ACR Manual On Contrast Media

2020

ACR Committee on Drugs and Contrast Media

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ACR Manual on Contrast Media

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ISBN: 978-1-55903-012-0

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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
2020

Version 2020 of the ACR Manual on Contrast Media was published in January 2020 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	Ch. 7 – Allergic-like and Physiologic Reactions to Intravascular Iodinated Contrast Media	Updated
2013	Ch. 8 – Contrast Media in Children	Updated
2013	Ch. 12 – Gastrointestinal (GI) Contrast Media in Adults: indications and Guidelines	Updated
2013	Ch. 19 - Administration of Contrast Media to Women Who Are Breast-Feeding	Updated
2014	Ch. 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 16 – Ultrasound Contrast Media	New chapter added
2017	Chapter 18 – 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 17 – Treatment of Contrast Reactions	Updated
2020	Table 4 – Equipment for Contrast Reaction Kits in Radiology	Updated

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) to ensure that the administration of contrast is appropriate for the patient and the indication; 2) to balance the likelihood of an adverse event with the benefit of the examination; 3) to promote efficient and accurate diagnosis and treatment; and 4) to 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 [3], 0.008% severe) [3, 4]. 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 [3]. 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) [5,6].

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 [3,7].

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 [8]. 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 [1,9] 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 [10]. 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 [11]. 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 [12]. 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 [13], 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 noncontrast CT, $p=0.01$) [14]. 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 [15]. 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 [16,17].

Normal Thyroid Function: Iodinated contrast medium does not affect thyroid function test results in patients with a normally functioning thyroid gland [15]. 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 [18]. 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 [19-21].

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 [22]. 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 [19]. 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 [20]. 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 [11], and development of “pseudoantigens” [23].

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 [24,25]. 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 [25]. 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) [3,26].

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 [22]. 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 [27].

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 [22,27].

Nonetheless, many experts believe that premedication does reduce the likelihood of a reaction in high- risk patients receiving low-osmolality iodinated contrast medium [28], although the number needed to treat to prevent a reaction is high [29,30]. 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 [29]. Another study estimated the number needed to treat to prevent a lethal reaction in high-risk patients to be 50,000 [30].

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 [31] and include transient leukocytosis, transient (24-48h) and usually asymptomatic hyperglycemia (non-diabetics: +20-80 mg/dL, diabetics: +100-150 mg/dL) [32, 33], 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 [29,34,35]. Allergic- like contrast reactions that occur despite premedication are called “breakthrough reactions” [34]. 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% [29]. In most cases (~81%), breakthrough reaction severity is similar to index reaction severity [34, 35]. Patients with a mild index reaction have a very low risk (<1%) of developing a severe breakthrough reaction [29].

The majority (~88%) of contrast injections in premedicated patients with a prior breakthrough reaction will not result in a repeat breakthrough reaction [34, 35]. 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 [34,35].

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 [22, 27]. The randomized trials of premedication in average-risk patients were conducted with oral methylprednisolone [22, 27]. Uncontrolled studies in high-risk patients were conducted with oral prednisone [36, 37].

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 [36].

The minimum duration of premedication necessary for efficacy is unknown. Lasser et al [27] 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 [27].

A dose-response study of single-dose IV methylprednisolone (1 mg/kg) [38] 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 [11, 27, 31, 38].

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 maybe 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 [22].

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 [39].

   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 [40]. 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 [40].

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 [41,42]. 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 [41,42]. 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 [34], 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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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 [27-29]. 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 [27,28]. Humeral placement is now the preferred site of access secondary to quick line placement and higher achievable flow rates compared to tibial access [27,30,31]. 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) [30,32-35]. 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 [27,31,36]. 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 [30]. 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.

Revision History

21 December 2017: Minor revision
10 June 2016: Major revision
29 October 2008: Major revisions
8 March 2004 (First version)

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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 OF CONTRAST MEDIA

Frequency

The reported incidence of intravenous (IV) contrast media extravasation related to power injection for CT has ranged from 0.1% to 1.2% [37-41] (1/1,000 patients to 1/83 patients). Extravasation can occur during hand or power injection. Extravasations may occur at both low and high flow rates [42]. Extravasation occurring with dynamic bolus CT may involve large volumes of contrast media [43]. Contrast injection rates have not been significantly associated with the frequency of extravasation; however, extravasations are more common when injections are made into more peripherally placed catheters [37].

Initial Signs and Symptoms

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 [43]. On physical examination, the extravasation site may be edematous, erythematous, and tender [43].

Sequelae of Extravasations

Extravasated iodinated contrast media can result in injury to surrounding tissues, particularly to the skin, producing an acute local inflammatory response may not peak for 24 to 48 hours [44]. The acute tissue injury resulting from extravasation of iodinated contrast media is likely, at least in part, related to its hyperosmolality [45,46]. Despite this, the vast majority of patients in whom extravasations occur recover without significant sequelae [43]. Only rarely will a low-osmolality contrast media (LOCM) extravasation injury proceed to a severe adverse event [43].

Most extravasations are limited to the immediately adjacent soft tissues (typically the skin and subcutaneous tissues). The most commonly reported severe injuries after extravasation of LOCM are compartment syndromes [43]. A compartment syndrome, which is produced as a result of mechanical compression, is probably more likely to occur after extravasation of larger volumes of contrast media; however, it also has been observed after extravasation of relatively small volumes, especially when these occur in less capacious areas (such as over the ventral or dorsal surfaces of the wrist) [43]. Compartment syndromes may develop soon after an extravasation [43] or result from increasing swelling that sometimes occurs hours after the extravasation [47].

Less commonly encountered severe injuries include skin ulceration and tissue necrosis [48]. These can occur within hours or days of the extravasation event.

A large series has previously illustrated the infrequency of severe injuries after LOCM extravasation. In this report by Wang and colleagues [43], 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.

Evaluation

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, active and passive range of motion of the fingers, and perfusion [49].

Extravasation of Gadolinium Based Contrast Media

Gadolinium-based MRI contrast media have similar to lower toxicity in comparison to iodinated contrast agents [50]; however, extravasations of these agents usually do not cause severe injury, likely due to the smaller total volumes of contrast material that are injected at MRI.

Treatment

There is no known effective treatment for contrast medium extravasation. Elevation of the affected extremity above the level of the heart to decrease capillary hydrostatic pressure and thereby promote resorption of extravasated fluid is recommended [49,51], but controlled studies demonstrating the efficacy of this treatment are lacking [52]. There is no clear evidence favoring the use of warm over cold compresses or vice versa [52]. Those who have used cold have reported that it may be helpful for relieving pain or the size of any subsequent ulceration at the injection site. Those who have used heat have found it helpful in improving absorption of the extravasation as well as in improving blood flow, particularly distal to the site [52]. Nonetheless, many surgeons recommend initial use of cold compresses [49,51].

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 [49,53]. Therefore, aspiration is not recommended.

There is no consistent evidence that local injection of other agents such as corticosteroids is beneficial. [44,54,55]. 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 [56-58]. However, no adequate studies have been conducted assessing its utility with contrast media. Therefore, use of hyaluronidase for the management of contrast material extravasation is not recommended [49].

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, should there be any worsening of pain, swelling, or should the patient develop paresthesias, diminished range of motion of the fingers (active or passive), skin ulceration, or other neurologic or circulatory symptoms [49].

Surgical Consultation

Surgical consultation prior to discharge should be obtained whenever there is concern for a severe extravasation injury [43,49]. An immediate surgical consultation is indicated for any patient in whom one or more of the following signs or symptoms develops: progressive swelling or pain, altered tissue perfusion as evidenced by decreased capillary refill at any time after the extravasation has occurred, change in sensation in the affected limb, worsening passive or active range of motion of the elbow, wrist, or fingers, and skin ulceration or blistering [46]. It is important to note that initial symptoms of a compartment syndrome may be absent or relatively mild (such as limited to the development of focal paresthesia) [47].

Reliance on an extravasation volume threshold to indicate the need for surgical consultation is unreliable [43]. The need for surgical consultation should be based on patient signs and symptoms [43]. If the patient is asymptomatic or has only mild symptoms, appropriate evaluation and clinical follow-up are usually sufficient.

Patients at Increased Risk for Extravasations

Certain patients have been found to be at increased risk for extravasations, including those 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 [59]. 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. Certain intravenous access sites (e.g., hand, wrist, foot, and ankle) are more likely to result in extravasation and should be avoided, if possible [37]. However, use of these alternate injection sites may be necessary due to lack of availability of the more traditional locations. Injection through indwelling peripheral intravenous lines that have been in place for more than 24 hours and multiple punctures into the same vein are associated with an increased risk of extravasation [60]

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

A severe extravasation injury is more likely to result from an extravasation in patients with arterial insufficiency or compromised venous or lymphatic drainage in the affected extremity [59]. 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 tissue injury.

Documentation

All extravasation events and their treatment should be documented in the medical record, especially in the dictated imaging report of the obtained study. If the extravasation is moderate or severe, the referring provider should be notified.

Revision History

23 January 2018 (Minor Revision)

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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° 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° C) and human body temperature (37° C) and concluded that extrinsic warming to 37° 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° C) and room temperature (20° 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° C) iohexol 350 mg I/mL and 2) 32 patients receiving non-warmed (24° 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 (20° C) and human body temperature (37° 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 24° C) or human body temperature (37° 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 (37° C) ionic HOCM compared to the same non-warmed (22° 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 (37° 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 (37° 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 30° C [59 to 86° F]) 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

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. PC-AKI may occur regardless of whether the contrast medium was the cause of the deterioration [*1-12*]. *PC-AKI is a correlative diagnosis*.

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, CIN is a subgroup of PC-AKI [*1-12*]. *CIN is a causative diagnosis*.

Unfortunately, very few published studies have a suitable control group to permit the separation of CIN from PC-AKI [*1-12*]. Therefore, the incidence of PC-AKI reported in clinical studies and the incidence of PC-AKI observed in clinical practice likely includes a combination of CIN (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 CIN and PC-AKI, but these terms are not interchangeable. PC-AKI is not synonymous with CIN.

At the current time, it is the position of ACR Committee on Drugs and Contrast Media that CIN is a real, albeit rare, entity. Published studies on CIN 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

PC-AKI may be caused by any nephrotoxic event (including CIN) that is coincident to the intravascular administration of contrast material. Because the diagnosis of PC-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 CIN 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. CIN may occur in children, but if so, it is rare [*27-30*]. Gadolinium-based contrast media either do not cause CIN when administered at FDA-approved doses, or this event is exceptionally rare [27-30]. 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

There are no standard criteria for the diagnosis of PC-AKI or CIN; criteria used in the past have included percent change in the baseline serum creatinine (e.g., an increase of variously 25% to 50%) and absolute elevation from baseline serum creatinine (e.g., an increase of variously 0.5 to 2.0 mg/dL). One of the most commonly used criteria has been an absolute increase of 0.5 mg/dL over a baseline serum creatinine [*15,39*].

