrated that certain age and gender combinations (e.g., young females) may have a higher incidence of allergic-like reactions compared to the general population. A retrospective case-control study by Lang et al [28] showed that individuals with asthma and those receiving beta-adrenergic blocker therapy may be at increased risk for moderate and severe reactions; however, this study did not match patients based on underlying diseases and it is possible that beta- blocker therapy merely indicated those patients with more comorbid conditions.

Pre-existing medical conditions may increase the risk of certain adverse events. For example, bronchospasm is a common adverse event among patients with a history of asthma. Hemodynamic changes are more common in patients with significant cardiovascular disease, such as aortic stenosis or severe congestive heart failure.

The effects of dose, route (intravenous vs. intra-arterial vs. other), and rate of delivery of contrast media on the incidence of adverse events are not entirely clear. Studies have shown that a "test injection" does not decrease the incidence of severe allergic-like reactions [29,30], and may actually increase it. Non-reaction to a "test injection" does not indicate that an allergic-like reaction will not occur with a standard injection [25]. Test injections are not recommended for predicting which patients will react to ICM.

Patients with Myasthenia Gravis

Myasthenia gravis has historically been considered a relative contraindication to intravascular iodinated contrast material exposure based on experimental and largely anecdotal clinical data with respect to HOCM. Due to a lack of clear evidence showing adverse effects for LOCM in this setting, only a few contrast material manufacturers continue to suggest precaution in patients with myasthenia gravis.

However, Somashekar et al [31] in 2013 studied 267 patients with clinically confirmed myasthenia gravis who underwent CT (112 with LOCM (CE-CT), 155 without LOCM (NC-CT)), and showed a significantly greater fraction of disease-related symptom exacerbations within 24 hours in the CE-CT group (6.3% [7/112] for CE-CT vs. 0.6% [1/155] for NC-CT, $p = 0.01$). These findings suggest that intravascular LOCM may be relatively contraindicated in patients with myasthenia gravis. This is the first evidence of such a relationship in the medical literature, and confirmatory studies will be needed before a more definitive recommendation can be made.

Other Risk Factors

Drug package inserts suggest precautions are necessary to avoid adverse events in patients with known or suspected pheochromocytoma, thyrotoxicosis, dysproteinemias, or sickle-cell disease. There are scant data, however, to support the need for specific precautions in these patients when LOCM is used (See the Chapter on Patient Selection and Preparation Strategies). For example, a small retrospective study by Bessell- Browne and O'Malley [32] demonstrated no adverse events following IV LOCM administration to patients with pheochromocytomas and paragangliomas.

Treatment

The proper treatment of an acute contrast reaction varies depending on the presentation. A variety of scenarios and possible treatment algorithms are discussed in Tables 2 and 3.

Delayed Adverse Events to Iodinated Contrast Media

Timing

Delayed allergic-like and non-allergic-like adverse events that occur following ICM exposure have long been a source of concern. Such reactions are most commonly cutaneous and may develop from 30 to 60 minutes to up to one week following contrast material exposure, with the majority occurring between three hours and two days [25,33].

Incidence

The incidence of delayed allergic-like reactions has been reported to range from 0.5% to 14% [33,34]. A prospective study of 258 individuals receiving intravenous iohexol demonstrated a delayed reaction rate of 14.3% compared to 2.5% in a control group undergoing imaging without intravascular contrast material [34]. In that same study, 26 of 37 delayed adverse reactions were cutaneous in nature [34]. For several reasons (lack of awareness of such adverse events, usual practice patterns, relatively low frequency of serious outcomes), such reactions are often not brought to the attention of the radiologist. Delayed reactions are more common in patients treated with interleukin-2 (IL-2) therapy [33,35,36].

There is some evidence that the iso-osmolar dimer iodixanol may have a slightly higher rate of delayed cutaneous adverse events when compared to other LOCM [36]. A prospective study by Schild et al [37] demonstrated an increased frequency of delayed cutaneous adverse events to nonionic dimeric contrast material compared to nonionic monomeric contrast material.

Symptoms

The most frequent delayed adverse events following ICM administration are allergic-like and cutaneous [2,33,34,36]. They occur more often than is generally recognized, can recur or have serious sequelae, and are often inadvertently ascribed to causes other than ICM.

Delayed cutaneous reactions commonly manifest as urticaria and/or a persistent rash [2,33,34,36], presenting as a maculopapular exanthem that varies widely in size and distribution [2,25,33,38], or a generalized exanthematous pustulosis [39]. Urticaria and/or angioedema may also occur, and is usually associated with pruritus [25,33]. Occasionally, pruritis may occur in the absence of urticaria.

Severe cutaneous reactions have also been described in individuals with systemic lupus erythematosus (SLE) [36,40,41]. A study by Mikkonen et al [42] suggested that delayed cutaneous adverse events may occur at an increased frequency during certain times of the year, and most commonly affect sun-exposed areas of the body. Cases have been also reported in which the reaction manifests similar to Stevens-Johnson syndrome [41,43], toxic epidermal necrolysis, or cutaneous vasculitis. Rare fatalities have been described [40,41].

A variety of delayed non-cutaneous symptoms and signs have been also reported. These include nausea, vomiting, fever, drowsiness, and headache. Severe delayed noncutaneous contrast reactions, while extremely rare, have been described, including severe hypotension [44] and cardiopulmonary arrest; however, at least some of the events may have been due to etiologies other than ICM.

Other Rare Delayed Adverse Events

Iodide “mumps” (iodine-related sialoadenopathy or salivary gland swelling) [45,46] and acute polyarthropathy [47] are two additional delayed contrast reactions that have been reported rarely after ICM administration. These reactions may be more frequent in patients with renal dysfunction.

Treatment

Since delayed reactions are generally self-limited, most require no or minimal therapy [36]. Treatment is usually supportive, with antihistamines and/or corticosteroids used for cutaneous symptoms, antipyretics for fever, antiemetics for nausea, and fluid resuscitation for hypotension. If manifestations are progressive or widespread, or if there are noteworthy associated symptoms, consultation with an allergist and/or dermatologist may be helpful.

Recurrence Rates and Prophylaxis

The precise recurrence rate of delayed contrast reactions is not known but anecdotally may be 25% or more [36]. Based on this tendency to recur, at least some of these reactions may be due to T cell-mediated hypersensitivity [2,33,34,36,38,48]. The efficacy of corticosteroid and/or antihistamine prophylaxis is unknown, though some have suggested this practice [36]. However, given the likely differing mechanisms between acute and delayed reactions, as well as the extreme rarity or nonexistence of severe delayed reactions, premedication prior to future contrast-enhanced studies is not specifically advocated in patients with solely a prior history of mild delayed cutaneous reaction.

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CONTRAST MEDIA WARMING

This chapter will discuss the relevant literature pertaining to the extrinsic warming of contrast media and provide suggestions of cases in which extrinsic warming of contrast media may be beneficial in the care of patients.

Introduction

Contrast media viscosity, like that of many other liquids, is related to temperature. As the temperature of a given contrast medium increases, there is a concomitant decrease in its dynamic viscosity [1]. Therefore, warmed contrast media are less viscous than room temperature contrast media. When a warmed contrast medium is hand- or power-injected into an intravenous (IV) or intra-arterial (IA) catheter, there will be less resistance than if the contrast medium had not been warmed. The relationship between viscosity and flow for contrast medium injections is typically non-linear because the flow through small bore IV catheters is turbulent and does not obey traditional laminar flow kinetics (Poiseuille's law) [2].

Iodinated Contrast Media – Contrast Material Warming and Injection Kinetics

Several investigators have studied the effects of extrinsic warming of iodinated contrast media on IV and IA injection kinetics [1-9].

Halsell [5] studied the in vitro flow rates through different sized angiographic catheters with and without extrinsic contrast media warming (37$_{o}$C). Contrast warming resulted in a flow rate improvement of 8% or more only when using high-viscosity contrast media (a highly concentrated ionic high-osmolality monomer and an ionic low-osmolality dimer from among the tested agents) through 4 to 5F catheters. Lower viscosity contrast media (including a nonionic monomer at 300 mg I/mL) and larger catheters did not show this flow improvement.

Hughes and Bisset [2] measured the iodine delivery rates for a variety of low-osmolality contrast media (LOCM) at both room (24$_{o}$C) and human body temperature (37$_{o}$C) and concluded that extrinsic warming to 37$_{o}$C improved iodine delivery rates for forceful hand injection through a 5F angiocatheter by 20% to 27% (average of 23.5%). They also found that the iodine delivery rates closely mimicked the dynamic viscosity of the tested contrast media. Contrast media with a greater viscosity tended to be delivered at substantially fewer milligrams of iodine per second compared to those with a lesser viscosity. The authors suggested that vascular opacification with forceful hand injection, such as that used during catheter angiography, could be maximized by reducing the viscosity of the utilized contrast media, either by using a lower viscosity contrast material or by extrinsic warming.

Roth et al [3] tested four different ionic and nonionic iodinated contrast media through 12 different-sized catheters at both human body (37$_{o}$C) and room temperature (20$_{o}$C), and measured the power injection pressure of each combination using a 7 mL injection at 3 mL/second with an electronic pressure transducer. Their results supported some of Halsell's [5] findings by showing that warmed contrast media have a lower viscosity, and this viscosity translates into a reduction in injection pressure, but primarily for smaller diameter (< 6 French) catheters.

Busch et al [4] studied the iodine delivery rates of four different contrast media through five different catheters used for coronary angiography at power injections of 100, 200, and 400 psi. Iodine delivery rates were treated as a surrogate for vascular opacification. The iodine delivery rate improved with increasing pressure, increasing iodine content (mg I/mL) and decreasing contrast media viscosity. Although the authors did not test the effect of extrinsic warming, they speculated that the reduction in viscosity associated with warming may be a method by which iodine delivery rates might be improved. This benefit might be greatest for lower pressure injections, such as hand injections.

Hazirolan et al [8] randomized patients undergoing cardiac CT angiography into two groups: 1) 32 patients receiving warmed (37$_{o}$C) iohexol 350 mg I/mL and 2) 32 patients receiving non-warmed (24$_{o}$C) iohexol 350 mg I/mL, and then compared the timing and degree of subsequent arterial opacification for a test bolus injection rate of 5 mL/second through an 18-gauge peripheral IV catheter. They found that the degree of maximal enhancement within the ascending aorta, descending aorta, and pulmonary arteries was significantly greater ($p = 0.005$) for group 1. They also found that group 1 patients reached 100 Hounsfield Units of enhancement within the ascending aorta significantly faster than group 2 patients ($p = 0.03$). The authors concluded that extrinsic warming of the relatively viscous iohexol 350 improved the speed and degree of enhancement for high-rate cardiac CT angiography. However, their data was solely based on the test injection (not the diagnostic injection).

Schwab et al [9] tested the maximum injection pressures of iopamidol 300, iomeprol 350, and iomeprol 400 at both room (20o C) and human body temperature (37o C) through 18, 20 and 22-gauge IV catheters using a variety of injection rates (1 to 9 mL/second) with a pressure-limited (300-psi) power injector. They concluded that warming of contrast media led to significant ($p < 0.001$) reductions in injection pressures across all tested media. Despite the fact that the manufacturer's recommended pressure thresholds were exceeded with high- rate injections (e.g., 8 mL/second), there were no instances of IV catheter malfunction.

Iodinated Contrast Media – Contrast Material Warming and Adverse Events

Although there is good evidence that warming of contrast media changes the bolus kinetics and injection pressure of iodinated contrast media, there has been little evidence that it affects clinical adverse event rates in a meaningful way [10-12].

In 1982, Turner et al [10] randomly assigned 100 patients in a double-blind fashion to receive either room temperature (20 to 24o C) or human body temperature (37o C) ionic high osmolality contrast media (HOCM), and then compared the anaphylactoid and non-anaphylactoid adverse event rates between these two groups. The authors were unable to show a significant difference, although their study was likely underpowered for a non-inferiority design. They did not report extravasation events.

Vergara et al [11] conducted a non-randomized prospective study of 4,936 IV injections of iodinated contrast media in which each group of patients received a specific contrast media and temperature combination. These groups were then compared with respect to their allergic-like and physiologic adverse events. Again, extravasation rates were not assessed. The authors showed a small but significant reduction in overall adverse events for warmed (37o C) ionic HOCM compared to the same non-warmed (22o C) ionic HOCM (89/894 [10.0%] vs. 204/1607 [12.7%]). The dominant effect was a reduction in mild adverse events (49/894 [5.5%] vs. 138/1607 [8.6%]) rather than a reduction in adverse events that were moderate (36/894 [4.0%] vs. 59/1607 [3.7%]) or severe (4/894 [0.45%] vs. 7/1607 [0.44%]).

Based on the above work, as well as the package inserts for many iodinated contrast media, many institutions heat their iodinated contrast media (both HOCM and LOCM) to human body temperature (37o C) prior to routine clinical intravascular administration. In most instances, this is performed using an external incubator in which the bottles of contrast media are placed. The temperature of the device is typically kept at or near human body temperature (37o C). In addition to these stand-alone warming machines, there also exist warming "sleeves" that can be used to keep pre-warmed bottles (or syringes filled from pre-warmed bottles) of contrast media at a stable (warmed) temperature for approximately one hour or more in cases where the contrast media is removed from the warming device but not immediately injected. These sleeves can be a component to the power injector itself or can function independently.

Because contrast media are designated as medications, the warming of contrast media has fallen under the regulation of The Joint Commission, which mandates that if contrast media are to be extrinsically warmed, there must be both a daily temperature log for each warmer and evidence of regular maintenance for the warming device(s). This regulation has led some institutions to reconsider the use of these warming devices and reevaluate whether warming iodinated contrast media to human body temperature has a significant practical, rather than just a theoretical, benefit for IV LOCM administration. Although some institutions have discontinued the routine use of contrast media warmers for low-rate (< 5 mL/second), non-angiographic, non-cardiac applications, there are little published data investigating what effect this may have on patient adverse events.

The largest study investigating the effect of extrinsic warming on IV LOCM adverse events was published in 2012 [12]. In this non-inferiority retrospective analysis of 24,830 power-injections (< 6 mL/ second) of IV LOCM, the authors compared the rates of allergic-like reactions and extravasations before and after the discontinuation of contrast media warming at a single institution for both iopamidol 300 (dynamic viscosity: 8.8 centiPoise (cP) at 20°C and 4.7 cP at 37°C) and the more viscous iopamidol 370 (dynamic viscosity: 20.9 cP at 20°C and 9.4 cP at 37°C). Discontinuation of contrast media warming had no significant effect on the allergic-like reaction or extravasation rates of iopamidol 300. However, it did result in nearly tripling of the extravasation rate (0.27% [five of 1851] vs. 0.87% [18 of 2074], $p = 0.05$) and combined allergic- like and extravasation event rate (0.43% [eight of 1851] vs 1.25% [26 of 2074], $p = 0.02$) for iopamidol 370. These results suggest that contrast media warming may not be needed for iopamidol 300 but may be needed for iopamidol 370 (and possibly other similarly viscous contrast media) if the primary goal is to minimize contrast media-related adverse events. However, the authors did note that there was no difference in clinical outcome between the warmed and non-warmed iopamidol 370 groups, likely because the vast majority of extravasation events and allergic-like reactions do not result in long-term morbidity or mortality. The authors did not have any data to permit evaluation of the effect of extrinsic contrast media warming on patient

comfort or physiologic (e.g., nausea, vomiting, sensation of warmth) adverse events.

Warming of Iodinated Contrast Media – Suggestions

Based on the available literature, the validity of extrinsic warmers seems predicated on the intended outcome.

Extrinsic warming of iodinated contrast material to human body temperature (37°C) may be helpful to minimize complications and improve vascular opacification in the following circumstances:

- For high-rate (> 5 mL/second) IV LOCM power injections
- For injections of viscous iodinated contrast (e.g., iopamidol 370, and presumably other contrast media with a similar or higher viscosity)
- For direct arterial injections through small-caliber catheters (5 French or smaller)
- For intravenously injected arterial studies in which timing and peak enhancement are critical features

Extrinsic warming of iodinated contrast material may not be needed or beneficial in the following circumstances:

- For low-rate (≤ 5 mL/second) IV LOCM power injections or hand injections
- For injections of iodinated contrast media with a relatively low viscosity (e.g., iopamidol 300, and presumably other contrast media with a similar or lower viscosity)
- For direct arterial injections through large-bore catheters (6 French or larger)
- For IV injections in which peak opacification and timing are not critical (e.g., routine portal venous phase chest/abdomen/pelvis CT imaging)

Package inserts for iodinated contrast media contain information about recommended storage temperatures.

Warming of Gadolinium-Based Contrast Media—Suggestions

Gadolinium-based contrast media are administered at room temperature (15 to 30₀C [59 to 86₀F]) and according to package inserts, should not be externally warmed for routine clinical applications.

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POST-CONTRAST ACUTE KIDNEY INJURY AND CONTRAST-INDUCED NEPHROPATHY IN ADULTS

Definitions and Terminology

Contrast-associated acute kidney injury (CA-AKI) (formerly known as post-contrast acute kidney injury (PC-AKI)) is a general term used to describe a sudden deterioration in renal function that occurs within 48 hours following the intravascular administration of iodinated contrast medium. CA-AKI may occur regardless of whether the contrast medium was the cause of the deterioration [1-12]. *CA-AKI is a correlative diagnosis.*

Contrast-induced acute kidney injury (CI-AKI) (formerly known as contrast-induced nephropathy (CIN) is a specific term used to describe a sudden deterioration in renal function that is caused by the intravascular administration of iodinated contrast medium; therefore, CI-AKI is a subgroup of CA-AKI [1-12]. *CI-AKI is a causative diagnosis.*

Unfortunately, very few published studies have a suitable control group to permit the separation of CI-AKI from CA-AKI [1-12]. Therefore, the incidence of CA-AKI reported in clinical studies and the incidence of CA-AKI observed in clinical practice likely includes a combination of CI-AKI (i.e., AKI caused by contrast medium administration) and AKI unrelated to contrast medium administration (i.e., AKI coincident to but not caused by contrast medium administration).

This document will address both CI-AKI and CA-AKI, but these terms are not interchangeable. CA-AKI is not synonymous with CI-AKI.

At the current time, it is the position of ACR Committee on Drugs and Contrast Media that CI-AKI is a real, albeit rare, entity. Published studies on CI-AKI have been heavily contaminated by bias and conflation. Future investigations building on recent methodological advancements [3,4,7,9], are necessary to clarify the incidence and significance of this disease.

Pathogenesis

CA-AKI may be caused by any nephrotoxic event (including CI-AKI) that is coincident to the intravascular administration of contrast material. Because the diagnosis of CA-AKI is based on changes in serum creatinine [2,13-15] physiologic fluctuation in this value can also contribute to its incidence, particularly in patients with chronic kidney disease. Patients who have an elevated serum creatinine at baseline have a greater variance in daily serum creatinine measurements than those with a normal baseline serum creatinine [10].

The exact pathophysiology of CI-AKI is not understood. Etiologic factors that have been suggested include renal hemodynamic changes (vasoconstriction) and direct tubular toxicity, among others [16-26]. Both osmotic and chemotoxic mechanisms may be involved, and some investigations suggest agent-specific chemotoxicity. The nephrotoxic effect of iodinated contrast medium may be proportional to dose for cardiac angiography; there is no evidence of a dose-toxicity relationship following intravenous (IV) administration when administered at usual diagnostic doses. CI-AKI may occur in children, but if so, it is rare [27-30]. Gadolinium-based contrast media either do not cause CI-AKI when administered at FDA-approved doses, or this event is exceptionally rare [31-35]. If administered at extreme above-FDA-label doses to achieve X-ray attenuating effects during angiography (not recommended), gadolinium-based contrast media are more nephrotoxic than iso-attenuating doses of iodinated contrast media [36-38].

Diagnosis

Kidney Disease Improving Global Outcomes (KDIGO) criteria are recommended for the diagnosis of CA-AKI and endorsed by the NKF Kidney Disease Outcomes Quality Initiative as a consensus definition for epidemiologic and clinical research applications [39-41]. The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for acute kidney injury were developed to assist practitioners caring for patients at risk for or with AKI following an explicit process of evidence review and appraisal [40,42].

KDIGO Definition of Acute Kidney Injury

The diagnosis of AKI is made according to the KDIGO criteria if one of the following occurs within 48 hours after a nephrotoxic event (e.g., intravascular iodinated contrast medium exposure) [40]:

1. Absolute serum creatinine increase ≥0.3 mg/dL (>26.4 μmol/L).
2. A percentage increase in serum creatinine ≥ 50% (≥1.5-fold above baseline).

3. Urine output reduced to ≤ 0.5 mL/kg/hour for at least 6 hours.

This system has been advocated as a common definition of intrinsic acute kidney injury, regardless of etiology [40]. Therefore, it can be used to define the parameters of CA-AKI as well as CI-AKI. The KDIGO criteria also outline a system for staging the degree of renal injury that is present following the diagnosis of AKI; the interested reader is referred to the original manuscript [40].

Elevations in serum creatinine are neither sensitive nor specific for individual types of AKI. Any serum creatinine-based criteria, used in isolation, will be unable to separate CI-AKI from generic CA-AKI. This applies to scientific studies lacking appropriate control groups and to clinical evaluations of individual patients [2-4,7-9,11].

Laboratory Tests of Renal Function

Laboratory tests may be used both to estimate the risk of CI-AKI prior to administering contrast medium and to determine whether AKI has occurred after contrast medium administration. Serum creatinine concentration is the most commonly used measure of renal function, but it has limitations as an accurate measure of glomerular filtration rate (GFR) [43-47]. Serum creatinine is considerably influenced by the patient's gender, muscle mass, nutritional status, and age. Impaired renal function can exist when the serum creatinine is "normal". Normal serum creatinine is maintained until the GFR – at least as reflected in creatinine clearance – is reduced by nearly 50%.

Calculated estimated glomerular filtration rate (eGFR) is more accurate than is serum creatinine at predicting true GFR [48]. As a result, eGFR is gaining attention as a potentially better marker of CI-AKI risk [49,50].

Although the formula for estimating GFR has intrinsic error due to the reliance on serum creatinine, and lack of validation in patients with AKI, low muscle mass or patients on dialysis, it is the most accurate and least biased method commonly available to stratify KDIGO CKD stages.

Route of Contrast Administration

In the last two decades, the CI-AKI literature has been dominated by reports of patients who have undergone cardiac angiography with iodinated contrast medium. Cardiac angiography differs from IV contrast medium administration in three major ways: 1) the injection is intra-arterial and supra-renal, 2) the injection requires a catheter that can dislodge atheroemboli, and 3) the contrast medium dose to the kidneys will be more abrupt and concentrated [2,6,51,52].

The overall incidence of CA-AKI in studies of cardiac angiography is higher than it is in studies of patients who receive IV iodinated contrast medium. Therefore, data from cardiac angiography studies likely over-estimate the risk of CI-AKI for patients undergoing IV contrast-enhanced studies [2,6].

CI-AKI Studies

Much of the literature investigating the incidence of CI-AKI has failed to include a control group of patients not receiving contrast medium [8,12]. This is problematic because several studies have shown that the frequency and magnitude of serum creatinine change in patients who have not received contrast medium is similar to the changes in patients who have received it [7-9,53-60]. In more than 30,000 patients at a single institution who did not receive any contrast medium, more than half showed a change in serum creatinine of at least 25%, and more than 40% showed a change of at least 0.4 mg/dL [10]. The authors noted that had some of these patients received iodinated contrast medium temporally related to the rise in serum creatinine, the rise would have been undoubtedly attributed to it, rather than to physiologic variation or another etiology.

Since 2007, an increasing number of published studies have included control groups of patients not exposed to iodinated contrast medium [53,55-60]. Most have found no evidence of CI-AKI, but most also utilized non- randomized non-matched controls who happened to receive unenhanced CT as part of routine clinical care [53,55-60]. The clinical population of patients imaged with unenhanced CT is enriched with patients who are at risk for AKI and therefore is contaminated by selection bias. This selection bias has been shown objectively in a meta-analysis by McDonald et al [8].

Four large studies released in 2013 and 2014 (each with >10,000 patients) have addressed selection bias in the unenhanced CT population through use of propensity score adjustment and propensity score matching [3,4,7,9]. Although the conclusions from these studies differ somewhat, all four have shown that CI-AKI is much less common than previously believed. In patients with a stable baseline eGFR ≥45 mL / min/1.73m2, IV iodinated contrast media are not an independent nephrotoxic risk factor [3,4,7,9], and in patients with a stable baseline eGFR 30-44 mL / min/1.73m2, IV iodinated contrast media are either not nephrotoxic or

rarely so [3,4,7,9].

Despite this common ground, there are differences among these studies [3,4,7,9] in the covariates chosen for inclusion, the method of controlling baseline renal function instability, the definitions of AKI, and the nuances of the statistical methodology. These differences likely explain the different conclusions drawn between these studies for patients with Stage IV and Stage V chronic kidney disease (eGFR <30 mL / min/1.73m2). In particular, two propensity-score matched studies [3,4] have shown that IV iodinated contrast material is an independent nephrotoxic risk factor in patients with Stage IV and Stage V chronic kidney disease, while two others were unable to find such evidence [7,9].

Risk Factors

Numerous studies have attempted to isolate risk factors for CI-AKI. There is consensus that the most important risk factor is pre-existing severe renal insufficiency [3,4,15,61,62]. Multiple other risk factors have been proposed, including diabetes mellitus, dehydration, cardiovascular disease, diuretic use, advanced age, hypertension, hyperuricemia, and multiple iodinated contrast medium doses in a short time interval (<24 hours) [3,4,15,61-64], but these have not been rigorously confirmed. In particular, multiple myeloma is not supported as a risk factor for CA-AKI [65-67]. Two studies have shown that CA-AKI may occur after two closely spaced doses of IV iodinated contrast medium [63,64], but neither study was designed to show that the risk was higher than after one or no dose of IV contrast medium.

Risk Thresholds

There is no agreed-upon threshold of serum creatinine elevation or eGFR declination beyond which the risk of CI-AKI is considered so great that intravascular iodinated contrast medium should never be administered. In fact, since each contrast medium administration always implies a risk-benefit analysis for the patient, contrast medium administration for all patients should always be taken in the clinical context, considering all risks, benefits and alternatives [2,6].

