ACR Manual on Contrast Media

Version 9

2013

ACR Committee on Drugs and Contrast Media

ACR
American College of
Radiology
Quality is Our Image

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Preface

This Ninth 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. 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 committee offers this document to practicing radiologists as a consensus of scientific evidence and clinical experience concerning the use of iodinated contrast media. The general principles outlined here also pertain to the administration and systemic effects (e.g., adverse effects) of noniodinated contrast media such as gadolinium or other compounds used for magnetic resonance imaging and gastrointestinal imaging.

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 Ms. Margaret Wyatt and other supporting members of the ACR staff.

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 4, and 5*). 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 patent 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

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 for the procedures listed. 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. First, either the CT scout scan or a recent chest radiograph should be checked to confirm the proper location of the catheter tip. 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 cardiopulmonary arrest occurs, closed-chest cardiopulmonary resuscitation should be initiated immediately.

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

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Extravasation Of Contrast Media

Frequency

The reported incidence of intravenous (IV) contrast media extravasation related to power injection for CT has ranged from 0.1% to 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 hyper-osmolality 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.

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

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Allergic-Like And Physiologic Reactions To Intravascular Iodinated Contrast Media

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

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

Acute Adverse Events

Classification of Acute Adverse Events

Acute adverse events can be categorized as either allergic-like or physiologic, and organized into three general categories of severity (mild, moderate, or severe). A suggested classification system (which can be utilized for both ICM and gadolinium-based contrast media [GBCM]), stratifying adverse events by severity and type, is presented in *Table 3*.

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

Allergic-Like Reactions

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

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

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

Physiologic reactions

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

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

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

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

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

Patient anxiety may also contribute to or exacerbate nonvagal adverse events.

Similar to allergic-like reactions, some additives and contaminants have been associated with physiologic reactions [12,13].

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

Frequency of Acute Adverse Events

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

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

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

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

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

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

Common Risk Factors for Acute Contrast Reactions

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

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

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

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

Patients with Myasthenia Gravis

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

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

Other risk factors

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

Treatment

The proper treatment of an acute contrast reaction varies depending on the presentation. A variety of scenarios and possible treatment algorithms are discussed in *Tables 4 and 5*.

Delayed Adverse Events to Iodinated Contrast Media

Timing

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

Incidence

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

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

Symptoms

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

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

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

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

Other rare delayed adverse events

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

Treatment

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

Recurrence rates and prophylaxis

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

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Contrast Media Warming

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

Introduction

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

Iodinated Contrast Media – Contrast Material Warming and Injection Kinetics

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

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

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

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

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

Hazirolan et al [8] randomized patients undergoing cardiac CT angiography into two groups: 1) 32 patients receiving warmed (37° 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 ($\leq$ 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^{o} C [59 to 86^{o} F]) and according to package inserts, should not be externally warmed for routine clinical applications.

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Contrast-Induced Nephrotoxicity

Definition

Contrast-induced nephrotoxicity (CIN) is a sudden deterioration in renal function following the recent intravascular administration of iodinated contrast medium in the absence of another nephrotoxic event. Unfortunately, very few published studies adequately isolate patients in whom iodinated contrast medium exposure is the only nephrotoxic event [1]. CIN occurs in children, but is rare [2-5]. Gadolinium-based contrast media either do not cause CIN when administered at FDA-approved doses, or this event is exceptionally rare.

Pathogenesis

The exact pathophysiology of CIN is not understood. Etiologic factors that have been suggested include: 1) renal hemodynamic changes (vasoconstriction), and 2) direct tubular toxicity. Both osmotic and chemotoxic mechanisms may be involved, and some investigations suggest agent-specific chemotoxicity. There is evidence that the nephrotoxic effect of iodinated contrast medium is proportional to dose for angiocardiography; data are conflicting with respect to the dose-toxicity relationship following intravenous (IV) administration.

Diagnosis

There are no standard criteria for the diagnosis of 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.

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 CIN varies inversely with the magnitude of the change in serum creatinine used to establish the diagnosis. The same threshold has not been used for all studies investigating CIN. The variable definitions of acute kidney injury (AKI) in the literature 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 [6] and the AKIN system was proposed by AKIN in 2007 [7]. The AKIN system is a modified version of RIFLE and is briefly defined below. This standard method of diagnosing and staging acute kidney injury may be helpful in the design of future CIN studies.

AKIN Definition of Acute Kidney Injury

The diagnosis of acute kidney injury 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) [7]:

1) Absolute serum creatinine increase of ≥ 0.3 mg/dL (> 26.4 µmol/L).
2) A percentage increase in serum creatinine of ≥ 50% (1.5-fold above baseline).
3) Urine output reduced to ≤ 0.5 mL/kg/hour for at least 6 hours.

This system has not been directly studied with respect to CIN, but has been advocated as a common definition of intrinsic acute kidney injury, regardless of etiology [7]. 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 [7].

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 CIN 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. 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 glomerular filtration rate (GFR) – at least as reflected in creatinine clearance – is reduced by nearly 50%.

Although direct measurement of GFR with inulin or a similar clearance marker would be more accurate in defining renal function before and after contrast administration, this is impractical and not advised. An alternative is to use one or more formulae to estimate renal function based on age, gender, body weight, and serum creatinine (e.g., the Cockcroft-Gault [8] or Modification of Diet in Renal Disease [MDRD]). Calculators are available on various web pages.

These formulae 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 acute kidney injury, neither renal function nor serum creatinine is stable. Therefore, using formulae that attempt to estimate GFR (eGFR) or creatinine clearance to make clinical decisions in the setting of acute kidney injury is inadvisable.

Route of Contrast Administration

A confounding variable in the literature is related to the route of contrast medium injection and presence of concurrent procedures. In the last two decades, the CIN literature has been dominated by reports of patients who have undergone angiocardiography with iodinated contrast medium. The overall incidence of CIN in these studies is higher than it is in studies of patients who receive IV iodinated contrast medium. Several publications that compare the incidence of CIN after angiocardiography and IV contrast administration have found the risk after angiocardiography to be higher [1]. Therefore, data from angiocardiography studies likely over-estimate the risk for patients undergoing IV contrast-enhanced studies.

CIN Studies

Much of the literature investigating the incidence of CIN has failed to include a control group of patients not receiving contrast medium. This is problematic because several studies have shown that the frequency and magnitude of serum creatinine change in patients who have not received contrast is similar to the changes in patients who have received it. 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% a change of at least 0.4 mg/dL [9]. The authors indicate that had some of these patients received iodinated contrast, the rise would have been undoubtedly attributed to it, rather than to physiologic variation or another etiology.

To date, only eight published studies of IV iodinated contrast media use have included a control group of patients not exposed to iodinated contrast medium [10-17]. All but one [10] found no evidence of CIN.

Bruce et al [10] showed that the frequency and magnitude of post-CT serum creatinine elevation (i.e., +0.5 mg/dL or +25% mg/dL) was equivalent in a control group of patients who did not receive contrast medium to patients who received either iodixanol or iohexol with a similar baseline serum creatinine (≤ 1.8 mg/dL). Only patients with a baseline serum creatinine greater than 1.8 mg/dL had a greater risk of post-CT renal dysfunction after exposure to LOCM (iohexol) when compared with patients not receiving intravenous contrast medium.

The development of clinically significant nephrotoxicity in patients with normal renal function after the intravascular administration of iodinated contrast medium is either extraordinarily rare or does not occur.

Risk Factors for CIN

Numerous studies have attempted to isolate risk factors for CIN. There is consensus that the most important risk factor for CIN is pre-existing renal insufficiency. Multiple others 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) [18-23], but these have not been rigorously confirmed as independent risk factors. Two studies have shown that CIN may occur after two closely spaced doses, but neither was designed to show that the risk was higher than after one or no dose of IV contrast medium [18,23].

Risk Thresholds

There is no universally agreed upon threshold of serum creatinine elevation (or degree of renal dysfunction) beyond which intravascular iodinated contrast medium should not be administered. In a 2006 survey of radiologists by Elicker et al [24], 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, thirty-five percent 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).

We believe that there is insufficient good data at this time to prescribe a specific recommended threshold. However, we also believe that the risk of CIN from intravenous iodinated contrast media is sufficiently low that a threshold of 2.0 mg/dL in the setting of stable chronic renal insufficiency is probably safe for most patients. As previously stated, no serum creatinine threshold is adequate to stratify patients with acute kidney injury because serum creatinine in this setting is unreliable.