Studies vary in the time when serum creatinine measurements were obtained following contrast medium administration and in the number of measurements made. Few studies have followed patients for more than 72 hours.

The incidence of PC-AKI varies inversely with the magnitude of the change in serum creatinine used to establish the diagnosis, and the same threshold has not been used for all studies. These variable definitions of acute kidney injury (AKI) have been addressed by two consensus groups—the Acute Dialysis Quality Initiative (ADQI) and the Acute Kidney Injury Network (AKIN). Both groups have attempted to standardize the diagnosis and staging of acute kidney injury irrespective of etiology. The RIFLE system (Risk, Injury, Failure, Loss, ESKD) was proposed by ADQI in 2004 [40] and the AKIN system was proposed by AKIN in 2007 [41]. The AKIN system is a modified version of RIFLE and is briefly defined below; only recently have the AKIN criteria been employed scientifically in the study of CIN [*1*, *3*, *4*, *42-44*]. This standard method of diagnosing and staging AKI may be helpful in the design of future CIN studies.

AKIN Definition of Acute Kidney Injury

The diagnosis of AKI is made according to the AKIN criteria if one of the following occurs within 48 hours after a nephrotoxic event (e.g., intravascular iodinated contrast medium exposure) [*41*]:

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 [*41*]. Therefore, it can be used to define the parameters of PC-AKI as well as CIN. The AKIN 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 [*41*].

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 CIN from generic PC-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 CIN 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*, *45-47*]. 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 CIN risk [*49,50*].

However, the formulae for estimating GFR rely in part on serum creatinine, and therefore are subject to some of the same limitations (e.g., confounding AKI, physiologic variation, muscle mass). Moreover, eGFR determinations have limitations because they were created from studies on narrow populations; one particular limitation is their applicability only to stable levels of renal dysfunction. This is because serum creatinine levels lag behind changes in renal function. In AKI, neither renal function nor serum creatinine is stable. Therefore, using these formulae to estimate GFR or creatinine clearance in the setting of AKI in order to make risk determinations for contrast medium use is inadvisable.

Route of Contrast Administration

In the last two decades, the CIN 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 PC-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 CIN for patients undergoing IV contrast-enhanced studies [*2,6*].

CIN Studies

Much of the literature investigating the incidence of CIN 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 CIN, 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 CIN is much less common than previously believed. In patients with a stable baseline eGFR ≥45 mL / min/1.73m^2, 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/1.73m^2, 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/1.73m^2). 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 CIN. There is consensus that the most important risk factor is pre-existing severe renal insufficiency [*3,4,15,39,61*]. Multiple other risk factors have been proposed, including diabetes mellitus, dehydration, cardiovascular disease, diuretic use, advanced age, multiple myeloma, hypertension, hyperuricemia, and multiple iodinated contrast medium doses in a short time interval (<24 hours) [*3,4,15,39,61-63*], but these have not been rigorously confirmed. Two studies have shown that PC-AKI may occur after two closely spaced doses of IV iodinated contrast medium [*62,63*], 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 CIN 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*].

In a 2006 survey of radiologists by Elicker et al [*64*], the cutoff value for serum creatinine beyond which intravascular iodinated contrast medium would not be administered varied widely among radiology practices. For patients with no risk factors other than elevated serum creatinine, 35% of respondents used 1.5 mg/dL, 27% used 1.7 mg/dL, and 31% used 2.0 mg/dL (mean, 1.78 mg/dL). Threshold values were slightly lower in patients with diabetes mellitus (mean: 1.68 mg/dL).

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 [*65-67*], but there are now two large propensity score-adjusted studies that stratify CIN risk by eGFR [*3,7*]. One showed no risk of CIN from IV iodinated contrast material, regardless of baseline eGFR [*7*], while another identified patients with an eGFR <30 mL / min/1.73m^2 to be at significant risk (patients with eGFR 30-44 mL / min/1.73m^2 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 CIN.

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/1.73m^2. Therefore, if a threshold for CIN risk is used at all, 30 mL / min/1.73m^2 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 CIN 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

A baseline serum creatinine (with or without eGFR) should be available or obtained before the injection of contrast medium in all patients considered at risk for CIN (see below for a list of suggested indications).

Choyke et al [*68*] identified a small list of risk factors that, if screened, would allow a radiologist to identify patients with impaired renal function with a high degree of specificity; when none of these risk factors was present, 94% of such patients had a normal serum creatinine and 99% had a serum creatinine less than 1.7 mg/dL. The risk factors screened in this study included: preexisting renal dysfunction, proteinuria, prior kidney surgery, hypertension, and gout. Patients without these risk factors (especially outpatients [*69*]) could therefore be reasonably excluded from serum creatinine screening prior to contrast medium injection resulting in significant cost savings.

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 [*68,69*] and expert opinion:

- Age > 60
- History of renal disease, including:
  - Dialysis
  - Kidney transplant
  - Single kidney
  - Renal cancer
  - Renal surgery
- History of hypertension requiring medical therapy
- History of diabetes mellitus
- Metformin or metformin-containing drug combinations*

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.

* Metformin does not confer an increased risk of CIN. However, patients who develop AKI while taking metformin may be susceptible to the development of lactic acidosis.

Morbidity and Mortality

The clinical course of PC-AKI (and, presumably, CIN) 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 [*65*,*67*].

Several studies have shown that patients with PC-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 [*40*,*41*,*44*,*70*,*71*]. These observations have led to widespread hesitance in the use of intravascular iodinated contrast medium when the risk of CIN is felt to be high. However, many studies investigating CIN and its consequences following intravascular iodinated contrast medium administration have failed to include a control group of patients not receiving contrast medium [*44*,*70*,*71*]; therefore, it is possible that much of the morbidity and mortality previously attributed to CIN in the literature may in fact be due to other etiologies (i.e., contrast-independent causes of PC-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 CIN is a relative but not absolute contraindication to the administration of intravascular iodinated contrast medium in at-risk patients. The risk of clinically relevant renal dysfunction is very low in many situations. However, patients with AKI or severe chronic kidney disease are considered at risk for CIN [*3*,*4*]. In these scenarios, the information that may be obtained by using no contrast medium (e.g. noncontrast CT) and/or other modalities (e.g., ultrasound, noncontrast 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 CIN risk. Although it seems logical to use the lowest possible dose of contrast medium to obtain the necessary diagnostic information, robust data supporting a dose-toxicity relationship for IV iodinated contrast medium administration are lacking. There does seem to be a directly proportional dose- toxicity relationship for intracardiac iodinated contrast medium [*72*].

One purported risk factor for the development of CIN is the administration of multiple doses of intravascular iodinated contrast medium within a short period of time [*62*,*63*]. 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 [*73*] 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 [*74-77*] have failed to establish a clear advantage of IV iso-osmolality iodixanol over IV LOCM with regard to PC-AKI or CIN. A 2009 meta-analysis using data pooled from 25 trials found no difference in the rate of PC-AKI between iodixanol and low osmolality agents after intravenous administration [*78*].

Volume Expansion

The major preventive action to mitigate the risk of CIN is to provide intravenous volume expansion prior to contrast medium administration [*79-85*]. The ideal infusion rate and volume is unknown, but isotonic fluids are preferred (Lactated Ringer's or 0.9% normal saline). One possible protocol would be 0.9% saline at 100 mL/hr, beginning 6 to 12 hours before and continuing 4 to 12 hours after, but this is only practical in the inpatient setting. Oral hydration has also been utilized, but with less demonstrated effectiveness.

Not all clinical studies have shown dehydration to be a major risk factor for PC-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 [*86*] studied adult patients with chronic kidney disease who underwent cardiac angiography. The reported incidence of PC-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 PC-AKI risk reduction [*80*].

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 PC-AKI [*81,82*], but these results have been challenged by other meta-analyses [*84*] and cannot be considered definitive at this time.

N-acetylcysteine

The efficacy of N-acetylcysteine to reduce the incidence of CIN is controversial. Multiple studies and a number of meta-analyses have disagreed whether this agent reduces the risk of PC-AKI [*87,88*]. There is evidence that it

reduces serum creatinine in normal volunteers without changing cystatin-C (cystatin-C is reported to be a better marker of GFR than serum creatinine). This raises the possibility that N-acetylcysteine might be simply lowering serum creatinine without actually preventing renal injury. At the current time, there is insufficient evidence of its efficacy to recommend its use [*89*]. N-acetylcysteine should not be considered a substitute for appropriate pre-procedural patient screening and adequate volume expansion.

Diuretics: Mannitol and Furosemide

Solomon et al [*90*] 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 CIN risk reduction.

Other Agents

The evidence for other theoretically renal-protective medications, such as theophylline, endothelin-1, and fenoldopam is even less convincing. Use of these agents to reduce the risk of CIN is not recommended.

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.

Patients receiving dialysis are also at theoretical risk from the osmotic load imposed by intravascular iodinated contrast medium because they cannot readily clear the excess intravascular volume. This osmotic load can theoretically result in pulmonary edema and anasarca, an issue that may have been more significant in the past when high-osmolality IV contrast media were utilized. Complications were not observed in one study of patients on dialysis who received intravascular nonionic iodinated contrast medium [*91*], though the number of patients in that study was small. In patients at risk for fluid overload, low osmolality or iso- osmolality contrast media should be employed with dosing as low as necessary to achieve a diagnostic result.

Most low-osmolality iodinated contrast media are not protein-bound, have relatively low molecular weights, and are readily cleared by dialysis. Unless an unusually large volume of contrast medium is administered, or there is substantial underlying cardiac dysfunction, there is no need for urgent dialysis after intravascular iodinated contrast medium administration [91].

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[1]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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Revision History

19 November 2014: Major revisions

15 April 2013: Minor revisions

23 June 2010: Major revisions

29 October 2008: First version

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 the susceptible patient. 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.

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[1]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.

TableA
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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Revision History

12 December 2014: Minor revisions

29 June 2012: Minor revisions

29 October 2008: First version

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 material differs from adult use and will attempt to avoid repeating recommendations that are similar for both patient populations.

Iodinated Intravascular Contrast Media

Unique Considerations in Children

Contrast Agent Osmolality

Osmolality is an important physical property of contrast media. A variety of the adverse effects attributed to intravascularly administered iodinated contrast agents seem to be related, at least in part, to this physical property, including physiologic side effects, allergic-like reactions, complications following contrast medium extravasation, and fluid shifts. There is noteworthy variation in the osmolality of the various nonionic iodinated contrast agents approved for use in the United States with equivalent iodine concentrations (see *Appendix A*).

Contrast media osmolality is of particular importance in neonates and small children. These patients are thought to be especially susceptible to fluid shifts and have a lower tolerance for intravascular osmotic loads when compared to adults. Intravascular administration of hyperosmolar contrast medium may result in migration of fluid from extravascular soft tissues into blood vessels, consequently 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.