Some practices have advocated stratification of potential risk by eGFR instead of serum creatinine because it is a better indicator of baseline renal function [49,50]. This has been limited in the past by insufficient data [68-70], but there are now two large propensity score-adjusted studies that stratify CI-AKI risk by eGFR [3,7]. One showed no risk of CI-AKI from IV iodinated contrast material, regardless of baseline eGFR [7], while another identified patients with an eGFR <30 mL / min/1.73m2 to be at significant risk (patients with eGFR 30-44 mL / min/1.73m2 were at borderline but not statistically significant risk) [3].

Herts et al [50] showed that when patients' eGFR was calculated by the MDRD formula, a significantly higher percentage of patients presenting for contrast-enhanced CT scans had an eGFR <60 mL / min than had a serum creatinine of >1.4 mg/dL. Davenport et al [49] showed that the use of eGFR thresholds (instead of serum creatinine-based thresholds) more appropriately identified patients who may be at risk for CI-AKI.

At the current time, there is very little evidence that IV iodinated contrast material is an independent risk factor for AKI in patients with eGFR ≥30 mL / min/1.73m2. Therefore, if a threshold for CI-AKI risk is used at all, 30 mL / min/1.73m2 seems to be the one with the greatest level of evidence [3]. Any threshold put into practice must be weighed on an individual patient level with the benefits of administering contrast material.

Contrast-enhanced CT has superior diagnostic performance compared to unenhanced CT for a wide array of indications. Failure to diagnose an important clinical entity carries its own risk.

As previously stated, no serum creatinine or eGFR threshold is adequate to stratify risk for patients with AKI because serum creatinine in this setting is unreliable. However, in patients with AKI, the administration of iodinated contrast medium should only be undertaken with appropriate caution, and only if the benefit to the patient outweighs the risk. There have been no published series demonstrating that IV iodinated contrast medium administration to patients with AKI leads to worse or prolonged renal dysfunction than would occur in a control group. However, patients with AKI are particularly susceptible to nephrotoxin exposure and therefore it is probably prudent to avoid intravascular iodinated contrast medium in these patients when possible.

Anuric patients with end-stage renal disease who do not have a functioning transplant kidney are not at risk for CI-AKI because their kidneys are nonfunctional; these patients may receive intravascular iodinated contrast material without risk of additional renal injury (see Renal Dialysis Patients and the Use of Iodinated Contrast Medium, below).

Screening

Screening based on eGFR should be used to identify patients at potential risk of CI-AKI [61,71] . A variety of patient risk factors

have been investigated as screening data elements which vary in their sensitivity and specificity, although the most useful may be a personal history of kidney disease (i.e. CKD, remote AKI, kidney surgery, kidney ablation, albumineria) [72,73]. Diabetes mellitus may be an additional optional factor for screening [72,73]. Patient age and treated or untreated hypertension as independent triggers for kidney function assessment may result in a large false-positive rate in identifying patients with eGFR less than 30 mL/min/1.73 m2.

There is no agreed-upon acceptable maximum interval between baseline renal function assessment and contrast medium administration in at-risk patients. Some accept a 30-day interval in outpatients. It seems prudent to have a shorter interval for inpatients, those with a new risk factor, and those with a heightened risk of renal dysfunction.

Suggested Indications for Renal Function Assessment before the Intravascular Administration of Iodinated Contrast Medium

The following is a suggested list of risk factors that may warrant renal function assessment (e.g., serum creatinine, eGFR) prior to the administration of intravascular iodinated contrast medium. This list should not be considered definitive and represents a blend of published data [73,74] and expert opinion:

- Personal history of renal disease, including:
  - Known chronic kidney disease (CKD)
  - Remote history of AKI
  - Dialysis
  - Kidney surgery
  - Kidney ablation
  - Albuminuria
- History of diabetes mellitus (optional)
- Metformin or metformin-containing drug combinations[1]

Patients who are scheduled for a routine intravascular study but do not have one of the above risk factors do not require a baseline serum creatinine determination before iodinated contrast medium administration.

Morbidity and Mortality

The clinical course of CA-AKI (and, presumably, CI-AKI) depends on baseline renal function, coexisting risk factors, degree of hydration, and other factors. However, the usual course consists of a transient asymptomatic elevation in serum creatinine. Serum creatinine usually begins to rise within 24 hours of intravascular iodinated contrast medium administration, peaks within 4 days, and often returns to baseline within 7 to 10 days. It is unusual for patients to develop permanent renal dysfunction [68,70].

Several studies have shown that patients with CA-AKI, including those with only transient injury, tend to have longer hospital stays, higher mortality, and higher incidences of cardiac and neurologic events than contrast medium-receiving patients whose kidney function remains stable [41,75-78]. These observations have led to widespread hesitance in the use of intravascular iodinated contrast medium when the risk of CI-AKI is felt to be high. However, many studies investigating CI-AKI and its consequences following intravascular iodinated contrast medium administration have failed to include a control group of patients not receiving contrast medium [76-78]; therefore, it is possible that much of the morbidity and mortality previously attributed to CI-AKI in the literature may in fact be due to other etiologies (i.e., contrast-independent causes of CA-AKI). Larger studies with proper control groups and longitudinal outcomes data are needed.

Prevention

Prior to contrast medium administration, adequate patient assessment and communication between radiologist and referring clinician are important. Consideration of alternative imaging strategies and an individualized risk-benefit assessment are fundamental.

Avoidance of Iodinated Contrast Medium

Concern for the development of CI-AKI is a relative but not absolute contraindication to the administration of intravascular iodinated contrast medium in at-risk patients that have AKI or an eGFR less than 30 mL/min/1.73 m2 and are not undergoing

[1] Metformin does not confer an increased risk of CI-AKI. However, patients who develop AKI while taking metformin may be susceptible to the development of lactic acidosis.

maintenance dialysis [3,4,70,79,80]. In these scenarios, the information that may be obtained by using no contrast medium (e.g., non-contrast CT) and/or other modalities (e.g., ultrasound, non-contrast magnetic resonance imaging [MRI]) may be sufficiently useful that contrast medium administration can be avoided. (See the Chapter on Nephrogenic Systemic Fibrosis [NSF] for a full discussion of the use of gadolinium chelates in patients with renal disease.) In some clinical situations, the use of intravascular iodinated contrast medium may be necessary regardless of CI-AKI risk. Although there is data suggesting a directly proportional dose- toxicity relationship for intracardiac iodinated contrast medium [81], there is no analogous robust data for intravenous iodinated contrast media within the range of clinically administered doses. Therefore, it is not recommended to reduce doses to attempt to mitigate the risk of CI-AKI as this may result in suboptimal or nondiagnostic images. Instead, standard contrast dosing is recommended if the benefits have been deemed to outweigh the risks for intravenous iodinated contrast media administration in high-risk patients for CI-AKI.

One purported risk factor for the development of CI-AKI is the administration of multiple doses of intravascular iodinated contrast medium within a short period of time [63,64]. Most low-osmolality iodinated contrast media have a half-life of approximately two hours. Therefore, it takes approximately 20 hours for one administered dose of contrast medium to be eliminated in a patient with normal renal function. Therefore, it has long been suggested that dosing intervals shorter than 24 hours be avoided except in urgent situations.

We do not believe that there is sufficient evidence to specifically endorse the decision to withhold a repeat contrast medium injection until more than 24 hours have passed since the prior injection, nor to recommend a specific threshold of contrast medium volume beyond which additional contrast media should not be given within a 24-hour period.

Further, obtaining a serum creatinine measurement between two closely spaced iodinated contrast medium enhanced studies are unlikely to be of any benefit given the slow nature of change of serum creatinine in patients with AKI.

Therefore, the decision to administer closely spaced contrast-enhanced studies is clinical and subjective, with high-risk patients (e.g., Stage IV and Stage V chronic kidney disease, AKI) treated with greater caution than the general population.

Choice of Iodinated Contrast Medium

Barrett and Carlisle [82] reported a meta-analysis of the literature concerning the relative nephrotoxicity of high osmolality contrast media (HOCM) and low osmolality contrast media (LOCM). They concluded that LOCM are less nephrotoxic than HOCM in patients with underlying renal insufficiency. LOCM were not shown to be significantly different in patients with normal renal function. Most centers no longer use intravascular HOCM due to the greater incidence of various adverse effects associated with its use.

Studies [83-86] have failed to establish a clear advantage of IV iso-osmolality iodixanol over IV LOCM with regard to CA-AKI or CI-AKI. A 2009 meta-analysis using data pooled from 25 trials found no difference in the rate of CA-AKI between iodixanol and low osmolality agents after intravenous administration [87].

Volume Expansion

The major preventive action to mitigate the risk of CI-AKI is to provide intravenous volume expansion prior to contrast medium administration [88-94]. The ideal infusion rate and volume is unknown, but isotonic fluid such as 0.9% normal saline (NS) is preferred. Typical prophylaxis regiments begin 1 hour prior to the exam and continue 3-12 hours after with longer regiments (approximately 12 hours) shown to lower the risk of CA-AKI compared with shorter regiments [61,95]. Typical doses may be fixed volume (e.g., 500 mL NS) before and after or weight-based volumes (1-3mL/kg per hour) [61,79]. Oral hydration has not been well studied for patients with eGFR less than 30 mL/min/1.73 m2 or in patients with AKI.

Not all clinical studies have shown dehydration to be a major risk factor for CA-AKI. However, in the dehydrated state, renal blood flow and GFR are decreased, the effect of iodinated contrast medium on these parameters is accentuated, and there is a theoretical concern of prolonged tubular exposure to iodinated contrast medium due to low tubular flow rates. Solomon et al [96] [86] studied adult patients with chronic kidney disease who underwent cardiac angiography. The reported incidence of CA-AKI was decreased by periprocedural IV volume expansion (0.45% or 0.9% saline, 100 mL/h, 12 hours before to 12 hours after intravascular contrast medium administration). In another study, IV volume expansion with 0.9% saline was superior to IV volume expansion with 0.45% saline in CA-AKI risk reduction [89].

Prophylaxis is indicated for patients who have AKI or severe CKD with an eGFR less than 30 mL/min/1.73m2, although the risks of volume expansion (i.e., heart failure or other hypervolemic conditions) should be considered before initiation [97,98].

Prophylaxis is not indicated for the general population of patients with stable eGFR greater than or equal to 30 mL/min 1.73 m2 or patients on chronic dialysis [98]. Prophylaxis may also be considered on an individual basis for high-risk circumstances (e.g. numerous risk factors, recent AKI, borderline eGFR) in patients with an eGFR of 30-44 mL/min./1.73 m2 at the discretion of the ordering provider.

Sodium bicarbonate

Some studies and meta-analyses of patients undergoing cardiac angiography have shown intravenous volume expansion with sodium bicarbonate to be superior to 0.9% saline in reducing the risk of CA-AKI [90,91], but these results have been challenged by other meta-analyses and studies [93,99]. Bicarbonate is likely similar to normal saline for the prevention of CA-AKI, but it is not preferred due to the additional requirement for pharmacist compounding.

N-acetylcysteine

Recent randomized trial showed that N-acetylcysteine was no more effective than placebo at preventing CA-AKI for intra-arterial iodinated contrast media administration and is therefore not recommended for intravenous contrast media prophylaxis [99].

Diuretics: Mannitol and Furosemide or Other Agents

Solomon et al [100] reported no beneficial effects from the osmotic diuretic mannitol when it was added to IV saline solution in patients with or without diabetes mellitus. There was an exacerbation of renal dysfunction when the loop diuretic furosemide was used in addition to IV saline solution. Neither mannitol nor furosemide is recommended for CI-AKI risk reduction. Other theoretical renal-protective medications such as theophylline, endothelin-1, and fenoldopam are also not recommended for CI-AKI reduction as strong supporting data is lacking.

Renal Dialysis Patients and the Use of Iodinated Contrast Medium

Patients with anuric end-stage chronic kidney disease who do not have a functioning transplant can receive intravascular iodinated contrast medium without risk of further renal damage because their kidneys are no longer functioning. However, there is a theoretical risk of converting an oliguric patient on dialysis to an anuric patient on dialysis by exposing him or her to intravascular iodinated contrast medium. This remains speculative, as there are no conclusive outcomes data in this setting. Therefore, patients undergoing dialysis who make more than 1-2 cups of urine/day (236-473 mL) should be considered nonanuric and treated as high-risk patients similar to patients with AKI or eGFR less than 30 mL/min/1.73m2 who are not undergoing hemodialysis.

Patients should not have acute dialysis nor continuous renal replacement therapy initiated or alter their schedule solely based on iodinated contrast media administration regardless of renal function due to the risks, costs and lack of benefit [39,61,72,79,80,101-103].

The U.S. Food and Drug Administration (FDA) has issued guidelines and drug labeling for metformin since 1995, and the component of these FDA guidelines related to administration of iodinated contrast material in patients taking metformin has been made progressively less rigorous since the original version. The ACR Committee on Drugs and Contrast Media recognizes that the latest (as of this writing, dated 4-8-2016) FDA guidelines and drug labeling are still more restrictive than those in this chapter of the ACR Manual on Contrast Media. Nevertheless, the committee authoring this Manual has reviewed the evidence and believes that the prevailing weight of clinical evidence on this matter allows less stringent yet safe patient management which should reduce patient cost and inconvenience. This footnote is designed to alert readers that the ACR recommendations differ in case their personal philosophy or institutional policies necessitate adherence to the more restrictive FDA guidelines.

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METFORMIN

Metformin is a biguanide oral anti-hyperglycemic agent used primarily, but not exclusively, to treat patients with non-insulin-dependent diabetes mellitus [1-3]. It is available as a generic drug as well as in proprietary formulations, alone and in combination with other drugs (see Table A for some of the brand name formulations). The drug was approved in the United States in December of 1994 for use as monotherapy or combination therapy in patients with non-insulin-dependent diabetes mellitus whose hyperglycemia is not controlled by diet or sulfonylurea therapy alone.

Metformin is thought to act by decreasing hepatic glucose production and enhancing peripheral glucose uptake as a result of increased sensitivity of peripheral tissues to insulin. Only rarely does it cause hypoglycemia.

The most significant adverse effect of metformin therapy is the potential for the development of metformin-associated lactic acidosis in susceptible patients. This condition is estimated to occur at a rate of 0 to 0.084 cases per 1,000 patient years. Patient mortality in reported cases is about 50%. However, in almost all reported cases, lactic acidosis occurred because one or more patient-associated contraindications for the drug were overlooked. In one extensive 13-year retrospective study [4] of patients in Sweden, 16 cases were found, and all patients had several comorbid factors, most often cardiovascular or renal disease. There are no documented cases of metformin-associated lactic acidosis in properly selected patients.

Metformin is excreted unchanged by the kidneys, probably by both glomerular filtration and tubular excretion. The renal route eliminates approximately 90% of the absorbed drug within the first 24 hours. Metformin seems to cause increased lactic acid production by the intestines. Any factors that decrease metformin excretion or increase blood lactate levels are important risk factors for lactic acidosis. Renal insufficiency, then, is a major consideration for radiologists.

Also, factors that depress the ability to metabolize lactate, such as liver dysfunction or alcohol abuse, or that increase lactate production by increasing anaerobic metabolism (e.g., cardiac failure, cardiac or peripheral muscle ischemia, or severe infection) are contraindications to the use of metformin. Iodinated X-ray contrast media are not an independent risk factor for patients taking metformin but are a concern only if post-contrast acute kidney injury (AKI) should develop. Please refer to the chapter on Postcontrast Acute Kidney Injury and Contrast-Induced Nephropathy in Adults for information about the risk of these events.

The metformin package inserts approved by the U.S. Food and Drug Administration state that metformin should be withheld temporarily for patients undergoing radiological studies using IV iodinated contrast media. If acute kidney injury were to be caused by the iodinated contrast media, an accumulation of metformin could occur, with resultant lactate accumulation.

Management

The management of patients taking metformin should be guided by the following:

1. Patients taking metformin are not at higher risk than other patients for post-contrast acute kidney injury.

2. Iodinated contrast is a potential concern for furthering renal damage in patients with acute kidney injury, and in patients with severe chronic kidney disease (stage IV or stage V).

3. There have been no reports of lactic acidosis following intravenous iodinated contrast medium administration in patients properly selected for metformin administration.

The Committee recommends that patients taking metformin be classified into one of two categories based on the patient's renal function (as measured by eGFR).

Category I

In patients with no evidence of AKI and with eGFR ≥30 mL / min/1.73m$_2$, there is no need to discontinue metformin either prior to or following the intravenous administration of iodinated contrast media, nor is there an obligatory need to

reassess the patient's renal function following the test or procedure.[1]

Category II

In patients taking metformin who are known to have acute kidney injury or severe chronic kidney disease (stage IV or stage V; i.e., eGFR< 30), or are undergoing arterial catheter studies that might result in emboli (atheromatous or other) to the renal arteries, metformin should be temporarily discontinued at the time of or prior to the procedure and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

Metformin and Gadolinium

It is not necessary to discontinue metformin prior to contrast medium administration when the amount of gadolinium-based contrast material administered is in the usual dose range of 0.1 to 0.3 mmol per kg of body weight.

1The U.S. Food and Drug Administration (FDA) has issued guidelines and drug labeling for metformin since 1995, and the component of these FDA guidelines related to administration of iodinated contrast material in patients taking metformin has been made progressively less rigorous since the original version. The ACR Committee on Drugs and Contrast Media recognizes that the latest (as of this writing, dated 4-8-2016) FDA guidelines and drug labeling are still more restrictive than those in this chapter of the ACR Manual on Contrast Media. Nevertheless, the committee authoring this Manual has reviewed the evidence and believes that the prevailing weight of clinical evidence on this matter allows less stringent yet safe patient management which should reduce patient cost and inconvenience. This footnote is designed to alert readers that the ACR recommendations differ in case their personal philosophy or institutional policies necessitate adherence to the more restrictive FDA guidelines.

Table A
Medications containing Metformin*

Generic Ingredients	Trade Names
Metformin	Glucophage
	Glucophage XR
	Fortamet
	Glumetza
	Riomet
Glyburide/metformin	Glucovance
Glipizide/metformin	Metaglip
Linigliptin.metformin	Jentadueto
Pioglitazone/metformin	ActoPlus Met
	ActoPlus Met XR
Repaglinide/metformin	Prandimet
Rosiglitazone/metformin	Avandamet
Saxagliptin/metformin	Kombiglyze XR
Sitagliptin/metformin	Janumet
	Janumet XR
(Metformin and several of the combination drugs also available in generic versions)	
*List most recently revised on 4/17/2014	

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CONTRAST MEDIA IN CHILDREN

Principles regarding contrast media utilization and associated adverse events are generally similar in children and adults. This section will address specific areas in which pediatric use of contrast medium differs from adult use and will attempt to avoid repeating recommendations that are similar for both patient populations.

Iodinated Intravascular Contrast Media
Osmolality

Osmolality, a measure of the concentration of a solution, is an important physical property of contrast media. There is variation in the osmolality of the nonionic iodinated contrast media approved for use in the United States, even when the iodine concentration is equivalent (see Appendix A). Contrast media osmolality is of particular importance in neonates and small children who are especially susceptible to fluid shifts and have a lower tolerance for intravascular and enteric osmotic loads compared to adults. Intravascular administration of hyperosmolar contrast medium can result in the shift of fluid from the extravascular space into the intravascular space, expanding blood volume [1,2]. If the fluid shift is large, cardiac failure and pulmonary edema can result; children with significant pre-existing cardiac dysfunction may be at particular risk.

Viscosity
Viscosity, a measure of fluid resistance to stress, is another important physical property of contrast media and varies between different contrast media (see Appendix A). Contrast medium viscosity is especially relevant in pediatric patients due to the use of small gauge angiocatheters for contrast medium injection. Smaller gauge catheters and higher contrast medium viscosity both slow the injection flow rate per Poiseuille's law. If rapid injection of a high viscosity contrast medium through a small angiocatheter is attempted, catheter failure, vessel injury, or failure to achieve the desired rapid injection rate may result. Viscosity of contrast media is inversely affected by temperature (see Appendix A). As temperature increases, viscosity decreases, thereby allowing for increased flow rates at lower pressures. However, there is a lack of data demonstrating the benefits of contrast media warming in children [3,4].

Safe Intravascular Injection of Contrast Media in Children
Several additional issues complicate the administration of intravascular contrast media to neonates and children, including the use of small volumes of contrast medium, small gauge angiocatheters, and unusual vascular access sites. First, very small volumes of contrast media are typically administered to neonates and infants (typically 1.5–2 mL/kg) [5]. As a result, timing of image acquisition with regard to contrast medium administration may be important when performing certain imaging studies, such as CT angiography. In some instances, a slower injection rate (compared to that used in older children and adults) may be useful to prolong intravascular enhancement. Second, small-gauge angiocatheters (e.g., 24-gauge) located in very small peripheral veins (e.g., in the hand or foot) or other unusual vascular access sites are commonly utilized in neonates and infants. A study by Amaral et al [6] showed that 24-gauge angiocatheters in a peripheral location can be safely power injected using a maximum flow rate of approximately 1.5 mL/sec and a maximum pressure of 150 psi. Recently, new small gauge intravenous catheter systems (e.g., BD Nexiva™ Diffusics™ closed IV catheter system) have been developed that allow injection rates and pressures higher than traditional peripheral intravenous cannulas, although there is a paucity of data describing their use in children undergoing power injection of contrast medium. When access is thought to be tenuous, careful hand injection of contrast medium should be strongly considered to minimize risk of vessel injury and extravasation, noting that smaller syringes can generate substantially greater injection pressures than larger syringes. Since some central venous catheters may not be approved for power injection, one should always verify in advance that any catheter to be utilized for bolus contrast material instillation can tolerate the anticipated injection and is appropriately positioned. It is also important to ensure that the pressure used does not exceed the catheter's pressure rating.

Extravasation of Contrast Media in Children
The frequency of contrast media extravasation in children is likely similar to that observed in the adult population, despite the use of lower intravascular contrast medium volumes. An extravasation rate of 0.3% was documented in a study of 554 children in which a power injector was used to administer iodinated contrast medium [6]. Another study of 2429 children who underwent intravenous power injection of iodinated contrast medium found an extravasation rate of 0.7% without an association with age [7]. Most extravasations in the pediatric population resolve without complication. A study by Wang et al [8] showed that 15 of 17 cases of contrast medium extravasation in children were mild in severity with minimal or no adverse effects. In the study by Barrera et al [7], none of the 18 children who experienced a contrast extravasation suffered a long-term substantial

injury or required surgery, although moderate and severe cases were documented. Furthermore, this study demonstrated positive associations between contrast media extravasation and both power injection peak pressure and flow rate.

Particular attention should be paid to the injection sites of neonates, infants, young children and developmentally delayed patients, as they cannot verbalize symptoms of an injection site complication. Please refer to the Extravasation of Contrast Media Chapter or download the ACR Guidance – Contrast Reaction App for the treatment of a contrast extravasation, as treatment in a child is similar to that in an adult.

Physiologic Side Effects in Children

Physiologic side effects to intravascular contrast medium administration in children have the potential for greater consequence than in adults [9]. For example, local warmth at the injection site or nausea may cause a child to move or cry. Such a response to contrast medium injection may result in a nondiagnostic imaging study, necessitating repeat imaging and additional exposure to contrast medium and possibly ionizing radiation. Management of physiologic side effects is generally supportive.

Incidence of Allergic-Like Reactions

There are several difficulties in interpreting the available literature on the incidence of allergic-like reactions to IV iodinated contrast media in children. First, some studies have failed to discriminate between physiologic side effects and allergic-like reactions and have used heterogeneous definitions of what constitutes mild, moderate, or severe reactions. Second, there is a lack of controlled prospective pediatric studies on the topic. Prospective investigations are difficult to perform because allergic-like reactions to contrast media in children are rare, and large numbers of patients would be needed to acquire statistically meaningful results. Third, in some studies in the published literature, the methodology for tracking contrast reactions is such that it is difficult to guarantee that all adverse reactions were documented, and none were overlooked.

Therefore, the reported incidence of pediatric allergic-like reactions to contrast media is variable. It is generally agreed, however, that the incidence of allergic-like reactions in children is lower than that in adults [3,8-10]. A very large retrospective study by Katayama et al of more than 150,000 nonionic contrast medium administrations [10], when stratified by age, showed that patients less than 10 years of age and greater than 60 years of age have the lowest rates of adverse reactions overall; the rate of severe reactions was more uniform across age groups but the numbers were small. A study by Dillman et al [11] retrospectively reviewed more than 11,000 intravascular injections of low-osmolality nonionic iodinated contrast media in children and neonates and documented an allergic-like reaction rate of 0.18%. Of the 20 reactions documented in their study, 16 were mild, one was moderate, and three were severe. A study by Callahan et al [12] of 12,494 consecutive patients up to 21 years of age revealed a 0.46% incidence of adverse reactions to ioversol, the majority of which were mild and none of which were severe. A smaller study by Fjelldal et al [13] documented five allergic-like reactions to iohexol following a total of 547 injections, for a rate of reaction of 0.9%. Although fatal reactions to contrast media in children are extremely rare (and may be due to co-morbid conditions), infants, young children, and developmentally delayed patients require close observation during and immediately following intravascular contrast medium administration, as they are unable to verbalize reaction-related discomfort or symptoms.

Prevention of Allergic-Like Reactions

General guidelines for the prevention of allergic-like reactions in children are similar to those used for adult patients. However, it should be noted that there has been no prospective, controlled investigation performed to assess the efficacy of premedication for the prevention of allergic-like reactions to iodinated contrast media in children. A sample pediatric premedication regimen, using a combination of corticosteroid and antihistamine, is described in Table A at the end of this chapter. Allergic-like reactions following premedication may still occur, although the frequency of such reactions is unknown [11].

