



ACR Manual on Contrast Media

Version 10.2

2016

**ACR Committee on
Drugs and Contrast Media**

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and Contrast Media**



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Preface

This 10th 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.

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VERSION HISTORY

Version 10.2

Version 10.2 of the ACR Manual on Contrast Media was published in June 2016 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:

Date	Chapter	Change
6-15-2016	Chapter 13	A collaborative statement on gadolinium deposition was added to the manual
6-15-2016	Table 1	Deleted
6-15-2016	Table 2	Deleted
6-15-2016	Chapter 9 – Metformin	Updated footnote based on new FDA advisory
6-15-2016	Chapter 4 – Injection of Contrast Media	New section on intra-osseous injection

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

General Considerations

The approach to patients about to undergo a contrast-enhanced examination has three general goals: 1) to assure that the administration of contrast is appropriate for the patient and the indication; 2) to minimize the likelihood of a contrast reaction; and 3) to be fully 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, preparing the patient appropriately for the examination, having equipment available to treat reactions, and ensuring that expertise sufficient to treat even the most severe reactions is readily at hand. Although mild reactions to contrast media are relatively common, they are almost invariably self-limited and of no consequence. Severe, life-threatening reactions, although rare, can occur in the absence of any specific risk factors with any type of media.

The history obtained should focus on identification of factors that may indicate either a contraindication to contrast media use or an increased likelihood of a reaction.

Risk Factors for Adverse Intravenous Contrast Material Reactions

Allergy: With regard to specific risk factors, a history of a prior allergy-like reaction to contrast media is associated with an up to five fold increased likelihood of the patient experiencing a subsequent reaction [1]. Additionally, any allergic diathesis predisposes individuals to reactions. This relationship is a difficult one to define, since many individuals have at least a minor allergy, such as seasonal rhinitis, and do not experience reactions. True concern should be focused on patients with significant allergies, such as a prior major anaphylactic response to one or more allergens.

The predictive value of specific allergies, such as those to shellfish or dairy products, previously thought to be helpful, is now recognized to be unreliable [2-3]. A significant number of health care providers continue to inquire specifically into a patient's history of "allergy" to seafood, especially shellfish [4]. There is no evidence to support the continuation of this practice [4-5].

Any patient who describes an "allergy" to a food or contrast media should be questioned further to clarify the type and severity of the "allergy" or reaction, as these patients could be atopic and at increased risk for reactions [2]. Most forms of atopy result in a 2 to 3 times likelihood of contrast reaction compared with non-atopic patients [2]. However, considering the rarity of severe life-threatening anaphylaxis, this level of incremental risk remains low and should be considered in the context of risk versus benefit.

Asthma: A history of asthma may indicate an increased likelihood of a contrast reaction [1,6].

Renal Insufficiency: Another specific risk category is renal insufficiency [7]. Discussion of contrast-induced nephrotoxicity (CIN) and nephrogenic systemic fibrosis (NSF) can be found in the Chapters on [Contrast-Induced Nephrotoxicity](#) and [NSF](#).

Cardiac Status: Patients with significant cardiac disease may be at increased risk for contrast reactions. These include symptomatic patients (e.g., patients with angina or congestive heart failure symptoms with minimal exertion) and also patients with severe aortic stenosis, primary pulmonary hypertension, or severe but well-compensated cardiomyopathy. In all such patients, attention should be paid to limiting the volume and osmolality of the contrast media.

Anxiety: A general category that deserves attention is emotional state. There is anecdotal evidence that severe adverse effects to contrast media or to procedures can be mitigated at least in part by reducing anxiety. It may be useful, therefore, to determine whether a patient is particularly anxious and to reassure and calm that patient before contrast injection. This issue was studied with reference to anxiety thought to be generated by informed consent of risks associated with intravenous (IV) contrast procedures [8]. Using a standardized anxiety index, it was concluded that the majority of patients who were and were not informed had equally elevated anxiety, and there was no increase in adverse reactions in the informed group.

Miscellaneous Risk Factors: There are several other specific risk factors that deserve attention.

Paraproteinemias, particularly multiple myeloma, are known to predispose patients to irreversible renal failure after high-osmolality contrast media (HOCM) administration due to tubular protein precipitation and aggregation; however, there is no data predicting risk with the use of low-osmolality or iso-osmolality agents.

Age, apart from the general health of the patient, is not a major consideration in patient preparation [1]. In infants and neonates, contrast volume is an important consideration because of the low blood volume of the patient and the hypertonicity (and potentially detrimental cardiac effects) of even nonionic monomeric contrast media. Gender is not considered a major risk factor for IV contrast injection.

Some retrospective case control studies suggest a statistically significant risk that the use of beta-adrenergic blocking agents lowers the threshold for and increases the severity of contrast reactions, and reduces the responsiveness of treatment of anaphylactoid reactions with epinephrine [9].

Others have suggested that sickle cell trait or disease increases the risk to patients; however, in neither case is there evidence of any clinically significant risk, particularly after the injection of low-osmolality contrast media (LOCM) [10].

Concomitant use of certain intra-arterial injections, such as papaverine, is believed to lead to precipitation of contrast media during arteriography. There have been reports of thrombus formation during angiography using nonionic as opposed to ionic agents. In both cases, there are in-vitro studies that suggest possible explanations.

Some patients with pheochromocytoma develop an increase in serum catecholamine levels after the IV injection of HOCM. A subsequent study showed no elevation of catecholamine levels after the IV injection of nonionic contrast media [11]. Direct injection of either type of contrast medium into the adrenal or renal artery is to be avoided, however, as this may cause a hypertensive crisis.

Some patients with hyperthyroidism or other thyroid disease (especially when present in those who live in iodine-deficient areas) may develop iodine-provoked delayed hyperthyroidism. This effect may appear 4 to 6 weeks after the IV contrast administration in some of these patients. This can occur after the administration of any iodinated contrast media. It is usually self-limited.

Patients with carcinoma of the thyroid deserve special consideration before the IV or oral administration of iodinated contrast media (ionic or nonionic). Uptake of I-131 in the thyroid becomes moderately decreased to about 50% at one week after iodinated contrast injection but seems to become normal within a few weeks. Therefore, if systemic radioactive iodine therapy is part of planned treatment, a pretherapy diagnostic study of the patient using an iodinated radiographic contrast medium (intravascular or oral) may

be contraindicated; consultation with the ordering clinician prior to contrast administration is recommended in these patients.

Intravenous injections may cause heat and discomfort but rarely cause pain unless there is extravasation. Intra-arterial contrast injections into peripheral vessels in the arms, legs, or head can be quite painful, particularly with HOCM. For such injections, iso-osmolality contrast media (IOCM) are associated with the least amount of discomfort.