Contrast Media Viscosity

Viscosity, a measure of fluid resistance to stress, is another important physical property of contrast media. As viscosity increases, the pressure associated with an intravascular contrast medium injection increases. This physical property is especially important for pediatric patients due to the use of small gauge angiocatheters in tiny blood vessels. Contrast medium viscosity and angiocatheter size are important factors in determining maximum injection rates. If a rapid injection rate is desired through a small angiocatheter and if contrast medium viscosity is high, two problems can potentially result: First, the desired injection flow rate may not be achieved. Second, high pressure may cause catheter failure and/or vessel injury. There is distinct variation in viscosity between different contrast agents (see *Appendix A*). Additionally, contrast medium viscosity is not directly proportional to the concentration of iodine. Using iopamidol (Isovue) as an example, at body temperature, viscosity increases from 2.0 centipoise (cps) at 200 mgI/mL to 9.4 cps at 370 mgI/mL.

Viscosity of contrast media is affected by temperature (see *Appendix A*). As temperature increases, viscosity decreases, allowing for increased flow rates at lower pressures. A study by Vergara and Seguel [*3*] that included both adult and pediatric patients showed that warming contrast media resulted in fewer adverse events following injection when compared to contrast media administered at room temperature. In another study of 24,826 intravenous (IV) contrast material administrations in children and adults [*4*], warming of iopamidol-370 to body temperature reduced the extravasation rate, but warming of iopamidol-300 to body temperature had no effect. The authors concluded that higher viscosity agents may benefit more from warming than lower viscosity agents.

Other Unique Issues 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, the use of 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 tiny peripheral veins (e.g., in the hand or foot) 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. When access is thought to be tenuous, hand injection of contrast medium should be strongly considered to minimize risk of vessel injury and extravasation. Since many currently used central venous catheters are not 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. It is also important to ensure that the pressure used does not exceed the catheter's pressure rating.

Particular attention should be paid to the injection sites of neonates and infants, as such individuals cannot effectively communicate the possibility of an injection site complication. Extravasation rates in children appear to be similar to those of the adult population. 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*]. Most extravasations in the pediatric population resolve without untoward sequelae. A study by Wang et al [*7*] showed that 15 of 17 cases of contrast medium extravasation in children were mild in severity with minimal or no adverse effects.

Physiologic Side Effects in Children

Although most minor physiologic side effects to IV contrast medium administration in adults are of minimal significance, such events are often of increased importance in children [*8*]. For example, local warmth at the injection site and nausea, generally regarded as physiologic side effects to contrast medium administration, may cause a child to move or cry. Such a response to contrast medium injection may result in the acquisition of a nondiagnostic imaging study, necessitating repeat imaging and additional exposure to contrast medium and radiation. There may be differences between the various nonionic low-osmolality iodinated contrast agents with regard to the incidence of injection-related side effects [*8*].

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, many 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. Also, much of the existing literature is retrospective in nature, for which it is difficult to ensure that all adverse reactions are appropriately documented.

Therefore, not surprisingly, the reported incidence of pediatric allergic-like reactions to contrast media is variable, due at least in part to the factors mentioned above. It is generally agreed, however, that the incidence of allergic-like reactions in children is lower than that in adults [*3*,*8*,*9*] . A very large retrospective study by

Katayama et al of more than 100,000 contrast medium administrations [*8*], when stratified by age and the use of nonionic iodinated contrast media, showed that patients less than 10 years of age and the elderly have the lowest rates of adverse reactions. A study by Dillman et al [*10*] retrospectively reviewed more than 11,000 IV 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 [*9*]. A similarly performed study by Wang et al [*11*] in adult patients from the same institution over a similar time period revealed an adult reaction rate of approximately 0.6%. 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. 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 in some cases), infants and young children require close observation during and immediately following IV 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. A sample pediatric premedication regimen, using a combination of corticosteroid and antihistamine, is described in the Table A at the end of this chapter. Allergic-like reactions following premedication may still occur, although the frequency of such reactions is unknown [*10*]. 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.

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. Dedicated pediatric emergency resuscitation equipment (including various sizes of supplemental oxygen facemasks) also 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.

Contrast-Induced Nephrotoxicity in Children

There has been no large prospective investigation dealing with the possible nephrotoxic effects of intravascular low-osmolality iodinated contrast agents in children. Consequently, the effects of contrast media on the kidneys are generally assumed to be similar between children and adults. A few key differences 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, even in the presence of preserved renal function. It is important to recognize that normal adult creatinine concentrations cannot be applied to the pediatric population. Normal pediatric serum creatinine concentrations increase with age, with the upper limits of normal always 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 patient would be clinically significant 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. A patient, therefore, may have impaired renal function and a normal serum creatinine concentration.

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 popular manner 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 and height. In addition, the assay used to measure serum creatinine concentration must be known.

GFR Calculator for Children

There is no perfect manner of estimating the 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 is the Bedside Schwartz equation. This formula is for use with creatinine methods with calibration traceable to isotope dilution mass spectroscopy (IDMS). Using the Original Schwartz equation (which is no longer recommended) with a serum creatinine value from a method with calibration traceable to IDMS will overestimate GFR by 20– 40%.

Equation: Bedside Schwartz Equation

GFR (mL / min/1.73 m^2) = (0.41 × height) / serum creatinine

- Height in cm
- Serum creatinine in mg/dL

Although other methods of estimating GFR exist (such as cystatin C measurement or nuclear medicine GFR study), the Bedside Schwartz equation remains the most readily available and easiest to use in pediatric patients.

Prevention of Contrast-Induced Nephrotoxicity in At-Risk Children

Risk factors for contrast-induced nephrotoxicity (CIN) in children are thought to be similar to those in adults. Unfortunately, there are no established evidence-based guidelines for the prevention of CIN in children with impaired renal function. As no pediatric-specific measures for the prevention of CIN have been established in the literature, strategies described in adults should be considered when using IV iodinated contrast media in children with renal dysfunction. A noncontrast imaging examination should be performed if the clinical question can be answered without IV iodinated contrast media. In addition, the use of alternative imaging modalities, such as ultrasound and MR (with or without gadolinium-based contrast medium, depending on exact degree of renal impairment and the clinical question to be answered), should be

considered.

Gadolinium-Based IV Contrast Agents

There are only a few published studies that address adverse reactions to gadolinium-based IV contrast media in children. The guidelines for IV use of gadolinium-based contrast agents are generally similar in both the pediatric and adult populations. There are currently nine gadolinium-based contrast agents approved for IV use in the United States. These agents are most commonly used off-label in children as several of these agents are not approved for use in all age groups. A few pediatric-specific issues regarding these contrast agents are discussed below.

Osmolality and Viscosity

As with iodinated contrast media, there is a significant range in osmolality and viscosity of gadolinium- based MR contrast agents (see *Appendix A*). For example, the osmolality of gadoteridol (ProHance) is 630 mosm/kg H_2O, and the osmolality of gadobenate dimeglumine (MultiHance) is 1,970 mosm/kg H_2O. 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 agents 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 agents result in lower injection-related pressures and decreased risk for vessel injury and extravasation.

Allergic-Like Reactions and Other Adverse Events

Though rare, allergic-like reactions to IV gadolinium-based contrast media in children do occur. A study by Dillman et al [14] documented a 0.04% (48 reactions/13,344 injections) allergic-like reaction rate for these contrast agents in children. A more recent 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% [15]. Although mild reactions are most common, more signifi reactions that require urgent medical management may occur [15]. Pediatric allergic-like reactions to gadolinium-based contrast media are treated similarly to those reactions to iodinated contrast agents (Table2).While no investigation has studied the efficacy of corticosteroid and antihistamine premedication regimens for the prevention of allergic-like reactions to gadolinium-based contrast agents in children or adults, regimens, such as those presented in Table A at the end of the chapter, are thought to provide some protective benefit.

A variety of physiologic side effects may also occur following administration of gadolinium-based contrast media, including coldness at the injection site, nausea, headache, and dizziness (see package inserts). There is no evidence for pediatric renal toxicity from gadolinium-based contrast media at approved doses. Extravasation of gadolinium-based contrast media is usually of minimal clinical significance because of the small volumes injected.

Nephrogenic Systemic Fibrosis and Gadolinium-Based Contrast Media

There are only a small number of reported cases of nephrogenic systemic fibrosis (NSF) in children. As of September 2012, there were 23 unique pediatric NSF cases, and all patients were 6 years of age or older [*15*]. Seventeen of these children had documented exposure to gadolinium-based contrast material. 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 or peritoneal dialysis (or both). In 10 children, renal status was unknown. A few early cases were described prior to this condition's known apparent association with gadolinium-based contrast media [*16-22*]. Only 10 children (all older than 8 years of age) with biopsy-confirmed NSF have been reported to the Yale Registry, with no new cases reported between 2007

and 2013 after guidelines were published in 2007 limiting the use of gadolinium- based contrast media in children with impaired renal function [*23*].

As there are no evidence-based guidelines for the prevention of NSF in children in particular, 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 [*24*]. Children at risk for renal impairment 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, gadolinium-based contrast media should be avoided in the setting of acute kidney injury or chronic kidney disease with an eGFR <30 mL / min/1.73 m^2. Though not based on specific evidence, some have suggested the avoidance of high-risk gadolinium agents in very young children (e.g., neonates younger than 4 weeks of age). Though there has been no reported case of NSF in a very young child to date, we believe caution should be used when administering these contrast agents, especially to preterm neonates and infants [*25*] due to renal immaturity and potential glomerular filtration rates under 30 mL / min/1.73m^2 [*26*]. As always, the use of IV gadolinium-based contrast media in children of all ages should be justified, and the benefit of administration should outweigh potential risks.

Gastrointestinal Contrast Media

The most commonly used gastrointestinal contrast agents in children are barium-based. These agents can be administered by mouth, rectum, ostomy, or catheter residing in the gastrointestinal tract. These contrast agents are generally contraindicated in patients with suspected or known gastrointestinal tract perforation.

Iodinated contrast agents are usually preferred in the setting of suspected gastrointestinal tract perforation. As with intravascular iodinated contrast agents, osmolality should be considered when deciding which iodinated contrast agent to administer orally due to significant variability. Hyperosmolality iodinated contrast agents within the gastrointestinal tract may cause fluid shifts between bowel wall and lumen and, once absorbed, between extravascular soft tissues and blood vessels [*27-31*]. 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 agents should be considered for imaging of the upper gastrointestinal tract. Regarding rectal use, higher osmolality contrast agents can usually be diluted to a lower osmolality and still have sufficient iodine concentration to allow diagnostic imaging.

High-osmolality iodinated contrast agents should be avoided in children who are at risk for aspiration. Aspirated hyperosmolality contrast medium may cause fluid shifts at the alveolar level and chemical pneumonitis with resultant pulmonary edema [*32-35*]. Aspiration of large volumes of both barium-based and iodinated oral contrast agents rarely may be fatal [*36*].