Treatment of Allergic-Like Reactions

General guidelines for the treatment of allergic-like reactions in children are similar to those used for adult patients. Pediatric medication dosages, however, may be significantly different from adult dosages used in the management of such reactions (Table 2 and Table 3). It can be helpful to have a pediatric medication chart with weight-based dosages placed on the emergency cart or posted in the rooms where intravascular contrast media is to be injected into children, noting that for IM epinephrine administration, most pediatric patients can be treated with an autoinjector (i.e., EpiPen® or EpiPen Jr®) to maximize speed of administration and minimize dosing errors. Dedicated pediatric emergency resuscitation equipment (including various sizes of supplemental oxygen facemasks) should be available in all such locations (Table 4). A separate box of pediatric airway equipment attached to the emergency cart may be useful in areas where both children and adults receive contrast media.

Acute Kidney Injury after Iodinated Contrast Media Administration in Children

Acute kidney injury (AKI) after contrast media administration is subdivided into two entities per the ACR-NKF consensus statement: contrast-induced acute kidney injury (CI-AKI), which implies a causal relationship between iodinated contrast material and AKI, and contrast-associated acute kidney injury (CA-AKI) [also referred to as post-contrast acute kidney injury (PC-AKI)], which represents a correlative relationship between iodinated contrast material (ICM) and acute kidney injury [14]. Recent studies in which children exposed to intravenous iodinated contrast media were propensity score matched with groups of nonexposed control patients have showed no significant difference in the frequencies of subsequent acute kidney injury (CI- and CA-AKI) [15,16]. A study by Gilligan et al of 925 ICM-exposed children 18 years of age and younger propensity score matched to a group who underwent abdominal ultrasound showed no significant difference in the frequency of CI-AKI between the exposed and unexposed groups and found that, in children with an eGFR of 60 and greater, iodinated contrast medium exposure was not predictive of CI-AKI [15]. A similar large propensity score-based study by Calle-Toro et al. yielded similar findings [17]. A study by Guo et al of 192 ICM-exposed children 3-years-old or younger prior to cardiac surgery propensity score matched to a group without preoperative iodinated contrast media exposure found no significant difference in postoperative AKI [16]. A retrospective study of 211 trauma patients aged 15 years or younger (164 exposed to contrast, 47 not exposed to contrast) showed no significant difference in frequency of subsequent AKI [18]. The effects of contrast media on the kidneys are generally assumed to be similar between children and adults as no evidence currently available suggests otherwise. A few key differences between CI-AKI and CA-AKI in children and adults are discussed below.

Measurement of Renal Function in Children

Serum creatinine concentration reflects the balance between creatinine production and excretion. Creatinine is a breakdown product of skeletal muscle, and its rate of production is proportional to muscle mass. Muscle mass depends on a variety of factors, including patient age, gender, and level of physical activity. Normal serum creatinine concentrations, thus, are quite variable in pediatric patients. Normal pediatric serum creatinine concentrations increase with age, with the upper limits of normal typically less than adult values. Age-based normal serum creatinine concentrations also may vary slightly from laboratory to laboratory.

There are problems with using serum creatinine concentration as the sole marker of renal function. First, a normal serum creatinine value does not mean that renal function is preserved. For example, an increase in creatinine from 0.4 mg/dL to 0.8 mg/dL in a 10-year-old child would be clinically important and suggest some degree of renal impairment, even though both measurements may be within acceptable limits for patient age. Serum creatinine concentration may not become abnormal until glomerular filtration has decreased substantially. Second, it may take several days in the setting of acute renal failure for serum creatinine concentration to rise. Therefore, a patient may have impaired renal function in the setting of a normal serum creatinine concentration. This phenomenon is not unique to the pediatric population.

Measurement of blood urea nitrogen (BUN) concentration is a poor indicator of renal function. BUN concentration depends on numerous variables in addition to renal function, including daily dietary protein intake, hepatic function, and patient hydration.

A more appropriate method by which to express renal function in children is the estimated glomerular filtration rate (eGFR). It is important to note that the formula used to calculate pediatric eGFR (see below) is different from that used in adults. eGFR calculation in children requires knowledge of patient serum creatinine concentration, height, and/or cystatin C. In addition, the assay used to measure serum creatinine concentration must be known.

EGFR Calculation in Children

There is no perfect manner of estimating GFR in children. The National Kidney Disease Education Program, an initiative of the National Institutes of Health, provides an *online calculator* for estimating purposes and has published the following information regarding the estimation of GFR in children.

Currently, the best equation for estimating GFR from serum creatinine in children and young adults ages 1-25 years is the CKiD Under 25 (U25) eGFR [19]. This formula has improved validity across a broader age range compared to the previously recommended Bedside Schwartz Equation, which was developed using a narrow age range of 8-15 years old. The CKiD U25 eGFR equation can be used with the serum creatinine level or with the IFCC-calibrated serum cystatin C level; both require age, sex, and height.

Equation: CKiD U25 eGFR

eGFR (mL/min/1.73 m2) = (K × height) / serum creatinine AND/OR
eGFR (mL/min/1.73 m2) = K x (1/cystatin C)

- K is multiplier that is dependent on age and sex
- Height in cm
- Serum creatinine in mg/dL
- Cystatin C in mg/L

It is also important to note that in the immediate newborn period (approximately the first 3 weeks of life), blood creatinine concentration represents at least in part the maternal creatinine concentration which freely crosses the placenta [20]. Thus, infant plasma creatinine is not a reliable measure of renal function or glomerular filtration rate. Iodinated contrast media can be generally considered safe in the neonate and infant regardless of serum creatinine and eGFR in the absence of known kidney disease [21].

Prevention of Contrast-Induced and Contrast-Associated Acute Kidney Injury in At-Risk Children
Risk factors for CI-AKI and CA-AKI in children are thought to be similar to those in adults. Unfortunately, there are no established evidence-based guidelines for the prevention of CI-AKI and CA-AKI in children with impaired renal function. As no pediatric-specific measures for the prevention of acute kidney injury have been established in the literature, strategies described in adults should be considered when using IV iodinated contrast media in children with renal dysfunction. Please refer to the chapter Post-Contrast Acute Kidney Injury And Contrast-Induced Nephropathy In Adults. A noncontrast imaging examination can be performed if the clinical question can be answered without intravascular iodinated contrast medium. In addition, the use of alternative imaging modalities, such as ultrasound (with or without intravenous microbubble contrast medium) and MRI (with or without intravenous gadolinium-based contrast medium) could also be considered.

Thyroid Dysfunction after Iodinated Contrast in Children
Some published data suggests an increased risk of thyroid dysfunction after the administration of iodinated contrast media in particular pediatric cohorts, including infants with congenital heart disease and very low birth weight. Supraphysiologic levels of iodine can potentially result in suppression of thyroid hormone production, a phenomenon known as the Wolff-Chaikoff effect (a protective autoregulatory mechanism). This effect in most individuals is transient, and thyroid hormone production typically returns to normal after 1-2 weeks. However, it is thought that in particularly susceptible populations, some individuals are unable to escape the Wolff-Chaikoff effect, resulting in true hypothyroidism.

The United States Food and Drug Administration (FDA) issued a safety announcement in 2015 regarding 10 cases of hypothyroidism reported after ICM administration in infants less than 4 months of age that occurred between 1969 and 2012 [22]. Each of those infants had congenital heart disease or a history of prematurity.

There is a small number of prospective studies that have evaluated the association between thyroid dysfunction and intravascular iodinated contrast media exposure in children. These studies have shown mixed results and are generally very small with regards to the number of participants, may or may not have a control group, and study specific pediatric cohorts which limit the generalizability of observations. There are some retrospective studies with larger (e.g., n >100) patient populations that also have assessed the impact of intravascular iodinated contrast media on thyroid function. These latter studies are also mostly limited due to a lack of control groups and/or a variety of biases and confounders. A review of this literature can be found in the ACR Statement on Use of Iodinated Contrast Material for Medical Imaging in Young Children and Need for Thyroid Monitoring [23].

In summary, there is an overall lack of high-quality data available regarding the risk of thyroid dysfunction after intravascular iodinated contrast media exposure and further investigation is needed.

Thyroid Monitoring after Iodinated Contrast in Children
The FDA issued an updated Drug Safety Communication in March 2022 recommending that newborns and children through 3 years of age undergo thyroid monitoring within 3 weeks after receiving intravascular iodinated contrast media [24]. This announcement cited 11 studies, nearly all of which have considerable limitations, as detailed in the section above. The ACR's position statement on this topic, referred to above, indicates that based on the available evidence the risk for clinically relevant hypothyroidism related to iodinated contrast media is quite low in children younger than 3 months and minimal to absent in

children 3 months and older. Furthermore, the ACR statement suggests that universal testing in all young children is not currently supported by the published literature [23].

Gadolinium-Based Intravascular Contrast Media

Guidelines for intravenous (IV) use of gadolinium-based contrast media are generally similar in both the pediatric and adult populations. The prescribing information sheets from gadolinium-based contrast media approved for intravascular use in the United States show variable labeling with regards to the pediatric population, with differences between contrast media relating to indications (most often MRI of the brain and spine, and less often other parts of the body) and age of approval for usage. For example, for certain contrast media, safety and efficacy have been established for pediatric patients over 2 years of age but not for children under 2 years of age. No gadolinium-based contrast media has been approved for use in premature infants to date. The prescribing information for gadoxetate disodium (Eovist), a hepatobiliary contrast media, does not specifically specify patient age for which the drug is approved. Instead, it indicates that an observational study was performed in patients aged >2 months and <18 years and identified no safety issues. Based on the above information, it can be concluded that these contrast media are commonly used off-label in children in the U.S. with regards to patient age, clinical indication for imaging, or both. Pediatric-specific issues regarding these contrast media are discussed below.

Osmolality and Viscosity

As with iodinated contrast media, there are significant ranges in osmolality and viscosity of gadolinium- based contrast media (see Appendix A). For example, the osmolality of gadoteridol (ProHance) is 630 mosm/kg H2O, and the osmolality of gadobenate dimeglumine (MultiHance) is 1,970 mosm/kg H2O. Viscosities (at 37°C) can also vary, for example from 1.19 cps for gadoxetate disodium (Eovist) to 5.3 cps for gadobenate dimeglumine (MultiHance). These physical properties, however, potentially are less important when using gadolinium-based contrast media in children compared to iodinated contrast agents. The much smaller volumes of gadolinium-based contrast agents typically administered to pediatric patients likely result in only minimal fluid shifts. The slower injection flow rates generally used for gadolinium-based contrast result in lower injection-related pressures and decreased risk for vessel injury and extravasation. While there is a lack of published literature describing the frequency and clinical relevance of extravasation of these contrast media in children, it is usually of no or minimal clinical significance because of the small volumes injected.

Allergic-Like Reactions and Other Adverse Events

Although uncommon, allergic-like reactions to IV gadolinium-based contrast media in children do occur. A study by Dillman et al [25] documented a 0.04% (48 reactions/13,344 injections) allergic-like reaction rate for these contrast media in children. Another study by Davenport et al that included 15,706 administrations of gadolinium-based contrast media in children (under the age of 18 years) documented only eight allergic-like reactions, for a reaction rate of 0.05% [26]. A more recent study by Forbes-Amrhein et al. documented 21 allergic-like reactions in 32,365 pediatric gadolinium-based contrast media administrations [27]. Although mild reactions are most common, more significant reactions that require urgent medical management may occur [27]. Pediatric allergic-like reactions to contrast media are treated in the same manner as other allergic and allergic-like reactions, including similar reactions to iodinated contrast media (Table 2). While no investigation has studied the efficacy of corticosteroid and antihistamine premedication regimens for the prevention of allergic-like reactions to gadolinium-based contrast media in children, commonly used regimens, such as the ones presented in Tables A and B at the end of the chapter, are thought to provide some protective benefit.

A variety of physiologic side effects also may occur following administration of gadolinium-based contrast media, including coldness at the injection site, nausea, vomiting, headache, and dizziness (see prescribing information for different contrast media). There is no evidence for pediatric renal toxicity from gadolinium-based contrast media at approved doses, and there is no role for intravenous or oral hydration prior to IV administration of gadolinium-based contrast media.

Nephrogenic Systemic Fibrosis

There are only a small number of reported cases of nephrogenic systemic fibrosis (NSF) in children. As of September 2012, there were only 23 unique pediatric NSF cases, and all patients were 6 years of age or older [28]. Seventeen of these children had documented exposure to a gadolinium-based contrast media. Thirteen of 13 children with available clinical data pertaining to renal disease had substantial renal dysfunction (acute kidney injury and/or chronic kidney disease), and 10 were on hemodialysis and/or peritoneal dialysis at the time of gadolinium-based contrast medium administration. Renal status was unknown in 10 children. There have been no published reports of NSF since 2012 in the pediatric population using currently approved contrast media.

As there are no pediatric-specific evidence-based guidelines for the prevention of NSF, we recommend that adult guidelines be followed for identifying at-risk patients and administering gadolinium-based contrast media in the presence of impaired renal function [see Chapter 16 –Nephrogenic Systemic Fibrosis]. If use of a Group I or III GBCA is being considered, children at risk for renal dysfunction should be identified (e.g., those with known medical renal disease [chronic kidney disease or acute kidney injury] or those with known renal/urinary tract structural abnormalities) and screened for impaired renal function. As in adults, the risks and benefits of gadolinium-based contrast media administration should be carefully considered in pediatric patients with acute kidney injury as well as chronic kidney disease with an eGFR less than 30 mL/min/1.73 m2. Although there has been no reported case of NSF in a very young child to date, some authors have urged caution with regards to administering these contrast media to preterm neonates and infants [29] due to renal immaturity and potential glomerular filtration rates under 30 mL/min/1.73m2 [30]. However, as mentioned above, there have been no cases of NSF in neonates and infants, and these contrast media may be administered to these populations if clinically warranted. Similar to older pediatric patients both without and with impaired renal function, the use of IV gadolinium-based contrast media should be justified in very young children, and the benefit of administration should outweigh potential risks.

Gadolinium Retention in the Body

Like adults, retention of gadolinium in the body has been observed by both imaging and/or pathology in children in multiple tissues (including the brain) and with a variety of gadolinium-based contrast media, including macrocyclic media [31-33]. The literature is conflicting and attributes these apparent signal alterations in the brain to a variety of causes including a particular contrast media, previous brain irradiation, and/or patient age [34-39]. Also, similar to adults, we believe that IV gadolinium-based contrast media can provide crucial diagnostic medical information. To date, no adverse health effects related to gadolinium retention have been confirmed in the pediatric population. Despite this fact, each time a contrast-enhanced MRI study is considered, it remains prudent to consider the clinical benefit of the diagnostic information that will be obtained while avoiding overutilization. Retention is of particular concern in children with chronic medical conditions that may receive multiple contrast-enhanced MRI studies over the course of their lifetimes. Reduced dose (e.g., half dose) contrast-enhanced MRI has been described as a method to further reduce contrast media exposure in children [40], although further investigations are needed before this practice can be commonplace. We will continue to assess the safety of these contrast media and modify our recommendations accordingly as new data become available. See Chapter 14 – ACR-ASNR Position Statement on the Use of Gadolinium Contrast Agents for additional information.

Gastrointestinal and Urogenital Contrast Media

Contrast media can be introduced into the gastrointestinal or urogenital tracts by mouth, rectum, vagina, urethra, urinary bladder, ostomy, or indwelling gastrointestinal or urinary tract catheter. The most commonly used contrast media for gastroenteric indications in infants, children, and adolescents are barium-based or water-soluble iodinated contrast media [41] (Appendix A). Although iohexol is the only iodinated low osmolar contrast medium that is approved by the FDA for gastrointestinal administration, any iodinated contrast medium that is FDA-approved for intravascular use is safe to administer off-label into the gastrointestinal or urinary tract. Contrast media for urogenital imaging is typically iodine-based, although the use of ultrasound microbubble contrast medium is becoming increasingly more common for pediatric studies involving the urogenital tract.

Barium sulfate suspension is used in the assessment of the upper gastrointestinal tract and small bowel when there is no clinical concern for perforation or leak. Barium sulfate is insoluble in water and absorption by the gut into the body is negligible. Barium has a high atomic number (Z=56) and attenuates more x-rays than water-soluble contrast, making it preferred for fine detail evaluation of the gastrointestinal system. Patients should be advised to stay well hydrated following an imaging study with barium due to its water insolubility and tendency to constipate. Barium should not be administered retrograde into a defunctionalized colon or bowel segment (e.g., mucous fistula or Hartman pouch), since intraluminal contents will likely not pass and barium can become inspissated and difficult to remove. Barium is generally contraindicated in patients with suspected or known gastrointestinal tract perforation because of the risk of peritonitis [42]. Barium contrast material is not directly toxic to the airways; however, it does have the potential to plug distal airways, resulting in post-obstructive pneumonia or diminishing the capacity for gas exchange [43]. Aspiration of large volumes of barium-based contrast can be fatal [44]. Allergic-like reactions to barium sulfate preparations are extremely rare and are likely related to the presence of additives to the commercial preparations rather than the barium sulfate [45]. Treatment of pediatric allergic-like reactions to enteric administration of barium sulfate suspension is the same as for allergic-like reactions to intravascular iodine-based and gadolinium-based contrast media and is outlined in Table 2.

Iodinated contrast media are commonly used for infant, pediatric, and adolescent contrast enemas, postoperative gastrointestinal tract assessment, when there is concern for gastrointestinal tract perforation, and upper gastrointestinal tract studies in

premature and very-low-birthweight neonates. They are generally preferred in the setting of suspected gastrointestinal tract perforation because they are quickly resorbed through the peritoneal surface and have a low risk of inducing peritonitis. The exact iodinated contrast media used for a particular exam typically relates to a combination of availability, cost, iodine concentration, and safety profile related to the route of administration.

As with intravascular iodinated contrast media, osmolality should be considered when deciding which iodinated contrast media to administer via the gastrointestinal tract. Hyperosmolar, typically ionic iodinated contrast media such as diatrizoate meglumine (i.e., Gastrografin or Gastroview) within the gastrointestinal tract may result in dangerous fluid shifts into the bowel from the intravascular space and therefore are capable of causing dehydration and hypotension [46-50]. Neonates, infants of very low birthweight, and older children with cardiac and renal impairment may be most susceptible to such fluid shifts. In such patients, low-osmolality or iso-osmolality contrast media should be considered for imaging of the gastrointestinal tract. Higher osmolality water soluble contrast media can be administered into the upper gastrointestinal tract or per rectum to assist in the resolution of a bowel obstruction, such as in the setting of cystic fibrosis [51], adhesive bowel disease, or meconium ileus [52]. Use of such contrast media is also commonly carried out only after some degree of dilution [53-55]. However, per mouth administration of high-osmolality iodinated contrast media should be generally avoided in children, in part due to the potential consequences of aspiration. This risk can be mitigated by using of a nasogastric tube to deliver the contrast material into the stomach. Aspirated hyperosmolality contrast medium may cause fluid shifts at the alveolar level and chemical pneumonitis with resultant pulmonary edema [44,56-58]. Aspiration of large volumes of iodinated oral contrast media rarely may be fatal [44]. The taste of barium sulfate preparations is usually tolerated quite well by children, given the presence of flavoring and sugar substitutes in the formulation. Barium sulfate suspensions also lend themselves well to flavor-mix-ins, such as chocolate syrup, fruit syrups, or drink mix powders. The taste of some iodinated contrast media are bitter and can be a limitation in its oral acceptability in pediatric patients. In this circumstance, placement of an enteric tube for contrast material administration can be useful.

Urogenital contrast media typically include ionic iodine-based contrast media and ultrasound microbubble contrast media. The iodinated contrast media are utilized in the setting of fluoroscopy and CT, whereas the ultrasound microbubbles are utilized in the setting of contrast-enhanced voiding ultrasonography. Lumason® is the only ultrasound contrast media approved for pediatric urinary tract use (see Ultrasound Contrast Media chapter). As with the gastrointestinal tract, any iodinated contrast medium that is FDA-approved for intravascular use is safe to administer into the vagina, urethra, urinary bladder, or renal collecting system.

Neutral oral contrast media are used for cross-sectional enterography imaging to promote distension of the bowel. These media demonstrate water or near water attenuation on CT and biphasic signal intensity on MRI. Commercially available preparations with imaging indications include a low-density barium sulfate suspension, which also contains sorbitol and a thickening agent (NeuLumEX [formerly VoLumen]; Bracco Diagnostics, Milan, Italy) and a lemon-lime flavored beverage containing sorbitol, mannitol, and a thickening agent (Breeza; Beckley Medical, Bristol, Conn). A study by Dillman et al showed that both media provide adequate bowel distension for imaging, but pediatric patients are more likely to consume the entirety of their prescribed oral preparation of Breeza versus NeuLumEX (VoLumen) due to the preferred flavor profile [59]. Other oral contrast media options for cross sectional enterography include water, methylcellulose, and polyethylene glycol electrolyte solution (Golytely; Braintree Laboratories, Inc, Braintree, Mass), each having unique advantages and disadvantages. Of these latter options, polyethylene glycol has been demonstrated to have bowel distension similar to low-density barium suspension [60].

Table A
Sample Pediatric Corticosteroid and Antihistamine Premedication Regimen

	Dosage	Timing
Prednisone	0.5–0.7 mg/kg PO (up to 50 mg)	13, 7, and 1 hr prior to contrast injection
Diphenhydramine	1.25 mg/kg PO (up to 50 mg)	1 hr prior to contrast injection

Note: Appropriate intravenous doses may be substituted for patients who cannot ingest PO medication.

Table B
Sample Pediatric Corticosteroid and Antihistamine Premedication Regimen for Urgent, ED, Inpatient, or NPO Patients

	Dosage	Timing
Hydrocortisone	2 mg/kg IV (up to 200 mg)	5 and 1 hr prior to contrast injection
Diphenhydramine	1 mg/kg IV, IM, or PO (up to 50 mg)	1 hr prior to contrast injection

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Ferumoxytol as MRI Contrast Medium

Ferumoxytol (Feraheme; AMAG Pharmaceuticals, Waltham, MA and ferumoxytol; Sandoz Inc., Princeton, NJ) is approved by the Food and Drug Administration (FDA) for intravenous (IV) treatment of iron deficiency anemia in adults [1-6]. However, off-label use of this iron oxide nanoparticle compound as a magnetic resonance imaging (MRI) contrast medium is growing [7,8]. Benefits of ferumoxytol as an intravenous MRI imaging medium include a prolonged blood pool phase and delayed intracellular uptake, allowing use as a pure intravascular contrast medium, and high T1 and T2 relaxivities compared to gadolinium-based contrast media [9]. Ferumoxytol has no known acute nephrotoxicity and may be considered in patients with severely impaired renal function [5,6].

Uses

Vascular imaging—The long circulating time of ferumoxytol, with a plasma half-life of 14–21 h [10], is exploited for cardiovascular [11,12] and peripheral vascular MRI examinations [13]. Ferumoxytol has been used in MRA of coronary artery stenosis [12], abdominal aortic aneurysms [12], renal artery stenosis [14], renal transplant [12], deep vein thrombosis [15], pulmonary thromboembolism [12], central venous occlusion [16], pediatric cardiovascular imaging, and peripheral arterial disease [8]. Ferumoxytol has also been used for steady-state [17-19] and dynamic [20] cerebral blood volume mapping of the brain.

Delayed phase imaging — Slow leakage of ferumoxytol from blood vessels results in intracellular MRI signal changes peaking around 24 h after administration. Signal decrease on T2-weighted and T2*-weighted images may represent accumulation of iron stores, macrophage or phagocytic uptake, and/or sequestration in tissue interstitium. This characteristic has useful applications in central nervous system (CNS) lesions [21,22], abdominal organs [23], atherosclerotic plaques [24], and evaluation for endoleaks after aortic aneurysm stent-graft repair [12]. Macrophage uptake of ferumoxytol allows the assessment of macrophage activity and identify localized cellular inflammation [25]. Thus, the immune response to tumors, such as gliomas and lymphomas, may enable the imaging of tumor extent. Macrophage influx related to stem cell death or immune-mismatched stem cell transplants can be imaged in stem cell transplant rejection [26]. Similarly, ferumoxytol uptake in macrophages has been associated with instability and impending rupture of vascular lesions, including intracranial aneurysms, arteriovenous malformations, and carotid plaques [22]. Conversely, lymph nodes replaced by metastatic tumor may show reduced or absent uptake [27].

Ferumoxytol administration for MRI Imaging

Imaging with ferumoxytol can be performed at both 1.5 and 3 Tesla [28].

Diagnostic imaging use of ferumoxytol differs from therapeutic use in two important ways: 1) lower total iron dose with dilution, and 2) lower average injection rate. Typical ferumoxytol doses for imaging range from 1 to 7.5 mg/kg, with most doses between 2 and 4 mg/kg in both adults and children [29,30]; whereas the standard therapeutic dose for anemia is 1020 mg (14.6 mg/kg for a 70-kg adult over 3-8 day period).

Injection rates reflect specific imaging indications and range from a slow infusion (for lymph node and steady-state imaging) to bolus injections of 3–15 sec for angiographic applications [30]. All reporting groups dilute the administered dose with saline (total volume of ~24–60 mL for adults). High injection rates and concentrations may be limited by artifacts from T2* effects.

In the therapeutic ferumoxytol boxed warning, the FDA recommends a slow intravenous infusion over at least 15 minutes of a diluted medium [31]. For imaging, the ferumoxytol is diluted to 1 part ferumoxytol in ~2-4 parts normal saline, resulting in a concentration of no higher than 10 mg/mL [30]. However, the infusion time varies depending on the imaging indication.

As with other contrast media, injection should be performed in a setting with personnel and therapies immediately available for the treatment of anaphylaxis and other hypersensitivity reactions [29]. For therapeutic ferumoxytol administration, FDA recommends close monitoring of patients for signs and symptoms of hypersensitivity reaction, including monitoring blood pressure and heart rate during the infusion and for at least 30 minutes after completion of the infusion [29,32].