In patients with acute kidney injury, the administration of iodinated contrast medium should only be undertaken with appropriate caution and only if the benefit to the patient clearly outweighs the risk. There has been no published series demonstrating that IV iodinated contrast medium administration to patients with acute kidney injury leads to worse or prolonged renal dysfunction than would occur in a control group. However, patients with acute kidney injury are particularly susceptible to nephrotoxin exposure and therefore it is probably prudent to avoid intravascular iodinated contrast medium in these patients (when possible), regardless of the generally low nephrotoxic risk.

Anuric patients with end-stage renal disease are no longer at risk for CIN and may receive intravascular iodinated contrast material without risk of additional renal injury (see *Renal Dialysis Patients and the Use of Iodinated Contrast Medium*, below).

The clinical benefit of using eGFR or calculated creatinine clearance in assessing preprocedural CIN risk in patients with stable renal function is uncertain because much of our published knowledge comes from studies that used only serum creatinine measurements. The threshold values at which different clinical actions should be taken (e.g., active IV hydration, avoidance of contrast medium administration) are neither proven nor generally agreed upon for either serum creatinine measurement or calculated creatinine clearance. In addition, the accuracy of these formulae has only been validated in the patient population for whom they were developed. The MDRD formula is known to underestimate eGFR in patients with normal and near normal renal function [25]. Herts et al [26] showed that when patients' eGFR was calculated by the MDRD formula, a significantly higher percentage of patients had an eGFR of < 60 mL/min than had a serum creatinine of > 1.4 mg/dL. These patients might have been denied contrast medium administration had eGFR been used to determine suitability for injection (15.3% vs. 6.2%).

Thomsen et al [27] reviewed the relative risk of CIN from two randomized trials using eGFR calculated from serum creatinine by the MDRD formula in patients who received IV contrast for computed tomography (CT) examinations. The risk of CIN was found to be 0.6% in patients with eGFR greater than 40 mL/min/1.73m^2 and 4.6% in patients with an eGFR of 30 to 40 mL/min/1.73m^2. The CIN rate was 7.8% in patients with an eGFR > 30 mL/min/1.73m^2. In a study of 421 patients with an eGFR < 60 mL/min/1.73m^2 who did not have end-stage kidney disease, Weisbord and colleagues [28] found that the rate of CIN following contrast-enhanced CT was 2.5% (8 of 316) in those patients who had an eGFR > 45 mL/min/1.73 m^2 and 9.8% (5 of 51) in patients with an eGFR between 30 and 45 mL/min/1.73 m^2. In a study by Kim and colleagues [29], which included 520 patients undergoing contrast-enhanced CT, none of the 253 patients who had an eGFR between 45 and 59 mL/min/1.73 m^2 developed CIN, while six (2.9%) of 209 patients with an eGFR between 30 and 44 mL/min/1.73 m^2 and seven (12.1%) of 58 patients with an eGFR lower than 30 mL/min/1.73 m^2 developed CIN. All of these studies lacked a group of patients not exposed to contrast medium. Therefore, it is difficult to determine if these cases of "CIN" were due to contrast medium administration, another etiology, or background fluctuations in serum creatinine.

Screening

A baseline serum creatinine should be available or obtained before the injection of contrast medium in all patients considered at risk for contrast nephrotoxicity (see below for a list of suggested indications for pre-contrast serum creatinine measurement). Choyke et al [30] identified several patient risk factors that could exclude patients with abnormal serum creatinine with a high specificity, and suggested that if all of these were answered in the negative, 94% would have a normal serum creatinine and 99% would have a serum creatinine under 1.7 mg/dL. These risk factors included: preexisting renal dysfunction, proteinuria, prior kidney surgery, hypertension, and gout. Patients without these risk factors (especially outpatients [31]) could be reasonably excluded from serum creatinine screening prior to contrast injection, resulting in a significant cost savings.

There is no universally agreed upon acceptable interval between the baseline serum creatinine measurement and contrast medium administration. Some accept a 30-day interval as adequate, although it seems prudent to shorten this interval for inpatients and those with a new or heightened risk factor for renal dysfunction.

Suggested Indications for Serum Creatinine Measurement before Intravascular Administration of Iodinated Contrast Medium

The following is a suggested list of risk factors that may warrant pre-administration serum creatinine screening in patients who are scheduled to receive intravascular iodinated contrast medium. This list should not be considered definitive and represents a blend of published data [30,31] and expert opinion:

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

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

*Metformin does not confer an increased risk of CIN. However, metformin can very rarely lead to lactic acidosis in patients with renal failure. Therefore, patients who develop CIN while taking metformin are susceptible to the development of lactic acidosis (see the Chapter on *Metformin* for recommendations). To assess the risk of lactic acidosis, it is probably prudent to stratify the risk of CIN in patients taking metformin who will be exposed to intravascular iodinated contrast medium (please also see the separate Chapter on *Metformin*).

Morbidity and Mortality

The clinical course of CIN depends on baseline renal function, coexisting risk factors, degree of hydration, and other factors. The usual course of CIN is 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. When chronic renal failure develops, it is usually in the setting of multiple risk factors and associated with lifelong morbidity.

Several studies have shown that patients with transient CIN tend to have longer hospital stays, higher mortality, and higher incidences of cardiac and neurologic events than contrast-receiving patients whose kidney function remains stable. 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; 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. 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 acute kidney injury or severe chronic kidney disease are considered at risk for CIN. In these scenarios, the information that may be obtained by using no contrast medium (e.g. noncontrast CT) or other modalities (e.g., ultrasound or 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 discussion of the risk of developing NSF following the administration of gadolinium chelates to 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.

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. Low osmolality contrast medium has a half-life of approximately two hours. Therefore, it takes approximately 20 hours for the entire administered dose of contrast media to be excreted in patients 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 justify a specific prohibition against this practice, nor a specific threshold of contrast media volume beyond which additional contrast media should not be given within a 24-hour period. Obtaining a serum creatinine measurement between two closely spaced iodinated contrast medium-enhanced studies is unlikely to be of any benefit.

Choice of Iodinated Contrast Medium

Barrett and Carlisle [32] 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. Rudnick et al found similar results in a large prospective study. Most centers no longer use intravascular HOCM due to the greater incidence of various adverse effects associated with its use.

Studies [33-37] have failed to establish a clear advantage of IV iso-osmolality iodixanol over IV LOCM with regard to CIN. A 2009 meta-analysis using data pooled from 25 trials found no difference in the rate of CIN between iodixanol and low osmolality agents after intravenous administration [38].

Hydration

The major preventive action against CIN is to ensure adequate hydration. 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 intravascular iodinated contrast medium administration. Oral hydration has also been utilized, but with less demonstrated effectiveness. Pediatric infusion rates are variable and should be based on patient weight.

Not all clinical studies have shown dehydration to be a major risk factor for CIN. 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 [37] studied adult patients with chronic kidney disease who underwent cardiac angiography. The reported incidence of CIN was decreased by periprocedural IV hydration (0.45% or 0.9% saline, 100 mL/h, 12 hours before to 12 hours after intravascular contrast administration). In another study, IV hydration with 0.9% saline was superior to IV hydration with 0.45% saline in reported CIN risk reduction [39]. A protocol for patients with mild to moderate renal dysfunction combining pre-cardiac catheterization oral hydration and post procedural IV hydration was proved effective in one series [40].

Sodium bicarbonate

Some studies and meta-analyses of patients undergoing angiocardiography have shown intravenous hydration with sodium bicarbonate to be superior to 0.9% saline in reducing the risk of CIN [41,42], but these results have been challenged by other meta-analyses [43] and cannot be considered definitive at this time, particularly for patients receiving IV iodinated contrast material.

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 as to whether this agent reduces the risk of CIN [44,45]. 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. There is insufficient evidence of its efficacy to make a definitive recommendation. N-acetylcysteine should not be considered a substitute for appropriate pre-procedural patient screening and adequate hydration.

Diuretics: Mannitol and Furosemide

Solomon et al [46] reported no beneficial effects from the osmotic diuretic mannitol when it was added to saline hydration in patients with or without diabetes mellitus. There was an exacerbation of renal dysfunction when the loop diuretic furosemide was used in addition to saline hydration. 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 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 dialysis patient to an anuric dialysis patient by exposing him or her to intravascular iodinated contrast medium. This remains speculative, as there are no conclusive outcome data in oliguric dialysis patients in this setting.

Patients receiving dialysis are also at theoretical risk from the osmotic load imposed by intravascular iodinated contrast medium because they cannot clear the excess intravascular volume. This osmotic load can theoretically result in pulmonary edema and anasarca. To mitigate this possible risk, contrast medium dosing should be as low as necessary to achieve a diagnostic result (as in all patients). However, complications were not observed in a study of dialysis patients who received intravascular nonionic iodinated contrast medium [47], though the number of patients was small.