Premedication

The primary indication for premedication is pretreatment of “at-risk” patients who require contrast media. In this context, “at risk” means at higher risk for an acute allergic-like reaction.

The etiological mechanisms of anaphylactoid contrast reactions are incompletely understood as well as the basis of prevention with the use of corticosteroids [12]. Approximately 90% of such adverse reactions are associated with direct release of histamine and other mediators from circulating basophils and eosinophils. It is now generally accepted that most adverse allergy-like reactions are not associated with the presence of increased IgE and, therefore, unlikely to be truly allergic. However, some studies show definite evidence of IgE mediation [13]. No antibodies to IV contrast media have been consistently identified, and according to skin testing and basophil activation, IgE-mediated allergy is uncommon, occurring in 4% of patients having anaphylaxis symptoms [14]. Pathophysiologic explanations include activation of mast cells and basophils releasing histamine, activation of the contact and complement systems, conversion of L-arginine into nitric oxide, activation of the XII clotting system leading to production of bradykinin [10], and development of “pseudoantigens” [15].

Considerable evidence exists in the medical literature that radiographic contrast media reactions arise from mediators released by circulating basophils. Dose response studies in humans of the suppression of whole blood histamine and basophil counts by IV methylprednisone [16] show a reduction in circulating basophils and eosinophils by the end of the first postinjection hour, reaching statistical significance compared with controls by the end of the second hour, and maximal statistical significance at the end of 4 hours. The reduction of basophils is greater than eosinophils. A reduction of histamine in sedimented leukocytes is also noted at 4 hours. Many of these effects reach their maximum at 8 hours.

The foregoing may provide some rationale for the use of IV steroids for “at risk” patients in emergency situations. Although some corticosteroid preventative effect may be gained as quickly as 1 hour after IV injection of corticosteroids, the experimental data would support a much better prophylactic effect if the examination can be delayed for at least 4 to 6 hours after giving premedication [10,17-18]. If this time interval is not clinically possible, some would omit the use of corticosteroids entirely and give only H1 blockers prior to injection of contrast [17]. However, it should be emphasized that no clinical studies have unequivocally demonstrated prevention of contrast reactions using short-term IV corticosteroid premedication.

The osmolality of the contrast agent as well as the size and complexity of the molecule has potential influence on the likelihood of contrast reactions. Hyperosmolality is associated with the stimulation of release of histamine from basophils and mast cells. Increase in the size and complexity of the contrast molecule may potentiate the release of histamine [19-20]. There is some evidence to suggest that nonionic monomers also produce lower levels of histamine release from basophils compared with high-osmolality ionic monomers, low-osmolality ionic dimers and iso-osmolality nonionic dimers [20]. A large nonrandomized nonblinded study suggests significantly greater safety of nonionic contrast agents [1]. Similar safety margins have been

claimed in other nonrandomized trials [21]; however, no definitive unbiased randomized clinical trials exist that demonstrate significant reduction in severe reactions and fatality [21]. Low-osmolality contrast agents also reduce the non-idiosyncratic physiologic reactions that are not related to allergy. For these reasons there is general agreement that the safety margin for low-osmolality contrast agents is better than that for ionic high-osmolality agents.

Before deciding to premedicate an “at risk” patient, some consideration should be given to the goals of such premedication. Ideally, one would like to prevent all contrast reactions, including minor, moderate, and severe ones. However, it is most important to target premedication to those who, in the past, have had moderately severe or severe reactions requiring treatment. Unfortunately, studies have thus far indicated that the main contrast reactions that benefit from premedication are minor ones requiring no or minimal medical intervention [18]. No randomized controlled clinical trials have demonstrated premedication protection against severe life-threatening adverse reactions [10,22-23]. But this may be attributed to the rarity of life-threatening reactions to contrast and the prohibitive numbers of subjects necessary for enough statistical power to demonstrate any beneficial effect of premedication in preventing the most severe contrast reactions.

Risk of Corticosteroids: Although the risk of a few doses of oral corticosteroids is extremely low [17], precautions must be taken when administering a short course of steroids to some patients. Corticosteroids should be used with caution in patients with uncontrolled hypertension, diabetes [24], tuberculosis, systemic fungal infections, peptic ulcer disease or diverticulitis [17]. The relative risk for the use of corticosteroids compared to the likelihood of severe or fatal contrast reaction must be considered. Anaphylactoid reactions to oral glucocorticoids have been rarely reported [36].

In comparison, there have been more frequent reports of serious reactions to IV injections of frequently used corticosteroids [17,25-29]. The most common offenders are the succinate esters of methylprednisolone sodium (Solu-Medrol®) [26,29] and hydrocortisone sodium succinate (Solu-Cortef®) [30]. Some have suggested that non-succinate glucosteroids, such as betamethasone or dexamethasone sodium sulfate (Decadron®), may be safer for intravenous use [29,31], based on follow-up skin prick tests on patients showing anaphylactic symptoms. Cross reactivity of topical and systemic steroids has been described in asthmatics resulting in bronchospasm after injecting the latter [30]. Increased risk for adverse reactions to corticosteroids has been seen more commonly in patients with asthma, particularly if those patients also have acetylsalicylic acid/nonsteroidal anti-inflammatory drug intolerances [26,30].

Pretesting: Preliminary intradermal skin testing with contrast agents is not predictive of adverse reactions, may itself be dangerous, and is not recommended [13-14,32].

Premedication strategies

Oral administration of steroids is preferable to IV administration, and prednisone and methylprednisolone are equally effective. It is preferred that steroids be given beginning at least 6 hours prior to the injection of contrast media regardless of the route of steroid administration whenever possible. It is unclear if administration for 3 hours or fewer prior to contrast reduces adverse reactions. Dunsky et al [16] experimentally established a theoretical scientific basis for such a strategy, but actual demonstration of clinical effects is not, to date, proved. Supplemental administration of an H-1 antihistamine (e.g., diphenhydramine), orally or intravenously, may reduce the frequency of urticaria, angioedema, and respiratory symptoms.

Additionally, ephedrine administration has been suggested to decrease the frequency of contrast reactions, but the use of this medication is not advised in patients with unstable angina, arrhythmia, or hypertension. In fact, inclusion of ephedrine in a routine premedication protocol is not recommended.

In one clinical study, addition of the H-2 antihistamine cimetidine to the premedication protocol resulted in a slight increase in the repeat reaction rate [33].

Specific Recommended Premedication Regimens

Several premedication regimens have been proposed to reduce the frequency and/or severity of reactions to contrast media.