TableA
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 hrs 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.

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Revision History

2 June 2014: Minor revision

15 April 2013: Minor revision

29 June 2012: Minor revision

29 October 2008: First version

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

Introduction

Oral, rectal, and intravenous contrast agents are utilized in a variety of ways for imaging of the gastrointestinal system. Oral contrast agents are used for fluoroscopic studies, such as dynamic pharyngography, esophagography, upper gastrointestinal (UGI) series, and small bowel follow-through (SBFT) examinations. They are also used to highlight the gastrointestinal tract in routine computed tomography (CT) of the abdomen and pelvis, CT enterography, magnetic resonance imaging (MRI), magnetic resonance enterography, CT colonography, CT positron emission tomography (PET), and MRI-PET. Oral agents are also occasionally used to opacify the biliary tree.

Rectal contrast media is given for conventional fluoroscopic colon studies and colon cleansing. Rectal contrast media may also opacify the colonic lumen during CT imaging of the abdomen and pelvis.

Intravenous contrast media of various types may be used to opacify the biliary tree during CT and MRI cholangiopancreatography, as well as for generalized enhancement of vascularized structures and organs in routine CT and MR of the abdomen and pelvis. Direct injection of contrast media into the biliary and pancreatic ductal systems is performed during endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous antegrade studies of the biliary tree.

This chapter discusses indications, contraindications, and adverse reactions resulting from the administration of contrast agents used to assess the gastrointestinal system. Ancillary drugs utilized in gastrointestinal tract imaging and additives to gastrointestinal contrast media will also be reviewed along with their contraindications and adverse/allergic potential.

Conventional fluoroscopic examinations

Diagnostic use of barium and water soluble contrast media

Barium sulfate contrast media continue to be the preferred agents for opacification of the gastrointestinal tract for conventional fluoroscopic examinations [1,2]. They provide greater delineation of mucosal detail and are more resistant to dilution than iodinated agents [1,3]. In adult patients, it is also generally agreed upon that in most non- acute clinical situations, barium is the preferred oral contrast medium for the diagnosis of most etiologies of obstruction (with the exception of suspected proximal small bowel obstruction). This is because dilution of water-soluble contrast media in dilated fluid-filled distal small bowel loops may render the contrast media nonvisible. Barium is also routinely used in patients undergoing GI studies performed via oral or nasoenteric tubes terminating in the stomach or small intestine.

The current use of iodinated water-soluble contrast media is primarily limited to select situations. These include patients in who there is suspected bowel perforation or leak (including bowel fistula, sinus tract, or abscess) or to confirm percutaneous feeding tube position. Less commonly, water-soluble oral contrast media may be preferred over barium contrast media in patients who are to be studied just before endoscopic procedures of the bowel or in patients with likely small bowel obstruction in whom timely surgery is anticipated. Very rarely, iodinated contrast media may be chosen for patients who report prior allergic-like reactions to barium agents.

Therapeuticuses 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 [4-6]. Given as an enema, HOCM has proved useful in some adults with barium impaction [7] as well as in patients with cystic fibrosis who have distal intestinal obstruction syndrome (DIOS) (obstipation) [8]. This is because HOCMs are hypertonic and draw fluid into the bowel lumen.

Administration of barium for opacification of the GI tract

Barium sulfate is a micropulverized white powder that is supplied in various forms, including in bulk for mixing with distilled or tap water. Barium may be obtained in prepackaged aliquot mixtures ready for individual use in patients requiring oral or rectal examinations. For the typical single contrast UGI series or SBFT contrast study, the usual mixture for optimal stability in suspension and bowel wall coating is 60% weight/volume (w/v) [9]. The volume of barium required varies with the procedure, anatomy, and the patient's transit time (for SBFT examinations). Administration of at least 500 ml of 40% w/v barium suspension is suggested for SBFT examinations [10]. High density barium (up to 250% w/v) is used in conjunction with air or effervescent gas for double contrast GI studies. High density barium (85% to 100% w/v suspension) has been recommended for optimal imaging in the colon for double contrast examinations. [10]. Generally, 1,000 to 2,000 ml is needed to study an average colon.

The formulae provided from vendors are altered in different areas of the gastrointestinal tract by local conditions, such as luminal acidity which affects flocculation out of suspension and coating. Also, local differences in tap water composition obtained from municipal sources alter the qualities of barium, so that there is not one formula that works equally well everywhere [3].

Colonic preparation cleansing regimens

Commonly employed full bowel cathartic agents include bisacodyl tablets, polyethelyne glycol (PEG), and magnesium citrate. One study concluded that oral sodium phosphate preparation results in higher patient compliance, less residual stool, and higher reader confidence for the diagnosis of polyps, but it is generally believed that polyethylene glycol (PEG) and sodium phosphates perform similarly for polyp detection [11]. Magnesium citrate resulted in greater residual stool in this study, but the results in other studies have been more variable. Additionally, some favor the routine use of magnesium citrate instead of sodium phosphate in the elderly and patients with renal insufficiency or hypertension, especially those being treated with angiotensin-converting enzyme inhibitors, to reduce the risk of acute phosphate nephropathy (a form of acute kidney injury) [12,13]. At the present time, however, no firm recommendation can be made for a preferred or superior cleansing method.

Administration of iodinated contrast agents for opacification of the GI tract

Two commercial water-soluble iodinated HOCMs specifically designed for enteric opacification are in common use. 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 of iodine per ml. Inactive ingredients includes edetate disodium, flavor, polysorbate 80, purified water, saccharin sodium, simethicone, and sodium citrate.

Gastrografin and Gastroview are hypertonic and may lead to hypovolemia and hypotension due to fluid loss from the intestine. These are usually used undiluted in the upper gastrointestinal tract in adults. However, in some children and elderly adults, the loss of plasma fluid may be sufficient to cause a shock- like state. In this situation, the contrast material can be diluted with water.

Iodinated contrast media supplied for intravenous use also can be administered safely by mouth or per rectum.

This is generally “off label”, with the exception of iohexol (Omnipaque, GE Healthcare; Princeton, NJ) which has an FDA-approved indication for oral use in select concentrations (see package insert for specifics). High or low-osmolality “intravenous” agents can be used full strength or diluted within the GI tract; dilution is required for typical CT use to avoid streak artifact from contrast media that is too attenuating, however. In general, there is no advantage of “intravenous” LOCMs over Gastroview or Gastrografin for GI tract use; however, low-osmolality agents may reduce risk of contrast-related pneumonitis in aspiration- prone patients (see below). Furthermore, the taste of low-osmolality agents may be more palatable, though this seems more important at full strength iodine concentrations than when these agents are diluted (and often mixed with flavorings) for CT scanning. Some institutions prefer to use intravenous contrast agents for oral/rectal use in the CT suite to avoid stocking Gastrografin or Gastroview in the same location, and thus reducing the risk of accidental intravenous misadministration of Gastrografin or Gastroview.

Complications from use of barium and water soluble contrast agents

The most serious complication from the use of barium in the GI tract is leakage into the mediastinum or peritoneal cavity [1]. The potential complications of a barium leak depend on the site from which the spill occurs. Esophageal leakage may cause mediastinitis. Stomach, duodenal, and small intestinal leakage may result in peritonitis. Escape of barium from the colon, where the bacterial count is highest, carries high mortality (with the mortality likely primarily related to leakage of stool).

Water-soluble contrast media are absorbed rapidly from the interstitial spaces and peritoneal cavity, a feature that makes them uniquely useful in examining patients with a suspected perforation of a hollow viscus. No permanent deleterious effects from the presence of water-soluble contrast media in the mediastinum, pleural cavity, or peritoneal cavity have been shown to occur [14]. Many investigators, therefore, recommend that iodinated water-soluble oral contrast media be utilized initially in any study in which a bowel perforation is suspected or known to exist. If an initial study with iodinated contrast agent fails to demonstrate a suspected perforation, barium sulfate can then be administered. Such follow-up studies may be important as some small leaks that are undetected with water-soluble media may be seen only when barium sulfate media are administered [15,16].

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 [9]. If not completely expectorated, retained barium in the lungs can remain indefinitely and may cause inflammation [14]. High volume aspiration can lead to acute respiratory distress or pneumonia, as might be true for aspiration of any nonsterile liquid.

HOCM may, if aspirated, cause life-threatening pulmonary edema [2,17,18]. Therefore, if water-soluble contrast media are to be used in patients at risk for aspiration, low-osmolality or iso-osmolality contrast media are preferred, as these contrast agents, if aspirated, are associated with only minimal morbidity and mortality [17].

Adverse 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 “reactions” are likely not allergic-like, but are part of a physiologic response resulting from distention of a viscus. Vasovagal reactions can also be encountered, after the colon is distended during a double contrast barium enema.

Allergic-like reactions

Allergic-like (anaphylactoid) reactions to enteric barium are very uncommon. The frequency of allergic-like adverse reactions have been reported to be 1 in 750,000 examinations, with most of the manifestations being mild [19]. The most common allergic-like responses are transient rashes, urticaria, itching, and mild bronchospasm.

Moderate and severe allergic reactions to barium are exceedingly unusual, estimated to occur in 1 in 2.5 million exposures [20], with manifestations including more extensive dermal responses, respiratory symptoms, and vascular events, such as hypotensive episodes, that may require pharmacotherapy. Angioedema of the stomach and small bowel has also been described [21].

An extreme allergic dermal condition, toxic epidermal necrolysis, has been reported following an UGI examination. This condition sometimes requiring extended hospitalization, and is associated with a 30% mortality rate [22].

There have been isolated reports of life-threatening reactions from double contrast colon examinations, especially those performed following the parenteral injection of glucagon [19]. Anaphylactic fatalities have also been very rarely reported in association with lower and UGI studies [23-26].

An association between a history of asthma and allergic-like reaction to barium has been raised [23]; however, there is no conclusive evidence of cause and effect. It is possible that if a contrast reaction occurs in an asthmatic, it may be more difficult to treat [23].

Possible etiologies of allergic-like reactions during barium studies

The cause of allergic-like reactions during barium studies is unknown. There are many candidates for allergens besides the barium itself, some of which are discussed below.

Barium: Although barium is generally considered insoluble, miniscule amounts can dissociate, resulting in availability of free barium ions that can dissolve into solution and potentially be absorbed from the GI tract [27]. The clinical significance of absorption of such tiny amounts is speculative, particularly in view of the presence of spectrometrically measurable trace amounts of barium in many water supplies in U.S. cities [28]. Tiny amounts of absorbed barium during a GI examination would be an unlikely allergen [29].

Ancillary medical products: In the past, ancillary medical products, such as products containing latex, were thought to be responsible for at least some of the allergic-like reactions occurring after the administration of barium agents [30], but after latex was eliminated from enema tips and gloves in 1991 reactions continued to occur, and attention turned toward other causes [31], including silicone (which is less common than sensitivity to latex) [29] and rectal lubricant jelly sensitivity [32].