Contrast agents 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 [47].

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Metformin

Metformin is a biguanide oral anti-hyperglycemic agent used to treat patients with non-insulin-dependent diabetes mellitus. 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 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.

Also, factors that depress the ability to metabolize lactate, such as liver dysfunction or alcohol abuse, or 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 (see *Table B*). Iodinated X-ray contrast media are not an independent risk factor for patients taking metformin but are a concern only in the presence of underlying renal dysfunction. Although contrast media-induced renal failure is very rare in patients with normal renal function, elderly patients with reduced muscle mass (and thus reduced ability to make creatinine) can have a "normal" serum creatinine level in the presence of a markedly depressed glomerular filtration rate.

Intravascular (IV) administration of iodinated contrast media to a patient taking metformin is a potential clinical concern. Of metformin-associated lactic acidosis cases reported worldwide between 1968 and 1991, 7 of the 110 patients received iodinated contrast media before developing lactic acidosis. 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 renal failure or a reduction in renal function were to be caused by the iodinated contrast media, an accumulation of metformin could occur, with resultant lactate accumulation. The major clinical concern, then, is confined to patients with known, borderline, or incipient renal dysfunction.

Limiting the amount of contrast medium administered and hydrating the patient lessen the risk of contrast media-induced dysfunction; both of these measures should be considered in patients with known or incipient renal dysfunction. The efficacy of other measures thought to limit contrast nephrotoxicity (e.g., administration of N-acetylcysteine) in preventing lactic acidosis related to metformin is not known (also see Chapter on *Contrast-Induced Nephrotoxicity*).

Management

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

1. Evidence suggesting clinically significant contrast-induced nephrotoxicity (CIN) induced by IV contrast injection is weak to nonexistent in patients with normal renal function [4].
2. Iodinated contrast is not an independent risk factor for patients taking metformin, but it is a concern in the presence of underlying conditions of delayed renal excretion of metformin or decreased metabolism of lactic acid or increased anaerobic metabolism.
3. There have been no reports of lactic acidosis following IV contrast injection in properly selected patients.
4. In elderly patients, preliminary estimates of renal function relying on serum creatinine levels may be misleading and overestimate the adequacy of renal function.

The Committee recommends that patients taking metformin be classified into one of three categories, each of which has slightly different suggested management.

Category I

In patients with normal renal function and no known comorbidities (see *Table B*), there is no need to discontinue metformin prior to intravenously administering iodinated contrast media, nor is there a need to check creatinine following the test or procedure.[1]

Category II

In patients with multiple comorbidities (see *Table B*) who apparently have normal renal function, metformin should be discontinued at the time of an examination or procedure using IV iodinated contrast media and withheld for 48 hours. Communication between the radiologist, the health care practitioner, and the patient will be necessary to establish the procedure for reassessing renal function and restarting metformin after the contrast-enhanced examination. The exact method (e.g., serum creatinine measurement, clinical observation, hydration) will vary depending on the practice setting. A repeat serum creatinine measurement is not mandatory.1 If the patient had normal renal function at baseline, was clinically stable, and had no intercurrent risk factors for renal damage (e.g., treatment with aminoglycosides, major surgery, heart failure, sepsis, repeat administration of large amounts of contrast media), metformin can be restarted without repeating the serum creatinine measurement.

Category III

In patients taking metformin who are known to have renal dysfunction, metformin should be suspended at the time of contrast injection, and cautious follow-up of renal function should be performed until safe reinstitution of metformin can be assured.

Metformin and Gadolinium

It is not necessary to discontinue metformin prior to gadolinium-enhanced MR studies when the amount of gadolinium administered is in the usual dose range of 0.1 to 0.3 mmol per kg of body weight.

Table A
Medications containing Metformin*

Generic Ingredients	Trade Names
Metformin	Glucophage Glucophage XR Fortamet Glumetza Riomet
Glyburide/metformin	Glucovance
Glipizide/metformin	Metaglip
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 as of June, 2012.

Table B
Comorbidities for Lactic Acidosis with use of Metformin

Decreased Metabolism of Lactate
Liver dysfunction Alcohol abuse
Increased Anaerobic Metabolism
Cardiac failure Myocardial or peripheral muscle ischemia Sepsis or severe infection

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

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CONTRAST MEDIA IN CHILDREN

Principles regarding contrast media utilization and associated adverse events are generally similar between children and adults. This section will address specific areas in which pediatric use of contrast material differs from adult use and 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 (IV) osmotic loads when compared to adults. IV administration of a hyperosmolality contrast medium may theoretically result in migration of fluid from extravascular soft tissues into blood vessels, consequently expanding blood volume. If the fluid shift is large, cardiac failure and pulmonary edema can result. In children with significant pre-existing cardiac dysfunction, consideration should be given to the use of an iso-osmolality intravascular contrast agent.

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 IV 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 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 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 at body temperature.

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 [1] 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.

Other Unique Issues in Children

Several additional issues complicate the administration of IV 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 2 ml/kg). As a result, timing of image acquisition with regard to contrast medium administration may be important when performing certain imaging studies, such as computed tomography (CT) angiography. A slower injection rate (compared to that used in older children and adults) may be useful to prolong IV enhancement. Second, small gauge angiocatheters (for example, 24-gauge) located in tiny peripheral veins (for example, in the hand or foot) are commonly utilized in neonates and infants.

A study by Amaral et al [2] 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 pounds per square inch (psi). When access is thought to be tenuous, hand injection of contrast medium should be strongly considered in order to minimize risk of vessel injury and extravasation. As many currently used central venous catheters are not approved for power injection, one should always verify that the catheter is approved for such injection and that the pressure used does not exceed its 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 [2]. Most extra-vasations in the pediatric population resolve without untoward sequelae. A study by Wang et al [3] 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

While 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 [4]. For example, local warmth at the injection site and nausea, generally regarded to be 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 [4].

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, there are no standard definitions for such reactions. For example, many studies fail to discriminate between physiologic side effects and allergic-like reactions. In addition, these studies lack agreement on what constitutes mild, moderate, or severe reactions. Second, there is a lack of controlled prospective pediatric studies on the topic. Such investigations are difficult to perform as allergic-like reactions to contrast media in children are rare and large numbers of patients would be needed to acquire statistically meaningful results. Much of the existing literature is retrospective in nature, for which it is impossible 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, at least in part due 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 [1,5]. A very large study by

Katayama et al [6], 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 [5] retrospectively reviewed greater than 11,000 IV injections of low-osmolality nonionic iodinated contrast media 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 [5]. A similarly performed study in adult patients from the same institution over a similar time period revealed an adult reaction rate of approximately 0.6% [7]. A study by Callahan et al 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 [8]. A smaller study by Fjelldal et al [9] documented 5 allergic-like reactions to iohexol following a total of 547 injections, for a rate of reaction of 0.9%. While 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 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 [5].

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 (*Tables 4 and 5*). It is recommended that a pediatric medication chart with weight-based dosages be placed on the emergency cart or posted in the room wherever intravascular contrast media is to be injected into children. Dedicated pediatric emergency resuscitation equipment (including various sizes of emergency airway devices and supplemental oxygen facemasks) also should be available in all such locations (*Table 6*). 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 (CIN) in Children

There has been no large prospective investigation dealing with the possible nephrotoxic effects of IV 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 break-down 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 (note: 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/ml 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 estimated glomerular filtration rate (eGFR). It is important to note that the two formulae used to calculate pediatric eGFR (see below) are different from those used in adults. eGFR calculations in children require knowledge of patient serum creatinine concentration and height. In addition, the assay used to measure serum creatinine concentration must be known.

GFR Calculators for Children

There is no perfect manner of estimating the GFR in children. The National Kidney Disease Education Program (NKDEP) (an initiative of the National Institutes of Health (NIH)) has published the following information regarding the estimation of GFR in children (*http://nkdep.nih.gov/lab-evaluation/gfr-calculators/children-conventional-unit.shtml*):

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 IDMS. Using the original Schwartz equation with a serum creatinine value from a method with calibration traceable to IDMS will overestimate GFR by 20-40%.