Elective Premedication

Two frequently used regimens are:

1. Prednisone – 50 mg by mouth at 13 hours, 7 hours, and 1 hour before contrast media injection, plus Diphenhydramine (Benadryl®) – 50 mg intravenously, intramuscularly, or by mouth 1 hour before contrast medium [12].

or

2. Methylprednisolone (Medrol®) – 32 mg by mouth 12 hours and 2 hours before contrast media injection. An anti-histamine (as in option 1) can also be added to this regimen injection [34].

If the patient is unable to take oral medication, 200 mg of hydrocortisone intravenously may be substituted for oral prednisone in the Greenberger protocol [35].

Emergency Premedication (In Decreasing Order of Desirability)

1. Methylprednisolone sodium succinate (Solu-Medrol®) 40 mg or hydrocortisone sodium succinate (Solu-Cortef®) 200 mg intravenously every 4 hours (q4h) until contrast study required plus diphenhydramine 50 mg IV 1 hour prior to contrast injection [35].
2. Dexamethasone sodium sulfate (Decadron®) 7.5 mg or betamethasone 6.0 mg intravenously q4h until contrast study must be done in patient with known allergy to methylpred-nisolone, aspirin, or non-steroidal anti-inflammatory drugs, especially if asthmatic. Also diphenhydramine 50 mg IV 1 hour prior to contrast injection.
3. Omit steroids entirely and give diphenhydramine 50 mg IV.

Note: IV steroids have not been shown to be effective when administered less than 4 to 6 hours prior to contrast injection.

Changing the Contrast Agent to be Injected

In patients who have a prior, documented contrast reaction, the use of a different contrast agent, has been advocated and may sometimes be protective [36]. However, a change from one to another low-osmolality agent generally appears to provide little or no benefit [37]. An optional switch to a different agent may be combined with a pre-medication regimen.

Breakthrough Reactions

Studies to date have demonstrated a decrease in overall adverse events after steroid premedication before contrast injection, but no decrease in the incidence of repeat severe adverse events [34]. This may be due to the infrequency of severe life-threatening reactions to iodinated contrast. Frequency and severity of repeat contrast reactions in premedicated patients (so-called breakthrough reactions) was recently studied [37-38] resulting in several important conclusions: 1) Breakthrough reaction severity, signs, and symptoms are most often similar to the index reaction; 2) The majority of low-osmolality contrast injections in premedicated patients with a prior breakthrough reaction will not result in a repeat breakthrough reaction; 3) Patients with a mild index reaction have an extremely low risk of developing a severe breakthrough reaction; 4) Patients with a moderate or severe index or breakthrough reaction are at higher risk for developing another moderate or severe reaction should breakthrough occur; 5) Severe allergies to any other substance (which includes IV iodinated contrast) are associated with a somewhat higher risk of developing a moderate or severe breakthrough reaction. This is also true of patients with more than four allergies, any drug allergy, and chronic use of oral corticosteroids [37].

Other considerations

No premedication strategy should be a substitute for the preadministration preparedness discussed in this manual. Contrast reactions occur despite premedication prophylaxis [38]. The radiologist must be prepared and able to treat these reactions. Most commonly, a repeat reaction will be similar to the patients' initial reaction; however, there is a chance that a recurrent reaction will be more or less severe [38].

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Injection of Contrast Media

Last updated: 10 June 2016

General Considerations

Injection methods vary depending on vascular access, clinical problems, and type of examination. 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 Guideline for the Use of Intravascular Contrast Media](#).

Referring to the FDA-mandated package inserts may be appropriate in determining the 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 clots forming. 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 the proper technique is used, contrast medium can be safely administered intravenously by power injector, even at high-flow rates.

Technique

To avoid potential complications, the patient's full 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. 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 higher. 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 is used, a flow rate of no greater than 1.5 ml/sec may be more appropriate.

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. Before initiating the injection, the position of the catheter tip should be checked for venous backflow. If backflow is not obtained, the catheter may need adjustment, and a saline test flush or special monitoring of the site during injection may be appropriate. If the venipuncture site is tender or infiltrated, an alternative site should be sought. If

venous backflow is obtained, the power injector and tubing should be positioned to allow adequate table movement without tension on the intravenous line.

A critical step in preventing significant extravasation is direct monitoring of the venipuncture site by palpation during the initial portion of the contrast medium injection. If no problem is encountered during the first 15 seconds, the individual monitoring the injection exits the CT scan room before the scanning begins. If extravasation is detected, the injection is stopped immediately. Communication between the technologist and the patient via an intercom or television system should be maintained throughout the examination.

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.

It cannot be assumed that all vascular catheters including a peripherally inserted central catheter (PICC) can tolerate a mechanical injection. However, a number of manufacturers have produced power injector compatible vascular catheters. The manufacturer's specifications should be followed.

Air Embolism

Clinically significant venous air embolism is a potentially fatal but extremely rare complication of IV contrast media injection. Clinically "silent" venous air embolism, however, commonly occurs when an IV contrast medium is administered by hand injection. Care when using power injection for contrast-enhanced CT minimizes the risk of this complication. 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. Air embolism has also been identified in intracranial venous structures.

Inadvertent injection of large amounts of air into the venous system may result in air hunger, dyspnea, cough, chest pain, pulmonary edema, tachycardia, hypotension, or 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, helping to restore circulation and oxygenation. If cardio-pulmonary arrest occurs, closed-chest cardiopulmonary resuscitation should be initiated immediately.

Intra-osseous Injection

Intra-osseous (IO) lines allow rapid access for administration of fluids and medications in critically ill patients without intravenous access. There has been a resurgence of IO usage in the last 2 decades secondary to improvements in product design, speed of line placement, and low complication rate [1-3]. The three most popular devices on the market are 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 [2]. Humeral placement is now the preferred site of access secondary to quick line placement and higher achievable flow rates when compared to tibial access [1,4,5]. High pressures are needed to infuse through IO lines secondary to high intramedullary compartmental pressure. 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 agents exist, several case reports document successful acquisition of contrast-enhanced CT with no reported complications using injection rates up to 5 ml/sec (max PSI of 300) [4,6-9]. Intra-osseous injection of gadolinium-based contrast media has not been studied, but there is no reason to think it would not be similarly efficacious, with low risk of adverse event.

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 pain of infusion [1,5,10]. One suggested pretreatment reported from a single institution with the EZ-IO device is 40 mg 2% (2 ml) of epinephrine-free lidocaine slowly infused over 2 minutes after the line is primed with 1 ml lidocaine. The medication is allowed to dwell for one minute, and then the line is 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 is used, with 0.5 mg/kg as the initial dose (not to exceed 40 mg), followed by a 2-5 ml saline flush and a second 0.25 mg/kg lidocaine dose [4].