Pharmacodynamics and pharmacokinetics

Ferumoxytol can be administered as a bolus, allowing dynamic imaging of the arterial vasculature and first-pass perfusion of the liver and kidneys [33]. There is slow migration of the ferumoxytol across the capillary endothelium (12-14 hours), so imaging in this time frame allows for venography [34]. The iron-oxide nanoparticles are then sequestered and cleared by the

mononuclear phagocytic system (MPS) [35], which includes liver, spleen, and bone marrow, and to a lesser extend lymph nodes. As the cells of MPS accumulated iron, they progressively lose T2- and T2*-weighted signal intensity. Iron deposition in the mononuclear phagocytic system (liver, spleen, and bone marrow) can cause signal change on MRI for up to 11 months [22,35,36], which may affect tissue and lesion characterization on subsequent MRI examinations.

The body has no active excretory pathways to remove excess iron from administration. For MRI, the amount of contrast administered (<4 mg/kg) is much lower than doses resulting in acute systemic toxicity (>60 mg/kg) or chronic iron overload [36]. However, evaluation for preexisting iron overload could be considered in high-risk groups, either through liver T2* measurements or serum ferritin levels.

As mentioned above, ferumoxytol is FDA approved for therapeutic use in adult patients with iron deficiency anemia in the setting of chronic kidney disease [6]. It is important for the radiologist to be aware of the common interactions of ferumoxytol and other intravenous iron formulations on subsequent MR imaging, particularly those studies that are performed within 72 hours of administration.

Ferumoxytol and other ultrasmall superparamagnetic iron oxide compounds result in T1, T2, and T2* shortening effects on MRI. These phenomena are used clinically for vascular imaging and other specific clinical indications [37], but can also result in unwanted artifacts, and may impact image interpretation [38]. Maximum intravascular signal alterations occur within 2 days of administration. The effects of T1 shortening and prolonged intravascular half-life of ferumoxytol can also result in interactions with conventional gadolinium-based contrast media for MRI [39], occasionally rendering typical enhancement patterns undetectable if ferumoxytol was administered within 72 hours of the MR examination. The package insert for ferumoxytol warns of potential prolonged MR effects [40], and can increase the R2* signal in hematopoietic bone marrow for up to a period of 3 months and liver for up to 6 months [41], mimicking hemosiderosis.

Other parenteral iron formulations are available, but are not used as contrast media. These preparations can also affect MR signal, and recommended times between infusion and MR imaging have been published [41]. There may be usefulness in reimaging with MRI soon after parenteral iron administration, however, the interpreting radiologist should be aware that MR signal may be impacted in this time frame. In brain pathologies, enhancement can persist for several days following ferumoxytol administration [35]. Ferumoxytol has no effect on radiography, computed tomography, positron emission tomography, single photon emission computed tomography, ultrasound, or nuclear medicine imaging [42].

Safety profile

Serious and rarely fatal adverse reactions to therapeutic doses of ferumoxytol, including anaphylaxis associated with cardiac/cardiorespiratory arrest, have been reported. From 2009 to 2015, approximately 1.2 million therapeutic doses of ferumoxytol were administered for treatment of iron deficiency anemia. In March 2015, the US Food & Drug Administration (FDA) placed a boxed warning on ferumoxytol for serious, potentially fatal allergic reactions after the FDA Adverse Event Reporting System showed 79 anaphylactic reactions, with 18 fatalities despite immediate intervention [31]. Twenty-four percent of these patients had multiple drug allergies, and nearly half of these anaphylactic reactions occurred within 5 minutes of administration.

The largest experience for diagnostic use of ferumoxytol is a retrospective, observational study using data from the FeraSafe™ Multicenter MRI Registry, consisting of 11 institutional partners in the U.S. and U.K. [43]. Between 2003 and 2018, a total of 3,215 unique patients (13% children, 87% adults) had 4,240 ferumoxytol injections for MRI. Ferumoxytol dose ranged from 1-11mg/kg (≤510mg Fe; rate ≤45mg Fe/s). There were no systematic changes reported in heart rate, blood pressure or oxygen saturation following ferumoxytol administration. No severe, life-threatening, or fatal adverse events occurred. Eighty-three adverse events (1.9%) were related or possibly related to ferumoxytol infusions (1.8 % mild; 0.2% moderate). Thirty-one were classified as allergic-like using ACR criteria but were consistent with known minor infusion reactions observed with parenteral iron. Other studies have shown similar results of an overall adverse event rate of 2%, serious hypersensitivity reactions in 0.01% of patients, and no reports of death [44].

Similar to other contrast media, hypersensitivity/allergic-like reactions may occur after the first dose or subsequent doses, even in patients who have previously tolerated the drug [1]. Patients with a history of multiple medication allergies have an increased risk of hypersensitivity reaction to parenteral iron preparations, therefore, potential risks and benefits of ferumoxytol administration should be considered carefully in such patients. The current FDA recommendation is that ferumoxytol should not be administered to patients with a history of allergic reactions to IV iron preparations [29,45].

A study in pigs showed no significant differences in the brain MRI of pigs exposed to ferumoxytol doses of 5-10 mg/kg compared to unexposed pigs [15]. A study of 17 pediatric patients who received between one and four doses of ferumoxytol for evaluation of arteriovenous malformations were compared to control patients, and showed no differences in susceptibility and R* values of the deep gray structures of the brain between the two groups [46].

Pregnant and breastfeeding patients

There is insufficient available data about ferumoxytol use in pregnant women to make conclusions regarding any risk of adverse developmental outcomes. There are risks to the mother and fetus associated with maternal severe hypersensitivity reactions [47,48]. Severe adverse reactions, including severe hypotension and shock, may occur in pregnant women with parental iron products which may cause fetal bradycardia, especially during the second and third trimester [1,49].

In animal studies, administration of ferumoxytol to pregnant rabbits at doses up to 2 times the estimated therapeutic human daily dose during organogenesis did not result in maternal or fetal effects [1]. In rabbits and rats, administration of ferumoxytol during organogenesis at approximately 6 times the estimated human daily dose caused adverse developmental outcomes including fetal malformations and decreased fetal weights [1]. One study that looked at ferumoxytol administration in rhesus macaques for MRI placental imaging showed placental ferumoxytol retention similar to levels of maternal liver ferumoxytol retention, which returned to baseline by day 4 post injection [50]. No increase in ferumoxytol was measured in the fetal tissues or maternal-fetal interface (decidua, placenta, fetal membranes) on MRI or post-delivery histopathologic evaluation, suggesting ferumoxytol may not enter the fetal circulation. Placental function, as measured by peripheral blood steroid hormone levels, was unaffected.

No data is available on the presence of ferumoxytol in human milk, the effects on breastfed children, or the effects on milk production.

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GASTROINTESTINAL (GI) CONTRAST MEDIA IN ADULTS: INDICATIONS AND GUIDELINES

Introduction

This chapter discusses indications, contraindications, and adverse reactions resulting from the administration of contrast agents used to assess the gastrointestinal system. Barium, iodinated, and negative GI contrast agents will be primarily discussed. Ancillary drugs utilized in gastrointestinal tract imaging will also be reviewed along with contraindications and risks. Allergic-like reactions and premedication strategies are covered at the end of the chapter.

Barium-based and iodinated contrast agents are commonly used to opacify the bowel lumen during fluoroscopic, computed tomography (CT), or magnetic resonance imaging (MRI) of the gastrointestinal system. Oral or rectal administration may be during the study (e.g., during fluoroscopic examinations), or in advance (e.g., prior to CT or MRI). Less commonly, contrast media can enter the bowel following intravenous injection and hepatobiliary clearance (e.g., with vicarious excretion of iodinated contrast, or following injection of gadobenate dimeglumine or gadoxetate disodium), or after direct injection of contrast media into the biliary and pancreatic ducts (e.g., during ERCP).

Barium Sulfate Enteric Contrast Media

Barium sulfate is a micropulverized white powder that is supplied in various forms, including in bulk for mixing with distilled or tap water, in prepackaged aliquots ready for suspension, or in prepared doses. Barium sulfate has a long history of use in diagnostic imaging, having been first described as a gastrointestinal contrast medium in 1910. Barium was the default enteric contrast medium for the evaluation of the GI tract for almost a century, and it retains value with both fluoroscopy and cross-sectional imaging.

Barium Sulfate in Fluoroscopy

Barium sulfate preparations remain the contrast media of choice for fluoroscopic imaging due to the delineation of mucosal detail and resistance to dilution. This is particularly helpful when performing double contrast studies and studies of swallowing mechanics using differing consistencies.

During a single contrast fluoroscopic examination, the optimal mixture for stability in suspension and bowel wall coating is 60% weight/volume (w/v) [1]. The volume of barium required varies by procedure and individual patient anatomy. For double contrast GI studies, high density barium (up to 250% w/v) is used in conjunction with air or effervescent material with a suspension of 85-100% weight/volume recommended for optimal double contrast imaging in the colon [2].

The composition of barium mixtures is altered in different areas of the gastrointestinal tract by local conditions including the presence of fluid and luminal acidity, which affects flocculation (clumping out of suspension) and coating. Also, local differences in tap water composition obtained from municipal sources alter the qualities of barium, so that trial and error may be needed to obtain the optimal constitution [3].

Water-soluble contrast media (discussed below) are generally preferred as oral contrast agents when a bowel perforation is suspected or known to exist. If an initial study with an iodinated contrast medium fails to demonstrate a suspected perforation, barium sulfate can then be administered. Such follow-up studies may be important as some small leaks may be undetectable with water-soluble media but subsequently seen when using barium-based media [4,5].

Barium Sulfate in Cross Sectional Imaging

Extremely dilute barium sulfate solutions are commonly used for opacification of the GI tract with CT, and less commonly with PET/CT. Its use varies among radiology departments, with some opacifying the GI tract routinely and others seldom or for specific indications only. The principal disadvantage is the time taken to opacify the GI tract which becomes relevant in emergency care [6,7]. Many feel that its routine use cannot be justified as it is seldom necessary to repeat a study with oral contrast following a study without it [7,8]. Targeted utilization (for example, for postoperative evaluation or in, patients who cannot receive intravenous (IV) contrast) is often suggested. Barium sulfate is avoided in patients with suspected perforation and known barium allergy in favor of water-soluble contrast (see below). There is no difference in opacification of the bowel on CT with barium sulfate or water-soluble alternatives [9].

For evaluation of the small bowel with CT or MR enterography, routine oral preparations of dilute barium should not be used as they may obscure mural or mucosal abnormalities due to the density. Instead, negative contrast agents are often used (discussed below).

Non-Allergic Complications of Barium Sulfate

The most serious complication from the use of barium in the GI tract is leakage into the mediastinum or peritoneal cavity [10]. The potential complications of a barium leak depend on the site from which the spill occurs. Esophageal leakage may cause mediastinitis. Gastric, duodenal, and small intestinal leakage may result in peritonitis. Escape of barium from the colon, where the bacterial count is highest, carries the highest mortality (likely primarily related to leakage of stool). Water-soluble contrast media (discussed below) are generally preferred as oral contrast agents when a bowel perforation is suspected or known to exist. If an initial study with an iodinated contrast medium fails to demonstrate a suspected perforation, barium sulfate can then be administered. Such follow-up studies may be important as some small leaks may be undetectable with water-soluble media but subsequently seen when using barium-based media [4,5].

Although barium sulfate is inert, it can occasionally produce symptoms if aspirated, particularly in patients who have underlying lung disease. While barium is usually mobilized proximally by ciliary action of normal bronchial epithelium, damaged epithelium from bronchial disease delays the normal elimination of barium [1]. If not completely expectorated, retained barium in the lungs can remain indefinitely and may cause inflammation [11]. High volume aspiration can lead to acute respiratory distress or pneumonia [12].

Other reactions to GI tract barium

Adverse reactions to oral and rectal barium contrast media are almost always mild, with the most common symptoms including nausea, vomiting, and abdominal cramping or discomfort during and/or after the examination. These symptoms are likely not hypersensitivity reactions but are part of a physiologic response resulting from distention of a viscus. Vasovagal reactions can also be encountered, when the colon is distended during a double contrast barium enema.

Direct barium toxicity

Direct toxicity of orally or rectally administered barium has been reported on very rare occasions [13,14]. Any barium that dissociates from the stable barium sulfate compound may form other chemical compounds that become soluble and are absorbed into the blood stream resulting in toxicity – for example, barium chloride, barium sulfide, or barium carbonate [15]. This is more likely to occur if industrial grade barium contaminates pharmaceutical grade barium distributed for diagnostic use [16]. Case reports of toxicity with pharmaceutical grade barium also exist [14,17].

Acute symptoms of barium toxicity are usually rapid in onset and include nausea, vomiting, and watery diarrhea. Absorption of barium can result in changes in electrolyte balance, causing rapid and severe hypokalemia [18,19]. Untreated, this can lead to a cascade of severe muscle weakness, respiratory arrest, coma, cardiac arrhythmia, and death [16,20]. Therapy consists of aggressive potassium infusion with monitoring and correction of electrolyte imbalances [16,21].

Contraindications to administration of barium

There are no absolute contraindications for the use of barium compounds, although as noted above, it is generally recommended that barium not be administered to individuals who are suspected or known to have bowel perforations or suspected allergy to barium and/or barium components.

Iodinated (Water-Soluble) Enteric Contrast Media

Two commercial iodinated contrast agents are commonly used for enteric opacification: Gastrografin® (Bracco Diagnostics, Inc.; Princeton, NJ) and Gastroview® (Covidien; Hazelwood, MO) are solutions comprising 660 mg/ml diatrizoate meglumine and 100 mg/ml diatrizoate sodium. The result is a solution that has 367 mg (37%) of iodine per ml [22,23]. Gastrografin® and Gastroview® are hypertonic solutions and are considered High Osmolar Contrast Media (HOCM).

Low osmolar iohexol (Omnipaque™ GE Healthcare; Princeton, NJ) has an FDA-approved indication for oral use in select concentrations. Omnipaque™350 is approved for oral or rectal administration in adults, with lower concentrations approved for pediatric patients. Diluted and oral solutions of iohexol are approved for use in conjunction with intravenous administration of iohexol for CT imaging of the abdomen (see prescribing information for further detail) [24,25]. Dilution for CT applications aims to avoid artifacts that may occur from high attenuation of the contrast media.

Diagnostic use of water-soluble enteric contrast media for Conventional Fluoroscopic Examinations

As discussed above, barium sulfate formulations are generally the preferred agents for opacification of the gastrointestinal tract for conventional fluoroscopic examinations [1,2]. The use of water-soluble contrast media during fluoroscopy is typically reserved for selected situations, including:

- Possible bowel perforation, postoperative leak, enteric fistula/sinus tract, or abscess
- Confirmation of feeding tube positioning
- Prior to planned endoscopic procedures
- In small bowel obstruction when surgery may be planned
- In patients with prior allergic-like reactions to barium

Diagnostic use of water-soluble enteric contrast media for CT

Common indications for the use of enterically administered water soluble contrast in Abdominopelvic CT include [26]:

- Oncologic imaging
- Suspected bowel leak, fistula, abscess, or fluid collection
- Abdominal pain
- CT colonography

Water-soluble contrast media are the preferred agents when evaluating for hollow viscus/bowel perforation because it is rapidly absorbed in the peritoneum and interstitial spaces. No deleterious effects from the presence of water-soluble contrast media in the mediastinum, pleural cavity, or peritoneal cavity have been demonstrated [11]. If an initial exam performed with water soluble contrast in a patient with suspected bowel perforation fails to demonstrate a leak, one can then consider barium sulfate.

Therapeutic use of water-soluble enteric contrast media

Oral iodinated high-osmolality contrast media (HOCM) have been used successfully for the treatment of postoperative adynamic (or paralytic) ileus and adhesive small-bowel obstruction [27-30]. Given as an enema, HOCM has proved useful in some adults with barium impaction [31] as well as in patients with cystic fibrosis who have distal intestinal obstruction syndrome (DIOS) (obstipation) [32]. This is because HOCMs are hypertonic and draw fluid into the bowel lumen.

Non-allergic Complications of water-soluble contrast agents

Diarrhea, nausea, and vomiting may occur following enteric administration of diatrizoate meglumine/diatrizoate sodium solutions as well as iohexol solutions. Mucosal irritation has also been reported [22,24,25,33]. Mucosal inflammation, mucosal infection, or bowel obstruction can increase the amount absorbed by several fold [34-36]. As a result, it is not rare to see opacification of the urinary tract after enteric administration of water-soluble contrast media [37].

Enteric HOCM in hypertonic concentrations may draw fluid into the lumen of the bowel. This can lead to hypovolemia and/or dehydration, so should also be avoided in patients with fluid and electrolyte imbalances [10,38]. Preparations made from nonionic LOCM may be preferable for these patients.

Because of the oral route of administration, aspiration is a risk for enteric contrast administration. Low osmolality and iso-osmolar contrast agents are preferred due to lower risks of life-threatening pulmonary edema if aspirated as compared to high osmolar agents [39-41]. Further, water soluble contrast agents should be avoided in patients with tracheoesophageal fistula due to risk of pulmonary complications [22,33].

Thyroid function tests may be altered for variable periods of time [42], even in normal patients, following administration of iodinated water-soluble biliary contrast agents such as orally administered iopanoate (Telapaque®; Winthrop Pharmaceuticals, New York, NY) or intravenously administered water-soluble contrast such as iodipamide (Cholografin®; Bracco Diagnostic, Inc., Princeton, NJ). Cases of hyperthyroidism have been reported following oral contrast [22,33].

Neutral and Negative Enteric Contrast Media

Neutral oral contrast agents (i.e., attenuation or signal intensity similar to water) are used to distend bowel without interfering with evaluation of mural enhancement. They are commonly used with MR and CT enterography, and to improve evaluation of the pancreaticobiliary tree.

Negative oral contrast agents (i.e., attenuation or signal intensity less than water) are used to suppress background luminal contents to improve visualization of the pancreaticobiliary tree.

Some neutral contrast agents contain nonabsorbable additives (resins, polyethylene glycol, mannitol, sorbitol, or other sugar alcohols) that help retain intraluminal water and prevent absorption. For example, NeuLumEx (formerly VoLumen, Bracco Diagnostics, Princeton, NJ) is a thin (0.1% w/v) barium sulfate solution approved that is widely used for CT and MRI enterography and contains a small amount of sorbitol. Sorbitol is hyperosmolar and retains water, improving bowel distention [43,44]. Breeza (Beekley Medical, Bristol, Conn) is a well-tolerated alternative neutral contrast agent containing sorbitol, mannitol and xantham gum. It is marketed as a "flavored beverage" and may be better tolerated than NeuLumEx [43,45].

There have been very few reported serious adverse reactions to neutral or negative oral contrast media. Examples include nausea, cramping, GI distress, and diarrhea. Barium-based solutions are relatively contraindicated in patients with bowel leak due to the potential for barium peritonitis.

Neutral Enteric Contrast Media with CT

Neutral oral contrast agents used with CT can include dilute barium-based media, water, milk, and dilute iodinated media. Negative oral contrast agents are not generally used with CT.

Water is the least expensive, safest, and most accessible neutral contrast medium [46]. Water will distend the lumen of the stomach and proximal duodenum but not the distal small bowel or colon due to interval absorption.

Commercially available neutral contrast agents containing sorbitol and/or mannitol are commonly used for purposes like CT Enterography. These include NeuLumEx (Bracco Diagnostics, Princeton, NJ) and Breeza (Beekley Medical, Bristol, Conn).

Milk has been tested as an inexpensive neutral oral contrast material for CT [47,48]. Milk contains fat, which slows intestinal peristalsis and transit. One comparison of whole milk to VoLumen (now NeuLumEX) in 215 adult patients found no significant difference with respect to bowel distention or bowel wall visualization but better patient acceptance [47].

Other less common neutral oral contrast agents have been used with CT, including lactulose solution, polyethylene glycol (PEG), and methylcellulose. In general, these uncommon agents are not favored due to side effects such as diarrhea and dehydration.

Neutral and Negative Enteric Contrast Media with MRI

Neutral and negative oral contrast agents are used during MRI to improve visualization of the pancreaticobiliary tree at MRCP (i.e., by suppressing background fluid within the stomach and small bowel) or improve visualization of the bowel during MR enterography (i.e., by distending the bowel lumen and enhancing evaluation of the bowel wall). In general, these agents function via T1 and T2/T2* effects which improve visualization of mucosal enhancement.

Neutral oral contrast agents used at MRI can include paramagnetic agents containing manganese (e.g., pineapple or blueberry juice). Use of diamagnetic agents (i.e., barium or kaopectate) or superparamagnetic substances (e.g., oral iron) is rare. Perfluorochemicals (i.e. molecules where protons are replaced by flourine atoms) have been studied but are not in routine clinical use [49].

Contrast Agents in the Biliary and Pancreatic Ductal Systems

Orally ingested barium contrast material can reflux into the biliary tree following biliary surgery, sphincteroplasty, or biliary stent placement. Normally this is of no consequence, as the barium empties back into the bowel promptly with physiological bile flow [50,51]. However, rare clinical reports of complications like suppurative cholangitis, shock, or disseminated intravascular coagulation exist, particularly when there is retention of barium beyond 24 hours [52-55]. Although some authors have theorized that barium could dehydrate and occlude the biliary system or indwelling stents, this has not been well documented [51,56].

Water-soluble iodinated contrast media (ICM) is instilled into the biliary ductal system during endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography, or during intraoperative cholangiography. Studies have demonstrated that small amounts may be absorbed and result in systemic exposure [57-59]. However, hypersensitivity reactions to ICM instilled during ERCP are rare [60-63]. Opacification of the biliary tree can also be achieved via intravenous injection of iodipamide (Cholografin®, Bracco Diagnostics, Milan, Italy) before fluoroscopy or CT, although this is now rarely (if ever) performed in the United States due to increased utilization of MRCP and the higher frequency of contrast reactions with this agent [64-67].

Two commonly used gadolinium-based contrast agents (GBCA) – gadobenate dimegumine (MultiHance® Bracco Diagnostics, Inc., Location) and gadoxetate disodium (Eovist®; Bayer Healthcare Pharmaceuticals, Wayne, NJ) – also have properties that result in transportation into hepatocytes and subsequent excretion into the biliary tree [68-70]. There are also small case series describing retrograde injection of GBCA into the pancreaticobiliary tree during ERCP, although there is limited research on resulting adverse events and the potential for absorption and systemic exposure [62,71].

Ancillary drugs

Glucagon and Anticholinergic Agents

Glucagon is FDA-approved to temporarily inhibit movement of the gastrointestinal tract in adults undergoing radiologic examinations [72-74]. Most often, glucagon is used to relax the bowel during double contrast studies of the upper GI tract or colon, or during MR enterography, although it can also be advantageous during intravascular or image-guided percutaneous procedures [75-79]. The dose in adults can depend on which portion of the GI tract is targeted for relaxation; beneficial effects are seen in the stomach with doses of 0.5 mg IV (or 2 mg IM), in small bowel with doses of 0.1 to 0.25 mg IV (or 1 mg IM), and in colon with doses of 1 mg IV (or 2 mg IM given 10 minutes in advance) [76,80]. A standard dose of 0.5-1 mg IV glucagon is commonly used for MR enterography in order to minimize motion artifacts from bowel peristalsis. Onset occurs within 1 minute when given IV or within 10 minutes when given IM and lasts at least 30 minutes [81-83]. Side effects of IV glucagon include nausea and vomiting which can be reduced by slow administration over 1 to 5 minutes [78], as well as vasovagal reactions [73]. Delayed hypoglycemia has been documented in some patients [78], although this is usually not clinically significant. Notably, some package inserts for glucagon (for example, GlucaGen; Bedford Laboratories; Bedford, OH) recommend oral carbohydrates after administration of glucagon to rebuild body glycogen stores and avoid hypoglycemia. The package insert for the specific drug used at each practice should be consulted.

Other anticholinergic agents like hyoscyamine sulfate and hyoscine butylbromide (scopolamine) have been explored as alternative options to IV glucagon due to cost and side effect profiles. One study found that using sublingual hyoscyamine tablets resulted in subjectively equivalent quality of upper GI examinations when compared to IV glucagon [84]. Another study found no significant difference in colonic distension or abdominal discomfort when using sublingual hyoscyamine, although less nausea was reported by patients [73]. However, other studies have shown lower effectiveness and overall reduced the use of hyoscyamine [73,85-88].

Metoclopramide

Metoclopramide (Reglan®; Pfizer, New York, NY) can be administered to stimulate motility of the upper GI tract and relax the pyloric sphincter without stimulating gastric, biliary, or pancreatic secretions. This can be helpful to hasten gastric emptying and small bowel transit or ease the placement of post-pyloric feeding tubes. Metoclopramide can be given at doses of 10 mg IV (slowly, over 1-2 minutes), 10 mg IM, or 20 mg PO. The onset of action is 1 to 3 minutes with IV dosing, 10 to 15 minutes with IM dosing, and 20 to 60 minutes following an oral dose. Pharmacological effects persist for 1 to 2 hours [89,90].

Contraindications to metoclopramide include pheochromocytoma, as it may stimulate release of catecholamines from the tumor. Epileptics may also be sensitive to its extrapyramidal effects [91]. Other adverse reactions from single doses as given in a radiology department are exceedingly rare. While adverse reactions from larger or regular dosing exist (e.g., tardive dyskinesia), this is outside of the scope of this document.

Secretin

A synthetic version of secretin (ChiRhoClin®, Inc., Silver Springs, MD) can be administered to stimulate pancreatic secretion and improve delineation of the main pancreatic duct or assess for leak during MRCP [92-94]. The manufacturer recommends an intravenous dose of 0.2 mcg/kg (slowly, over 1 minute) [95].

A relative contraindication to secretin administration is acute pancreatitis, as symptoms can be exacerbated [96]. Other side effects include nausea, flushing, abdominal pain, and vomiting [95]. Allergic-like reactions are rare, with few (if any) reported [97]. Nonetheless, the manufacturer recommends giving a test dose of 0.2 mcg to assess for reactions for 1 minute before giving the remainder of the dose [95].

Immediate hypersensitivity reactions to enteric contrast media

Nonvascular (enteric or nonenteric) administration of contrast agents results in some systemic absorption of the agent [98]. Studies suggest that approximately 1% to 2% of enteric iodinated contrast media are normally absorbed and subsequently excreted into the urinary tract after oral or rectal administration [99,100]. As allergic-like reactions are not considered to be dose related and can occur with less than 1 ml of IV contrast media, it is generally accepted that allergic-like reactions can occur even from the small amounts of contrast medium absorbed from the gastrointestinal tract. However, these reactions allergic-like reactions after nonvascular administration of contrast remain infrequent compared to reactions after intravenous administration [101-103], with only very rare reports of moderate or severe allergic-like reactions to orally or rectally administered iodinated contrast media [36].