Additives: It is quite possible that allergic-like reactions to commercial barium products result from exposure to various additives to barium preparations, such as antifoaming agents (e.g., dimethyl polysiloxane), flavoring agents (e.g., chocolate and citrus), preservative stabilizers (e.g., carrageenan) [29,33], and antiflocculants. Carbomethylcellulose has been used to improve coating and flow of barium suspensions. Various forms of methylcellulose have been identified to act as allergens when injected with corticosteroids into joints [34,35], muscle [36], and when ingested with large amounts of barium [37]. Effervescent granules, which are used for double contrast studies of the esophagus and upper gastrointestinal tract, also contain additives, including tartaric acid, citric acid, and

antifoaming agents. These substances can also potentially induce an allergic response when given orally for esophagrams and UGI examinations [20].

All of the above additives are also ubiquitous in food products, cosmetics, and pharmaceuticals, albeit in small amounts, and they are considered safe by the U.S. Food and Drug Administration, appearing on their generally regarded as safe (GRAS) list [20]. However, recent studies have shown that 9% of a population screened for IgE carboxymethylcellulose-specific antibodies have tested positive, and, of these, 1/6th (1.6% of the total population sampled) had strongly positive responses [38]. Since a significant percentage of the population is sensitized, methylcellulose should be given to patients with caution.

Direct barium toxicity

Direct toxicity of orally or rectally administered barium has been reported on very rare occasions [38,39]. Any barium that dissociates from the stable barium sulfate compound may form other chemical compounds that become soluble and absorbed into the blood stream resulting in toxicity. Barium chloride, barium sulfide, and barium carbonate [40] fall into this category. This is more likely to occur if industrial grade barium contaminates pharmaceutical grade barium distributed for diagnostic use [41]. Case reports of toxicity with pharmaceutical grade barium have been reported [39,42].

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 [43,44]. If left untreated, this can lead to a cascade of severe muscle weakness, respiratory arrest, coma, cardiac arrhythmia, and death [41,45]. Therapy for acute barium intoxication of this nature consists of aggressive potassium infusion with monitoring and correcting electrolyte imbalance [41,46].

Adverse reactions to GI tract water-soluble iodinated contrast media

Allergic-like reactions: A small volume of iodinated contrast media (approximately 1% to 2%) is normally absorbed and subsequently excreted into the urinary tract after oral or rectal administration [47,48]. Mucosal inflammation, mucosal infection, or bowel obstruction can increase the amount absorbed by several fold [49- 51]. As a result, it is not rare to see opacification of the urinary tract after enteric administration of water soluble contrast media [52]. Because anaphylactoid reactions are not considered to be dose related and can occur with less than 1 ml of intravenous (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. Somewhat surprisingly, there are only very rare reports of moderate or severe allergic-like reactions to orally or rectally administered iodinated contrast media [51].

Alterations in thyroid function: Thyroid function tests may be altered for variable periods of time [53], 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). It has also been theorized, although not shown clinically, that a small amount of iodine can be absorbed from orally administered iodinated contrast media and interfere with studies involving protein-bound and radioactive iodine uptake as well as with spectrophotometric trypsin assay [54,55].

Bacteremia during and after contrast media enemas: Single-contrast barium enemas have been shown to be associated with transient bacteremia in 11.4% and 23% of patients studied in two series [56,57]. However, a third study failed to demonstrate this phenomenon [58]. Similarly, bacteremia could not be found in a study of patients undergoing double-contrast enemas [59].

Contraindications to administration of barium

There are no absolute contraindications for the use of barium compounds, although, for reasons already mentioned, 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.

Contraindications to administration of water soluble contrast agents

HOCM at standard fluoroscopic concentrations are contraindicated for oral administration in patients at risk for aspiration. Iso-osmolality or low-osmolality agents are safer for these patients [2,17]. Enteric HOCM in hypertonic concentrations should also be avoided in patients with fluid and electrolyte imbalances, particularly the very young or elderly patients with hypovolemia or dehydration. The very hypertonic HOCM solutions draw fluid into the lumen of the bowel, leading to further hypovolemia [1,60]. Preparations made from nonionic LOCM may be preferable for these patients because, for any given required radiographic density, LOCM will have lower osmolality and will draw less fluid into the bowel lumen.

Small bowel-follow-through examinations

A common dedicated radiographic study of the small intestine is the small bowel follow-through (SBFT) performed using single contrast oral barium and serial overhead radiographs of the abdomen and pelvis in association with selective fluoroscopic imaging and focal abdominal compression. In the recent past (and still today at some institutions), this imaging test has been the routine initial diagnostic study for assessment of the non-obstructed small bowel [61,62], although many small bowel evaluations are now performed with CT or MR enterography.

The SBFT often follows an UGI examination, but sometimes is requested by itself to assess the small bowel for Crohn disease, neoplasm, malabsorption, and a variety of other conditions. Conventional barium may be used, but special barium mixtures with additives, such as citrate or sorbitol, are often added to stimulate the small bowel and to reduce overall transit time of the contrast media to the colon, also potentially reducing the radiation dose. However, there is little evidence-based literature to support this contention, and no specific barium formula can be recommended that satisfy all requirements in all clinical situations. The SBFT may also be useful in the management of small bowel obstruction [63]. While most SBFT examinations are often performed with barium, searches for the presence and location of mechanical obstructions may be undertaken with water-soluble agents if immediate surgery is anticipated or if a proximal small bowel obstruction is suspected.

The peroral SBFT is limited by effects of gastric pH on the barium [3,64,65], intermittency of gastric emptying resulting in loss of continuity of the contrast media bolus, degradation and dilution of the contrast medium in the distal small bowel, and the unpredictable length of the examination.

Small bowel enteroclysis

Enteroclysis was developed in an attempt to obviate the weaknesses of SBFT by bypassing the stomach, gaining more control of the continuity of the contrast bolus, improving small bowel distension, and reducing barium dilution, while also substantially decreasing transit time. This is performed by direct instillation of barium through a nasoenteric or oroenteric tube, and then by rapidly infusing contrast media through the bowel. The resultant examination produces improvements in the depiction of anatomy [66,67].

Later, double contrast enteroclysis was introduced using a large bolus of high density barium followed by an infusion of methylcellulose. The methylcellulose serves the purpose of advancing the barium column more distally, while at the same time producing double contrast images of proximal and mid small bowel loops (since the bowel mucosa of these remains coated with barium after the neutral density methylcellulose has filled the bowel lumen [68-71].

Excellent reviews of small bowel enteroclysis [62,72] and comparison of enteroclysis with the peroral SBFT have demonstrated the efficacy of technical improvements, especially with use of a constant flow infusion pump [73,74].

Patient acceptance of this study is low primarily because of substantial discomfort associated with tube placement, although the degree of discomfort depends upon on the skill of the radiologist performing the examination. Fewer than 1% of patients refused intubation in one study [62]; however, there are no studies documenting the frequency of patient acceptance of subsequent repeat examinations involving intubation. As a consequence, small bowel enteroclysis has now been largely replaced by CT and MRI enterography (see below).

Computed Tomography

A variety of CT techniques are now utilized during which the gastrointestinal tract can be evaluated. Many of these involve administration of oral contrast agents.

Standard abdominal/pelvic computed tomography

Orally administered contrast media are used for gastrointestinal opacification during routine abdominopelvic CT [75]. There is no significant difference in the diagnostic quality of the subsequently obtained CT examinations with barium agents, HOCM, or LOCM, assuming appropriate dilution of contrast material [75].

Oral contrast material administration

Various iodine concentrations of water-soluble contrast media ranging from 4 to 48 mg I/ml have been suggested for bowel opacification with CT. Because dilute, hypotonic contrast solutions become concentrated during their passage through the bowel, the concentration used for oral administration is a compromise between lower Hounsfield unit opacity in the proximal bowel and higher Hounsfield unit opacity in the distal bowel. In general, a solution containing 13 to 15 mg I/ml is recommended for oral and rectal administration in adults [75,76]. Barium products for oral use in CT are commercially available in appropriate concentrations.

Contraindications to oral contrast material

As with conventional fluoroscopic imaging, there are a few specific clinical situations in which water-soluble contrast agents are strongly favored over barium agents for use in CT (see above). The water-soluble HOCMs used for CT are very dilute and hypotonic. Therefore, aspiration and hypovolemia are not specific contraindications to their use. While some concerns have been expressed about possible aspiration in unconscious or severely traumatized patients, dilute water-soluble agents have been used safely in both adults and children [77,78].

Allergic-like reactions to orally administered iodinated contrast media remain a theoretical risk, and are felt to be more relevant to patients known to have had prior reactions to intravascular iodinated contrast agents and those who also have active inflammatory bowel disease in whom studies have shown that active mucosal protection against contrast absorption may be reduced [47].

CT enterography/CT enteroclysis

Indications for CT enterography: CT enterography is currently used for the CT diagnosis and assessment of inflammatory bowel disease, localizing sites of GI tract bleeding [79], and, less commonly, for detection of small bowel neoplasms [80,81]. While small bowel distention can be achieved by the use of high attenuation oral contrast agents (e.g., dilute barium or water-soluble iodinated contrast media) [75,76], there is increasing use of neutral (low attenuation) contrast agents (e.g., 0.1% w/v ultra-low-dose barium with 2% sorbitol - VoLumen; Bracco Diagnostics, Monroe Township, NJ).

In the assessment of Crohn's disease, neutral or low attenuation agents provide the benefit of increasing conspicuity of diseased segments due to the striking contrast between the lower luminal density and the mucosal/mural hyperenhancement and stratification that is produced following intravenous contrast media administration. Also, hypervascular bowel lesions and active bleeding can be detected much more easily on studies performed with neutral oral contrast media as well, since the high attenuation of enhancing lesions or active extravasation of contrast material into bowel lumen stands out when surrounded by the lower attenuation distended bowel lumen. Positive oral contrast media, including both dilute barium and dilute water soluble iodinated contrast media can obscure such abnormalities and is problematic for creating three- dimensional images [75].

Use of neutral contrast agents for CT enterography: VoLumen includes a very small amount of barium as well as sorbitol to promote luminal distention and limit reabsorption of water. It has an attenuation of approximately 20 Hounsfield units (HU) [81], and has been demonstrated to distend the small bowel better than water or water- methylcellulose solutions and equally well as PEG, with fewer side effects than the latter [82,83].

There have been very few reported serious adverse reactions to VoLumen. Some patients experience self- limited side effects, such as nausea, cramping, gassiness, and diarrhea. Similar precautions extend to VoLumen that exist for more concentrated barium. Enteric barium in any concentration should be avoided in any patient who has a known barium allergy or who has a known or suspected non-localized/non- contained bowel perforation. VoLumen is administered by many to patients with contained perforations/ fistulae, however.