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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 0.9% (1/1,000 patients to 1/106 patients). Extravasation can occur during hand or power injection. The frequency of extravasation is not related to the injection flow rate. Extravasation occurring with dynamic bolus CT may involve large volumes of contrast media.

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

Sequelae of Extravasations

Extravasated iodinated contrast media are toxic to the surrounding tissues, particularly to the skin, producing an acute local inflammatory response that sometimes peaks in 24 to 48 hours. The acute tissue injury resulting from extravasation of iodinated contrast media is possibly related primarily to the hyperosmolality of the extravasated fluid. Despite this, the vast majority of patients in whom extravasations occur recover without significant sequelae. Only rarely will a low-osmolality contrast media (LOCM) extravasation injury proceed to a severe adverse event.

Most extravasations are limited to the immediately adjacent soft tissues (typically the skin and subcutaneous tissues). Usually there is no permanent injury.

The most commonly reported severe injuries after extravasation of LOCM are compartment syndromes. A compartment syndrome may be produced as a result of mechanical compression. A compartment syndrome is 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 this occurs in less capacious areas (such as over the ventral or dorsal surfaces of the wrist).

Less commonly, skin ulceration and tissue necrosis can occur as severe manifestations and can be encountered as early as six hours after the extravasation has occurred.

A recent study has illustrated the infrequency of severe injuries after LOCM extravasation. In this report by Wang and colleagues, only one of 442 adult LOCM extravasations resulted in a severe injury (a compartment syndrome), although three other patients developed blisters or ulcerations that were successfully treated locally.

Evaluation

Because the severity and prognosis of a contrast medium extravasation injury are difficult to determine on initial evaluation of the affected site, close clinical follow-up for several hours is essential for all patients in whom extravasations occur.

Treatment

There is no clear consensus regarding 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, but controlled studies demonstrating the efficacy of this treatment are lacking. There is no clear evidence favoring the use of either warm or cold compresses in cases of extravasation. As a result there are some radiologists who use warm compresses and some who use cold compresses. Those who have used cold have reported that it may be helpful for relieving pain 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.

There is no consistent evidence that the effects of an extravasation can be mitigated effectively by trying to aspirate the extravasated contrast medium through an inserted needle or angiocatheter, or by local injection of other agents such as corticosteroids or hyaluronidase.

Outpatients who have suffered contrast media extravasation should be released from the radiology department only after 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 symptoms, skin ulceration, or the development of any neurologic or circulatory symptoms, including paresthesias.

Surgical Consultation

Surgical consultation prior to discharge should be obtained whenever there is concern for a severe extravasation injury. 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, and skin ulceration or blistering. It is important to note that initial symptoms of a compartment syndrome may be relatively mild (such as limited to the development of focal paresthesia).

In a previous edition of this manual, it was recommended that surgical consultation should be obtained automatically for any large volume extravasations, particularly those estimated to be in excess of 100 ml; however, more recently it has been suggested that reliance on volume threshold is unreliable and that the need for surgical consultation should be based entirely on patient signs and symptoms. If the patient is totally asymptomatic, as is common with extravasations in the upper arm, careful evaluation and appropriate 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 adequately (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. 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. In addition, 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.

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. 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 damage.

Documentation

All extravasation events and their treatment should be documented in the medical record, especially in the dictated imaging report of the obtained study, and the referring physician should be notified.

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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 (HOICM) to nonionic low-osmolality contrast media (LOICM) [1-11]. The majority of adverse side effects to LOICM 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 angiocardiology 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 has affected the reported incidence of these events.

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

LOEM 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 LOEM 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 LOEM 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 LOEM are rare, with an historical rate of approximately four in 10,000 (0.04%) [6].

The mortality incidence related to intravascular IEM is unknown. In a large Japanese study by Katayama et al [6], no fatal reactions were attributed to LOEM 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 LOEM 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 LOEM. 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 LOEM [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 IEM, contrast reactions remain sporadic and unpredictable.

A prior allergic-like reaction to IEM 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 IEM 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, pruritus 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

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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 $\mu\text{mol/L}$).
- 2) A percentage increase in serum creatinine $\geq 50\%$ (≥ 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/1.73m², IV iodinated contrast media are not an independent nephrotoxic risk factor [3,4,7,9], and in patients with a stable baseline eGFR 30-44 mL / min/1.73m², IV iodinated contrast media are either not nephrotoxic or rarely so [3,4,7,9].

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

Risk Factors

Numerous studies have attempted to isolate risk factors for 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/1.73m² to be at significant risk (patients with eGFR 30-44 mL / min/1.73m² were at borderline but not statistically significant risk) [3].

Herts et al [50] showed that when patients' eGFR was calculated by the MDRD formula, a significantly higher percentage of patients presenting for contrast-enhanced CT scans had an eGFR <60 mL / min than had a serum creatinine of >1.4 mg/dL. Davenport et al [49] showed that the use of eGFR thresholds (instead of serum creatinine-based thresholds) more appropriately identified patients who may be at risk for 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/1.73m². Therefore, if a threshold for CIN risk is used at all, 30 mL / min/1.73m² seems to be the one with the greatest level of evidence [3]. Any threshold put into practice must be weighed on an individual patient level with the benefits of administering contrast material.

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

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

Anuric patients with end-stage renal disease who do not have a functioning transplant kidney are not at risk for 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:
 - o Dialysis
 - o Kidney transplant
 - o Single kidney

- o Renal cancer
- o 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 is 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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METFORMIN

Last updated: 23 May 2016

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 $eGFR \geq 30$ mL / min/1.73m², 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 reinstated only after renal function has been re-evaluated and found to be normal.

Metformin and Gadolinium

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

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

Table A
Medications containing Metformin*

Generic Ingredients	Trade Names
Metformin	Glucophage Glucophage XR Fortamet Glumetza Riomet
Glyburide/metformin	Glucovance
Glipizide/metformin	Metaglip
Linagliptin/metformin	Jentadueto
Pioglitazone/metformin	ActoPlus Met ActoPlus Met XR
Repaglinide/metformin	Prandimet
Rosiglitazone/metformin	Avandamet
Saxagliptin/metformin	Kombiglyze XR
Sitagliptin/metformin	Janumet Janumet XR

(Metformin and several of the combination drugs also available in generic versions)

*List most recently revised on 4/17/2014

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CONTRAST MEDIA IN CHILDREN

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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 Fjellidal 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

$$\text{GFR (mL / min/1.73 m}^2\text{)} = (0.41 \times \text{height}) / \text{serum creatinine}$$

- 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 pediatric patients, and no agent is approved for administration to individuals younger than two years of age. 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 H₂O, and the osmolality of gadobenate dimeglumine (MultiHance) is 1,970 mosm/kg H₂O. Viscosities (at 37° C) can also vary, for example from 1.19 cps for gadoxetate disodium (Eovist) to 5.3 cps for gadobenate dimeglumine (MultiHance). These physical properties, however, potentially are less important when using gadolinium-based contrast 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 significant 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 ([Table 2](#)). While no investigation has studied the efficacy of corticosteroid and antihistamine premedication

regimens for the prevention of allergic-like reactions to gadolinium-based contrast 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 m². 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/1.73m² [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].