Equation: Bedside Schwartz Equation

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

- Height in cm
- Serum creatinine in mg/dL

Prevention of CIN in At-Risk Children

Risk factors for 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 for use 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 magnetic resonance imaging (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 Intravascular Contrast Agents

There are only a few published studies that address adverse reactions to IV gadolinium-based 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 six gadolinium-based contrast agents approved for IV use in the United States. These agents are 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 less 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. Osmolality of gadolinium-based contrast media ranges from approximately 630 mosm/kg H_2O for gadoteridol (Prohance) to 1,970 mosm/kg H_2O for gadobenate dimeglumine (Multihance). Viscosities (at 37 degrees Celsius) range from 1.3 cps for gadoteridol (Prohance) to 5.3 cps for gadobenate dimeglumine (Multihance). These physical properties, however, 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 that are 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

While rare, allergic-like reactions to intravascular gadolinium-based contrast media in children do occur. A study by Dillman et al [12] documented a 0.04% allergic-like reaction rate to these contrast agents in children. While mild reactions are most common, more significant reactions that require urgent medical management may occur [12]. Pediatric allergic-like reactions to gadolinium-based contrast media are treated similarly to those reactions to iodinated contrast agents (*Table 4*). 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 (NSF) and Gadolinium-Based Contrast Media

There are only a small number of reported case of NSF in children (fewer than 10 as of 2008), the majority of which were described prior to this condition's known apparent association with gadolinium-based contrast agents [13-19]. The youngest reported affected pediatric patient is 8 years of age [20], and all reported pediatric patients had significant renal dysfunction. As there are no evidence-based guidelines for the prevention of NSF in children, we recommend that adult guidelines for identifying at-risk patients and administering gadolinium-based contrast media in the presence of impaired renal function be followed. While there has been no reported case of NSF in a very young child, caution should be used when administering these contrast agents to preterm neonates and infants [20] due to renal immaturity and potential glomerular filtration rates under 30 ml/min/1.73m^2 [21].

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 IV 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 [22]. Neonates 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 [23,24]. Aspiration of large volumes of both barium-based and iodinated oral contrast agents rarely may be fatal [24].

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Table A
Sample Pediatric Corticosteriod 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.

Gastrointestinal (GI) Contrast Media In Adults: Indications And Guidelines

Introduction

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

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

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

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

Conventional fluoroscopic examinations

Diagnostic use of barium and water soluble contrast media

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

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

Administration of iodinated contrast agents for opacification of the GI tract

Two commercial water-soluble iodinated HOCMs specifically designed for enteric opacification are in common use. Gastrografin® (Bracco Diagnostics, Inc.; Princeton, NJ) and Gastroview (Covidien; Hazelwood, MO) are solutions comprising 660 mg/ml diatrizoate meglumine and 100 mg/ml diatrizoate sodium. The result is a solution that has 367 mg of iodine per ml. Inactive ingredients includes edetate disodium, flavor, polysorbate 80, purified water, saccharin sodium, simethicone, and sodium citrate.

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

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

Complications from use of barium and water soluble contrast agents

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

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

Although barium sulfate is inert, it can occasionally produce symptoms if aspirated, particularly in patients who have underlying lung disease. While barium is usually mobilized proximally by ciliary action of normal bronchial epithelium, damaged epithelium from bronchial disease delays the normal elimination of barium [9]. If not completely expectorated, retained barium in the lungs can remain indefinitely and may cause inflammation [14]. High volume aspiration can lead to acute respiratory distress or pneumonia, as might be true for aspiration of any nonsterile liquid.

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

Adverse reactions to GI tract barium

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

Allergic-like reactions

Allergic-like (anaphylactoid) reactions to enteric barium are very uncommon. The frequency of allergic-like adverse reactions 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 CO2by the colonic mucosa compared to room air reduces the gas dissolution time following the procedure, making the entire experience better tolerated [107]. However, a consensus on the adoption of CO2 vs. room air has not yet materialized [103].

CT and Positron Emission Tomography (PET) Scanning

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

Magnetic Resonance Imaging (MRI)

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

Magnetic resonance enterography, enteroclysis, and colonography

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

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

Biphasic oral agents

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

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

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

Negative oral agents: 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 T1-0 and T2-weighted images [120]. The resultant negative intraluminal contrast can be useful in the detection of both soft tissue tumors and bowel inflammation [121-123]. Negative oral MR contrast agents can also be beneficial in decreasing the fluid signal in bowel, thereby improving visualization of the pancreatic ducts.

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

Contraindications

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

Contrast Agents in the Biliary and Pancreatic Ductal Systems

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

Potential complications can occur, however, when barium does not drain out of the biliary tree promptly, with most adverse manifestations resulting from overdistention. Delayed emptying or retention of barium beyond 24 hours has been associated with suppurative cholangitis [126]. Choledocholiths forming after progressive water absorption may occlude the biliary ductal system [127]. Indwelling stents may become occluded, also predisposing patients to cholangitis [128]. Shock and disseminated intravascular coagulation have been encountered in occasional patients [128-130]. Very rarely, in individuals sensitive to barium agents, allergic reactions have been encountered.

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

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

Fluoroscopic/conventional radiographic biliary studies with positive oral biliary agents

Imaging of the gallbladder and the lumen of the biliary tree can be accomplished with the use of twelve 500 mg oral iopanoic acid tablets (Telapaque®, Winthrop Pharmaceuticals, New York, NY) administered the prior evening, with overnight fasting [138-140]. Although rarely performed in North America, intravenous infusions of iodipamide (Cholografin®, Bracco Diagnostic, Inc., 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.

Hyocyamine Sulfate

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

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 metoclopromide is unclear; however, it appears to sensitize tissues to the actions of acetylcholine. Metoclopramide increases the tone and amplitude of gastric (especially antral) contractions, relaxes the pyloric sphincter and the duodenal bulb, and increases peristalsis of the duodenum and jejunum, resulting in accelerated gastric emptying.

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

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

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

Secretin

Biologic secretin in no longer available, but is manufactured in a synthetic version (ChiRhoClin®, Inc., Silver Springs, MD). Secretin can be administered to stimulate pancreatic fluid and bicarbonate secretion during MRCP. This improves ductal delineation as the increased generated ductal fluid volume results in greater ductal distension [149,164,165].

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

Treatment of adverse reactions to GI contrast agents and ancillary drugs

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

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Adverse Reactions To Gadolinium-Based Contrast Media

Gadolinium chelates have been approved for parenteral use since the late 1980s. Although these agents can be differentiated on the basis of stability, viscosity, and osmolality, they cannot be differentiated on the basis of efficacy. Gadolinium chelates 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 frequency of all acute adverse events after an injection of 0.1 or 0.2 mmol/kg of gadolinium chelate ranges from 0.07% to 2.4%. The vast majority of these reactions are mild, including coldness at the injection site, nausea with or without vomiting, headache, warmth or pain at the injection site, paresthesias, dizziness, and itching. Reactions resembling an “allergic” response are very unusual and vary in frequency from 0.004% to ¬0.7%. A rash hives, or urticaria are the most frequent of this group, and very rarely there may be bronchospasm. Severe, life-threatening anaphylactoid or nonallergic anaphylactic reactions are exceedingly rare (0.001% to 0.01%). In an accumulated series of 687,000 doses there were only 5 severe reactions. In another survey based on 20 million administered doses there were 55 cases of severe reactions. Fatal reactions to gadolinium chelate agents occur but are extremely rare.

Gadolinium chelates administered to patients with acute renal failure or severe chronic kidney disease can result in a syndrome of nephrogenic systemic fibrosis (NSF). (See the Chapter on *Nephrogenic Systemic Fibrosis - NSF*)

Risk Factors

The frequency of acute adverse reactions to gadolinium contrast media is about 8 times higher in patients with a previous reaction to gadolinium-based contrast media. Second reactions to gadolinium-based media (GBCM) can be more severe than the first. Persons with asthma and various other allergies, including to other medications or foods are also at greater risk, with reports of adverse reaction rates as high as 3.7%. Although there is no cross-reactivity, patients who have had previous allergic-like reactions to iodinated contrast media are also in this category.

In the absence of any widely accepted policy for dealing with patients with prior contrast reactions (especially to gadolinium-based media) and the need for subsequent exposure to magnetic resonance (MR) agents, it does seem prudent to at least take precautions in a patient who previously had a reaction to GBCM. It should be determined if gadolinium-based contrast medium is necessary, if a different brand could be used, and if 12 to 24 hours of premedication with corticosteroids and antihistamines could be initiated. This administration is particularly applicable in patients who had prior moderate to severe reactions.

Nephrotoxicity

Gadolinium agents are considered to have no nephrotoxicity at approved dosages for MR imaging. MR with gadolinium has been used instead of contrast-enhanced CT in those at risk for developing worsening renal failure if exposed to iodinated contrast media. However, in view of the risk of NSF in patients with severe renal dysfunction, this practice should only be considered after reviewing the recommendations for use of gadolinium-based contrast in this group of patients.