Use of Gastrografin® and Gastroview® is contraindicated in patients with allergy to salts of diatrizoic acid or other ingredients of the solution [22,23].

Strategies for Premedication or Agent-Switching

There is variability in the approach to premedication for patients with a history of contrast allergies who are scheduled for exams involving nonvascular administration of contrast. Some favor following the same guidelines as for vascular administration of contrast (see "Indications for Premedication" in Chapter 4). Others do not recommend premedication for these patients given the rarity of immediate hypersensitivity reactions after nonvascular administration [98]. This latter approach has also been adopted by some outside of radiology, with a study showing that most urologists do not prescribe prophylaxis for contrast allergies prior to endourologic procedures [104]. Yet another approach is to only premedicate patients with a history of a severe immediate hypersensitivity reaction to the same class of contrast agent being administered extravascularly (see Table 1 for description of categories of acute reactions) [105].

It is known that premedication does not prevent all repeat reactions. Another mitigation strategy is to change contrast agents, whether choosing a different agent in the same class or selecting a different class of agent (iodinated contrast media vs. barium vs. gadolinium-based agent). Changing contrast media, even within the same class, may be more effective than premedication in preventing repeat reaction [98,106-109]. This is also discussed in Chapter 4 of the manual (link to "Changing Contrast Media Within the Same Class").

Treatment of adverse reactions to GI contrast agents and ancillary drugs

Facilities should be equipped with basic supplies and medications to evaluate and treat adverse reactions to oral contrast agents and ancillary drugs. Treatment of allergic-like reactions to oral contrast agents can follow the same algorithmic approach as treatment of reactions to intravenous contrast agents. Algorithms, scenarios, and potential supplies for contrast reaction kits are provided in Table 2, Table 3, and Table 4. Treatment of other non-allergic adverse reactions can vary and should be based on patient symptoms.

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ACR–ASNR POSITION STATEMENT ON THE USE OF GADOLINIUM CONTRAST AGENTS

Following U.S. Food and Drug Administration (FDA) approval in 1988, gadolinium-based contrast agents (GBCAs) have been used for diagnosis and treatment guidance in more than 300 million patients worldwide. GBCAs increase the conspicuity of diseased tissues. All GBCAs share a common structure of an organic ligand that tightly binds to and improves the stability, solubility, and safety of the central gadolinium heavy metal ion. In typical patients, the chelate is mostly eliminated via the kidneys, with some amount of liver excretion demonstrated for a few of the agents.

Since 2006, radiologists have withheld some GBCAs from patients with acute kidney injury and/or severe chronic kidney disease, if the estimated glomerular filtration rate (GFR) is <30 mL/min/1.73 m_2, because of the increased risk of nephrogenic systemic fibrosis (NSF). NSF is a rare but serious systemic disease characterized by fibrosis of the skin and other tissues throughout the body in renally impaired individuals. As a result of judicious use of GBCAs among patients with compromised renal function and a decrease in utilization of those GBCAs that are more highly associated with NSF, there has been a drastic reduction in the number of cases encountered since restrictive guidelines were put into place after the association of NSF with GBCAs was identified in 2006.

Recently, residual gadolinium has been found within the brain tissue of patients who received multiple doses of GBCAs over their lifetimes. For reasons that remain unclear, gadolinium deposition appears to occur preferentially in certain specific areas of the brain, even in the absence of clinically evident disease and in the setting of an intact blood brain barrier. Such deposition is not expected, and led the FDA to publish a Safety Alert in July of 2015 indicating that they were actively investigating the risk and clinical significance of these gadolinium deposits. To date, no adverse health effects have been uncovered, but the radiology community has initiated a rigorous investigation.

Gadolinium deposition in the brain may be dose dependent and can occur in patients with no clinical evidence of kidney or liver disease. Fortunately, there have been no reports to date to suggest these deposits are associated with histologic changes that would suggest neurotoxicity, even among GBCAs with the highest rates of deposition. Although there are no known adverse clinical consequences associated with gadolinium deposition in the brain, additional research is warranted to elucidate the mechanisms of deposition, the chelation state of these deposits, the relationship to GBCA stability and binding affinity, and theoretical toxic potential, which may be different for different GBCAs. Until we fully understand the mechanisms involved and their clinical consequences, the safety and tissue deposition potential of all GBCAs must be carefully evaluated.

GBCAs provide crucial, life-saving medical information. Each time a gadolinium-enhanced MRI study is considered, it would be prudent to consider the clinical benefit of the diagnostic information or treatment result that MRI or MRA may provide against the unknown potential risk of gadolinium deposition in the brain for each individual patient. Particular attention should be paid to pediatric and other patients who may receive many GBCA-enhanced MRI studies over the course of their lifetimes. If the decision for an individual patient is made to use a GBCA for an MRI study, multiple factors need to be considered when selecting a GBCA, including diagnostic efficacy, relaxivity, rate of adverse reactions, dosing/concentration, and propensity to deposit in more sensitive organs such as the brain. As this gadolinium deposition phenomenon remains a relatively undefined clinical phenomenon, and accurate and complete data may be useful as investigations proceed, the identity and dose of GBCA used should be recorded after each intravenous administration.

The radiology community will continue to assess the safety of GBCAs and modify clinical practice recommendations accordingly as new data becomes available.

ADVERSE REACTIONS TO GADOLINIUM-BASED CONTRAST MEDIA

Gadolinium-based contrast media (GBCM) have been approved for parenteral use since the late 1980s. These agents can be differentiated on the basis of chelate chemistry, stability, viscosity, osmolality, and, in some cases, effectiveness for specific applications. GBCM are extremely well tolerated by the vast majority of patients in whom they are injected. Acute adverse reactions are encountered with a lower frequency than is observed after administration of iodinated contrast media.

Adverse Reactions

The adverse event rate for GBCM administered at clinical doses (0.1–0.2 mmol/kg for most GBCM) ranges from 0.07% to 2.4%. Most reactions are mild and physiologic, including coldness, warmth, or pain at the injection site; nausea with or without vomiting; headache; paresthesias; and dizziness. Allergic- like reactions are uncommon and vary in frequency from 0.004% to –0.7%. The manifestations of an allergic- like reaction to a GBCM are similar to those of an allergic-like reaction to an iodinated contrast medium. Severe life-threatening anaphylactic reactions occur [1-6] but are exceedingly rare (0.001% to 0.01%) [7-9] In an accumulated series of 687,000 doses there were only five severe reactions [10]. In a survey of 20 million administered doses, there were 55 severe reactions. A large single-institution study that included more than 100,000 GBCM injections demonstrated an allergic-like reaction frequency of 0.15%, with 0.13% mild reactions and 0.006% severe reactions (six reactions) [11]. Fatal reactions to gadolinium chelate agents occur but are extremely rare [12].

GBCM administered to patients with acute kidney injury or severe chronic kidney disease can result in a syndrome of nephrogenic systemic fibrosis (NSF) [13,14]. For more information, see the chapter on Nephrogenic Systemic Fibrosis. GBCM are not considered nephrotoxic at dosages approved for MR imaging.

Risk Factors

The frequency of acute adverse reactions to GBCM is about eight times higher in patients with a previous reaction to GBCM. At many institutions, a prior allergic-like reaction to GBCM is often an indication for corticosteroid prophylaxis prior to subsequent exposures. One GBCM, gadobenate dimeglumine, has FDA labeling contraindicating use in patients who have a history of an allergic-like reaction to GBCM. Some reports have suggested that GBCM that have been most commonly associated with NSF are less likely to be associated with allergic-like reactions and vice versa [15].

Patients with asthma and various other allergies may have a mild increased risk for an allergic-like reaction to GBCM compared to the general population, but many institutions do not have special procedures for these patients given the extremely low overall reaction rate for GBCM. There is no cross-reactivity between GBCM and iodinated contrast media.

In a patient with previous moderate or severe allergic-like reactions to a specific GBCM, it may be prudent to use a different GBCM and premedicate for subsequent MR examinations, although there are no published studies to confirm that this approach is efficacious in reducing the likelihood of a repeat contrast reaction.

The Safety of Gadolinium-Based Contrast Media in Patients with Sickle Cell Disease

Early in vitro research investigating the effects of a strong external magnetic field (e.g., MR magnet) on red blood cells (erythrocytes) suggested that fully deoxygenated sickle erythrocytes align perpendicularly to a magnetic field. It was hypothesized that this alignment could further restrict sickle erythrocyte flow through small vessels and promote vaso-occlusive complications in sickle cell patients [16]. Based on this supposition, FDA package inserts suggested caution in patients with sickle cell disease for two GBCM approved for use in the United States (gadoversetamide [OptiMARK, Guerbet] and gadoteridol [Prohance, Bracco Diagnostics]).

To the best of our knowledge and noted in a review of the literature [17], there has been no documented in vivo vaso-occlusive or hemolytic complication directly related to the IV administration of GBCM in a sickle cell disease patient. A small retrospective study with a control group showed no significantly increased risk of vaso- occlusive or hemolytic adverse events when administering GBCM to sickle cell disease patients [18]. Additionally, several small scientific studies [19-21] of patients with sickle cell disease have employed MR imaging with GBCM without reported adverse effects.

Therefore, the risk to patients with sickle cell disease from IV-administered GBCM at approved dosages is very low or nonexistent, and there is no reason to withhold these agents from these patients when their use is otherwise indicated.

Breath-holding Difficulty with Gadoxetate Disodium

Several studies have noted that gadoxetate disodium may be associated with transient severe respiratory motion-related artifact that manifests in the arterial phase of dynamic T1-weighted gradient echo imaging and resolves shortly thereafter [22-26]. This manifestation has been described as "transient dyspnea". At one institution, patient surveys showed that significantly more patients complained of subjective shortness of breath following gadoxetate disodium compared to gadobenate dimeglumine exposure [22]. The reported rate of occurrence of "transient dyspnea" has varied by site, imaging acquisition parameters, and administered volume, ranging from 4% to 14% [22-26].

Based on the volume-effect relationship and the lack of identifiable atopic covariates, this appears to be a physiologic reaction, manifesting as dyspnea or breath-holding difficulty that is unique to this agent [25]. The event is self-limited and does not appear to relate to allergic-like bronchospasm [22,24,25]. Therefore, corticosteroid prophylaxis is unlikely to be beneficial and is not felt to be indicated. Strong risk factors include a larger administered volume irrespective of patient weight (20 mL doses are twice as likely to cause the artifact as 10 mL doses) [25], chronic obstructive pulmonary disease (patients with COPD have a 35–40% event rate) [25], and re-administering the agent to patients who have previously had a similar reaction (previously affected patients have a 60% event rate on subsequent studies compared to a 5% event rate in the unaffected population) [26]. Imaging strategies to avoid the artifact include minimizing the injected volume (≤10 mL), avoiding the agent in patients who have experienced it before, and acquiring more than one arterial phase with a short temporal footprint [22-26]

Treatment of Acute Adverse Reactions

Treatment of acute adverse reactions to GBCM is similar to that for acute reactions to iodinated contrast media (see Tables 2 and 3). In any facility where contrast media are injected, it is imperative that personnel trained in recognizing and handling reactions and the equipment and medications to do so be on site or immediately available. Most MR facilities take the position that patients requiring treatment should be taken out of the imaging room immediately and away from the magnet so that none of the resuscitative equipment becomes a magnetic hazard.

Extravasation

Extravasation events to GBCM are rare, with one series demonstrating a rate of 0.05% (28,000 doses). Laboratory studies in animals have demonstrated that both gadopentetate dimeglumine and gadoteridol are less toxic to the skin and subcutaneous tissues than are equal volumes of iodinated contrast media [27,28]. The small volumes typically injected for MR studies limit the chances of developing compartment syndrome. For these reasons the likelihood of a significant injury resulting from extravasated MR contrast media is extremely low.

Serum Calcium Determinations

Some linear nonionic GBCM (e.g., gadoversetamide, gadodiamide) may interfere with total serum calcium values as determined with some calcium assay methods [29,30]. These GBCM do not cause actual reductions in serum calcium. Rather, they interfere with the test, leading to falsely low serum calcium laboratory values. In one report by Brown and associates [30], calcium levels measured by only one of three different assays (the orthocresolphthalein assay) showed a temporary decrease for just two of four studied GBCM (gadopentetate and gadoteridol had no effect), the length and severity of which closely mirrored the concentration of the measured GBCM in blood.

Off-Label Use of MRI Contrast Agents

In the past, radiologists often used GBCM in an off-label fashion (e.g., off-label higher doses or off-label indications). By definition, such usage is not approved by the FDA. However, physicians have some latitude in off-label GBCM use as guided by clinical circumstances as long as they can justify such usage in individual cases. Extremely high doses of GBCM much greater than FDA labeling (which were used frequently in the past) have largely been abandoned, especially in patients with severe chronic kidney disease and acute kidney injury due to concerns regarding nephrogenic systemic fibrosis.

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Gadolinium Pregnancy Screening Statement

It has been shown that some gadolinium-based contrast agents (GBCAs) pass the placental barrier into the fetal circulation of nonhuman primates [1]. While multiple small sample size studies have not shown convincing evidence of adverse effects from fetal exposure to GBCAs [2,3], a 2016 retrospective study cited an increased risk of stillbirth/neonatal death as well as increased risk of rheumatologic, inflammatory, or infiltrative skin conditions in the offspring after GBCA exposure during pregnancy [4]. While, questions have been raised regarding study methodology, and these results have not been independently confirmed, both uncertainty and an abundance of caution in general about the effect of GBCA exposure and retention on the developing fetus has led to statements in the ACR Manual on Contrast Media [5] and the ACR Manual on MR Safety [6] recommending avoidance of routine administration of GBCAs to pregnant patients. A decision to administer GBCAs to a pregnant woman should only be made when there is the potential for significant clinical benefit that outweighs the unknown risk of fetal exposure and should be the product of discussion that involves the referring provider and patient.

A 2019 study cited increased prevalence of GBCA administration during the first trimester as opposed to later in pregnancy, indicating that many exposures have occurred without pregnancy screening and/or prior to recognition of pregnancy. This suggests a potential need for more vigilant pregnancy screening protocols [7]. The current standard of practice is to avoid routine GBCA administration during pregnancy due to the unknown risk of fetal exposure [5,6,8]; and we recommend that imaging facilities have an established standardized system of screening in place that includes screening for unsuspected pregnancy prior to GBCA administration within existing institutional protocols that similarly screen patients prior to exposure to ionizing radiation and/or anesthesia. Protocols regarding pregnancy testing and reporting of results for pediatric patients and patients with legal guardians must be in accordance with local and state regulatory statutes.

There is variability in the accuracy of pregnancy tests early in gestation, and at a minimum, testing will be falsely negative in the first two weeks of pregnancy. As such, there is no screening method that will be 100% effective in detection of unsuspected pregnancy. Regardless of which screening option is chosen, women of child-bearing age should be informed of the lack of certainty regarding risk of fetal GBCA exposure. An increased awareness of the issue by the patient may facilitate information sharing between patient and MRI staff regarding potential for pregnancy that would improve accuracy of screening. Any discussion with referring providers or patients acknowledging uncertain risks of GBCAs should always be coupled with an assessment of the known diagnostic benefits accrued from contrast-enhanced examinations on a per patient basis.

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NEPHROGENIC SYSTEMIC FIBROSIS

Definition

Nephrogenic systemic fibrosis (NSF) is a disease, primarily involving the skin and subcutaneous tissues but also known to involve other organs, such as the lungs, esophagus, heart, and skeletal muscles. Initial symptoms typically include skin thickening and/or pruritus. Symptoms and signs may develop and progress rapidly, with some affected patients developing contractures and joint immobility. In some patients, the disease may be fatal.

Associations

Gadolinium-based contrast agent (GBCA) administration

When first described in 2000, NSF was noted to occur predominantly in patients with end-stage chronic kidney disease (CKD), particularly in patients on dialysis. In 2006, several groups noted a strong association between gadolinium-based contrast agent (GBCA) administration in patients with advanced renal disease and the development of NSF [1,2], and it is now generally accepted that GBCA exposure is a necessary factor in the development of NSF, although in rare instances NSF can be diagnosed without known GBCA exposure. The time between injection of GBCA and the onset of NSF symptoms occurs within days to months in the vast majority of patients [1-6]; however, in rare cases, symptoms have appeared years after the last reported exposure [5].

The association between NSF development and exposure to GBCAs is widely accepted. It is now known that there are differences in the likelihood of a patient developing NSF after exposure to different formulations of GBCAs. Almost all unconfounded cases have been reported after exposure to gadodiamide, gadopentetate dimeglumine, and/or gadoversetamide, while some GBCAs have been associated with few, if any, confirmed unconfounded cases of NSF. If the prevailing hypothesis is true—that the development of NSF is related to the release of gadolinium from the chelates that constitute GBCAs—the differences in number of reported cases may, in part, be explained by differences in the chemical properties of different GBCAs. However, it remains possible that a combination of other factors, including market share, number of years that the agent has been in use, patient populations, and possible reporting bias, may have contributed, in part, to some of the differences in the number of reported cases associated with the various GBCAs.

Utilizing both empirical data and theoretical lines of reasoning, the ACR Committee on Drugs and Contrast Media, the European Medicines Agency (EMA), and the U.S. Food and Drug Administration (FDA) all have classified GBCAs into different groups based on reported associations with NSF in vulnerable patients, although the scheme used by each is not identical [7,8]. The ACR classification is given in Table 1 in this chapter.

Chronic kidney disease

Based on current knowledge, it is estimated that patients with end-stage CKD (CKD5, eGFR <15 ml/ min/1.73 m2) and severe CKD (CKD4, eGFR 15-29 ml/min/1.73 m2) have a 1% to 7% chance of developing NSF after one or more exposures to group 1 GBCAs with the strongest association with NSF [1-6,9].

However, most patients who developed NSF had end-stage kidney disease and were on dialysis at the time of exposure. Moreover, among patients with severe CKD (CKD4) that developed NSF (approximately 3% of all reported NSF cases), most had an eGFR closer to 15 ml/min/1.73 m2 than to 30 ml/min/1.73 m2. There have been rare, published case reports of patients with eGFR values above 30 ml/min/1.73 m2 [10-12].

Acute kidney injury (AKI)

Between 12% and 20% of confirmed cases of NSF have occurred in patients with AKI, often superimposed upon CKD [13,14]. Some cases of NSF have developed in patients with AKI without underlying CKD [15]. Hence, AKI alone is also a risk factor for NSF.

High-dose and multiple exposures

Cases of NSF have occurred following a single exposure to a GBCA, including a single exposure to a standard (0.1 mmol/kg) single dose [5,16]. Nevertheless, NSF occurs most commonly in patients who have received high doses of GBCA, either as a single administration or cumulatively, in multiple administrations over months to years [6,17].

Most patients with severe CKD exposed to high doses and/or many doses of GBCAs have not developed NSF [5]. One study [18] described 30 patients who had an eGFR of under 30 ml/min/1.73 m2 and who were exposed to high doses of gadodiamide (median dose of 90 ml and range of 40 to 200 ml). Only one of the 30 patients subsequently developed NSF, an observed incidence of about

3%.

A few cases of NSF also have been reported in patients with no known GBCA exposure [19]. In some of these cases, subsequent tissue biopsy evaluation revealed elevated gadolinium levels in the tissues of these patients, suggesting that at least some of these patients had prior unknown GBCA exposure [20, 21].

Other possible risk factors

It is not understood why some patients with severe CKD or AKI develop NSF following exposure to GBCAs and others do not, but a number of possible co-factors have been postulated to play a role. These include metabolic acidosis or medications that predispose patients to acidosis [1,21]; elevated iron, calcium, and/or phosphate levels [21,22]; high-dose erythropoietin therapy [13]; immunosuppression [6]; vasculopathy [23]; and infection [24] or other acute proinflammatory events [4,25]. However, none of these have been consistently confirmed as true cofactors. As a result, routine screening for these factors prior to GBCA administration is not recommended.

Hepatic insufficiency/hepatorenal syndrome

Initially, a number of researchers observed that a disproportionate number of affected patients had concomitant severe liver and renal dysfunction [4,5], prompting the FDA to warn against the use of GBCAs in patients with "…acute renal insufficiency of any severity due to the hepatorenal syndrome or in the perioperative liver transplantation period" [26]. However, most data do not support this conclusion. For example, in one study, a review of the literature found that of 335 patients with NSF, 35 (10%) had concomitant liver disease [27]; however, all but one of these patients also had known severe renal insufficiency (eGFR of <30 ml/min/1.73 m2) prior to GBCA administration. Thus, hepatic disease in and of itself, in the absence of AKI or severe CKD, is no longer considered an independent risk factor for NSF.

Postulated Mechanism

The exact mechanism of NSF causation is unknown. The most widely held hypothesis is that gadolinium ions dissociate from the chelates in GBCAs in patients with significantly degraded renal function due to the prolonged clearance times of the GBCAs, as well as to other metabolic factors associated with this level of renal disease. The free gadolinium then binds with an anion such as phosphate, and the resulting insoluble precipitate is deposited in various tissues [9,28]. A fibrotic reaction ensues, involving the activation of circulating fibrocytes [28,29]. This hypothesis is supported by the greater presence of gadolinium in affected tissues of NSF patients relative to unaffected tissues [30]. Nevertheless, the detection of gadolinium in tissues is complicated and is not considered a requirement for the diagnosis of NSF.

If the propensity for gadolinium to dissociate from various chelates is eventually proved to contribute to, or be primarily responsible for, the development of NSF, this may help explain, at least in part, why the various GBCAs differ in their apparent NSF safety profile in at-risk patients, since these agents have varying degrees of stability in vitro and in vivo [31].

Assessment of Risk (See Table 1 for the classification of GBCAs)

Group II agents

Based on the most recent scientific and clinical evidence [32-43] the ACR Committee on Drugs and Contrast Media considers the risk of NSF among patients exposed to standard or lower than standard doses of group II GBCAs is sufficiently low or possibly nonexistent such that assessment of renal function with a questionnaire or laboratory testing is optional prior to intravenous administration. As in all instances, group II GBCAs should only be administered if they are deemed necessary by the supervising radiologist, and the lowest dose needed for diagnosis should be used as deemed necessary by the supervising radiologist.[1]

Certain newer FDA-approved agents may be designated as a group II * provisional status based on favorable biochemical profile and available laboratory data. These agents are considered provisional due to a relative lack of in-use clinical performance data and/or incomplete clinical data related to use in higher risk populations. Agents in this category can be treated similar to a group III agent per local practice preference.

[1]The ACR Committee on Drugs and Contrast Media recognizes that as of this writing (4-6-2017), U.S. Food and Drug Administration (FDA) guidelines and drug labeling for GBCA have the same recommendations for each GBCA with respect to assessing renal function prior to GBCA administration. Nevertheless, the committee authoring this Manual has reviewed the evidence and believes that the prevailing weight of clinical evidence on this matter allows less stringent yet safe patient management which should reduce patient cost and inconvenience. This footnote is designed to alert readers that the ACR recommendations differ in case their personal philosophy or institutional policies necessitate adherence to the more restrictive FDA guidelines.

Group I and III agents
The ACR Committee on Drugs and Contrast Media concludes that patients receiving group I GBCAs should be considered at risk of developing NSF if any of the following conditions apply to the patient:

- On dialysis (of any form)
- Severe or end-stage CKD (CKD 4 or 5, eGFR < 30 mL / min/1.73 m2) without dialysis
- AKI [44,45]

There is insufficient real-life data to determine the risk of NSF from administration of group III agents. Thus, it is important to identify patients at risk of developing NSF, as defined above, prior to injection of group I and III GBCAs. The method used to identify such patients may differ for outpatients versus inpatients.

Identifying at-risk outpatients
Outpatients who may be receiving group I or group III agents should be screened for conditions and other factors that may be associated with renal function impairment.

Simply asking patients if they have a problem with their kidneys is not considered an effective screening tool, as this has been shown to fail to detect the majority of patients with chronic kidney disease, even those with eGFR<30 ml/min/1.73 m2 [46].

A more reliable method to identify outpatients who may have renal function impairment is to utilize a panel of questions that includes risk factors for compromised renal function. The following list of risk factors can be used to identify patients who have impaired renal function. This list represents a blend of published data [47,48] and expert opinion; alternative lists may be as or more effective depending on practice patterns:

- History of renal disease, including:
    - Dialysis
    - Kidney transplant
    - Single kidney
    - Kidney surgery
    - History of known cancer involving the kidney(s)
    - History of CKD or prior history of AKI
- History of diabetes mellitus (optional)

Many additional factors may have deleterious effects on renal function, including multiple myeloma, systemic lupus erythematosus, urinary tract infection, and use of some medications (e.g., nonsteroidal anti-inflammatory drugs, diuretics, aminoglycosides, cyclosporine A, amphotericin, and others); however, the ACR Committee on Drugs and Contrast Media currently does not recommend routinely screening for these additional possible risk factors, since the incremental benefit in patient safety from such screening has not been established and is considered to be low by the committee.

Once an outpatient is identified as being at risk for having reduced renal function based on screening, and group I or group III GBCA administration is contemplated, renal function should be assessed by laboratory testing (checking results of prior laboratory tests performed within an acceptable time window, and ordering new laboratory tests only if necessary) and calculation of eGFR. However, if the patient is on dialysis or has known AKI, laboratory testing and calculation of eGFR is not useful or necessary (i.e., eGFR is not accurate in this setting, and these patients would be considered at risk for NSF prior to group I or group III administration regardless of calculated eGFR).

Calculating eGFR
For adults, eGFR calculation is commonly performed using the Modification of Diet in Renal Disease (MDRD) equation or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The four-variable MDRD equation takes into account age, gender, and serum creatinine level. The updated Schwartz equation should be used for children (also see Chapter on Contrast Media in Children).

A number of websites and point-of-service tools are available that can calculate eGFR values in adults and children. For consistency, radiologists may wish to identify which equation(s) are in use in their laboratory facilities.