Table A
Sample Pediatric Corticosteroid and Antihistamine Premedication Regimen

	Dosage	Timing
Prednisone	0.5–0.7 mg/kg PO (up to 50 mg)	13, 7, and 1 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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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 nasogastric 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 whom 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.

Therapeutic uses 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, polyethylene 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 has 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, Princeton, NJ).

In the assessment of Crohn 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 CO₂ by 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: superparamagnetic 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- 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 superparamagnetic 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 cholangiography, 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., 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 (Chologafin[®], 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.

Hyocyanine Sulfate

Hyocyanine 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.

Hyoscyamine 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.

Hyoscine butylbromide (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 metoclopramide 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 is 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

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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 m², 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

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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, Mallinckrodt] 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 readministering 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. Examples include MR angiography, cardiac applications, and pediatric applications in patients younger than two years of age. In addition, no GBCM is approved in the United States for use in a power injector. Off-label dosing of GBCM is now used much less commonly. 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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Nephrogenic Systemic Fibrosis

Definition

Nephrogenic systemic fibrosis (NSF) is a fibrosing 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 pruritis.

Symptoms and signs may develop and progress rapidly, with some affected patients developing contractures and joint immobility. In some patients, the disease may be fatal.

Associations

Gadolinium-based contrast agent (GBCA) administration

When first described in 2000, NSF was noted to occur predominantly in patients with end-stage chronic kidney disease (CKD), particularly in patients on dialysis. In 2006 several groups noted a strong association between gadolinium-based contrast agent (GBCA) administration in patients with advanced renal disease and the development of NSF [1,2], and it is now generally accepted that GBCA exposure is a necessary factor in the development of NSF. 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].

While the association between NSF development and exposure to GBCAs is well accepted, the precise relationship between NSF and different formulations of GBCAs is controversial and incompletely understood. Some GBCAs have been associated with few, if any, confirmed cases of NSF, and most unconfounded cases have been reported after exposure to gadodiamide, gadopentetate dimeglumine, and/or gadoversetamide. 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 chemical properties of different GBCAs. However, a combination of other factors, including market share, number of years that the agent has been in use, and possible reporting bias, also may contribute to differences in 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 (see Table at end of chapter) based on reported associations with NSF in vulnerable patients, although the scheme used by each is not identical [7,8].

Chronic kidney disease

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

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

Acute kidney injury (AKI)

Between 12% and 20% of confirmed 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 development in the consensus opinion of the ACR Committee on Drugs and Contrast Media.

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]. A few cases of NSF also have been reported in patients with no known GBCA exposure [15]. 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 [16].

Nevertheless, NSF is believed to occur most commonly in patients who have received high doses of GBCA, either as a single administration or cumulatively in multiple administrations over months to years [6,17]. Thus, the reported frequency of associations with the various types of GBCAs may be skewed if specific agents were preferentially used at higher doses or more often than others, especially in vulnerable patients.

Importantly, most patients with severe CKD exposed to high doses and/or many doses of GBCAs have not developed NSF [5]. One study [18] described 30 patients who had an eGFR of under 30 mL / min/1.73m² and who were exposed to high doses of gadodiamide (median dose of 90 ml and range of 40 to 200 ml). One of the 30 patients subsequently developed NSF, an observed incidence of about 3%.

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 pro-inflammatory events [4,23]. However, none of these have been consistently confirmed as true co-factors. As a result, routine screening for them prior to GBCA administration is not recommended, although such screening may be performed on an optional basis.

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 NSF patients, 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 m²) prior to GBCA administration. Thus, hepatic disease in and of itself, in the absence of AKI or severe CKD, is no longer considered a 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 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, it may help explain, at least in part, why the various GBCAs differ in their apparent NSF safety profiles in at-risk patients [29].

Patients at Risk for NSF

Based on the above, the ACR Committee on Drugs and Contrast Media believes that patients receiving any GBCA should be considered at risk of developing NSF if any of the following conditions applies:

- on dialysis (of any form)
- severe or end-stage CKD (CKD 4 or 5, eGFR < 30 mL / min/1.73 m²) without dialysis
- eGFR 30 to 40 mL / min/1.73 m² without dialysis*
- AKI [30,31]

*As further discussed below (see “Patients with CKD 3 [eGFR 30 to 59 mL / min/1.73 m²]”), patients with eGFR 30 to 40 mL / min/1.73 m² should also be considered at risk because eGFR levels may fluctuate (e.g., from the 30 to 40 mL / min/1.73 m² range one day to below < 30 mL / min/1.73 m² on another day).

Identifying Patients at Risk for NSF Prior to Any GBCA Injection

It is important to identify patients at risk of developing NSF, as defined above, prior to any GBCA injection. The method used to identify such patients may differ for outpatients and inpatients.

Identifying At-Risk Outpatients

Regardless of the GBCA employed, outpatients 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 many patients with chronic kidney disease, regardless of severity [32].

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 is a suggested list of risk factors that warrants pre-administration eGFR calculation in individuals scheduled to receive any GBCA injection. This list should not be considered comprehensive and represents a blend of published data [33,34] and expert opinion:

- Age > 60
- 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 some medications (e.g., non-steroidal anti-inflammatory drugs, diuretics, amino-glycosides, 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, 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, laboratory testing and calculation of eGFR is not useful.

For adults, eGFR calculation should be performed using the Modification of Diet in Renal Disease (MDRD) equation. The four-variable MDRD equation takes into account age, race, gender, and serum creatinine level. Commercially available point-of-service devices may facilitate this in an outpatient setting. The updated Schwartz equation should be used for children (also see [Chapter on Contrast Media in Children](#)).

MDRD equation:

$$eGFR \text{ (mL / min/1.73 m}^2\text{)} = 175 \times (\text{serum creatinine in mg/dl})^{-1.154} \times (\text{age in years})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$$

Updated Schwartz equation:

$$eGFR \text{ (mL / min/1.73 m}^2\text{)} = (0.413 \times \text{height in cm})/\text{serum creatinine in mg/dl.}$$

A number of websites and point of service tools are available which can calculate eGFR values in adults and children.