Other low attenuation oral contrast agents that have been utilized, albeit much less frequently, for CT enterography include water, lactulose solution, polyethylene glycol (PEG) electrolyte solution [84], Mucofalk, and methylcellulose.

PEG combined with an electrolyte solution (Golytely®; Braintree Laboratories, Inc., Braintree, MA) is an osmotic laxative used routinely for bowel cleansing prior to radiographic colon studies and colonoscopy. On CT, PEG has a similar attenuation as water, but does not have any distal intestinal absorption, thus allowing for better distal bowel distention [84]. Adverse effects include nausea, gastric bloating, abdominal cramping, and diarrhea. Rare allergic reactions have been reported [85].

Lactulose, a synthetic non-digestible sugar that results from combining galactose and lactose, has been mentioned previously in the English literature for use with barium in speeding transit for SBFT examinations [86]. Lactulose creates an osmotic gradient across the intestinal lining, resulting in increased bowel distention. Lactulose diluted in 1250 ml of water has been studied as a contrast agent additive for use with CT enterography in conjunction with IV contrast media injection [87]. With the addition of lactulose, the resorption of water is delayed sufficiently to maintain homogeneous distention throughout the small bowel, including the terminal ileum and cecum. While the side effects of lactulose,

such as diarrhea and dehydration, are slightly greater than those of other contrast agents used for CT enterography, they are counterbalanced to some extent by better visualization of a very important, and sometimes the most important, segment of the small intestine, the terminal ileum. Still, there has been little research on the clinical application of lactulose for improving CT enterography, and it has not been widely adopted, likely due to the increased side effects.

Mucofalk contains psyllium fiber from the outer shell seeds of *Plantago ovata*. These husks retain water in quantities much greater than their weight and can be used to distend the bowel during MR or CT enterography. Allergic and other significant adverse effects may occur, but are rare [88].

CT enteroclysis

CT enteroclysis involves combining the techniques of conventional small bowel enteroclysis with those of CT enterography. Oral contrast agents are administered through an enteric tube whose tip is positioned in the proximal jejunum. This technique has attained favor with some examiners, as the cross-sectional imaging of CT obviates problems caused by overlapping bowel loops during conventional enteroclysis and, as with any CT examination, can evaluate abnormalities outside the GI tract. The administration of oral contrast material via an enteric tube promotes more rapid and uniform small bowel distention than is seen during CT enterography [89]. While CT enteroclysis has shown great reliability for defining sites of partial small bowel obstruction due to adhesions, neoplasms, or other causes [64], like conventional enteroclysis, this study has not been widely accepted due to its invasive nature.

Dosing of oral contrast agents for CT enterography: Discussion of the various dosing strategies that have been suggested for all of these contrast agents is beyond the scope of this review; however, many involve preloading the patient with the agent at least twice before imaging and timing the acquisition of images to assure maximal visualization of the distal ileum, especially when evaluating patients for Crohn disease [80,81]. The reader is referred to previous citations for more information.

CT Colonography (CTC, Virtual Colonography)

Advantages of using computed tomography for assessment of failed optical colonoscopy, for initial screening for colorectal cancer, or for surveillance of known polyps [13] include: high accuracy, full evaluation of the colon in virtually all patients, non-invasiveness, safety, patient comfort, detection of extracolonic findings, and cost-effectiveness [90].

Currently, full bowel preparation is required to achieve optimal results. (See previous section on bowel cleansing.) However, fecal tagging techniques will likely allow for less aggressive, milder and better tolerated, but less cleansing, preparation studies in the near future [91]. Reduced cathartic, mild laxatives and noncathartic methods in combination with contrast fecal tagging are gaining popularity [92,93]. “Electronic” cleansing using post-processing thresholding in conjunction with fecal tagging is also a developing model [94,95]. Further details on the techniques that can be employed for colonic preparation prior to CTC are provided in the paragraphs that follow.

All of these agents can be associated with undesirable levels of diarrhea, which is a challenge to full patient compliance. Reduced bowel cleansing using mild laxatives with oral contrast fecal tagging has demonstrated sufficient fecal tagging while reducing diarrhea [96,97]. The most serious adverse effect of bowel cleansing procedures is the loss of potassium. Hypokalemia is of particular concern in patients on diuretics without potassium supplements. Hypokalemia can be prevented in these patients by potassium administration during the preparation period. Please see reference [98] for more details, if desired.

Oral Contrast Stool Tagging Agents: Oral fecal tagging without cathartics or laxatives has been studied using electronic cleansing subtraction algorithms [95,99]. Several protocols have been advanced for contrast tagging of stool. Oral administration of thick barium, thin barium, and water-soluble iodinated solutions have been employed in variable doses alone or in combination [93,96,100-102], and given at variable intervals before and with oral bowel preparation. High doses of high-osmolality iodinated agents are associated with diarrhea, and efforts have been made to use the lowest dose possible [93]. Barium has the advantage of better tagging of solid stool without tagging liquid components which can cause inhomogeneous tagging [92]. Conversely, high- osmolality iodinated contrast media softens stool, resulting in a more homogeneous mixing with the iodine, a phenomenon that may improve ease of CTC interpretation [95].

Bowel Relaxation Agents: Spasmolytic agents such as glucagon are not routinely used for CTC. In a survey of 33 selected experts in CTC, only 15% responded that they use these agents routinely, while 38% limit use to patients with cramping pain or discomfort [103]. The complications for the use of glucagon are discussed below (see section on ancillary drugs at the end of this chapter).

Bowel Insufflation: In order to accurately detect polypoid and other lesions on CTC, adequate bowel distension is required [13]. Sedation is not required during bowel distention [104]. The least expensive and most easily available gas is room air. The latter is ordinarily introduced manually through a rectal tube. Rare colonic perforations have been reported during insufflation with room air [91,105,106]. As an alternative, CO2, may be insufflated (preferably via a small catheter to improve patient comfort), either manually or via an electronic pump. Faster absorption of CO2by the colonic mucosa compared to room air reduces the gas dissolution time following the procedure, making the entire experience better tolerated [107]. However, a consensus on the adoption of CO2 vs. room air has not yet materialized [103].

CT and Positron Emission Tomography (PET) Scanning

Several authors have shown that any oral contrast media can be used for co-registered PET/CT examinations without the introduction of artifacts [108]. There is no increase in FDG uptake in areas of oral contrast media concentration to confound interpretation. When oral and intravenous enhancement is administered for whole-body PET/CT examinations, good vascular and intestinal enhancement results, without sacrificing PET quality and resulting in potential improvement in diagnostic capability [109].

Magnetic Resonance Imaging (MRI)

Recent improvements in MR image quality and temporal resolution have increased the use of this imaging technique for evaluating the gastrointestinal tract.

Magnetic resonance enterography, enteroclysis, and colonography

As with CT, MR enterographic and colonographic techniques often require distension of the gastrointestinal tract with orally administered contrast media. In many cases, this is achieved with barium suspensions; however, other agents can be utilized that provide differing signal characteristics on the various MR sequences, thereby providing either neutral or positive intraluminal contrast between the bowel lumen and the bowel wall and adjacent structures [110,111].

For MR enterography and enteroclysis, biphasic oral contrast agents, as described below, can be employed to help document presence of disease and therapeutic response in inflammatory bowel disease, as well as to aid in the detection of disease complications, particularly fistulae [112,113].

Biphasic oral agents

Dilute barium suspensions (e.g., VoLumen), water, methylcellulose, and polyethylene glycol all demonstrate low signal intensity on T1-weighted and high signal intensity on T2-weighted images [114,115].

Administration: In general, 900 to 1350 mL (2-3 bottles) of a dilute barium solution will provide adequate distension of the small bowel for diagnostic purposes [116,117]. This will vary, especially in patients who have had multiple small bowel resections (short gut) and those with an ileostomy. Alternatively, a total volume of
1.5 liters of a non-absorbable agent such as a mannitol–locust bean gum mixture or PEG can be used for the examination [114]. Imaging may begin as early as 20 minutes after oral ingestion of the contrast agent in order to ensure that there is adequate distension and of the proximal jejunum [114]; but delayed imaging is also necessary to guarantee optimal distension of the ileum.

Regardless of the biphasic oral contrast agent utilized, a delay of 40 to 60 minutes generally is required from the time of oral ingestion to imaging in order to allow for complete filling of the small bowel [111,115,118]. In some centers, the contrast media is injected via an enteroclysis tube with an automatic electronic pump [119].

Negative oral agents: super paramagnetic contrast media

Previously available negative oral MR contrast agents containing superparamagnetic iron oxide, a substance that has high T1 and T2 relaxivity, resulting in low signal intensity on both T1- and T2-weighted MR images, are not currently available; however, pineapple juice has been used effectively as a substitute, as it is also hypointense on both T1-0 and T2-weighted images [120]. The resultant negative intraluminal contrast can be useful in the detection of both soft tissue tumors and bowel inflammation [121-123]. Negative oral MR contrast agents can also be beneficial in decreasing the fluid signal in bowel, thereby improving visualization of the pancreatic ducts.

The usual volume of negative oral contrast media needed to adequately distend the bowel ranges between 600 to 900 ml. While this can be administered over 30 minutes prior to the onset of imaging, a longer waiting period prior to imaging may be helpful in delineating the lower GI tract. The required administered volume will be decreased in patients with multiple small bowel resections (short gut). For details of concentrations required for optimal diagnostic studies, the reader is referred to the appropriate referenced articles.

Contraindications

The aqueous barium suspensions used for MR are dilute and hypotonic. Therefore, an increased risk of aspiration and concerns related to hypovolemia are not specific contraindications to their use. However, both barium suspension agents and the syperparamagnetic agents used for MR imaging should generally be avoided in cases of possible free non-contained gastrointestinal perforation or just before bowel surgery.

Contrast Agents in the Biliary and Pancreatic Ductal Systems

Following biliary surgery or sphincteroplasty, orally ingested barium commonly can freely reflux into the biliary tree. The placement of biliary stents may also facilitate reflux of enteric contents and barium during an UGI examination. Normally, this is of no consequence, as the barium empties back into the bowel promptly under the influence of gravity and physiological bile flow [124,125].

Potential complications can occur, however, when barium does not drain out of the biliary tree promptly, with most adverse manifestations resulting from overdistention. Delayed emptying or

retention of barium beyond 24 hours has been associated with suppurative cholangitis [126]. Choledocholiths forming after progressive water absorption may occlude the biliary ductal system [127]. Indwelling stents may become occluded, also predisposing patients to cholangitis [128]. Shock and disseminated intravascular coagulation have been encountered in occasional patients [128-130]. Very rarely, in individuals sensitive to barium agents, allergic reactions have been encountered.