When eGFR is recommended in outpatients with risk factor(s) for compromised renal function

For those patients identified by screening to have one or more risk factors for compromised renal function and in whom administration of a group I or group III agent is planned, there is no high-level scientific evidence to guide the optimal time interval between eGFR determination and GBCA injection. Nevertheless, the ACR Committee on Drugs and Contrast Media has made recommendations (see Table 2 in this chapter) that take into consideration the need to maintain patient safety while minimizing the burden associated with excessive laboratory testing.

Identifying at-risk inpatients

For all inpatients, an eGFR level should be obtained within 2 days prior to planned administration of a group I or group III GBCA. In addition, ordering health professionals should assess inpatients for the possibility of AKI, as eGFR calculation alone has limited accuracy for the detection of AKI.

General Recommendations for Imaging Patients at Risk for NSF

Group II agents are strongly preferred in patients at risk for NSF. Given the very low, if any, risk of NSF development with group II agents, regardless of renal function or dialysis status, informed consent is not recommended prior to GBCA group II injection, but deference is made to local practice preferences.

If use of a group I or group III agent is being considered in a patient with a risk of NSF, the potential benefit of a GBCA-enhanced MRI exam is felt to outweigh the risk of NSF in an individual patient, and there is no suitable alternative, the referring physician and patient should be informed of the risks of GBCA administration, and both should agree with the decision to proceed with GBCA injection. Group I agents (see Table 1), the GBCAs that have been most often associated with NSF, have been contraindicated by the FDA for use in these patients [26].

The lowest dose of GBCA required to obtain the needed clinical information should be used in at-risk patients, and it should generally not exceed the recommended single dose. (Note: the lowest diagnostic dose has not been thoroughly investigated for many indications; be careful not to minimize dose below diagnostic quality).

Exceptions to the above recommendations may be made at the discretion of the supervising radiologist, such as in the rare instance of an acute, life-threatening condition, and after consultation with the referring health care professional. Documentation of the rationale for the exception is recommended.

Limiting use of GBCAs in at-risk patients has already had a dramatic effect in reducing or even eliminating the number of new cases of NSF [49]. It must be remembered that the risks of administering a GBCA to a high-risk patient must always be balanced against the often substantial risks of not performing a needed contrast-enhanced imaging procedure.

Multiple doses of GBCA

In unusual circumstances, it may be necessary to administer multiple doses of a GBCA within a relatively short time frame. Examples include a rapid change in patient condition for which an additional enhanced MR exam may be of benefit or when the initial MR exam indicates an acute need for a more sophisticated enhanced MR exam. In patients not at risk of NSF, there is no contraindication if the examination(s) are determined to be necessary. In patients at risk of NSF, the committee recommends the use of group II agent(s).

Additional Specific Recommendations for Specific Groups of Patients

Patients with end-stage renal disease on chronic dialysis

If a contrast-enhanced cross-sectional imaging study is required in an anuric patient with no residual renal function, it would be reasonable to consider administering iodinated contrast media and performing a CT rather than an MRI, assuming the anticipated diagnostic yield is similar.

If a contrast-enhanced MR examination is to be performed in a patient with end-stage renal disease on chronic dialysis, injection of group I agents (see Table 1) is contraindicated, and the committee recommends the use of a group II agent. When using a group II agent, the risk of NSF is extremely low. The ACR Committee on Drugs and Contrast Media and National Kidney Foundation also recommend that elective GBCA-enhanced MRI examinations be performed as closely before a regularly scheduled hemodialysis as is possible, as dialysis can improve GBCM clearance. However, due to associated increased risk of catheter placement and infection,

the possibility of worsening kidney function in patients with AKI and CKD, the perceived very low risk of NSF from group II and probably III GBCM agents, dialysis should not be initiated or altered (i.e. daily dialysis or multiple per-day dialysis sessions) [42, 50].

Peritoneal dialysis may provide less NSF risk reduction compared to hemodialysis, but this has not been adequately studied.

Patients with CKD 4or5 (eGFR<30mL/min/1.73m2) not on chronic dialysis

Group I agents are contraindicated in this setting. If a GBCA-enhanced MRI study is to be performed, a group II agent should be used.

Patients with CKD 3 (eGFR 30 to 59 mL / min/1.73 m2)

NSF developing after GBCA administration to patients with stable eGFR 30-59 ml/min/1.73 m2 is exceedingly rare. No special precautions are necessary in this group.

Patients with CKD 1or2 (eGFR60to119mlmin/1.73m2)

There is no evidence that patients in these groups are at increased risk of developing NSF. Any GBCA can be administered safely to these patients.

Patients with acute kidney injury (AKI)

Patients with AKI who have been exposed to GBCA are at risk for developing NSF. Due to the temporal lag between eGFR (which is calculated using serum creatinine values) and actual glomerular filtration rates, it is not possible to determine whether a given patient has AKI based on a single eGFR determination. Accordingly, group I agents should be avoided in patients with known or suspected AKI. If GBCA is to be administered in this setting, a group II agent is preferred.

Children

A systematic search of databases published in 2014 [51] found only 23 reported pediatric cases of NSF, and no cases in children under the age of 6 years. Nevertheless, there is not enough data to demonstrate that NSF is less likely to occur in children than in adults with similarly significant renal disease. Therefore, it is prudent to follow the same guidelines for adult and pediatric patients as described in the remainder of this document. However, eGFR values in certain premature infants and neonates may be <30 ml/min/1.73 m2 simply due to immature renal function (and not due to pathologic renal impairment). In these individuals, the ACR Committee on Drugs and Contrast Media believes that caution should still be used when administering GBCAs, and group II agents should be used in this setting if feasible.

Caveat

Information on NSF and its relationship to GBCA administration continues to evolve, and the summary included here represents only the most recent opinions of the ACR Committee on Drugs and Contrast Media. If additional information becomes available, our understanding of causative events leading to NSF and recommendations for preventing it may change, leading to further revisions of this document.

TABLE 1. ACR Manual Classification of Gadolinium-Based Agents Relative to Nephrogenic Systemic Fibrosis

Group I: Agents associated with the greatest number of NSF cases:
• Gadodiamide (Omniscan® – GE Healthcare)
• Gadopentetate dimeglumine (Magnevist® – Bayer HealthCare Pharmaceuticals)
• Gadoversetamide (OptiMARK® – Guerbet)
Group II: Agents associated with few, if any, unconfounded cases of NSF:
• Gadobenate dimeglumine (MultiHance® – Bracco Diagnostics)
• Gadobutrol (Gadavist® – Bayer HealthCare Pharmaceuticals; Gadovist in many countries)
• Gadoteric acid (Dotarem® – Guerbet, Clariscan – GE Healthcare)
• Gadoteridol (ProHance® – Bracco Diagnostics)
• Gadopiclenol* (Elucirem® – Guerbet, Vueway® – Bracco Diagnostics)
• Gadoxetate disodium (Eovist – Bayer HealthCare Pharmaceuticals; Primovist in many countries)
Group III: Agents for which data remains limited regarding NSF risk, but for which few, if any unconfounded cases of NSF have been reported:
• No agents currently in this category (as of April 2024)

* Gadopiclenol demonstrates kinetic stability and long dissociation half-life that are comparable to other Group II macrocyclic agents. Based on the available evidence [52-55], the ACR Committee on Drugs and Contrast Media considers the risk of NSF among patients exposed to a standard or lower than standard dose of gadopiclenol to theoretically be sufficiently low or possibly non-existent such that it has been classified as a Group II* agent (provisional status).

However, in vivo long-term human data for potential NSF risk associated with gadopiclenol in patients with severe or end-stage kidney disease (eGFR < 30mL/min/1.73m^2) is not currentl (January, 2025) as well-established as other group II agents. It is at the discretion of local practices whether to treat this as a group II or group III agent.

TABLE 2. eGFR Evaluation of Renal Function to Group I or Group III GBCA Administration

Patient Condition	eGFR Requirement
Patient on dialysis (any type)	No eGFR required — eGFR is not helpful in this situation.
Patient with AKI	No eGFR required — eGFR is not helpful in this situation.
Inpatient	Obtain eGFR within 2 days of the MRI study.
Outpatient/ED with no prior eGFR at the time the MR exam is scheduled	If NO risk factors [1], no eGFR required. WITH risk factors [1], obtain eGFR.*
Outpatient/ED with most recent prior eGFR of 45 or above	If NO risk factor [1] and eGFR of 60 or above, no new eGFR is required. WITH risk factors [1] and/or eGFR 45-59, if most recent prior eGFR is within 6 weeks of the MRI, no new eGFR is needed; otherwise obtain a new eGFR.**
Outpatient/ED with most recent prior eGFR of 44 or below	Obtain eGFR within 2 days of the MRI study

** If the new eGFR is to be obtained expressly for evaluation of suitability for administration of GBCA, obtaining the eGFR within 2 days of the MRI exam would avoid the situation where the new eGFR might be less than 45 and require another eGFR within two days of the MRI exam, as per the last line in the table.

[1] **Risk Factors:**

1. History of renal disease, including:
    a. Prior dialysis
    b. Renal transplant
    c. Single kidney
    d. Kidney surgery
    e. Renal cancer
2. Diabetes mellitus (optional)

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July 2021: Updated to reflect the ACR-NKF Consensus Statement
15 May 2017: Major revisions

ACR Contrast Manual Update January 2025 : Clarification on gadolinium-based contrast agent groups:

In early 2024, two additional agents (gadoxetic acid and gadopiclenol) were classified as Group II gadolinium-based contrast agents in the ACR Manual on Contrast Media. Following feedback from the radiology community, the committee has revisited this decision. The committee would like to take this opportunity to share clarity on the decision-making process of gadolinium-based contrast agent classification.

Group II gadolinium-based contrast agents are defined as, "agents associated with few, if any, unconfounded cases of nephrogenic systemic fibrosis (NSF)". Restrictions and cautions concerning use of these agents have progressively been reduced over time based on favorable laboratory data, longitudinal clinical in vivo data with respect to NSF risk, and interdisciplinary practice consensus [1-3].

Gadopiclenol (Elucirem ® - Guerbet, Vueway ®- Bracco Diagnostics) is a newer agent, initially classified as a Group II * by the committee in 2024. A common question has arisen regarding the meaning of this *, and how this might be applied to clinical practice.

The * designation is now described as a provisional status, reflecting the lack of in vivo clinical data related to gadopiclenol and specifically the in vivo risk associated with NSF when administered to patients with severe and end stage CKD (CKD 4 and 5 without or with dialysis [eGFR < 30mL/min/1.73m^2]). Traditional group II agents (gadobenate dimeglumine, gadobutrol, gadoteric acid, gadoteridol), have a pooled upper bound risk of NSF from group II GBCA administration in stage 4 or 5 CKD likely less than 0.07%; upper bound risk stratification by individual agents varies between 0.12%-1.59% based on differences in sample sizes available at the time of meta-analysis [1]. Currently (January 2025) the published risk for gadopiclenol in patients with CKD 4 and 5 without or with dialysis is limited [4].

Additionally, traditional group II agents have been used in clinical practice for at least a decade, lending a degree of comfort based on established clinical track records. For these collective reasons, while the committee feels biochemically and theoretically gadopiclenol should behave similar to group II agents, the difference in real world data warrant a slightly different classification (Group II * - provisional status), until a time when the published literature and time-in-practice prove sufficient to classify this similarly to other Group II agents. As detailed within the 2025 contrast manual update:

*Certain newer FDA-approved agents may be designated as a group II * provisional status based on favorable biochemical profile and available laboratory data. These agents are considered provisional due to a relative lack of in-use clinical performance data and/or incomplete clinical data related to use in higher risk populations. Agents in this category can be treated similar to a group II agent or a group III agent per local practice preference.*

Gadoxetic acid (Eovist – Bayer HealthCare Pharmaceuticals; Primovist in many countries) has been classified previously as a group III agent but was changed to a group II classification in 2024. This is based on a longer clinical in use period and favorable data related to risk for NSF in patients with CKD 4 and 5 without or with dialysis [4]. The data used to make this determination was based on a combination of both published data and additional clinical administrations in higher risk patients provided to the committee. Based on published and clinical data available to the committee, the risk of NSF is felt to be within a safe upper limit margin, similar to other group II agents. Since its introduction in 2010, there have been over 10 million estimated world-wide gadoxetic acid exposures now compared to the 800,000 at the time of the initial classification. Reclassification of gadoxetic acid from a group III agent to a group II agent reflects integration of new data over time.

Gadolinium-based contrast agent groupings are designed to be fluid and evolve with new information and time. The changes made to gadolinium-based contrast agent classifications within the past two years reflect these changes.

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ULTRASOUND CONTRAST MEDIA

Contrast agents available for ultrasound, consisting of microbubbles or microspheres, allow for transient improvement in ultrasound contrast resolution, increased conspicuity of vascularity, and detection of blood flow.

With dedicated ultrasound software, these contrast agents, composed of an outer phospholipid or protein wall and a central inert echogenic gas, enhance the acoustic ultrasound signal from blood. Such contrast agents can be safely injected intravenously through a peripheral or central line, or instilled into hollow structures, such as the urinary bladder.

Approved Agents and Uses

There are three ultrasound contrast agents with FDA approval available in the United States [1-3]:

1. Definity® (perflutren lipid microspheres)
2. Lumason® (sulfur hexafluoride lipid-type A microspheres; also known as SonoVue®)
3. Optison® (perflutren protein-type A)

At the time of this publication, Definity, Lumason, and Optison are approved for intravenous administration in adults undergoing echocardiography to improve visualization of the left ventricular cavity and its endocardial borders. Lumason is also approved for liver imaging in both children and adults, and for imaging of the pediatric urinary tract for evaluation of suspected or known vesicoureteral reflux (voiding ultrasonography) [4-7].

In addition to these approved indications, ultrasound contrast agents also have been used off-label to assess for the presence and dynamics of blood flow in tumors [8], to differentiate benign cysts from solid masses in the kidney [9], to detect solid organ injury in the setting of trauma [10-12], to detect and characterize endoleaks after abdominal aortic aneurysm repair [13,14], to detect bowel wall inflammation in Crohn's disease [15-18], to discriminate abscess from phlegmon [19], and to guide and monitor ultrasound- guided interventions and ablative therapies [20]. Some of these off-label indications are in clinical use, while others remain investigatory.

Contrast Agent Administration and Ultrasound Imaging

As detailed in the package labeling, these contrast agents are approved for intravenous slow infusion and/or bolus injection. After reconstitution, they are typically hand injected through a moderate- or large- bore peripheral intravenous catheter followed by a saline flush. The maximum volume of contrast material that can be administered per injection and per imaging session differs by contrast agent.

Dedicated ultrasound software is available from most ultrasound vendors. Such software functions to suppress the background tissue signal and maximize the signal from the contrast agent due to a combination of soundwave reflection and microbubble resonance.

The likelihood of bubble rupture can and should be minimized by avoiding small intravenous catheters and using a low mechanical index during imaging. The safety of high mechanical index imaging (>0.8) has not been well studied and can cause microbubble cavitation or rupture.

Pharmacodynamics and Pharmacokinetics

Intravascularly administered ultrasound contrast agents generally remain in the blood pool because they are too large to enter the interstitium (mean microbubble diameter: Definity [1.1-3.3 μm], Lumason [1.5-2.5 μm], Optison [3.0-4.5 μm). This property differs from most CT and MRI contrast media.

Real-time assessment can be obtained over an approximately 10-minute period. After this time, the microbubbles spontaneously rupture and dissolve, releasing an inert gas that is mostly eliminated through the lungs.

Safety Profile

Ultrasound contrast agents are safe, with an adverse event rate similar to or less than that of modern CT and MRI contrast agents. A large retrospective investigation of more than 78,000 doses of Definity and Optison found a severe reaction rate of 0.01% (n=8); half of these reactions (4 of 8) were considered anaphylactoid and there were no deaths [21]. Another large retrospective study evaluating the use of SonoVue in 23,188 subjects documented 29 adverse events, with only two considered serious [22]. The majority of adverse events are mild and likely physiologic in etiology, including symptoms such as headache, a sensation of warmth or flushing, nausea, and altered taste. The majority of severe reactions occur within 30 minutes of administration.

A review performed by the Society for Pediatric Radiology in conjunction with the International Contrast Ultrasound Society concluded that noncardiac applications of contrast-enhanced ultrasound—including intravenous and intravesical administration—are safe, with side effects uncommon and typically minor [23]. A study [24] showed that that the intravenous injection of microspheres is also well-tolerated in the pediatric population, with only minor side effects.

Ultrasound contrast agents are contraindicated for intra-arterial injection and in patients with previous hypersensitivity reaction to microspheres. Old labeling included a contraindication for patients with a known or suspected right-to-left or bidirectional shunt, but that labeling has been removed from the package inserts by the FDA, and it is no longer considered a contraindication.

The risk for a serious cardiopulmonary reaction may be increased in patients who also have an unstable cardiopulmonary condition (e.g., acute myocardial infarction, unstable congestive heart failure). However, a study [25] of 1513 hospitalized patients with pulmonary hypertension showed that adverse reactions to Definity were very rare (0.002%).

Ultrasound contrast agents have no known renal toxicity in approved doses. There are no adequate and well- controlled studies of these agents in pregnant women. While there are no known risks, these agents should only be used when needed and the benefits outweigh any potential small risks to the fetus. As the effects of these contrast agents on human breast milk is currently unknown, temporary (~24 hours) pumping and discarding of milk may be considered. Optison contains human albumin, a derivative of human blood, and may confer a theoretical risk of viral or prion infection; additionally, it may be contraindicated in patients with religious or ethical objections to the intravascular receipt of human blood products.

As with all contrast agents, appropriate resuscitation equipment and trained personnel should be readily available at the time of injection in the event that an adverse reaction occurs.

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TREATMENT OF CONTRAST REACTIONS

Optimal treatment of contrast reactions starts with a well-designed plan and a properly trained staff. In addition to basic life support training, on-site personnel should be trained in the rapid recognition, assessment, diagnosis, and treatment of contrast reactions.

In evaluating a patient for a potential contrast reaction, five immediate assessments should be made if clinically feasible:

- What is the patient's general appearance?
- Can the patient speak? How does their voice sound?
- What is the quality of the patient's breathing?
- What is the patient's pulse?
- What is the patient's blood pressure?

The patient's level of consciousness, appearance of their skin, quality of phonation, lung auscultation, blood pressure, and heart rate assessment will allow the responding provider to quickly determine the severity of a reaction and properly diagnose it. Once diagnosed, effective treatment can be rapidly and effectively administered (see Tables 1, 4, and 3). Staff should be aware of how to activate the emergency response system to elevate the level of care if needed—for example, calling an emergency response phone number (e.g., 911 for emergency medical personnel assistance in an outpatient medical center setting).

Mild immediate reactions (both allergic-like and physiologic) typically do not require medical treatment. However, a mild reaction may evolve into a moderate or severe reaction. Vital signs should be obtained to detect hypotension that may be clinically silent while the patient is supine. Any patient with a mild allergic-like reaction should be observed for a minimum of 20 to 30 minutes to ensure clinical stability or recovery. Treatment with an antihistamine may be instituted for mild symptomatic allergic-like urticarial reactions, but often is not necessary.

Most moderate and all severe reactions will require prompt and aggressive treatment to reduce the likelihood of an adverse outcome. Treatment algorithms for adults and children are provided in Tables 1, 2, and 3.

Ongoing quality assurance and quality improvement programs with in-service training and review sessions are helpful in ensuring that responses to contrast reactions are prompt and appropriate. This includes training of onsite health care providers in resuscitation techniques such as basic life support.

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ADMINISTRATION OF CONTRAST MEDIA TO PREGNANT OR POTENTIALLY PREGNANT PATIENTS

Studies of low-molecular weight water-soluble extracellular substances such as iodinated and gadolinium- based contrast media in pregnancy have been limited, and their effects on the human embryo or fetus are incompletely understood. Iodinated contrast media have been shown to cross the human placenta and enter the fetus in measurable quantities [1,2]. A standard gadolinium-based contrast medium has been shown to cross the placenta in primates and appear within the fetal bladder within 11 minutes after intravenous (IV) administration [3]. It is likely that all iodinated and gadolinium-based contrast media behave in a similar fashion and cross the blood-placental barrier and into the fetus.

After entering the fetal blood stream, these agents will be excreted via the urine into the amniotic fluid and be subsequently swallowed by the fetus [4]. It is then possible that a small amount will be absorbed from the gut of the fetus, with the additional swallowed gadolinium-based contrast agents eliminated back into the amniotic fluid.

In a study in primates, placental enhancement could be detected up to 2 hours following IV administration of gadopentetate dimeglumine. When gadopentetate dimeglumine was injected directly into the amniotic cavity, it was still conspicuous at 1 hour after administration [3]. There are no data available to assess the rate of clearance of contrast media from the amniotic fluid.

Iodinated Low-Osmolality Contrast Media

Mutagenic effect of low-osmolality contrast media

Diagnostic iodinated contrast media have been shown to cross the human placenta and enter the fetus when given in usual clinical doses. In-vivo tests in animals have shown no evidence of either mutagenic or teratogenic effects with low-osmolality contrast media (LOCM). No well-controlled studies of the teratogenic effects of these media in pregnant women have been performed.

Effect of iodinated contrast media on fetal thyroid function

The fetal thyroid plays an important role in the development of the central nervous system. There have been rare reports of hypothyroidism developing in the newborn infant after the administration of an iodinated contrast medium during pregnancy; however, this occurred only following amniofetography using a fat- soluble iodinated contrast medium, which was performed in the past to detect congenital malformations.

Intravenous administration of iodinated contrast media does not affect short-term neonatal thyroid stimulating hormone (TSH), likely because the overall amount of excess iodide in the fetal circulation is small and transient. However, the long-term effects are unknown. To date, there has been no documented case of neonatal hypothyroidism from the maternal intravascular injection of water-soluble iodinated contrast agents [5,6]. Given the current available data and routine evaluation of all newborns for congenital hypothyroidism by measurement of TSH levels at the time of their birth, no extra attention is felt to be necessary [7-9].

Other adverse effects

No other adverse effects have been reported in the fetus or neonate following administration of LOCM. However, information in this area is sparse.

Recommendations prior to performing imaging studies requiring iodinated contrast material administration

Given that there are no available data to suggest any potential harm to the fetus from exposure to iodinated contrast medium via maternal IV or intra-arterial injection, we do not recommend routine screening for pregnancy prior to contrast media use. This recommendation is also supported by the FDA classifying of most iodinated contrast agents as category B medications.

Screening for potential pregnancy in women of child-bearing age receiving radiation to the pelvis, which is discussed separately, is therefore not affected by the use of iodinated contrast agents (See the ACR–SPR Practice Parameter for Imaging Pregnant or Potentially Pregnant Adolescents and Women With Ionizing Radiation). We do not recommend withholding the use of iodinated contrast agents in pregnant or potentially pregnant patients when it is needed for diagnostic purposes.

Gadolinium-Based Contrast Agents

Mutagenic effect of gadolinium-based contrast agents

To date, there have been no known adverse effects to human fetuses reported when clinically recommended dosages of gadolinium-based contrast agents (GBCAs) have been given to pregnant women. A single cohort study of 26 women exposed to gadolinium chelates during the fi trimester of pregnancy showed no evidence of teratogenesis or mutagenesis in their progeny [10]. However, no well-controlled studies of the teratogenic effects of these media in pregnant women have been performed. In a retrospective review [11] of a Canadian provincial database of births, the risk of a congenital anomaly did not differ between patients exposed to GBCAs at any time during pregnancy and those patients who did not undergo MRI.

Risk of nephrogenic systemic fibrosis

There are no known cases of nephrogenic systemic fibrosis (NSF) linked to the use of GBCAs in pregnant patients. However, gadolinium chelates may accumulate in the amniotic fluid Therefore, there is the potential for the dissociation of the toxic free gadolinium ion, conferring a potential risk for the development of NSF in the child or mother.

In a retrospective review [11] of a Canadian provincial database of births, exposure to GBCAs at any time during pregnancy was associated with an increased risk in the child of a broad set of rheumatological, inflammatory, or infiltrative conditions. With further analysis, only first-trimester GBCA exposure showed this association. However, the study had some substantial limitations. The control group was patients who did not undergo MRI during pregnancy, rather than patients who underwent MRI without GBCA. Also, the percentage of patients experiencing the condition was 31% in the GBCA exposed group and 27% in the unexposed group (adjusted hazard ratio 1.36), which was statistically significantly different given the large numbers in the unexposed group, but is a surprisingly large baseline percentage in the unexposed group. The number of cases of a connective tissue or skin disease resembling NSF was too small for statistical analysis. Whether any of the children were exposed after birth to GBCA was not investigated.

Risk of still birth or neonatal death

In a retrospective review [11] of a Canadian provincial database of births, exposure to GBCAs at any time during pregnancy was associated with an increased risk of stillbirth or neonatal death, although the number of deaths in the exposed group was small. In addition, the control group was patients who did not undergo MRI during pregnancy, rather than patients who underwent MRI without GBCA.

Recommendations for the use of GBCA-enhanced MRI examinations in pregnant patients

Because it is unclear how GBCAs will affect the fetus, these agents should be administered with caution to pregnant or potentially pregnant patients. GBCAs should only be used if their usage is considered critical and the potential benefits justify the potential unknown risk to the fetus. If a GBCA is to be used in a pregnant patient, one of the agents believed to be at low risk for the development of NSF [12] should be used at the lowest possible dose to achieve diagnostic results. In pregnant patients with severely impaired renal function, the same precautions should be observed as in non-pregnant patients. The ACR Committee on Drugs and Contrast Media recommends the following concerning the performance of contrast- enhanced MRI examinations in pregnant patients:

Each case should be reviewed carefully by members of the clinical and radiology service groups, and a GBCA should be administered only when there is a potential significant benefit to the patient or fetus that outweighs the possible but unknown risk of fetal exposure to free gadolinium ions.

A. The radiologist should confer with the referring physician and document the following in the radiology report or the patient's medical record:

    1. That information requested from the MRI study cannot be acquired without the use of IV contrast or by using other imaging modalities.
    2. That the information needed affects the care of the patient and/or fetus during the pregnancy.
    3. That the referring physician is of the opinion that it is not prudent to wait to obtain this information until after the patient is no longer pregnant.