When eGFR is recommended in Outpatients with Risk Factor(s) for Compromised Renal Function

There is no high-level scientific evidence to guide the time interval prior to GBCA injection with which an eGFR should be obtained in patients identified by screening to have one or more risk factor for compromised renal function. However, based on expert opinion and a need to maintain patient safety while minimizing the costs and burdens associated with additional laboratory testing, the ACR Committee on Drugs and Contrast Media recommends a new eGFR be obtained with the time intervals listed in the Chart below in outpatients who are identified by screening as at increased risk. The following guidelines are suggested:

If no risk factors for reduced renal function were identified at screening, new laboratory testing for eGFR does not need to be done.

Identifying At-Risk Inpatients

For all inpatients, eGFR level should be obtained within two days prior to any GBCA administration. In addition, the ordering health professional should assess inpatients for the possibility of AKI, as eGFR calculation alone has limited sensitivity for the detection of AKI.

General Recommendations for Imaging Patients at Risk for NSF

Once a patient at risk for NSF is identified, alternative diagnostic examinations that do not employ a GBCA should be considered. In nonemergent or nonurgent cases if the potential benefits of a GBCA-enhanced MRI 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. In emergent or urgent cases it may not always be possible to inform the patient or referring physician prior to GBCA administration.

If the decision is made to administer a GBCA to a patient at increased risk for developing NSF, the supervising radiologist (including the name) should document the reason for the examination and the rationale for use of intravenous GBCA.

Group I agents (see table at end of chapter), the GBCAs that have been most often associated with NSF, have been contraindicated by the FDA in these patients [24]. Alternative agents should be used.

When a new eGFR should be obtained in outpatients with risk factor(s) for compromised renal function

Prior eGFR level (mL / min/1.73 m²)	When was the last eGFR before MRI?	When should new eGFR be obtained prior to MRI?
None available	Not applicable	Within 6 weeks
> 60	> 6 months	Within 6 weeks
> 60	< 6 months (stable state*)	New eGFR not needed
> 60	< 6 months (possibly unstable state**)	Within 2 weeks
30–59	> 2 weeks	Within 2 weeks
< 30	> 1 week	Within 1 week
On dialysis	Not applicable	New eGFR not needed

* patient does not have a known condition that might result in acute deterioration of renal function

** patient has a known condition that might result in acute deterioration of renal function. Such conditions include severe dehydration, febrile illness, sepsis, heart failure, recent hospitalization, advanced liver disease, abdominal surgery

The lowest possible dose of GBCA required to obtain the needed clinical information should be used, and it should generally not exceed the recommended single dose. (Note: the lowest diagnostic dose has not been thoroughly investigated for many indications and caution should be exercised so as not to administer a dose that is too low to provide the diagnostic information sought from the examination).

Exceptions to the above recommendation 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. However, the rationale for the exception must be documented by the supervising radiologist.

Precautions such as these have already had a dramatic effect in reducing or even eliminating the number of NSF cases being encountered [35]. It must be remembered that the risks of administering GBCA to a given high-risk patient must always be balanced against the often substantial risks of not performing a needed contrast-enhanced imaging procedure.

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.

If a contrast-enhanced MR examination must be performed in a patient with end-stage renal disease on chronic dialysis, injection of group I agents (see *Tables at end of Chapter*) is contraindicated. Also, use of the lowest possible dose needed to obtain a diagnostic study is recommended and is appropriate. The ACR Committee on Drugs and Contrast Media also recommend that GBCA-enhanced MRI examinations be performed as closely before hemodialysis as is possible, as prompt post-procedural hemodialysis, although unproven to date, may reduce the likelihood that NSF will develop. Because it may be difficult for a dialysis center to alter dialysis schedules at the request of imaging departments, it may be more feasible for elective imaging studies to be timed to precede a scheduled dialysis session.

While it is possible that multiple dialysis sessions may be more protective than merely a single session, this possible incremental benefit remains speculative. Some experts recommend several dialysis sessions following GBCA administration, with use of prolonged dialysis times and increased flow rates and volumes to facilitate GBCA clearance.

Peritoneal dialysis probably provides less potential NSF risk reduction compared to hemodialysis and should not be considered protective.

Patients with CKD 4 or 5 (eGFR < 30 mL / min/1.73 m²) not on chronic dialysis

The correct course of action in this patient group is problematic, as administration of iodinated contrast media for CT may lead to further deterioration of renal function, while administration of GBCA for MRI could result in NSF.

It is recommended that any GBCA be avoided in this patient group. However if GBCA enhanced MRI is deemed essential, use of the lowest possible dose needed to obtain a diagnostic study is recommended (note: for many MRI examinations, the lowest diagnostic dose has not been determined, and care should be taken not to lower the dose below diagnostic levels). Although there is no absolute proof that any GBCA is completely safe in this patient group, group I agents (see *Table at end of Chapter*) have been contraindicated by the FDA. Further, it may be prudent to avoid readministration of GBCA for several days to a week (with the precise duration of delay balanced with the severity of renal disease and medical urgency in a particular patient).

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

NSF developing after GBCA administration to patients with eGFR > 30 mL / min/1.73 m² is exceedingly rare. However, eGFR determinations may fluctuate from one day to the next (with an eGFR level just above 30 on one day changing to an eGFR below 30 on another day). It is for this reason that the precautions described above for CKD4 and CKD5 patients are also recommended for inpatients with an eGFR < 40 mL / min/1.73 m². In comparison, no special precautions are required in patients with an eGFR of 40 to 59 mL / min/1.73 m² [36,37].

Patients with CKD 1 or 2 (eGFR 60 to 119 ml min/1.73 m²)

There is no evidence that patients in these groups are at increased risk of developing NSF. Current consensus is that 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 [15]. 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, caution should be exercised in use of GBCA in patients with known or suspected AKI regardless of measured serum creatinine or calculated eGFR values. GBCA should only be administered to these patients if absolutely necessary. When GBCA administration is required, agents associated with the greatest apparent NSF-associated risk (Group I agents, see [Table at end of Chapter](#)) should be avoided.

Children

At this time (August 2011) few pediatric cases of NSF have been reported, and no cases have been reported 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. It should be noted, however, that eGFR values in certain premature infants and neonates may be < 30 mL / min/1.73 m² simply due to immature renal function (and not due to pathologic renal impairment). In these individuals, the ACR Committee on Drugs and Contrast Media believes that caution should still be used when administering GBCAs, although an eGFR value < 30 mL / min/1.73 m² should not be considered an absolute contraindication to GBCA administration.