Gadolinium agents are radiodense and can be used for opacification in CT and angiographic examinations instead of iodinated radiographic contrast media. However, there is controversy about whether gadolinium contrast media are less nephrotoxic at equally attenuating doses. Caution should be used in extrapolating the lack of nephrotoxicity of intravenous (IV) gadolinium at MR dosages to its use for angiographic procedures, including direct injection into the renal arteries. No assessment of gadolinium versus iodinated contrast nephrotoxicity by randomized studies of equally attenuating doses is currently available. Initially, radiographic use of high doses of gadolinium agents was proposed as an alternative to nephrotoxic iodinated contrast media in patients with renal insufficiency. However, because of the risk of NSF following gadolinium-based contrast material administration, especially in patients with acute renal failure or severe chronic kidney disease, and because of the unknown nephrotoxicity of high doses of gadolinium agents, use of these contrast media for conventional angiography is no longer recommended.

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

Early in vitro research dealing with the effects of MRI 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, thus conceivably could promote vaso-occlusive complications in sickle cell patients [1]. The further supposition that the IV administration of GBCM might potentiate sickle erythrocyte alignment, thereby additionally increasing the risk of vaso-occlusive complications, is mentioned in the FDA package inserts (as of 2009) 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 [2] of the literature, there has been no documented *in vivo* vaso-occlusive or hemolytic complication directly related to the IV administration of a GBCM in a sickle cell disease patient. A small retrospective study by Dillman et al with a control group showed no significantly increased risk of vaso-occlusive or hemolytic adverse events when administering GBCM to sickle cell disease patients [3]. Additionally, several small scientific studies [4-6] of patients with sickle cell disease have employed MR imaging with GBCM without reported adverse effects.

Therefore, it is our opinion that any special risk to sickle cell patients from IV administered GBCM at currently approved dosages must be extremely low, and there is no reason to withhold these agents from patients with sickle cell disease. However, as in all patients, GBCM should be administered only when clinically indicated.

Treatment of Acute Adverse Reactions

Treatment of moderate or severe acute adverse reactions to gadolinium-based contrast media is similar to that for moderate or severe acute reactions to iodinated contrast media (see *Tables 3, 4 and 5*). 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

The incidence of extravasation in one series of 28,000 doses was 0.05%. Laboratory studies in animals have demonstrated that both gadopentetate dimeglumine and gadoteridol are much less toxic to the skin and subcutaneous tissues than are equal volumes of iodinated contrast media. The small volumes typically injected for MR studies limit the chances for a compartment syndrome. For these reasons the likelihood of a significant injury resulting from extravasated MR contrast media is extremely low. Nonionic MR contrast media are less likely to cause symptomatic extravasation than hypertonic agents such as gadopentate dimeglumine.

Serum Calcium Determinations

Some gadolinium-based MR contrast media interfere with total serum calcium values as determined with some calcium assay methods. It should be emphasized that these MR contrast media do not cause actual reductions in serum calcium, only that the contrast media interferes with the test, leading to falsely low serum calcium laboratory values. In one report by Brown [7] and associates, calcium levels measured by only one of three different assays (the orthocresolphthalein assay) showed a temporary decrease for just two of four studied gadolinium-based contrast media, the length and severity of which closely mirrored the concentration of the measured gadolinium-based media in blood. Specifically, this decrease was seen after injection of gadoversetamide and gadodiamide, but not with gadopentetate dimeglumine or gadoteridol.

Off-Label Usage

Radiologists commonly use contrast media for a clinical purpose not contained in the labeling and thus commonly use contrast media off-label. By definition, such usage is not approved by the Food and Drug Administration. However, physicians have some latitude in using gadolinium chelates off label 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 gadolinium chelate is approved in the United States for use in a power injector.

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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 (EMEA), 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 m^2) and severe CKD (CKD4, eGFR 15 to 29 ml/min/1.73 m^2) 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 m^2 than to 30 ml/min/1.73 m^2. There has been only one published case report of a patient with eGFR values above 30 ml/min/1.73 m^2 [10].

Acute kidney injury (AKI)

Between 12% and 20% of 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 3 0 ml/min/1.73m^2 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 m^2) prior to GBCA administration. Thus, hepatic disease in and of itself, in the absence of AKI or severe CKD, is no longer considered 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 m^2) without dialysis
- eGFR 30 to 40 ml/min/1.73 m^2 without dialysis*
- AKI [30,31]

*As further discussed below (see “Patients with CKD 3 [eGFR 30 to 59 ml/min/1.73 m^2]”), patients with eGFR 30 to 40 ml/min/1.73 m^2 should also be considered at risk because eGFR levels may fluctuate (e.g., from the 30 to 40 ml/min/1.73 m^2 range one day to below < 30 ml/min/1.73 m^2 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 erythematosis, 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:

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

Updated Schwartz equation:

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

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:

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

Prior eGFR level (ml/min/1.73 m^2)	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*

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.

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 m^2) 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 m^2)

NSF developing after GBCA administration to patients with eGFR > 30 ml/min/1.73 m^2 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 m^2. In comparison, no special precautions are required in patients with an eGFR of 40 to 59 ml/min/1.73 m^2 [36,37].

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

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 m^2 simply due to immature renal function (and not due to pathologic renal impairment). In these individuals, the ACR Committee on Drugs and Contrast Media believes that caution should still be used when administering GBCAs, although an eGFR value < 30 ml/min/1.73 m^2 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)
Gadoteridol (ProHance® – Bracco Diagnostics)
Gadoteric acid (Dotarem® – Guerbet [as of this writing not FDA-approved for use in the U.S.]
Gadobutrol (Gadavist® – Bayer HealthCare Pharmaceuticals)
Group III: Agents that have only recently appeared on the market:
Gadofosveset (Ablavar® – Lantheus Medical Imaging)
Gadoxetic acid (Eovist® – 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 3, 4, and 5*). 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 3, 4, and 5*.

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 6*). 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

Studies of low-molecular weight water-soluble extracellular substances such as iodinated diagnostic X-ray and computed tomography (CT) and gadolinium-based magnetic resonance imaging (MRI) contrast media in pregnancy have been limited, and their effects on the human embryo or fetus are incompletely understood. Iodinated diagnostic contrast media have been shown to cross the human placenta and enter the fetus in measurable quantities [1,2]. A standard gadolinium-based MRI contrast medium has been shown to cross the placenta in primates and appear within the fetal bladder within 11 minutes after intravenous administration [3]. It must be assumed that all iodinated and gadolinium-based contrast media behave in a similar fashion and cross the blood-placental barrier 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 the study in primates, placental enhancement could be detected up to 2 hours following the intravenous (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 LOCM

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 adequate and well-controlled teratogenic studies of the 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 iodinated contrast medium during pregnancy; however, this occurred only following amniofetography using fat-soluble iodinated contrast medium which was performed in the past to detect congenital malformations.

Intravenous administration of iodinated contrast medium does not affect short-term neonatal 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 thyroid stimulating hormone levels at the time of their birth, no extra attention is felt to be necessary[7,8,9].

Other adverse effects

There have been no other adverse effects that 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

We recommend that all imaging facilities should have policies and procedures in place to identify pregnant patients prior to the performance of any examination involving administration of iodinated contrast media. If a patient is known to be pregnant, the potential added risks of contrast media should be considered before proceeding with the study [10].

There is insufficient evidence to conclude that LOCM are without any risk with respect to the fetus. Consequently, the Committee on Drugs and Contrast Media recommends the following in patients in whom imaging studies are requested that may require the use of iodinated contrast material:

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

1. That the information requested cannot be acquired without contrast administration.
2. That the information needed affects the care of the patient and 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 pregnant patients undergoing a diagnostic imaging examination with iodinated contrast media and their referring physicians should indicate that they understand the potential risks and benefits of the procedure to be performed, the potential for risk to the fetus, and the alternative diagnostic options available to them (if any), and that they indicate the desire to proceed.

Gadolinium-Based Contrast Agents (GBCAs)

Mutagenic effect of GBCAs

To date, there have been no known adverse effects to human fetuses reported when clinically recommended dosages of 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 [11]. However, no adequate and well-controlled teratogenic studies of the effects of these media in pregnant women have been performed.

Risk of nephrogenic systemic fibrosis

There are no known cases of NSF linked to the use of GBCAs in pregnant patients to date. However, gadolinium chelates may accumulate in the amniotic fluid. Therefore, there is the potential for dissociation of the toxic free gadolinium ion, conferring a potential risk for the development of nephrogenic systemic fibrosis (NSF) in the child or mother. Because the risk is unknown, it is generally recommended that gadolinium chelates not be used routinely in pregnant patients.