Water-soluble iodinated contrast media is intentionally instilled into the biliary ductal system during endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiogaphy, or during intraoperative cholangiography. Small amounts of these agents may be absorbed, resulting in systemic exposure. In one study, serum concentrations of iodinated contrast media increased significantly in up to 76% of patients after ERCP [131]. Measured serum iodine also increases [132]. This is why some contrast media is often excreted into the urine after biliary studies [132,133] and likely why occasional allergic-like reactions are encountered [134].

The frequency of allergic-like reactions in the general population and even in those patients at high risk is quite low in patients undergoing ERCP. Nonetheless, a review of the practices of providers for ERCP in 2000 indicated that the majority were using prophylactic corticosteroids and nonionic low-osmolality iodinated contrast agents in patients perceived to be at higher risk of having adverse allergic-like reactions [135]. Only a minority of practitioners has concluded that routine prophylactic regimens are not needed prior to ERCP, even in high-risk patients [55,136]. Other investigators have recommended substitution of gadolinium based MR contrast media for iodinated contrast media in high-risk patients [137], but large- scale studies validating the efficacy of this substitution have not been performed.

Fluoroscopic/conventional radiographic biliary studies with positive oral biliary agents

Imaging of the gallbladder and the lumen of the biliary tree can be accomplished with the use of twelve 500 mg oral iopanoic acid tablets (Telapaque®, Winthrop Pharmaceuticals, New York, NY) administered the prior evening, with overnight fasting [138-140]. Although rarely performed in North America, intravenous infusions of iodipamide (Cholografin®, Bracco Diagnostic, Inc., and Princeton, NJ) may be administered. The latter is excreted into the biliary system within 20 to 40 minutes, permitting direct visualization of the biliary tree with x-rays or during fluoroscopy [141]. Its use has been diminished in recent decades due to high frequency of contrast reactions [142] and increasing utilization of MRCP.

Assessment of the biliary tree with standard CT

Conventional CT has been employed to evaluate the biliary system for obstruction. Unenhanced imaging may detect calcified bile duct stones, while CT with conventional intravenous contrast media enhancement may detect non-calcified stones associated with surrounding mural thickening and enhancement [143]. Minimum intensity projection images of the liver and biliary tree have been found to be effective in assessing dilated bile ducts during standard portal venous phase CT [144,145]. CT imaging of the biliary ductal lumen can also be accomplished with the use of twelve 500 mg oral iopanoic acid tablets (Telapaque®, Winthrop Pharmaceuticals, New York, NY) administered the prior evening with overnight fasting [138-140]. Although rarely performed in North America, intravenous infusion of iodipamide (Cholografin®, Bracco Diagnostic, Inc., Princeton, NJ) may be administered for use with CT, as well. The latter is excreted into the biliary system within 20 to 40 minutes [141]. Again, its use has been diminished in recent decades due to frequency of contrast reactions [142].

CT and MR cholangiopancreatography

MR and CT cholangiopancreatography are employed in the assessment of the hepatobiliary and

pancreatic ductal systems for evaluation of strictures, stones, and neoplasms. Their uses also extend to preoperative planning for anticipated liver transplantation and for postoperative assessment of patients who have received liver transplants. These modalities have advantages over ERCP since the latter is invasive and carries 3% to 9% complication and 0.2 % to 0.5% mortality rates [143]. Contrast-enhanced CT cholangiopancreatography has also been used in these clinical situations [141,146-148], but has not become as popular as MRCP. CT is less prone to certain artifacts [143] and is more easily performed in sick patients (who can be better monitored in the CT than the MR suite). However, MRCP has become most widely accepted. Modern respiratory-gated 3D T2-weighted MRCP studies better image the biliary tree when compared to traditional 2D techniques and have the advantage of not exposing patients to ionizing radiation.

Standard 2D and 3D MRCP techniques require no oral contrast material administration, and exploit the relatively high signal intensity of static fluids in the biliary tract and pancreatic ducts on heavily T2-weighted images [143,149]. Some authors have advocated the use of oral contrast materials that are of low signal intensity on both T1- and T2-weighted imaging (see above) when 2D imaging is being performed and the pancreatic duct is the primary structure of interest. Such oral contrast materials minimize superimposed signal hyperintensity from fluid in overlying bowel.

Intravenous contrast-enhanced MRCP may be performed with fat-saturated T1-weighted imaging using gadolinium-based contrast agents excreted into the bile. Agents such as gadobenate dimegumine (MultiHance® Bracco Diagnostics, Inc., Location) or gadoxetate disodium (Eovist®; Bayer Healthcare Pharmaceuticals, Wayne, NJ) are used for this purpose, especially for anatomic mapping of the biliary tree prior to living donor liver transplantation and for detection of biliary leaks after liver transplantation [143,150].

With respect to the use of gadolinium-based MR contrast agents, precautions must be taken in patient selection and renal function screening to preclude later development of nephrogenic systemic fibrosis (NSF) (See the chapter on NSF).

Ancillary drugs

Glucagon

The pharmacologic agent most widely used in the United States to prevent or treat bowel spasm or discomfort during imaging studies is glucagon [151,152]. Glucagon may be used to relax the bowel in double contrast studies of the upper GI tract, in conjunction with small bowel examinations such as CT or MR enterography, and during barium enema studies, most commonly during double contrast barium enemas. Most of the beneficial effects of glucagon on the upper GI tract can be gained with small IV doses of 0.1 to 0.25 mg lasting for 8 to 12 minutes [153]. During double contrast UGI exams, a dose of 0.1 mg is enough to relax the stomach in order to retain administered effervescent granules. The effective dose of glucagon when used during barium enemas is 1 to 2 mg given intravenously (usually 1 mg), a dose which limits the duration of pharmacologic activity to less than 30 minutes [154]. 0.5-1 mg IV or IM glucagon is also commonly used for MR enterography in order to minimize motion artifacts from bowel peristalsis.

Untoward side effects from IV glucagon include nausea and vomiting, which can be reduced by slow administration of the drug over 1 to 5 minutes [154], as well as vasovagal reactions [151]. Intramuscular glucagon has delayed onset of action when compared to IV administration and a longer duration of action [155]. Delayed hypoglycemia has been documented in some patients [154], although this is usually not clinically significant. The package insert for glucagon (GlucaGen; Bedford Laboratories; Bedford, OH) recommends oral carbohydrate administration after glucagon administration following diagnostic procedures to rebuild body glycogen stores and avoid hypoglycemia.

Hyocyamine Sulfate

Hyocyamine sulfate, an anticholinergic medication, is a naturally occurring tertiary amine isomer of atropine used in the GI tract as a spasmolytic agent in patients with irritable bowel syndrome. There has been interest in its use in diagnostic radiology as an oral option to parenteral glucagon, which is also far more expensive.

Hyocyamine has adverse effects limiting its use in patients where anticholinergic blockade might cause problems, such as in patients with bladder outlet obstruction, severe ulcerative colitis, myasthenia gravis, and cardiac arrhythmias [151]. Its effectiveness in reducing discomfort associated with diagnostic imaging studies and significantly maximizing bowel relaxation may not be as great as that of other agents [151,156], which explains why this agent alone has not been used widely.

Hyoscinebutylbromide (butylscopolamine)

The agent hyoscine butylbromide (scopolamine), which is another anticholinergic, has also been utilized to decreased peristalsis [157]; however, it has not been as effective as glucagon in some studies [158]. One investigation actually found that a combination of IV glucagon and IM hyoscine butylbromide to be most effective in inhibiting peristalsis [159].

Metoclopramide

Metoclopramide (Reglan®; Pfizer, New York, NY) can be administered as an intestinal stimulant. Metoclopramide promotes motility of the upper gastrointestinal tract without stimulating gastric, biliary, or pancreatic secretions. Administration can be performed to increase small bowel transit or to assist in passage of enteric feeding tubes. The mode of action of metoclopromide is unclear; however, it appears to sensitize tissues to the actions of acetylcholine. Metoclopramide increases the tone and amplitude of gastric (especially antral) contractions, relaxes the pyloric sphincter and the duodenal bulb, and increases peristalsis of the duodenum and jejunum, resulting in accelerated gastric emptying.

Metoclopramide can be given intravenously, intramuscularly, or orally. The intravenous dose is 10 mg given slowly over a 1 to 2 minute period, either undiluted or diluted in sterile saline solution. The intramuscular dose is 10 mg, while the oral dose usually consists of two 10 mg tablets. The onset of pharmacological action of metoclopramide is 1 to 3 minutes following an intravenous dose, 10 to 15 minutes following intramuscular administration, and 20 to 60 minutes following an oral dose of two 10 mg tablets. Pharmacological effects persist for 1 to 2 hours [83,160].

Metoclopramide should not be given to patients with pheochromocytoma, as it may stimulate release of catecholamines from the tumor, or to epileptics, who are sensitive to its extrapyramidal effects [161].

Other adverse reactions to the single doses of metoclopramide used in the fluoroscopy suite are exceedingly rare. However, in larger and more regularly administered dosages, adverse reactions are much more common, with manifestations including extrapyramidal symptoms, such as acute dystonia, Parkinsonian symptoms, depression, and tardive dyskinesia. Tardive dyskinesia, which occurs as a side effect of any drug that blocks dopamine [162,163], is a neurologic condition causing a tongue, mouth and jaw disorder in which eye-blinking and face and body jerking can occur, along with difficulty swallowing. Tardive dyskinesia can persist for years and may be permanent. The potential for this adverse effect is directly related to length of drug use. Since metoclopramide is only given once in conjunction with diagnostic gastrointestinal imaging studies, tardive dyskinesia is not a serious concern.

Secretin

Biologic secretin in no longer available, but is manufactured in a synthetic version (ChiRhoClin®, Inc.,

Silver Springs, MD). Secretin can be administered to stimulate pancreatic fluid and bicarbonate secretion during MRCP. This improves ductal delineation as the increased generated ductal fluid volume results in greater ductal distension [149,164,165].

Secretin is safely administered to most patients, but its use should be avoided in patients with acute pancreatitis, as symptoms can be exacerbated [166]. Other immediate side effects may be encountered, with the most common symptoms including flushing of the face, neck, and chest. Less commonly, some patients may develop vomiting, diarrhea, fainting, blood clot, fever, and tachycardia. Allergic-like reactions are rare, but have been reported, with symptoms of these including hives, redness of the skin, and even anaphylaxis.

Treatment of adverse reactions to GI contrast agents and ancillary drugs

Every radiology department should have an infrastructure in place wherever oral contrast media and drugs are administered, wherein the staff, from technologist to examining physician can be made aware of any allergic history, active asthma, or potential co-morbidities (e.g., dehydration, and known inflammatory bowel conditions that may alter permeability of the intestinal mucosa) that may place patients at increased risk for adverse events related to the administration of oral contrast agents (and the medications that are occasionally administered when these agents are used). Every department should also have a mechanism in place to evaluate and treat the rare adverse reactions to oral contrast agents, both non-allergic and allergic, that are encountered from time to time.