Caveat

Information on NSF and its relationship to GBCA administration is still evolving, and the summary included here represents only the most recent opinions of the ACR Committee on Drugs and Contrast Media (as of January, 2012). As 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

Group I: Agents associated with the greatest number of NSF cases:

Gadodiamide (Omniscan® – GE Healthcare)
Gadopentetate dimeglumine (Magnevist® – Bayer HealthCare Pharmaceuticals)
Gadoversetamide (OptiMARK® – Covidien)

Group II: Agents associated with few, if any, unconfounded cases of NSF:

Gadobenate dimeglumine (MultiHance® – Bracco Diagnostics)
Gadobutrol (Gadavist® – Bayer HealthCare Pharmaceuticals)
Gadoterate meglumine (Dotarem® – Guerbet)
Gadoteridol (ProHance® – Bracco Diagnostics)

Group III: Agents that have only recently appeared on the market:

Gadofosveset trisodium (Ablavar® – Lantheus Medical Imaging)
Gadoxetate disodium (Eovis – Bayer HealthCare Pharmaceuticals)

There is limited data for group III agents, although, to date, few, if any, unconfounded cases of NSF have been reported.

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Treatment Of Contrast Reactions

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

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

- How does the patient look?
- Can the patient speak? How does the patient's voice sound?
- How is the patient's breathing?
- What is the patient's pulse strength and rate?
- What is the patient's blood pressure?

The level of consciousness, the appearance of the skin, quality of phonation, lung auscultation, blood pressure and heart rate assessment will allow the responding physician to quickly determine the severity of a reaction. These findings also allow for the proper diagnosis of the reaction including urticaria, facial or laryngeal edema, bronchospasm, hemodynamic instability, vagal reaction, seizures, and pulmonary edema. Once identified, 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 in extreme cases; for example, calling 911 for emergency medical personnel assistance in an outpatient medical center setting.

Urticarial reactions are allergic-like and almost always mild, although hives can progress in severity and/or number, and can be associated with more serious symptoms. Mild angioedema (such as a scratchy throat, slight tongue/facial swelling, and paroxysmal sneezing) not requiring medical management may also be considered a mild allergic-like reaction.

Mild reactions (both allergic-like and non-allergic-like) typically do not require medical treatment, but they may presage or evolve into a more 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 20 to 30 minutes, or as long as necessary, to ensure clinical stability or recovery. Treatment with an antihistamine may be instituted for mild symptomatic allergic-like cutaneous contrast reactions, but is most often not necessary.

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

Facilities should be equipped with basic emergency equipment and medications needed to treat contrast reactions. This includes, but is not limited to, equipment needed to assess a patient such as stethoscope, blood pressure/pulse monitor, and a pulse oximeter, as well as medications and equipment needed to treat a patient, such as sterile saline for intravenous injection, diphenhydramine, beta agonist inhaler (e.g., albuterol), epinephrine, atropine, oxygen, intubation equipment, and a cardiac defibrillator (see [Table 4](#)). A periodic monitoring program to ensure equipment functionality and medication shelf life is recommended.

Ongoing quality assurance and quality improvement programs with in-service training and review sessions are very helpful in ensuring that responses to contrast reactions are prompt and appropriate. These would include training of onsite health care providers in cardiopulmonary resuscitation techniques, including basic life support or advanced cardiac life support whenever possible.

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ADMINISTRATION OF CONTRAST MEDIA TO PREGNANT OR POTENTIALLY PREGNANT PATIENTS

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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 assumed 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 amniocentesis using a fat-soluble iodinated contrast medium, which was performed in the past to detect congenital malformations.

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

Other adverse effects

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

Recommendations prior to performing imaging studies requiring iodinated contrast material administration

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

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.

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 [11] 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 reproduction 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 [12,13].

Recommendations for the use of corticosteroid premedication in pregnant patients

Expert opinion indicates that the use of steroids in pregnancy is generally safe [14,15], although common specific regimens for premedication prior to contrast media administration have not been tested. Severe anaphylaxis in a pregnant female represents an even greater risk to the fetus than to the mother herself [16]. 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 Premedication 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.

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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 from 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
<i>General comment: observe until hives are resolving. Further observation may be necessary if treatment is administered.</i>		
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	
<i>If profound or unresponsive to fluids alone can also consider</i>	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 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)
	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 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)
	AND Beta agonist inhaler (Albuterol®) (May work synergistically)	2 puffs (90 mcg/puff) for a total of 180 mcg; can repeat up to 3 times
	Call emergency response team or 911	

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

Note: It can be difficult to dose medications accurately in neonates and infants.

LARYNGEAL EDEMA

	Treatment	Dosing
All forms	Preserve IV access	
	Monitor vitals	
	O ₂ by mask	6–10 L / min
	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 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)		
<i>If mild</i>	No other treatment usually necessary	
<i>If severe (patient remains symptomatic despite above measures)</i>	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)		
<i>If severe (hypotension persists)</i>	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.

UNRESPONSIVE AND PULSELESS

	Treatment	Dosing
	Activate emergency response team (call 911)	
	Start CPR	
	Get defibrillator or automated electronic defibrillator (AED); apply as soon as available; shock as indicated	
Note: Please also see BLS and ACLS (PALS) booklets published by the American Heart Association	Epinephrine (between 2 min cycles)	0.1 mL / kg of 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
<i>If unremitting</i>	Call emergency response team or 911	

HYPOGLYCEMIA

	Treatment	Dosing
<i>All forms</i>	Preserve IV access	
	O ₂ by mask	6–10 L / min
<i>If patient is able to swallow safely</i>	Observe	
	Administer oral glucose	2 sugar packets or 15 g of glucose tablet or gel or ½ cup (4 oz) of fruit juice
<i>If patient is unable to swallow safely</i>		
<i>And IV access is available</i>	Dextrose 50% (IV)	IV D25 2 mL/ kg; IV injection over 2 min
<i>And IV access is not available</i>	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
<p><i>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.</i></p>	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	
<i>Consider</i>	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
<i>If profound or unresponsive to fluids alone can also consider</i>	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 (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) (0.3 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	
* 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	

	Treatment	Dosing
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

	Treatment	Dosing
	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
<i>All forms</i>	Preserve IV access	
	Monitor vitals	
	Pulse oximeter	
	O ₂ by mask	6–10 L / min
	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
	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
<i>All forms</i>	Preserve IV access	
	Monitor vitals	
	Pulse oximeter	
	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)		
<i>If mild</i>	No other treatment usually necessary	
<i>If severe (patient remains symptomatic despite above measures)</i>	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)		
<i>If hypotension persists</i>	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 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.		