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 only with caution. They should only be used if their usage is considered critical and the potential benefits justify the potential risk to the unborn fetus. If a GBCA is to be used in a pregnant patient, one of the agents believed to be at low risk for the development of NSF [12] should be used at the lowest possible dose to achieve diagnostic results. In pregnant patients with severely impaired renal function, the same precautions should be observed as in non-pregnant patients.

At the present time, the 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 and gadolinium-based contrast agent administered only when there is a potential significant benefit to the patient or fetus that outweighs the possible risk of exposure of the fetus 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 both pregnant patients undergoing an MRI examination and their referring physicians should indicate that they understand the potential risks and benefits of the MRI procedure to be performed, and the alternative diagnostic options available (if any), and that they wish to proceed.

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

Diphenhydramine and corticosteroids (most commonly prednisone and methyl-prednisolone) 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 also classified as a class C drug, carries a small risk of cleft lip if used before 10 weeks of gestation [16, 17].

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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 form both breast after contrast administration until breast feeding resumes. In anticipation of this, she may wish to use a breast pump to obtain milk before the contrast-enhanced study to feed the infant during the 24-hour period following the examination.

References

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Table 1: Indications for Use of Iodinated Contrast Media

Intravascular

- Intravenous
  - Computed tomography
  - Digital subtraction angiography
  - Intravenous urography
  - Venography (phlebography)
    - Inferior vena cava and its tributaries
    - Superior vena cava and its tributaries
    - Extremities
    - Other venous sites
      - Epidural venography
- Intra-arterial
  - Angiocardiography
  - Computed tomography
  - Coronary and pulmonary angiography
  - Aortography
  - Visceral and peripheral arteriography
  - Digital subtraction angiography
  - Central nervous system
    - Cerebral, vertebral, and spinal angiography

Intrathecal (Use U.S. Food and Drug Administration-approved contrast media only)

- Myelography (myelographic nonionic only)
- Cysternography (myelographic nonionic only)

Other

- Oral, rectal, or ostomy – gastrointestinal tract
  - Conventional fluoroscopy
  - Computed tomography
  - Therapeutic uses
- Body cavity use
  - Herniography
  - Peritoneography
  - Vaginography
- Hysterosalpingography
- Arthrography
- Endoscopic retrograde cholangiopancreatography
- Cholangiography
- Nephrostography
- Pyelography – antegrade, retrograde
- Urethrography – voiding, retrograde
- Cystography
- Sialography
- Ductography (breast)
- Miscellaneous
  - Sinus tract injection
  - Cavity delineation (including urinary diversions, such as loop and pouch)
  - Catheter localization studies

Table 2 : Organ and System-Specific Adverse Effects from the Administration of Iodine-Based or Gadolinium-Based Contrast Agents

Individual organs can manifest isolated adverse effects caused by the administration of contrast media.

Adrenal Glands

Hypertension (in patients with pheochromocytoma after intra-arterial injection)

Brain

Headache

Confusion

Dizziness

Seizure

Rigors

Lost or diminished consciousness

Lost or diminished vision

Gastrointestinal Tract

Nausea

Vomiting

Diarrhea

Intestinal cramping

Heart

Hypotension

Dysrhythmia (asystole, ventricular fibrillation/ ventricular tachycardia)

Pulseless electrical activity (PEA)

Acute congestive heart failure

Kidney

Oliguria

Hypertension

Contrast-induced nephropathy (CIN)

Pancreas

Swelling / pancreatitis

Respiratory System

Laryngeal edema

Bronchospasm

Pulmonary edema

Salivary Glands

Swelling / parotitis

Skin and Soft Tissues

Pain

Edema

Flushing

Erythema

Urticaria

Pruritus

Compartment syndrome (from extravasation)

Nephrogenic Systemic Fibrosis (NSF)

Thyroid

Exacerbation of thyrotoxicosis

Vascular System

Hemorrhage (due to direct vascular trauma from contrast injection or from the reduction in clotting ability)

Thrombophlebitis

Table 3: 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 4: Treatment of Acute Reactions to Contrast Media in Children

HIVES

	Treatment	Dosing
General comment: observe until hives are resolving. Further observation may be necessary if treatment is administered.		
Mild (scattered and/or transient)	No treatment often needed; however, if symptomatic, can consider	
	Diphenhydramine (Benadryl®)*	1 mg/kg (max = 50 mg) PO, IM, or IV; administer IV dose slowly over 1–2 min
Moderate (more numerous/ bothersome)	Monitor vitals	
	Preserve IV access	
Consider	Diphenhydramine (Benadryl®)*	1 mg/kg (max = 50 mg) PO, IM, or IV; administer IV dose slowly over 1–2 min
Severe (widespread and/or progressive)	Monitor vitals	
	Preserve IV access	
Consider	Diphenhydramine (Benadryl®)*	1 mg/kg (max = 50 mg) PO, IM, IV; administer IV dose slowly over 1–2 min
Can also consider	Epinephrine (IM)	IM 0.01 mg/kg of 1:1,000 dilution (or 0.01 mL/kg); max 0.15 mg (0.15 mL) if ≤ 30 kg; max 0.30 mg (0.30 mL) if > 30 kg
		or
		EpiPen® Jr. or equivalent (1:1,000 dilution) 0.15 mg (0.15 mL) if ≤ 30 kg 0.30 mg (0.30 mL) if > 30 kg

*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 mL/min
Normotensive	No other treatment usually needed	
Hypotensive	IV fluids: 0.9% normal saline	10–20 mL/ kg;
	or	Maximum of 500–1,000 mL
	Lactated Ringers	
If profound or unresponsive to fluids	Epinephrine (IV)*	IV 0.01 mg/kg of 1:10,000 dilution (or 0.1 mL/kg); administer slowly into a running IV infusion of saline; can repeat every 5–15 min, as needed; maximum single dose: 0.15 mg (1.5 mL) ≤ 30 kg; 0.3 mg (3.0 mL) > 30 kg; can repeat up to 1 mg total dose
	or (if no IV access available)	
	Epinephrine (IM)*	IM 0.01 mg/kg of 1:1,000 dilution (or 0.01 mL/kg); max 0.15 mg (0.15 mL) if ≤ 30 kg; max 0.30 mg (0.30 mL) if > 30 kg
		or
		EpiPen® Jr. or equivalent (1:1,000 dilution); 0.15 mg (0.15 mL) if ≤ 30 kg; 0.30 mg (0.30 mL) if > 30 kg
	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.

BRONCHOSPASM

	Treatment	Dosing
All forms	Preserve IV access	
	Monitor vitals	
	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 calling emergency response team or 911, based upon the completeness of the response	
Moderate	Consider adding epinephrine (IM)*	IM 0.01 mg/kg of 1:1,000 dilution (or 0.01 mL/kg); max 0.15 mg (0.15 mL) if ≤ 30 kg; max 0.30 mg (0.30 mL) if > 30 kg
		or
		EpiPen® Jr. or equivalent (1:1,000 dilution); 0.15 mg (0.15 mL) if ≤ 30 kg 0.30 mg (0.30 mL) if > 30 kg
	or	
	Epinephrine (IV)*	IV 0.01 mg/kg of 1:10,000 dilution (or 0.1 mL/kg); administer slowly into a running IV infusion of saline; can repeat every 5–15 min, as needed; maximum single dose: 0.15 mg (1.5 mL) ≤ 30 kg; 0.30 mg (3.0 mL) > 30 kg; 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 0.01 mg/kg of 1:10,000 dilution (or 0.1 mL/kg); administer slowly into a running IV infusion of saline; can repeat every 5–15 min, as needed; maximum single dose: 0.15 mg (1.5 mL) ≤ 30 kg; 0.30 mg (3.0 mL) > 30 kg; can repeat up to 1 mg total dose
	or	
	Epinephrine (IM)*	IM 0.01 mg/kg of 1:1,000 dilution (or 0.01 mL/kg); max 0.15 mg (0.15 mL) if ≤ 30 kg; max 0.30 mg (0.30 mL) if > 30 kg
		or