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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

Last updated: 2 June 2014

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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Revision History

2 June 2014: Major revisions

15 April 2013: Minor revisions

26 June 2012: Minor revisions May

2008: First version

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 fi 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*.

Chronic kidney disease

Based on current knowledge, it is estimated that patients with end-stage CKD (CKD5, eGFR <15 ml/min/1.73 m^2) and severe CKD (CKD4, eGFR 15-29 ml/min/1.73 m^2) 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 m^2 than to 30 ml/min/1.73 m^2. There has been only one published case report of a patient with eGFR values above 30 ml/min/1.73 m^2 [10].

Acute kidney injury (AKI)

Between 12% and 20% of confi cases of NSF have occurred in patients with AKI, often superimposed upon CKD [11,12]. Some cases of NSF have developed in patients with AKI without underlying CKD [13]. 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 [5,14]. 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 [6,15].

Most patients with severe CKD exposed to high doses and/or many doses of GBCAs have not developed NSF [5]. One study [16] described 30 patients who had an eGFR of under 30 ml/min/1.73 m^2 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 [17]. 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 [18].

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 [1,19]; elevated iron, calcium, and/or phosphate levels [19,20]; high-dose erythropoietin therapy [11]; immunosuppression [6]; vasculopathy [21]; and infection [22] or other acute proinflammatory events [4,23]. However, none of these have been consistently confi 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" [24]. However, most data do not support this conclusion. For example, in one study, a review of the literature found that of 291 patients with NSF, 34 (12%) had concomitant liver disease [25]; however, all but one of these patients also had known severe renal insufficiency (eGFR of <30 ml/min/1.73 m^2) 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 [9,26]. A fibrotic reaction ensues, involving the activation of circulating fibrocytes [26,27]. This hypothesis is supported by the greater presence of gadolinium in affected tissues of NSF patients relative to unaffected tissues [28]. 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 [29].

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

Group II agents

Based on the most recent scientific and clinical evidence [30-37] 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]

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 m^2) without dialysis
- AKI [38,39]

There is insufficient real-life data to determine the risk of NSF from administration of group III agents, despite an alternative excretion pathway for hepatobiliary 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 m^2 [40].

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 [41,42] and expert opinion; alternative lists may be as or more effective depending on practice patterns:

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[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.

- History of renal disease, including:
  - Dialysis
  - Kidney transplant
  - Single kidney
  - Kidney surgery
  - History of known cancer involving the kidney(s)
- History of hypertension requiring medical therapy
- History of diabetes mellitus

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, race, 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*) 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 are 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 [24].

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 [43]. 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 also recommends that elective GBCA-enhanced MRI examinations be performed as closely before hemodialysis as is possible, as prompt postprocedural hemodialysis, although unproven to date, may reduce the likelihood that NSF will develop. Some experts recommend multiple dialysis sessions following GBCA administration, with use of prolonged dialysis times and increased flow rates and volumes to

facilitate GBCA clearance, but the incremental benefits remain speculative. When using a group II agent, the risk of NSF is so low that the ACR Committee on Drugs and Contrast Media believes that the risk-benefit equation does not favor repeated dialysis sessions.

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/1.73m^2) 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 m^2)

NSF developing after GBCA administration to patients with stable eGFR 30-59 ml/min/1.73 m^2 is exceedingly rare. No special precautions are necessary in this group [44,45].

Patients with CKD 1or2 (eGFR60to119mlmin/1.73m^2)

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 [17]. 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 [46] 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 m^2 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)

Group III: Agents for which data remains limited regarding NSF risk, but for which few, if any unconfounded cases of NSF have been reported:

Gadoxetate disodium (Eovist – Bayer HealthCare Pharmaceuticals; Primovist in many countries)

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 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. Hypertension requiring medical therapy
3. Diabetes mellitus

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Revision History

15 May 2017: Major revisions

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 Imagings

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 [61]. Another large retrospective study evaluating the use of SonoVue in 23,188 subjects documented 29 adverse events, with only two considered serious [62]. 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.

Revision History

15 January 2020: Minor revisions

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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.

IIntravenous 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 classifiying 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 significicantly 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 premediction 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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Revision History

15 May 2017: Minor revisions

28 June 2015: Major revisions

23 June 2010: Minor revisions

ADMINISTRATION OF CONTRAST MEDIA TO WOMEN 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 [1,2]. In addition, less than 1% of the contrast medium ingested by the infant is absorbed from its gastrointestinal tract [3]. 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 related to an imaging study (usually 1.5 to 2 mL/kg). The potential risks to the infant include direct toxicity and allergic sensitization or reaction, which are theoretical concerns but have not been reported.

The likelihood of either direct toxic or allergic-like manifestations resulting from ingested iodinated contrast material in the infant is extremely low. As with other medications in milk, the taste of the milk may be altered if it contains contrast medium [1-4].

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, we believe that the available data suggest that it is safe for the mother and infant to continue breast-feeding after receiving such an agent.

Ultimately, 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. There is no value to stop breast feeding beyond 24 hours. 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.

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 [6].

Less than 0.04% of the intravascular dose given to the mother is excreted into the breast milk in the first 24 hours [4-6]. Because less than 1% of the contrast medium ingested by the infant is absorbed from its gastrointestinal tract [6,7], 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 [2]). 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 [5]. As in the case with iodinated contrast medium, the taste of the milk may be altered if it contains a gadolinium-based contrast medium [2].

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, we believe that the available data suggest that it is safe for the mother and infant to continue breast-feeding after receiving such an agent [6].

Ultimately, 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. There is no value to stop breast feeding beyond 24 hours. The mother should be told to express and discard breast milk form both breast 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.

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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: 28 August 2015

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	
	O_2 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 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 1:1,000 dilution (0.01 mg / kg); max 0.30 mL (0.30 mg); can repeat every 5-15 minutes up to
		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)
	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	
	O_2 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 1:1,000 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)
	or	
	Epinephrine (IV)*	IV 0.1 mL / kg of 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 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 1:1,000 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 (1:1,000 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	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	
	O_2 by mask	6–10 L / min
		IV 0.1 mL / kg of 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 1:1,000 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	
	O_2 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 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 1:1,000 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 (1:1,000 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.

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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	
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 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	
	O_2 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	
	O_2 by mask	6–10 L / min
If unremitting	Call emergency response team or 911	

HYPOGLYCEMIA

	Treatment	Dosing
All forms	Preserve IV access	
	O_2 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

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: 28 August 2015

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	
	O_2 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	Epinephrine (IV)*	IV 1 mL of 1:10,000 dilution
	or (if no IV access available)	
	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) (0.3mL of 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	
	O_2 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 1:1,000 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 1:1,000 dilution, fixed [0.3mg]); can repeat every 5-15 minutes up to three times
	or	
	Epinephrine (IV)*	IV 1 mL of 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 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 1:1,000 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	
	O_2 by mask	6–10 L / min
		IV 1 mL of 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 1:1,000 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 1:1,000 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**
	O_2 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 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 1:1,000 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 o1:1,000 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

(diastolicBP> 120mmHg; systolicBP> 200mm Hg; symptoms of endorgan compromise)

	Treatment	Dosing
All forms	Preserve IV access	
	Monitor vitals	
	Pulse oximeter	
	O_2 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	
	O_2 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	
	O_2 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	
	O_2 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

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

Lastupdated: 12December2014

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)
INTRAVASCULAR						
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
Cholografin® (Bracco)	iodipamide (520)	Ionic	257	6.6	5.6	664

[+] 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 20o 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 **continues on next page**

Appendix A – CONTRAST MEDIA SPECIFICATIONS (continued)

GASTROINTESTINAL – Non-Barium Oral Contrast [O]

Gastrografin® (Bracco)	diatrizoate meglumine sodium (660)	Ionic	367		8.4	1940
MD-Gastroview™ (Guerbet)	diatrizoate meglumine sodium (660)	Ionic	367			2000
Omnipaque™ 180 (GE Healthcare)	iohexol (388) pediatric use	Nonionic	180	3.1*	2.0	331
Omnipaque™ 240 (GE Heathcare)	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 58% w/w			
Liquid Polibar (Bracco)	barium sulfate		100% w/v			
E-Z-Paque / Pilibar ACB (Bracco)	barium Sulfate		96% w/w			
Liquid E-Z-Paque (Bracco)	barium sulfate		60% w/v 41% w/w			
Readi-cat (Bracco)	barium sulfate		1.3% w/v			
Readi-cat 2 (Bracco)	barium sulfate		2.1% w/v			
Esopho-Cat (Bracco)	Barium sulfate		3% w/v			
Entero Vu (Bracco)	barium sulfate		24% w/v			
Tagitol™ (Bracco)	barium sulfate		40% w/v 30% w/w			
Varibar® (Bracco)	Barium sulfate in variable consistency		40% w/v			
Volumen® (E-Z-EM Inc/Bracco)	barium sulfate		0.1% w/v 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 20o 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.

***Appendix A* continues on next page**

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+Osmolality Osm/kg H2O) 37° C (cp(m or mPa.s)
Cystografin® (Bracco)	diatrizoate	Ionic	141		
CystoConray™ II (Guerbet)	iothalamate (172)	Ionic	81	(Only for retrograde cystography and cystourethrography)	00
Conray™ 43 (Guerbet)	iothalamate (430)	Ionic	202	3	2 1000
Omnipaque™ Can be diluted for retrograde use. See package insert	iohexol	Nonionic			

INTRATHECAL

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/ kgH2O)	Log k Therm (cond7.4)
Magnevist® (Bayer Healthcare)	Gd-DTPA Linear Ionic	Gadopentetate	Dime-glumine	4.9*	2.9	4.1(3.7)	1960	22.5 (18.4)
Prohance® (Bracco)	Gd-HP-D03A Macro- cyclic	Gadoteridol	None	2.0*	1.3	4.1(3.7)	630	23.8 (17.2)
Multihance® (Bracco)	Gd-BOPTA Linear Ionic	Gadobenate	Dime-glumine	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™ (Mallinck-rodt)	Gd-DTPA-BMEA Linear Non-ionic	Gadoverset-amide	None	2.8**	2.0	4.7(4.5)	1110	16.8 (15)
EOVIST/Primovist® (Bayer Healthcare)	Gd-EOB-DTPALinear Ionic	Gadoxetate	Disodium		1.19	6.9(6.2)	688	23.5 (18.7)
Gadavist/Gadovost™ (Bayer Healthcare)	Gd-BT-D03A Macro- cyclic Non-ionic	Gadobutrol	None		4.96	5.2 (5)	1603	21.8 (15.5)
Dotarem® (Guerbet)	Gd-DOTA Macrocy- clic Ionic	Gadoterate	Meglu-mine	3.4*	2.4	3.6(3.5)	1350	25.6 (19.3)
Ablavar/Vasovist® (Lantheus)	MS-325 Linear Ionic	Gadofosveset	Trisodium	3.0*	2.1	19 (10)	825	22.1 (18.9)

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 20o 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

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