HYPERTENSIVE CRISIS

(diastolic BP > 120 mm Hg; systolic BP > 200 mm Hg; symptoms of end organ compromise)

	Treatment	Dosing
<i>All forms</i>	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
<i>If unremitting</i>	Call emergency response team or 911	
	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
<i>If patient is able to swallow safely</i>	Oral glucose	Two sugar packets or 15 g of glucose tablet/gel or ½ cup (4 oz) of fruit juice
<i>If patient is unable to swallow safely and IV access available</i>	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
<i>If no IV access is available</i>	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
<i>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.</i>	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: 29 June 2015

Depending on the size and function of the imaging site, it may be sufficient to have one reaction treatment cart designed to both treat contrast reactions and manage the initial steps in the treatment of cardiac/respiratory arrests. Other facilities may find it more cost-effective to have more widespread distribution of contrast reaction kits to treat non-arrest reactions with fewer full code carts. Some imaging sites will find that their institutions will have standard full code carts throughout the facility, but that smaller and more widely distributed contrast reaction kits may enable rapid implementation of treatment at considerably lower expense than opening an institutional full code cart to treat a non-arrest contrast reaction. When standard code carts are available, it may be efficient to place only the most frequently used or urgently needed items in contrast reaction kits. In general, these larger institutional carts have more equipment than strictly necessary for radiologists to use, and smaller facilities may find the suggestions below helpful in designing a dedicated reaction treatment cart that can be used to manage arrests until the arrival of other emergency responders.

The contact phone number of the cardiopulmonary arrest emergency response team should be clearly posted within or near any room in which contrast media is to be injected.

The following equipment must 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):

- Oxygen cylinders or wall-mounted oxygen source, flow valve, tubing, oxygen masks* (adult and pediatric sizes)
- Suction: wall-mounted or portable; tubing and catheters
- Oral and/or nasal airways: rubber/plastic
- "Ambu®-type" bag-valve-mask device; masks in adult and pediatric sizes; protective barriers for mouth-to-mouth respiration are optional if the bag-valve-mask device is stocked
- Stethoscope; sphygmomanometer
- Intravenous solutions (0.9% [normal] saline and/or Ringer's lactate) and tubing\
- Syringes and IV cannulas: variety of sizes; tourniquets
- Needles: variety of sizes
- Necessary medications:
 - Epinephrine 1:10,000, 10-mL preloaded syringe (for IV injection)
and/or
 - Epinephrine 1:1000, 1 mL (for IM injection)
and/or
 - Epinephrine IM auto-injector** (sizes for patients 15–30 kg and patients 30 kg and over)
 - Atropine, 1 mg in 10-ml preloaded syringe
 - Beta-agonist inhaler with or without spacer
 - Diphenhydramine for PO/IM/IV administration
 - Nitroglycerin (NTG) –, 0.4 mg tabs, sublingual
 - Aspirin, 325 mg (for chest pain where myocardial ischemia is a consideration)
- Optional medications:
 - Lasix, 20– 40 mg IV
 - Labetalol, 20 mg IV
 - Dextrose 50% 25mg/50mL syringe

The following items should be on the emergency/code cart*** or within or near any room in which contrast media is to be injected:

- Defibrillator or automated external defibrillator (AED)
- Blood pressure/pulse monitor
- Pulse oximeter

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

** Examples: EpiPen Jr.® (Mylan Specialty L.P.) or Auvi-Q® 0.15 mg (Sanofi-Aventis U.S. LLC); injects 0.15 mg epinephrine (as 0.3 mL of 1:2000 or 0.15 mL of 1:1000 epinephrine, respectively) or EpiPen® or Auvi-Q® 0.3 mg; injects 0.3 mg epinephrine (as 0.3 mL of 1:1000 epinephrine)

*** If in a hospital or clinic, the emergency/code cart should conform to hospital or departmental policies and procedures; it often includes these items.

Appendix A – Contrast Media Specifications

Last updated: 12 December 2014

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 H ₂ O)
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 (Mallinckrodt)	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 Healthcare)	iohexol (647)	Nonionic	300	11.8*	6.3	672
Optiray™ 300 (Mallinckrodt)	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 (Mallinckrodt)	ioversol (680)	Nonionic	320	9.9	5.8	702
Visipaque™ 320 (GE Healthcare)	iodixanol (652)	Nonionic	320	26.6	11.8	290
Optiray™ 350 (Mallinckrodt)	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 (Mallinckrodt)	diatrizoate/ meglumine/ sodium (760)	Ionic	370	16.4	10.5	1551
Ultravist® 370 (Bayer Healthcare)	loprokoi98mide	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.

° 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.

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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™ (Mallinckrodt)	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 Healthcare)	iohexol (518) pediatric use	Nonionic	240	5.8*	3.4	520
Omnipaque™ 300 (GE Healthcare)	iohexol (647) pediatric use	Nonionic	300	11.8*	6.3	672
Omnipaque™ 350 (GE Healthcare)	iohexol (755) adult use	Nonionic	350	20.4*	10.4	844
Gastromark™ (Mallinckrodt) 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.

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Appendix A – Contrast Media Specifications (continued)

GENITOURINARY

Product	Generic name (concentration in mg contrast/ml)	Ionicity	Iodine+ (mg/ml)	Viscosity+ 25° C (cp or mPa.s)	Viscosity+ 37° C (cp or mPa.s)	Osmolality (mOsm/kg H ₂ O)
Cystografin® (Bracco)	diatrizoate	Ionic	141			
Cysto-Conray™ II (Mallinckrodt)	iothalamate (172)	Ionic	81	(Only for retrograde cystography and cystourethrography)		~400
Conray™ 43 (Mallinckrodt)	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/kgH ₂ O)	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 Non-ionic	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™ (Mallinckrodt)	Gd-DTPA-BMEA Linear Non-ionic	Gadoversetamide	None	2.8**	2.0	4.7 (4.5)	1110	16.8 (15)
EOVIST/Primovist® (Bayer Healthcare)	Gd-EOB-DTPA Linear Ionic	Gadoxetate	Disodium		1.19	6.9 (6.2)	688	23.5 (18.7)
Gadavist/Gadovost™ (Bayer Healthcare)	Gd-BT-D03A Macro-cyclic Non-ionic	Gadobutrol	None		4.96	5.2 (5)	1603	21.8 (15.5)
Dotarem® (Guerbet)	Gd-DOTA Macro-cyclic Ionic	Gadoterate	Meglumine	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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