		EpiPen® Jr. or equivalent (1:1,000 dilution); 0.15 mg (0.15 mL) if ≤ 30 kg; 0.30 mg (0.30 mL) if > 30 kg
	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
	Preserve IV access	
	Monitor vitals	
	O_2 by mask	6–10 L/min
	Epinephrine (IV)*	IV 0.01 mg/kg of 1:10,000 dilution (or 0.1 mL/kg); administer slowly into a running IV infusion of saline; can repeat every 5–15 min, as needed; maximum single dose: 0.15 mg (1.5 mL) ≤ 30 kg; 0.30 mg (3.0 mL) > 30 kg; can repeat up to 1 mg total dose
	or	
	Epinephrine (IM)*	IM 0.01 mg/kg of 1:1,000 dilution (or 0.01 mL / kg); max 0.15 mg (0.15 mL) if ≤ 30 kg; max 0.30 mg (0.30 mL) if > 30 kg
		or
		EpiPen® Jr. or equivalent (1:1,000 dilution); 0.15 mg (0.15 mL) if ≤ 30 kg; 0.30 mg (0.30 mL) if > 30 kg
	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 Ringers	
Hypotension with bradycardia (min normal pulse varies for children of different ages) (Vasovagal reaction)		
If mild	No other treatment usually necessary	
If severe (patient remains symptomatic despite above measures)	In addition to above measures: Atropine (IV)	IV 0.02 mg/kg (0.2 mL/kg of 0.1 mg / mL solution); 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; Follow with saline flush
Hypotension with tachycardia (max normal pulse varies for children of different ages) (Anaphylactoid reaction)		
If severe (hypotension persists)	Epinephrine (IV)*	IV 0.01 mg/kg of 1:10,000 dilution (or 0.1 mL/kg); administer slowly into a running IV infusion of saline; can repeat every 5–15 min, as needed; maximum single dose: 0.15 mg (1.5 mL) ≤ 30 kg; 0.30 mg (3.0 mL) > 30 kg; can repeat up to 1 mg total dose
	or	
	Epinephrine (IM)*	IM 0.01 mg/kg of 1:1,000 dilution (or 0.01 mL/kg); max 0.15 mg (0.15 mL) if ≤ 30 kg; max 0.30 mg (0.30 mL) if > 30 kg
		or
		EpiPen® Jr. or equivalent (1:1,000 dilution); 0.15 mg (0.15 mL) if ≤ 30 kg; 0.30 mg (0.30 mL if > 030 kg
	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
	Check for responsiveness	
	Activate emergency response team (call 911)	
	Start CPR	
	Get defibrillator or automated electronic defibrillator (AED); apply as soon as available; shock as indicated	
	Epinephrine (between 2 min cycles)	IV 0.01 mg/kg of 1:10,000 dilution (or 0.1 mL/kg); administer quickly; max dose of 1 mg

Note: Please also see BLS and ACLS (PALS) booklets published by the American Heart Association.

PULMONARY EDEMA

	Treatment	Dosing
	Preserve IV access	
	Monitor vitals	
	O_2 by mask	6–10 L/min
	Elevate head of bed	
	Furosemide (Lasix®) (IV)	IV 0.5–1.0 mg/kg; over 2 min; maximum = 40 mg
	Call emergency response team or 911	

SEIZURES / CONVULSIONS

	Treatment	Dosing
	Observe and protect the patient	
	Turn patient on side to avoid aspiration	
	Suction airway, as needed	
	Preserve IV access	
	Monitor vitals	
	O_2 by mask	6–10 L/min
If unremitting	Call emergency response team or 911	

HYPOGLYCEMIA

	Treatment	Dosing
All forms	Preserve IV access	
	O_2 by mask	6–10 L/min
If patient is able to swallow safely	Observe	
	Administer oral glucose	2 sugar packets or 15 g of glucose tablet or gel or ½ cup (4 oz) of fruit juice
If patient is unable to swallow safely		
And IV access is available	Dextrose 50% (IV)	IV D50 ½ ampule (25 g); IV injection over 2 min
And IV access is not available	Glucagon (IM/SQ)	IM/SQ 0.5 mg if < 20 kg
		IM/SQ 1.0 mg if > 20 kg

ANXIETY (PANIC ATTACK)

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

REACTION REBOUND PREVENTION

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

Table 5 : Management of Acute Reactions to Contrast Media in Adults

HIVES

	Treatment	Dosing
Mild (scattered and/or transient)	No treatment often needed; however, if symptomatic, can consider:	
	Diphenhydramine (Benadryl®)*	25–50 mg PO
	or	
	Fexofenadine (Allegra®)**	180 mg PO
Moderate (more numerous/bothersome)	Monitor vitals	
	Preserve IV access	
	Consider diphenhydramine (Benadryl®)*	25–50 mg PO
	or	
	Fexofenadine (Allegra®)**	180 mg PO
	or	
	Consider diphenhydramine (Benadryl®)*	25–50 mg IM or IV (administer IV dose slowly over 1–2 min)
Severe (widespread and/or progressive)	Monitor vitals	
	Preserve IV access	
Consider	Diphenhydramine (Benadryl®)*	25–50 mg IM or IV (administer IV dose slowly over 1–2 min)
Can also consider	Epinephrine (IM)	IM 0.3 mg (0.3 mL of 1:1,000 dilution)
		or
		IM EpiPen® or equivalent (0.3 mL of 1:1,000 dilution, fixed)
	or	
	Epinephrine (IV)	IV 1–3 mL of 1:10,000 dilution; administer slowly into a running IV infusion of saline

* Note: all forms can cause drowsiness; IM/IV form may cause or worsen hypotension.

** Note: second generation antihistamines cause less drowsiness; may be beneficial in patients that 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	
Hypotensive	IV fluids 0.9% normal saline	1,000 mL rapidly
	or	
	Lactated Ringers	1,000 mL rapidly
If profound or unresponsive to fluids alone can also consider	Epinephrine (IV)*	IV 1–3 mL of 1:10,000 dilution; administer slowly into a running IV infusion of saline; can repeat every 5–10 minutes up to 10 mL total
	or (if no IV access available)	
	Epinephrine (IM)*	IM 0.3 mg (0.3 mL of 1:1,000 dilution); can repeat up to 1 mg total
		or
		IM EpiPen® or equivalent (0.3 mL of 1:1,000 dilution, fixed); can repeat 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
	Consider sending patient to the Emergency Department or calling emergency response team or 911, based upon the completeness of the response	
Moderate	Consider adding epinephrine (IM)*	IM 0.3 mg (0.3 mL of 1:1,000 dilution); can repeat up to 1 mg total
		or
		IM EpiPen® or equivalent (0.3 mL of 1:1,000 dilution, fixed; can repeat up to three times)
	or	
	Epinephrine (IV)*	IV 1–3 mL of 1:10,000 dilution; administer slowly into a running IV infusion of saline; can repeat up to 1 mg total
	Consider calling emergency response team or 911 based upon the completeness of the response	
Severe	Epinephrine (IV)*	IV 1–3 mL of 1:10,000 dilution; administer slowly into a running IV infusion of saline; can repeat up to 1 mg total
	or	
	Epinephrine (IM)*	IM 0.3 mg (0.3 mL of 1:1,000 dilution); can repeat up to 1 mg total
		or
		IM EpiPen® or equivalent (0.3 mL of 1:1,000 dilution, fixed); can repeat up to three times
	Call emergency response team or 911	

* Note: in hypotensive patients, the preferred route of epinephrine delivery is IV, as the extremities may not be perfused sufficiently to allow for adequate absorption of IM administered drug.

LARYNGEAL EDEMA

	Treatment	Dosing
All forms	Preserve IV access	
	Monitor vitals	
	Pulse oximeter	
	O_2 by mask	6–10 L /min
	Epinephrine (IV)*	IV 1–3 mL of 1:10,000 dilution; administer slowly into a running IV infusion of saline; can repeat up to 1 mg total
	or	
	Epinephrine (IM)*	IM 0.3 mg (0.3 mL of 1:1,000 dilution); can repeat up to 1 mg total
		or
		IM EpiPen® or equivalent (0.3 mL of 1:1,000 dilution, fixed); can repeat up to three times
	Consider calling emergency response team or 911 based upon the severity of the reaction and the completeness of the response	

* Note: in hypotensive patients, the preferred route of epinephrine delivery is IV, as the extremities may not be perfused sufficiently to allow for adequate absorption of IM administered drug.