B. It is recommended that informed consent be obtained from the patient after discussion with the referring physician.

Premedication of pregnant patients (with prior allergic-like reactions to iodinated or gadolinium-based contrast media)

Diphenhydramine and corticosteroids (most commonly prednisone and methylprednisolone) are commonly used for prophylaxis in patients at risk for allergic-like contrast reactions to contrast media. Diphenhydramine is classified as FDA category B. (FDA category B: Animal reproductive studies have failed to demonstrate a risk to the fetus, and there are no adequate well-controlled studies in pregnant women.) Prednisone (FDA category C) and dexamethasone (FDA category C) traverse the placenta; however, most of these agents are metabolized within the placenta before reaching the fetus and therefore are not associated with teratogenicity in humans. (FDA category C: Animal reproductive studies have shown an adverse effect on fetus, and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.) However, sporadic cases of fetal adrenal suppression have been reported. Methylprednisolone is also classified as a category C drug and carries a small risk to the fetus for the development of a cleft lip if used before 10 weeks of gestation [13,14].

Recommendations for the use of corticosteroid premedication in pregnant patients

Expert opinion indicates that the use of steroids in pregnancy is generally safe [15,16], although common specific regimens for premedication prior to contrast media administration have not been tested. Severe anaphylaxis in a pregnant female represents an even greater risk to the fetus than to the mother herself [17]. Given this information, we recommend that otherwise-indicated premedication to reduce the risk of contrast media reaction not be withheld because the patient is pregnant and a standard PO or IV regimen be employed (see Chapter on Patient Selection and Preparation Strategies). Both referring clinicians and their pregnant patients receiving premedication prior to contrast media administration should indicate that they understand the potential risks and benefits of the medications being used, as well as alternative diagnostic options [18].

Management of contrast reactions in pregnant patients

The management of contrast reactions in pregnant patients is generally the same as that of contrast reactions in non- pregnant adults [19], with minor additions.

For the treatment of hypotension in patients with an obviously gravid uterus, the patient may be placed in the left lateral decubitus position or positioned supine with a leftward tilt using a wedge. If cardiac compressions are required, these are usually best performed in the supine position; in this situation, manual displacement of the uterus upward and to the left is recommended (if there are sufficient personnel to perform this maneuver). These tactics reduce the compression of the inferior vena cava by the gravid uterus which may otherwise compromise venous return to the heart [19].

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Breast Feeding Recommendations with Associated Strength of Evidence

Below is a summary of the recommendations related to breast feeding and the associated strength of evidence for those recommendations using the ACR Appropriateness Criteria® Methodology.

Question 1. Should breast feeding be routinely ceased for 24 hours after maternal IV or IA exposure to iodinated contrast material?

Recommendation: Because of the very small percentage of iodinated contrast medium that is excreted into the breast milk and absorbed by the infant's gut (under 0.01%), the available data suggest that it is safe for the mother and infant to continue breast-feeding after receiving such an agent. Therefore, stopping breastfeeding for 24 hours after maternal IV or IA exposure to iodinated contrast material is not required. It is recommended patients make an informed decision on managing breastmilk after exposure to iodinated contrast material.

Strength of Evidence: Limited

Reference	Name	Study Quality
[1]	Webb 2005	4
[2]	Trembley 2012	4
[3]	Wang 2012	4
[4]	Nielsen 1987	4

Question 2. Should breast feeding be routinely ceased for 24 hours after maternal IV or IA exposure to gadolinium-based contrast agents?

Recommendation: Because of the very small percentage of gadolinium-based contrast medium that is excreted into the breast milk and absorbed by the infant's gut (estimated to be under 0.0004%), the available data suggest that it is safe for the mother and infant to continue breast-feeding after receiving such an agent [5]. Therefore, stopping breastfeeding for 24 hours after maternal IV or IA exposure to gadolinium based contrast material is not required. It is recommended patients make an informed decision on managing breastmilk after exposure to gadolinium based contrast material.

Strength of Evidence: Limited

Reference	Name	Study Quality
[6]	Rofsky 1993	4
[5]	Kubik-Huch 2000	3
[7]	Lin 2007	4

Question 3. Should routine thyroid function testing be performed in infants exposed to iodinated contrast material through maternal breast milk?

Recommendation: No strong data exists in the literature that the amount of iodinated contrast material absorbed systemically in an infant from maternal breast milk following a conventional contrast-enhanced CT is enough to place the infant at risk for hypothyroidism. Therefore, routine thyroid function testing is not recommended in this clinical setting.

Strength of Evidence: Limited

Reference	Name	Study Quality
[8]	Themelin 2019	4

ADMINISTRATION OF CONTRAST MEDIA TO PATIENTS WHO ARE BREAST-FEEDING

Imaging studies requiring either iodinated or gadolinium-based contrast media are occasionally required in patients who are breast feeding. Both the patient and the patient's physician may have concerns regarding potential toxicity to the infant from contrast media that is excreted into the breast milk.

The literature on the excretion into breast milk of iodinated and gadolinium-based contrast media and the gastrointestinal absorption of these agents from breast milk is very limited; however, several studies have shown that the expected dose of contrast medium absorbed by an infant from ingested breast milk is extremely low.

Iodinated X-ray Contrast Media (Ionic and Nonionic)
Background

The plasma half-life of intravenously administered iodinated contrast medium is approximately 2 hours, with nearly 100% of the media cleared from the bloodstream in patients with normal renal function within 24 hours. Because of its low lipid solubility, less than 1% of the administered maternal dose of iodinated contrast medium is excreted into the breast milk in the first 24 hours with one paper showing concentrations of iohexol (350 mg I/ml) of approximately 0.5% of weight-adjusted maternal dose in the first 24 hours after exposure [1,4,9]. In addition, less than 1% of the contrast medium ingested by the infant is absorbed from its gastrointestinal tract [2]. Therefore, the expected systemic dose absorbed by the infant from the breast milk is less than 0.01% of the intravascular dose given to the mother. This amount represents less than 1% of the recommended dose for an infant being prescribed iodinated contrast material intravenously related to an imaging study (usually 1.5 to 2 mL/kg). The potential risks to the infant from breast milk include allergic sensitization or reaction, which are theoretical concerns but have not been reported, and adverse effects on the infant's thyroid. The likelihood of either direct toxic or allergic-like manifestations resulting from ingested iodinated contrast material in the infant is extremely low. There is no high-quality literature on thyroid dysfunction in infants related to contrast media exposure through breast milk with a single case report inferring transient neonatal hypothyroidism induced by breast milk containing iodinated contrast media in a premature infant (despite withholding breast milk for 24 hours post exposure) [8]. As with other medications in milk, the taste of the milk may be altered if it contains contrast medium [1,2,4,9].

For further information on ACR recommendations / guidelines on thyroid testing after direct iodinated contrast exposure in infants please see the ACR Statement on Use of Iodinated Contrast Material for Medical Imaging in Young Children and Need for Thyroid Monitoring and the Contrast Media in Children *Chapter.*

Recommendation

Because of the very small percentage of iodinated contrast medium that is excreted into the breast milk and absorbed by the infant's gut, the available data suggest that it is safe for the mother and infant to continue breast-feeding after receiving such an agent. Ultimately, however, an informed decision to temporarily stop breast-feeding should be left up to the mother after these facts are communicated. If the mother remains concerned about any potential ill effects to the infant, she may abstain from breast-feeding from the time of contrast administration for a period of 12 to 24 hours. In this situation, the mother should be told to express and discard breast milk from both breasts during that period. In anticipation of this, she may wish to use a breast pump to obtain milk before the contrast-enhanced study to feed the infant during the 24-hour period following the examination. There is little value to stop breast-feeding beyond 24 hours.

While data remains limited, we do not recommend routine thyroid monitoring in infants (premature or term) after exposure to iodinated contrast material through ingested breast milk.

Gadolinium-Based Contrast Agents
Background

Like iodinated contrast media, gadolinium-based contrast media have a plasma half-life of approximately 2 hours and are nearly completely cleared from the bloodstream in patients with normal renal function within 24 hours. Also similar to iodinated contrast media, gadolinium-based contrast media are excreted into the breast milk. It is likely that the overwhelming bulk of gadolinium excreted in the breast milk is in a stable and chelated form [5].

Less than 0.04% of the intravascular dose given to the mother is excreted into the breast milk in the first 24 hours [3,5,6]. Because less than 1% of the contrast medium ingested by the infant is absorbed from its gastrointestinal tract [5,7], the expected systemic dose absorbed by the infant from the breast milk is less than 0.0004% of the intravascular dose given to the mother. This ingested amount is far less than the permissible dose for intravenous use in neonates. The likelihood of an adverse effect from such a minute fraction of gadolinium chelate absorbed from breast milk is remote [1]). However, the potential risks to the infant include direct toxicity (including toxicity from free gadolinium, because it is unknown how much, if any, of the gadolinium in breast milk is in the unchelated form) and allergic sensitization or reaction. These are theoretical concerns but none of these complications have been reported [6]. As in the case with iodinated contrast medium, the taste of the milk may be altered if it contains a gadolinium-based contrast medium [1].

Recommendation

Because of the very small percentage of gadolinium-based contrast medium that is excreted into the breast milk and absorbed by the infant's gut, the available data suggest that it is safe for the mother and infant to continue breast-feeding after receiving such an agent [5].

Ultimately, an informed decision to temporarily stop breast-feeding should be left up to the mother after these facts are communicated as survey data suggests that patient preference and radiologist's opinion may sometimes differ [10]. If the mother remains concerned about any potential ill effects to the infant, she may abstain from breast-feeding from the time of contrast administration for a period of 12 to 24 hours. In this situation, the mother should be told to express and discard breast milk from both breasts after contrast administration until breast feeding resumes. In anticipation of this, she may wish to use a breast pump to obtain milk before the contrast-enhanced study to feed the infant during the 24-hour period following the examination. There is little value to stop breast feeding beyond 24 hours, by which time the contrast media is nearly completely cleared from the mother's bloodstream.

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Table 1: CATEGORIES OF ACUTE REACTIONS

The following describes a classification system for acute adverse reactions to iodinated and gadolinium- containing contrast media. Acute adverse reactions can be either allergic-like or physiologic. Allergic-like reactions have clinical manifestations similar to allergic reactions. They are termed "allergic-like" rather than just "allergic" because they are often idiosyncratic and may differ immunologically from true allergies despite their similar clinical presentations. A history of prior allergic-like reaction may be an indication for corticosteroid premedication prior to future contrast-enhanced studies that utilize a similar contrast material. Physiologic reactions are not allergic-like and represent a physiologic response to the contrast material. A history of a prior physiologic reaction is not an indication for corticosteroid premedication.

Assessment of reaction severity is somewhat subjective, and it is difficult to succinctly describe all possible degrees of reaction severity. Sound clinical judgment should be used to determine when and how aggressively an acute reaction should be treated. However, many mild reactions resolve during a period of observation without treatment.

Acute contrast reaction management and delayed allergic-like and non-allergic (e.g., CIN, NSF) adverse events to contrast media, are described elsewhere in this Manual.

Mild

Signs and symptoms are self-limited without evidence of progression. Mild reactions include:

Allergic-like	**Physiologic**
Limited urticaria / pruritis	Limited nausea / vomiting limited
Cutaneous Edema	Transient flushing / warmth / chills
Limited "itchy"/"scratchy" throat	Headache / dizziness / anxiety / altered taste
Nasal congestion	Mild hypertension
Sneezing / conjunctivitis / rhinorrhea	Vasovagal reaction that resolves spontaneously

Moderate

Signs and symptoms are more pronounced and commonly require medical management. Some of these reactions have the potential to become severe if not treated. Moderate reactions include:

Allergic-like	**Physiologic**
Diffuse urticaria / pruritis	Protracted nausea / vomiting
Diffuse erythema, stable vital signs	Hypertensive urgency
Facial edema without dyspnea	Isolated chest pain
Throat tightness or hoarseness without dyspnea	Vasovagal reaction that requires and is responsive to treatment
Wheezing / bronchospasm, mild or no hypoxia	

Severe

Signs and symptoms are often life-threatening and can result in permanent morbidity or death if not managed appropriately. Cardiopulmonary arrest is a nonspecific end-stage result that can be caused by a variety of the following severe reactions, both allergic-like and physiologic. If it is unclear what etiology caused the cardiopulmonary arrest, it may be judicious to assume that the reaction is/was an allergic-like one.

Pulmonary edema is a rare severe reaction that can occur in patients with tenuous cardiac reserve (cardiogenic pulmonary edema) or in patients with normal cardiac function (noncardiogenic pulmonary edema). Noncardiogenic pulmonary edema can be allergic-like or physiologic; if the etiology is unclear, it may be judicious to assume that the reaction is/was an allergic-like one.

Severe reactions include:

Allergic-like	**Physiologic**
Diffuse edema, or facial edema with dyspnea	Vasovagal reaction resistant to treatment
Diffuse erythema with hypotension	Arrhythmia
Laryngeal edema with stridor and/or hypoxia	Convulsions, seizures
Wheezing / bronchospasm, significant hypoxia	Hypertensive emergency
Anaphylactic shock (hypotension + tachycardia)	

Table 2: TREATMENT OF ACUTE REACTIONS TO CONTRAST MEDIA IN CHILDREN

Last updated: October 2020

HIVES (Urticaria)

	Treatment	Dosing
General comment: observe until hives are resolving. Further observation may be necessary if treatment is administered.		
Mild (scattered and/or transient)	No treatment often needed; however, if symptomatic, can consider	
	Diphenhydramine (Benadryl®)*	1 mg/kg (max = 50 mg) PO, IM, or IV; administer IV dose slowly over 1 – 2 min
Moderate (more numerous/bothersome)	Monitor vitals	
	Preserve IV access	
Consider	Diphenhydramine (Benadryl®)*	1 mg/kg (max = 50 mg) PO, IM, or IV; administer IV dose slowly over 1 – 2 min
Severe (widespread and/or progressive)	Monitor vitals	
	Preserve IV access	
Consider	Diphenhydramine (Benadryl®)*	1 mg/kg (max = 50 mg) PO, IM, IV; administer IV dose slowly over 1 – 2 min

*Note: All forms can cause drowsiness; IV/IM form may cause or worsen hypotension.
Note: It can be difficult to dose medications accurately in neonates and infants. Also, with respect to IM delivery of epinephrine, EpiPen Jr® package insert does not provide dosing recommendations for children < 15 kg.

DIFFUSE ERYTHEMA

	Treatment	Dosing
All forms	Preserve IV access	
	Monitor vitals	
	O2 by mask	6 – 10 L / min
Normotensive	No other treatment usually needed	
	Treatment	**Dosing**
Hypotensive	IV fluids: 0.9% normal saline	10 – 20 mL / kg;
	or	Maximum of 500 – 1,000 mL
	Lactated Ringer's	
If profound or unresponsive to fluids alone can also consider	Epinephrine (IV)*	IV 0.1 mL/kg of 0.1 mg/mL (1:10,000) dilution (0.01 mg/kg); administer slowly into a running IV infusion of fluids; can repeat every 5 – 15 min, as needed; maximum single dose: 1.0 mL (0.1 mg); can repeat up to 1 mg total dose
	or (if no IV access available)	
	Epinephrine (IM)*	IM 0.01 mL/kg of 1.0 mg/mL (1:1,000) dilution (0.01 mg / kg); max 0.30 mL (0.30 mg); can repeat every 5-15 minutes up to 1 mL (1 mg) total
		or
		Epinephrine auto-injector (1.0 mg/mL (1:1,000) dilution equivalent) If < 30 kg, pediatric epinephrine auto-injector (EpiPen Jr® or equivalent) 0.15 mL equivalent (0.15 mg); If ≥ 30 kg, adult epinephrine auto-injector (EpiPen® or equivalent) 0.30 mL (0.30 mg)
	Consider calling emergency response team or 911	

*Note: In hypotensive patients, the preferred route of epinephrine delivery is IV, as the extremities may not be perfused sufficiently to allow for adequate absorption of IM administration. Also, with respect to IM delivery of epinephrine, the EpiPen Jr® package insert does not provide dosing recommendations for children < 15 kg.
Note: It can be difficult to dose medications accurately in neonates and infants.

BRONCHOSPASM

	Treatment	Dosing
All forms	Preserve IV access	
	Monitor vitals	
	O2 by mask	6–10 L / min
	Treatment	**Dosing**
Mild	Beta agonist inhaler (Albuterol®)	2 puffs (90 mcg/puff) for a total of 180 mcg; can repeat up to 3 times
	Consider calling emergency response team or 911, based upon the completeness of the response	
Moderate	Consider adding epinephrine (IM)*	IM 0.01 mL/kg of 1.0 mg/mL (1:1,000) dilution (0.01 mg/kg); max 0.30 mL (0.30 mg); can repeat every 5-15 minutes up to 1 mL (1 mg) total
		or
		Epinephrine auto-injector (1.0 mg/mL (1:1,000) dilution equivalent) If < 30 kg, pediatric epinephrine auto-injector (EpiPen Jr® or equivalent) 0.15 mL equivalent (0.15 mg); If ≥ 30 kg, adult epinephrine auto-injector (EpiPen® or equivalent) 0.30 mL (0.30 mg)
	or	
	Epinephrine (IV)*	IV 0.1 mL/kg of 0.1 mg/mL (1:10,000) dilution (0.01 mg/kg); administer slowly into a running IV infusion of fluids; can repeat every 5–15 min, as needed; maximum single dose:1.0 mL (0.1 mg); can repeat up to 1 mg total dose
	Consider calling emergency response team or 911 based upon the completeness of the response	
Severe	Epinephrine (IV)*	IV 0.1 mL / kg of 0.1 mg/mL (1:10,000) dilution (0.01 mg / kg); administer slowly into a running IV infusion of fluids; can repeat every 5-15 min, as needed; maximum single dose: 1.0 mL (0.1 mg); can repeat up to 1 mg total dose
	or	
	Epinephrine (IM)*	IM 0.01 mL/kg of 1.0 mg/mL (1:1,000) dilution (0.01 mg/kg); max 0.30 mL (0.30 mg); can repeat every 5-15 minutes up to1 mL (1 mg) total
		or

	Treatment	Dosing
		Epinephrine auto-injector (1.0 mg/mL (1:1,000) dilution equivalent) If < 30 kg, pediatric epinephrine auto-injector (EpiPen Jr® or equivalent) 0.15 mL equivalent (0.15 mg); If ≥ 30 kg, adult epinephrine auto-injector (EpiPen® or equivalent) 0.30 mL (0.30 mg)
	AND Beta agonist inhaler (Albuterol®) (May work synergistically)	2 puffs (90 mcg/puff) for a total of 180 mcg; can repeat up to 3 times
	Call emergency response team or 911	

*Note: In hypotensive patients, the preferred route of epinephrine delivery is IV, as the extremities may not be perfused sufficiently to allow for adequate absorption of IM administration. Also, with respect to IM delivery of epinephrine, the EpiPen Jr® package insert does not provide dosing recommendations for children < 15 kg.
Note: It can be difficult to dose medications accurately in neonates and infants.

LARYNGEAL EDEMA

	Treatment	Dosing
All forms	Preserve IV access	
	Monitor vitals	
	O2 by mask	6–10 L/min
		IV 0.1 mL/kg of 0.1 mg/mL (1:10,000) dilution (0.01 mg/kg); administer slowly into a running IV infusion of fluids; can repeat every 5–15 min, as needed; maximum single dose: 1.0 mL (0.1 mg); can repeat up to 1 mg total dose
		or
	Epinephrine (IM)*	IM 0.01 mL/kg of 1.0 mg/mL (1:1,000) dilution (0.01 mg/kg); max 0.30 mL (0.30 mg); can repeat every 5-15 minutes up to 1 mL (1 mg) total
		or
		Epinephrine auto-injector (1:1,000 dilution equivalent) If < 30 kg, pediatric epinephrine auto-injector (EpiPen Jr® or equivalent) 0.15 mL equivalent (0.15 mg); If ≥ 30 kg, adult epinephrine auto-injector (EpiPen® or equivalent) 0.30 mL (0.30 mg)
	Call emergency response team or 911	

*Note: In hypotensive patients, the preferred route of epinephrine delivery is IV, as the extremities may not be perfused sufficiently to allow for adequate absorption of IM administration. Also, with respect to IM delivery of epinephrine, the EpiPen Jr® package insert does not provide dosing recommendations for children < 15 kg.
Note: It can be difficult to dose medications accurately in neonates and infants.

HYPOTENSION (minimum normal blood pressure varies for children of different ages)

	Treatment	Dosing
All forms	Preserve IV access	
	Monitor vitals	
	O2 by mask	6–10 L/min
	Elevate legs at least 60 degrees	
	Consider IV fluids: 0.9% normal saline	10–20 mL/kg;
	or	Maximum of 500–1,000 mL
	Lactated Ringer's	
Hypotension with bradycardia (min normal pulse varies for children of different ages) (Vasovagal reaction)		
If mild	No other treatment usually necessary	
If severe (patient remains symptomatic despite above measures)	In addition to above measures: Atropine (IV)	IV 0.2 mL/kg of 0.1 mg/mL solution (0.02 mg/kg); Minimum single dose = 0.1 mg Maximum single dose = 0.6–1.0 mg Maximum total dose = 1 mg for infants and children 2 mg for adolescents administer into a running IV infusion of fluids
Hypotension with tachycardia (max normal pulse varies for children of different ages) (Anaphylactoid reaction)		
If severe (hypotension persists)	Epinephrine (IV)*	IV 0.1 mL/kg of 0.1 mg/mL (1:10,000) dilution (0.01 mg/kg); administer slowly into a running IV infusion of fluids; can repeat every 5–15 min, as needed; maximum single dose: 1.0 mL (0.1 mg); can repeat up to 1 mg total dose
	or	
	Epinephrine (IM)*	IM 0.01 mg/kg of 1.0 mg/mL (1:1,000) dilution (0.01 mL/kg); max 0.30 mL (0.30 mg); can repeat every 5–15 minutes up to 1 mL (1 mg) total
		or
	Treatment	**Dosing**
		Epinephrine auto-injector (1.0 mg/mL (1:1,000) dilution equivalent) If < 30 kg, pediatric epinephrine auto-injector (EpiPen Jr® or equivalent) 0.15 mL equivalent (0.15 Mg); If ≥ 30 kg, adult epinephrine auto-injector (EpiPen® or equivalent) 0.30 mL (0.30 mg)
	Call emergency response team or 911	

*Note: In hypotensive patients, the preferred route of epinephrine delivery is IV, as the extremities may not be perfused sufficiently to allow for adequate absorption of IM administration. Also, with respect to IM delivery of epinephrine, the EpiPen Jr® package insert does not provide dosing recommendations for children < 15 kg.
Note: It can be difficult to dose medications accurately in neonates and infants.

UNRESPONSIVE AND PULSELESS

	Treatment	Dosing
	Activate emergency response team (call 911)	
	Start CPR	
	Get defibrillator or automated electronic defibrillator (AED); apply as soon as available; shock as indicated	
Note: Please also see BLS and ACLS (PALS) booklets published by the American Heart Association	Epinephrine (between 2 min cycles)	0.1 mL/kg of 0.1 mg/mL (1:10,000) dilution (0.01 mg/kg); administer quickly with flush or IV fluids; max dose of 10 mL (1 mg)

PULMONARY EDEMA

	Treatment	Dosing
	Preserve IV access	
	Monitor vitals	
	O2 by mask	6–10 L/min
	Elevate head of bed	
	Furosemide (Lasix®) (IV)	IV 0.5–1.0 mg/kg; over 2 min; maximum = 40 mg
	Call emergency response team or 911	

SEIZURES/CONVULSIONS

	Treatment	Dosing
	Observe and protect the patient	
	Turn patient on side to avoid aspiration	
	Suction airway, as needed	
	Preserve IV access	
	Monitor vitals	
	O2 by mask	6–10 L/min
If unremitting	Call emergency response team or 911	

HYPOGLYCEMIA

	Treatment	Dosing
All forms	Preserve IV access	
	O2 by mask	6–10 L / min
If patient is able to swallow safely	Observe	
Administer oral glucose		2 sugar packets or 15 g of glucose tablet or gel or ½ cup (4 oz) of fruit juice
If patient is unable to swallow safely		
And IV access is available	Dextrose 50% (IV)	IV D25 2 mL/ kg; IV injection over 2 min
And IV access is not available	Glucagon (IM/SQ)	IM/SQ 0.5 mg if < 20 kg
		IM/SQ 1.0 mg if > 20 kg

ANXIETY (PANIC ATTACK)

	Treatment	Dosing
	Diagnosis of exclusion	
	Assess patient for developing signs and symptoms that might indicate another type of reaction	
	Preserve IV access	
	Monitor vitals	
	Pulse oximeter	
	If no identifiable manifestations and normal oxygenation, consider this diagnosis	
	Reassure patient	

REACTION REBOUND PREVENTION

	Treatment	Dosing
Note: While IV corticosteroids may help prevent a short-term recurrence of an allergic-like reaction, they are not useful in the acute treatment of any reaction. However, these may be considered for patients having severe allergic-like manifestations prior to transportation to an Emergency Department of inpatient unit.	Hydrocortisone (Solu-Cortef®) (IV)	IV 5 mg/kg; administer over 1-2 min; maximum: 200 mg
	or	
	Methylprednisolone (Solu-Medrol®) (IV)	IV 1 mg/kg; administer over 1–2 min; maximum: 40 mg

Revision History
14 October 2020: Minor revisions
28 August 2015: Major revisions
15 May 2015: Major revisions
7 June 2013: Major revisions
17 March 2010: Minor revisions
29 October 2008: First version

Table 3: MANAGEMENT OF ACUTE REACTIONS TO CONTRAST MEDIA IN ADULTS

Last updated: October 2020

HIVES (Urticaria)

	Treatment	Dosing
Mild (scattered and/or transient)	No treatment often needed; however, if symptomatic, can consider:	
	Diphenhydramine (Benadryl®)*	25–50 mg PO
	or	
	Fexofenadine (Allegra®)**	180 mg PO
Moderate (more numerous/bothersome)	Monitor vitals	
	Preserve IV access	
	Consider diphenhydramine (Benadryl®)*	25–50 mg PO
	or	
	Fexofenadine (Allegra®)**	180 mg PO
	or	
	Consider diphenhydramine (Benadryl®)*	25–50 mg IM or IV (administer IV dose slowly over 1–2 min)
Severe (widespread and/or progressive)	Monitor vitals	
	Preserve IV access	
Consider	Diphenhydramine (Benadryl®)*	25–50 mg IM or IV (administer IV dose slowly over 1–2 min)
* Note: all forms can cause drowsiness; IM/IV form may cause or worsen hypotension	** Note: second generation antihistamines cause less drowsiness; may be beneficial for patients who need to drive themselves home	

DIFFUSE ERYTHEMA

	Treatment	Dosing
All forms	Preserve IV access	
	Monitor vitals	
	Pulse oximeter	
	O2 by mask	6–10 L/min
Normotensive	No other treatment usually needed	
	Treatment	**Dosing**
Hypotensive	IV fluids 0.9% normal saline	1,000 mL rapidly
	or	
	Lactated Ringer's	1,000 mL rapidly
If profound or unresponsive to fluids alone can also consider	Epinephrine (IV)*	IV 1 mL of 0.1 mg/mL (1:10,000) dilution (0.1 mg); administer slowly into a running IV infusion of fluids; can repeat every few minutes as needed up to 10 mL (1 mg) total
	or (if no IV access available)	
	Epinephrine (IM)*	IM 0.3 mL of 1.0 mg/mL (1:1,000) dilution (0.3 mg); can repeat every 5-15 minutes up to 1 mL (1 mg) total
		or
		Epinephrine auto-injector (EpiPen® or equivalent) (0.3mL of 1.0 mg/mL (1:1,000) dilution, fixed [0.3mg]); can repeat every 5-15 minutes up to three times
	Consider calling emergency response team or 911	
* Note: in hypotensive patients, the preferred route of epinephrine delivery is IV, as the extremities may not be perfused sufficiently to allow for adequate absorption of IM administered drug.		

BRONCHOSPASM

	Treatment	Dosing
All forms	Preserve IV access	
	Monitor vitals	
	Pulse oximeter	
	O2 by mask	6–10 L/min
Mild	Beta agonist inhaler (Albuterol®)	2 puffs (90 mcg/puff) for a total of 180 mcg; can repeat up to 3 times
	Consider sending patient to the Emergency Department or calling emergency response team or 911, based upon the completeness of the response to the beta agonist inhaler	
Moderate	Beta agonist inhaler (Albuterol®)	2 puffs (90 mcg/puff) for a total of 180 mcg; can repeat up to 3 times
	Consider adding epinephrine (IM)*	IM 0.3 mL of 1.0 mg/mL (1:1,000) dilution (0.3 mg); can repeat every 5-15 minutes up to 1 mL (1 mg) total
		or
		Epinephrine auto-injector (EpiPen® or equivalent) (0.3 mL of 1.0 mg/mL (1:1,000) dilution, fixed [0.3mg]); can repeat every 5-15 minutes up to three times
	or	
	Epinephrine (IV)*	IV 1 mL of 0.1 mg/mL(1:10,000) dilution (0.1 mg); administer slowly into a running IV infusion of fluids or use saline flush; can repeat every few minutes as needed up to 10 mL (1 mg) total
	Consider calling emergency response team or 911 based upon the completeness of the response	
Severe	Epinephrine (IV)*	IV 1 mL of 0.1 mg/mL (1:10,000) dilution (0.1 mg); administer slowly into a running IV infusion of fluids or slow IV push followed by a slow saline flush; can repeat every few minutes as needed up to 10 mL (1 mg) total
	or	
	Epinephrine (IM)*	IM 0.3 mL of 1:1,000 dilution (0.3 mg); can repeat every 5-15 minutes up to 1 mL (1 mg) total
		or
		Epinephrine auto-injector (EpiPen® or equivalent) (0.3 mL of 1.0 mg/mL(1:1,000) dilution, Fixed [0.3mg]); can repeat every 5-15 minutes up to three times
	AND Beta agonist inhaler (Albuterol®) (may work synergistically)	2 puffs (90 mcg/puff) for a total of 180 mcg; can repeat up to 3 times
	Call emergency response team or 911	
* Note: in hypotensive patients, the preferred route of epinephrine delivery is IV, as the extremities may not be perfused sufficiently to allow for adequate absorption of IM administered drug.		

LARYNGEAL EDEMA

	Treatment	Dosing
All forms	Preserve IV access	
	Monitor vitals	
	Pulse oximeter	
	O2 by mask	6–10 L/min
		IV 1 mL of 0.1 mg/mL (1:10,000) dilution (0.1 mg); administer slowly into a running IV infusion of fluids or use saline flush; can repeat every few minutes as needed up to 10 mL (1 mg) total
	or	
	Epinephrine (IM)	IM 0.3 mL of 1.0 mg/mL (1:1,000) dilution (0.3 mg); can repeat every 5-15 minutes up to 1 mL (1 mg) total
	or	
		Epinephrine auto-injector (EpiPen® or equivalent) (0.3 mL of 1.0 mg/mL (1:1,000) dilution, fixed [0.3mg]); can repeat every 5-15 minutes up to three times
	Consider calling emergency response team or 911 based upon the severity of the reaction and the completeness of the response	
* Note: in hypotensive patients, the preferred route of epinephrine delivery is IV, as the extremities may not be perfused sufficiently to allow for adequate absorption of IM administered drug.		

HYPOTENSION (systolic blood pressure< 90 mm Hg)

	Treatment	Dosing
All forms	Preserve IV access	
	Monitor vitals	
	Pulse oximeter	
	Treatment	**Dosing**
	O2 by mask	6–10 L/min
	Elevate legs at least 60 degrees	
	IV fluids 0.9% normal saline	1,000 mL rapidly
	or	
	Lactated Ringer's	1,000 mL rapidly
	Treatment	**Dosing**
Hypotension with bradycardia (pulse < 60 bpm) (Vasovagal reaction)		
If mild	No other treatment usually necessary	
If severe *(patient remains symptomatic despite above measures)*	In addition to above measures: Atropine (IV)	0.6–1.0 mg; administer into a running IV infusion of fluids; can repeat up to 3 mg total
	Consider calling the emergency response team or 911	
Hypotension with tachycardia (pulse > 100 bpm) (Anaphylactoid reaction)		
If hypotension persists	Epinephrine (IV)*	IV 1 mL of 0.1 mg/mL (1:10,000) dilution (0.1 mg); administer slowly into a running IV infusion of fluids; can repeat every few minutes as needed up to 10 mL (1 mg) total
	or	
	Epinephrine (IM)*	IM 0.3 mL of 1.0 mg/mL (1:1,000) dilution (0.3 mg); can repeat every 5-15 minutes up to 1 mL (1 mg) total
		or
		Epinephrine auto-injector (EpiPen® or equivalent) (0.3 mL of 1.0 mg/mL (1:1,000) dilution, fixed [0.3mg]); can repeat every 5-15 minutes up to three times
	Consider calling emergency response team or 911 based upon the severity of the reaction and the completeness of the response	
* Note: in hypotensive patients, the preferred route of epinephrine delivery is IV, as the extremities may not be perfused sufficiently to allow for adequate absorption of IM administered drug.		

HYPERTENSIVE CRISIS

(diastolic BP> 120mmHg; systolic blood pressure > 200mm Hg; symptoms of endorgan compromise)

	Treatment	Dosing
All forms	Preserve IV access	
	Monitor vitals	
	Pulse oximeter	
	O2 by mask	6–10 L/min
	Labetalol (IV)	20 mg IV; administer slowly, over 2 min; can double the dose every 10 min (e.g., 40 mg 10 min later, then 80 mg 10 min after that)
	or (if labetalol not available)	
	Nitroglycerin tablet (SL)	0.4 mg tablet; can repeat every 5–10 min
	and	
	Furosemide (Lasix®) (IV)	20–40 mg IV; administer slowly over 2 min
	Call emergency response team or 911	

PULMONARY EDEMA

	Treatment	Dosing
	Preserve IV access	
	Monitor vitals	
	O2 by mask	6–10 L/min
	Pulse oximeter	
	Elevate head of bed, if possible	
	Furosemide (Lasix®)	20–40 mg IV; administer slowly over 2 min
	Call emergency response team or 911	

SEIZURES/CONVULSIONS

	Treatment	Dosing
	Observe and protect the patient	
	Turn patient on side to avoid aspiration	
	Suction airway, as needed	
	Preserve IV access	
	Monitor vitals	
	Pulse oximeter	
	O2 by mask	6–10 L/min
If unremitting	Call emergency response team or 911	
	Treatment	**Dosing**
	Lorazepam (IV)	IV 2–4 mg IV; administer slowly to maximum dose of 4 mg

HYPOGLYCEMIA

	Treatment	Dosing
	Preserve IV access	
	O2 by mask	6–10 L/min
If patient is able to swallow safely	Oral glucose	Two sugar packets or 15 g of glucose tablet/gel or ½ cup (4 oz) of fruit juice
If patient is unable to swallow safely and IV access available	Dextrose 50% (IV)	D50W 1 ampule (25 grams) IV administer over 2 min
	D5W or D5NS (IV) as adjunct therapy	Administer at a rate of 100 mL/hour
If no IV access is available	Glucagon (IM)	IM 1 mg

ANXIETY (PANIC ATTACK)

	Treatment	Dosing
	Diagnosis of exclusion	
	Assess patient for developing signs and symptoms that might indicate another type of reaction	
	Preserve IV access	
	Monitor vitals	
	Pulse oximeter	
	If no identifiable manifestations and normal oxygenation, consider this diagnosis	
	Reassure patient	

REACTION REBOUND PREVENTION

	Treatment	Dosing
Note: While IV corticosteroids may help prevent a short-term recurrence of an allergic-like reaction, they are not useful in the acute treatment of any reaction. However, these may be considered for patients having severe allergic-like manifestations prior to transportation to an Emergency Department or inpatient unit.	Hydrocortisone (Solu-Cortef®) (IV)	IV 5 mg / kg; administer over 1-2 min
	or	
	Methylprednisolone (Solu-Medrol®) (IV)	IV 1 mg / kg; administer over 1-2 min

Revision History
14 October 2020: Minor revisions
28 August 2015: Major revisions
15 April 2013: Major revisions
26 June 2012: Minor revisions
23 June 2010: Major revisions
15 March 2004: First version

Table 4:
EQUIPMENT FOR CONTRAST REACTION KITS IN RADIOLOGY
Last updated: January 2020

Facilities should be equipped with basic emergency equipment and medications needed to assess patients and treat contrast reactions. Equipment that can help assess a patient's clinical status include a stethoscope, blood pressure and pulse monitor, and a pulse oximeter. While no standard contrast reaction kit exists, sites should consider making key medications available for prompt reaction management. This would include epinephrine 1 mg/1 mL for intramuscular injection (this includes standard Epinephrine auto-injectors), albuterol, and an antihistamine. Additional medications and equipment are listed in Table 4. Due to financial and operational constraints related to frequent replacement of medications with a relatively short shelf life, many practices are choosing to stock only essential medications separate from standard code carts. A periodic monitoring program to ensure equipment functionality and medication shelf life is recommended.

Depending on the size and function of an imaging site, it may be sufficient to have one treatment cart designed for both contrast reactions and cardiopulmonary arrest. Other facilities may find it more cost-effective to have separate contrast reaction kits and code carts. Smaller distributed contrast reaction kits focused on the most frequently used or urgently needed items can enable rapid implementation of treatment at considerably lower expense. In general, "code carts" designed for treatment of cardiopulmonary arrest have more equipment than necessary for radiologists to use, and facilities may find the suggestions below helpful in designing a dedicated reaction treatment cart that can be used to manage patients experiencing a contrast reaction.

The contact phone number of the local emergency response team (if one is available) should be clearly posted within or near any room in which contrast media is to be injected. If there is no emergency response team, the emergency external phone number to be used (e.g., 911) should be displayed instead.

The following equipment is suggested to be readily available and within or nearby any room in which contrast media is to be injected. Adult or pediatric sizes are optional for facilities that do not inject adult or pediatric patients, respectively. Sites may opt to stock less equipment and medications if emergency response teams or ambulance support is readily available.

The following minimum equipment should be within or near any room in which contrast media is to be injected:

- Access to oxygen*
- Defibrillator or automated external defibrillator (AED)
- Blood pressure and pulse monitor
- Pulse oximeter
- Stethoscope

* Although oxygen can be administered in a variety of ways, use of non-rebreather masks is preferred because of their ability to deliver a larger dose of oxygen to the patient.

The following minimum medications should be within or near any room in which contrast media is to be injected:

- Epinephrine IM 1mg/1mL (auto-injector or vials with needle and syringe for use)
- Inhaled short-acting beta-agonist (inhaler or nebulizer)
- Anti-histamine

The following discretionary medications and equipment may be considered for inclusion within or near any room in which contrast media is to be injected:

- Equipment
  - Suction: wall-mounted or portable; tubing and catheters
  - "Ambu®-type" bag-valve-mask device; masks in adult and pediatric sizes; protective barriers for mouth-to-mouth respiration optional if bag-valve-mask device is stocked
  - Normal saline (0.9%) and tubing
  - Syringes and IV cannulas: variety of sizes; tourniquets
  - Needle(s) for IM drug administration

- Medications
  - Epinephrine IV 1mg/10mL, 10-mL preloaded syringe
  - Atropine IV, 1mg/10mL, 10-mL preloaded syringe
  - Corticosteroid IV
  - Nitroglycerin sublingual, 0.4 mg tab
  - Aspirin per oral, 325 mg (for chest pain where myocardial ischemia is a consideration)
  - Lasix IV, 20–40 mg (for pulmonary edema)
  - Labetalol IV, 20 mg (for hypertensive emergency)
  - Dextrose IV, 50% 25g/50mL syringe (for hypoglycemia)

Appendix A – CONTRAST MEDIA SPECIFICATIONS

Last updated: March 2023

INTRAVASCULAR

Product	Generic name (concentration in mg contrast/ml)	Ionicity	Iodine+ (mg/ml)	Viscosity+ 25°C (cp or mPa.s)	Viscosity+37°C (cp or mPa.s)	Osmolality (mOsm/kgH2O)
Omnipaque™ 140 (GE Healthcare)	Iohexol 302	Nonionic	140	2.3*	1.5	322
Conray™ 30 (Covidien)	iothalamate (300)	Ionic	141	2	1.5	600
Ultravist® 150 (Bayer HealthCare)	iopromide	Nonionic	150	2.3*	1.5	328
Omnipaque™ 180 (GE Healthcare)	iohexol (388)	Nonionic	180	3.1*	2	408
Isovue®-200 (Bracco)	iopamidol (408)	Nonionic	200	3.3*	2.0	413
Conray™ 43 (Covidien)	iothalamate (430)	Ionic	202	3	2	1000
Omnipaque™ 240 (GE Healthcare)	iohexol (518)	Nonionic	240	5.8*	3.4	520
Optiray™ 240 (Guerbet)	ioversol (509)	Nonionic	240	4.6	3.0	502
Ultravist® 240 (Bayer Healthcare)	iopromide	Nonionic	240	4.9*	2.8	483
Isovue® 250 (Bracco)	iopamidol (510)	Nonionic	250	5.1*	3.0	524
Visipaque™ 270 (GE Healthcare)	iodixanol (550)	Nonionic	270	12.7*	6.3	290
Conray™ (Covidien)	iothalamate (600)	Ionic	282	6	4	1400
Isovue® 300 (Bracco)	iopamidol (612)	Nonionic	300	8.8*	4.7	616
Omnipaque™300 (GE Health care)	iohexol (647)	Nonionic	300	11.8*	6.3	672
Optiray™ 300 (Guerbet)	ioversol (640)	Nonionic	300	8.2	5.5	651
Oxilan® 300 (Guerbet)	ioxilan (623)	Nonionic	300	9.4*	5.1	610
Ultravist® 300 (Bayer Healthcare)	iopromide	Nonionic	300	9.2*	4.9	607
Hexabrix™*** (Guerbet)	Ioxaglate meglumine/sodium (589)	Ionic	320	15.7*	7.5	≈600
Optiray™320 (Guerbet)	ioversol (680)	Nonionic	320	9.9	5.8	702
Visipaque™ 320 (GE Healthcare)	iodixanol (652)	Nonionic	320	26.6	11.8	290
Optiray™ 350 (Guerbet)	ioversol (740)	Nonionic	350	14.3	9.0	792
Omnipaque™ 350 (GE Healthcare)	iohexol (755)	Nonionic	350	20.4*	10.4	844
Oxilan® 350 (Guerbet)	ioxilan (727)	Nonionic	350	16.3*	8.1	721
Isovue® 370 (Bracco)	iopamidol (755)	Nonionic	370	20.9*	9.4	796
MD-76™ R (Guerbet)	diatrizoate/ meglumine/sodium (760)	Ionic	370	16.4	10.5	1551
Ultravist® 370 (Bayer Healthcare)	Ioprokoi98mide	Nonionic	370	22.0*	10.0	774

+ Data from product package inserts, product brochures, technical information services and Rohrer, M, et al., Comparison of Magnetic Properties of MRI Contrast Media Solutions at Different Field Strengths. Investigative Radiology 2005;40:715-724.

* Measured at 20°C.
** Data on file with Covidien
*** Hexabrix is a registered trademark of Guerbet, S.A. and is co-marketed in the U.S. by Guerbet LLC and Covidien.

o Viscosities of most products intended for oral administration are not reported by manufacturers.

Barium concentrations are expressed as percent by weight (%w/w) and percent weight-in volume (% w/v). Percent by weight is the number of grams of barium sulfate per 100 grams of final suspension. For barium powders, percent by weight is the proportion of total powder weight that is pure barium, and the remainder is additives (Ex., barium 100% w/w is pure barium with no additives). Percent weight-in volume is the number of grams of barium sulfate per 100 mL of final suspension

1 Adopted from Reiter et al. Minimizing risk of nephrogenic systemic fibrosis in cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2012; 14(1): 31.
Cond 7.4 refers to value at physiologic pH of 7.4.

Appendix A – CONTRAST MEDIA SPECIFICATIONS (continued)

GASTROINTESTINAL – Non-Barium Oral Contrast

Product	**Generic name (concentration in mg contrast/ml)**	**Ionicity**	**Iodine+ (mg/ml)**	**Viscosity+ 25°C (cp or mPa.s)**	**Viscosity+ 37°C (cp or mPa.s)**	**Osmolality (mOsm/kg H2O)**
Gastrografin® (Bracco)	diatrizoate meglumine sodium (660)	Ionic	367			
MD-Gastroview™ (Guerbet)	diatrizoate meglumine sodium (660)	Ionic	367			
Omnipaque™ 180 (GE Healthcare)	iohexol (388) pediatric use	Nonionic	180	3.1*	2.0	331
Omnipaque™ 240 (GE Healthcare)	iohexol (518) pediatric use	Nonionic	240	5.8*	3.4	520
Omnipaque™ 300 (GE Healthcare)	iohexol (647) pediatric use	Nonionic	300	11.8*	6.3	672
Omnipaque™ 350 (GE Healthcare)	iohexol (755) adult use	Nonionic	350	20.4*	10.4	844
Gastromark™ (Guerbet) **Discontinued in US**	ferrous-ferric oxide ferumoxsil	NA	NA			250

GASTROINTESTINAL – Barium-Based Oral Contrast

Product	**Chemical Structure**	**Concentration (w/v or w/w)#**
E-Z-HD (Bracco)	barium sulfate	98% w/w
Liquid Polibar Plus (Bracco)	barium sulfate	105% w/v or 58% w/w
Liquid Polibar (Bracco)	barium sulfate	105% w/v
E-Z-Paque / Pilibar ACB (Bracco)	barium Sulfate	96% w/w
Liquid E-Z-Paque (Bracco)	barium sulfate	60% w/v or 41% w/w
Readi-cat 2 (Bracco)	barium sulfate	2.1% w/v
E-Z-Paste (Bracco)	barium sulfate	60% w/w
Entero Vu (Bracco)	barium sulfate	24% w/v
Tagitol™ (Bracco)	barium sulfate	40% w/v or 30% w/w
Varibar® (Bracco)	Barium sulfate in variable consistency	40% w/v
E-Z-HD (Bracco)	barium sulfate	98% w/w
NeuLumEX™ (E-Z-EM Inc/Bracco)	barium sulfate	0.1% w/v or 0.1% w/w

+ Data from product package inserts, product brochures, technical information services and Rohrer, M, et al., Comparison of Magnetic Properties of MRI Contrast Media Solutions at Different Field Strengths. Investigative Radiology 2005;40:715-724.

* Measured at 20°C.
** Data on file with Covidien
*** Hexabrix is a registered trademark of Guerbet, S.A. and is co-marketed in the U.S. by Guerbet LLC and Covidien.

o Viscosities of most products intended for oral administration are not reported by manufacturers.

Barium concentrations are expressed as percent by weight (%w/w) and percent weight-in volume (% w/v). Percent by weight is the number of grams of barium sulfate per 100 grams of final suspension. For barium powders, percent by weight is the proportion of total powder weight that is pure barium and the remainder is additives (Ex., barium 100% w/w is pure barium with no additives). Percent weight-in volume is the number of grams of barium sulfate per 100 mL of final suspension

1 Adopted from Reiter et al. Minimizing risk of nephrogenic systemic fibrosis in cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2012; 14(1): 31. Cond 7.4 refers to value at physiologic pH of 7.4.

Appendix A – CONTRAST MEDIA SPECIFICATIONS (continued)

GENITOURINARY

Product	Generic name (concentration in mg contrast/ml)	Ionicity	Iodine+ (mg/ml)	Viscosity+ 25°C (cp or mPa.s)	Viscosity+ 37°C (cp or mPa.s)	Osmolality (mOsm/kg H2O)
Cystografin® (Bracco)	diatrizoate	Ionic	141			
Cysto-Conray™ II (Guerbet)	iothalamate (172) (Only for retrograde cystography and cystourethrography)	Ionic	81	(Only for retrograde cystography and cystourethrography)		~400
Conray™ 43 (Guerbet)	iothalamate (430)	Ionic	202	3	2	1000
Omnipaque™ Can be diluted for retrograde use. See package insert	iohexol	Nonionic				

INTRATHECAL

Product	Generic name (concentration in mg contrast/ml)	Ionicity	Iodine+ (mg/ml)	Viscosity+ 25°C (cp or mPa.s)	Viscosity+ 37°C (cp or mPa.s)	Osmolality (mOsm/kg H2O)
Omnipaque™ 180 (GE Healthcare)	iohexol	Nonionic	180	3.1*	2.0	408
Omnipaque™ 240 (GE Healthcare)	iohexol	Nonionic	240	5.8*	3.4	520
Omnipaque™ 300 (GE Healthcare)	iohexol	Nonionic	300	11.8*	6.3	672
Isovue-M® 200 (Bracco)	iopamidol	Nonionic	200	3.3*	2.0	413
Isovue-M® 300 (Bracco)	iopamidol	Nonionic	300	8.8*	4.7	616

GADOLINIUM-BASED INTRAVASCULAR

Product	Chemical Structure and Class	Anion	Cation	Viscosity+ 25°C (cp or mPa.s)	Viscosity+ 37°C (cp or mPa.s)	Relaxivity 1.5T (3T)	Osmolality (mOsm/kg H2O)	Log k Therm (cond7.4)
Elucirem® (Guerbet) Vueway® (Bracco)	Macrocyclic Non-ionic	Gadopiclenol****	None	12.6*	7.6	12.8 (11.6)	850	18.7
Magnevist® (Bayer Healthcare)	Gd-DTPA Linear Ionic	Gadopentetate	Dimeglumine	4.9*	2.9	4.1 (3.7)	1960	22.5 (18.4)
Prohance® (Bracco)	Gd-HP-D03A Macrocyclic Non-ionic	Gadoteridol	None	2.0*	1.3	4.1 (3.7)	630	23.8 (17.2)
Multihance® (Bracco)	Gd-BOPTA Linear Ionic	Gadobenate	Dimeglumine	9.2*	5.3	6.3 (5.5)	1970	22.6 (18.4)
Omniscan™ (GE Healthcare)	Gd-DTPA-BMA Linear Non-ionic	Gadodiamide	None	2.0	1.4	4.3 (4)	789	16.9 (14.9)
Optimark™ (Guerbet)	Gd-DTPA-BMEA Linear Non-ionic	Gadoversetamide	None	2.8**	2.0	4.7 (4.5)	1110	16.8 (15)
EOVIST/Primovist® (Bayer Healthcare)	Gd-EOB-DTPA Linear Ionic	Gadoxetate	Disodium		1.19	6.9 (6.2)	688	23.5 (18.7)
Gadavist/Gadovost™ (Bayer Healthcare)	Gd-BT-D03A Macrocyclic Non Ionic	Gadobutrol	None		4.96	5.2 (5)	1603	21.8 (15.5)
Dotarem® (Guerbet) Clariscan™ (GE Healthcare)	Gd-DOTA Macrocyclic Ionic	Gadoterate	Meglumine	3.4*	2.4	3.6 (3.5)	1350	25.6 (19.3)

Data from product package inserts, product brochures, technical information services and Rohrer, M, et al., Comparison of Magnetic Properties of MRI Contrast Media Solutions at Different Field Strengths. Investigative Radiology 2005; 40:715-724.

* Measured at 20°C.
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1 Adopted from Reiter et al. Minimizing risk of nephrogenic systemic fibrosis in cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2012; 14(1): 31. Cond 7.4 refers to value at physiologic pH of 7.4

****Gadopiclenol demonstrates kinetic stability and a long dissociation half-life that are comparable to other Group II macrocyclic agents. Based on the most recent scientific and clinical evidence, the ACR Committee on Drugs and Contrast Media considers the risk of NSF among patients exposed to standard or lower than standard doses of Gadopiclenol is sufficiently low or possibly nonexistent such that it has been classified as a Group II agent.

Revision History
September 2020: Minor Revision
April 2023: Minor Revision