HYPOTENSION (systolic blood pressure < 90 mm Hg)

	Treatment	Dosing
All forms	Preserve IV access	
	Monitor vitals	
	Pulse oximeter	
	O_2 by mask	6–10 L/min
	Elevate legs at least 60 degrees	
	Consider IV fluids: 0.9% normal saline	1,000 mL rapidly
	or	
	Lactated Ringers	1,000 mL rapidly
Hypotension with bradycardia (pulse < 60 bpm) (Vasovagal reaction)		
If mild	No other treatment usually necessary	
If severe (patient remains symptomatic despite above measures)	In addition to above measures: Atropine (IV)	0.6–1.0 mg; administer slowly, followed by saline flush; can repeat up to 3 mg total
	Consider calling the emergency response team or 911	

	Treatment	Dosing
Hypotension with tachycardia (pulse > 100 bpm) (Anaphylactoid reaction)		
If hypotension persists	Epinephrine (IV)*	IV 1–3 mL of 1:10,000 dilution; administer slowly into a running IV infusion of saline; can repeat up to 1 mg total
	or	
	Epinephrine (IM)*	IM 0.3 mg (0.3 mL of 1:1,000 dilution); can repeat up to 1 mg total
		or
		IM EpiPen® or equivalent (0.3 mL of 1:1,000 dilution, fixed); can repeat 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
All forms	Preserve IV access	
	Monitor vitals	
	Pulse oximeter	
	O_2 by mask	6–10 L/min
	Labetalol (IV)	20 mg IV; administer slowly, over 2 min; can double the dose every 10 min (e.g., 40 mg 10 min later, then 80 mg 10 min after that)
	or (if labetalol not available)	
	Nitroglycerin tablet (SL)	0.4 mg tablet; can repeat every 5–10 min
	and	
	Furosemide (Lasix®) (IV)	20–40 mg IV; administer slowly over 2 min
	Call emergency response team or 911	

UNRESPONSIVE AND PULSELESS

	Treatment	Dosing
	Check for responsiveness	
	Activate emergency response team (call 911)	
	CPR (30 compressions at a rate of 100 per min, then 2 respirations)	
	Get defibrillator or automated electronic defibrillator (AED); apply as soon as available; shock as indicated	
	Epinephrine (between 2 min cycles)	IV 10 mL of 1:10,000 dilution (administer entire ampule quickly)

Note: Please also see BLS and ACLS booklets published by the American Heart Association.

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
	Morphine (IV)	IV 1–3 mg; repeat every 5–10 min, as needed
	Call emergency response team or 911	

SEIZURES/CONVULSIONS

	Treatment	Dosing
	Observe and protect the patient	
	Turn patient on side to avoid aspiration	
	Suction airway, as needed	
	Preserve IV access	
	Monitor vitals	
	Pulse oximeter	
	O_2 by mask	6–10 L/min
If unremitting	Call emergency response team or 911	
	Lorazepam (IV)	IV 2–4 mg IV; administer slowly, to maximum dose of 4 mg

HYPOGLYCEMIA

	Treatment	Dosing
	Preserve IV access	
	O_2 by mask	6–10 L/min
If patient is able to swallow safely	Oral glucose	Two sugar packets or 15 g of glucose tablet/gel or ½ cup (4 oz) of fruit juice
If patient is unable to swallow safely and IV access available	Dextrose 50% (IV)	D50W 1 ampule (25 grams) IV administer over 2 min
	D5W or D5NS (IV) as adjunct therapy	Administer at a rate of 100 mL/hour
If no IV access is available	Glucagon (IM)	IM 1 mg

ANXIETY (PANIC ATTACK)

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

REACTION REBOUND PREVENTION

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

Table 6: Equipment for Contrast Reaction Kits in Radiology

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. 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:

- Oxygen cylinders or wall-mounted oxygen source, flow valve, nasal prongs, tubing, non-rebreather oxygen masks* (adult and pediatric sizes).
- Suction: wall-mounted or portable; tubing and catheters.
- Oral and/or nasal airways: rubber/plastic; and/or protective breathing barriers.
- "Ambu® – type" bag – valve mask and mouth mask (adult and pediatric sizes) with protective barrier.
- Stethoscope; sphygmomanometer, tourniquets.
- Intravenous solutions (0.9% [normal]saline and/or Ringer's lactate) and tubing.
- Syringes and IV cannulas: variety of sizes.
- Needles: variety of sizes.
- Necessary medications:
  - ➢ Epinephrine 1:10,000, 10-ml preloaded syringe (for IV injection)

    and/or
  - ➢ Epinephrine 1:1,000, 1 ml (for SC/IM injection)

    and/or
  - ➢ Epinephrine IM auto-injector.

    EpiPen Jr.®** (or equivalent) injects 0.15 mg or 0.3 ml of 1:2000

    EpiPen®** (or equivalent) injects 0.3 mg or 0.3 ml of 1:1000
  - ➢ Atropine 1 mg in 10-ml preloaded syringe.
  - ➢ Beta-agonist inhaler with or without spacer.
  - ➢ Diphenhydramine for PO/IM/IV injection.
  - ➢ Nitroglycerin (NTG) – 0.4 mg tabs, sublingual
  - ➢ Aspirin 325 mg.
  - ➢ Dextrose 50% 25mg/50mL syringe.
- Optional medications:
- Lasix 20 – 40 mg IV.
- Labetalol 20 mg IV

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.

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* 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.

** Dey, L.P., Napa, CA

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

Appendix A – Contrast Media Specifications

Product	Chemical Structure	Anion	Cation	% Salt Concentration	Iodine+ (mgl/ml)	Viscosity+ 25° C (cps)	Viscosity+ 37° C (cps)	Osmolality (mOsm/kg H_2O)
INTRAVASCULAR								
Omnipaque™ 140 (GE Healthcare)	Iohexol 302mg	Nonionic	Nonionic	None	140	2.3*	1.5	322
Conray™ 30 (Covidien)	Ionic	Iothalamate	Meglumine	30	141	2	1.5	600
Ultravist® 150 (Bayer HealthCare)	Iopromide	Nonionic	Nonionic	<0.1	150	2.3*	1.5	328
Isovue® –200 (Bracco)	Iopamidol 40.8%	Nonionic	Nonionic	None	200	3.3*	2.0	413
Conray™ 43 (Covidien)	Ionic	Iothalamate	Meglumine	43	202	3	2	1000
Omnipaque™ 240 (GE Healthcare)	Iohexol 518mg	Nonionic	Nonionic	None	240	5.8*	3.4	520
Optiray™ 240 (Covidien)	Ioversol 51%	Nonionic	Nonionic	None	240	4.6	3.0	502
Ultravist® 240 (Bayer Healthcare)	Iopromide	Nonionic	Nonionic	<0.1	240	4.9*	2.8	483
Isovue® –250 (Bracco)	Iopamidol 51%	Nonionic	Nonionic	None	250	5.1*	3.0	524
Visipaque™ 270 (GE Healthcare)	Iodixanol 550mg	Nonionic	Nonionic	None	270	12.7*	6.3	290
Conray™ (Covidien)	Ionic	Iothalamate	Meglumine	60	282	6	4	1400
Isovue® –300 (Bracco)	Iopamidol 61.2%	Nonionic	Nonionic	None	300	8.8*	4.7	616
Omnipaque™ –300 (GE Healthcare)	Iohexol 647mg	Nonionic	Nonionic	None	300	11.8*	6.3	672
Optiray™ 300 (Covidien)	Ioversol 64%	Nonionic	Nonionic	None	300	8.2	5.5	651
Oxilan® 300 (Guerbet)	Ioxilan 62.3%	Nonionic	Nonionic	None	300	9.4*	5.1	610
Ultravist® 300 (Bayer Healthcare)	Iopromide	Nonionic	Nonionic	<0.1	300	9.2*	4.9	607
Hexabrix™ (Covidien)	Ionic	Ioxaglate	Meglumine Sodium	39.3 19.6	320	15.7*	7.5	≈600
Optiray™320 (Covidien)	Ioversol 68%	Nonionic	Nonionic	None	320	9.9	5.8	702
Visipaque™ –320 (GE Healthcare)	Iodixanol 652mg	Nonionic	Nonionic	None	320	26.6	11.8	290
Optiray™ 350 (Covidien)	Ioversol 74%	Nonionic	Nonionic	None	350	14.3	9.0	792
Omnipaque™ –350 (GE Healthcare)	Iohexol 755mg	Nonionic	Nonionic	None	350	20.4*	10.4	844
Oxilan® 350 (Guerbet)	Ioxilan 72.7%	Nonionic	Nonionic	None	350	16.3*	8.1	721
Isovue® –370 (Bracco)	Iopamidol 75.5%	Nonionic	Nonionic	None	370	20.9*	9.4	796
MD-76™ (Covidien)	Ionic	Diatrizoate	Meglumine Sodium	66 10	370	16.4	10.5	1551
Ultravist® 370 (Bayer Healthcare)	Iopromide	Nonionic	Nonionic	<0.1	370	22.0*	10.0	774
Cholografin® (Bracco)	Ionic	Iodipamide	Meglumine	52	257	6.6	5.6	664

+ Data from product package inserts, product brochures, or technical information services.
* Measured at 20° C
** Data on file with Covidien
*** Hexabrix is a registered trademark of Guerbet, S.A. and is co-marketed in the U.S. by Guerbet LLC and Covidien.
o Viscosities of most products intended for oral administration are not reported by manufacturers.

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

Appendix A – Contrast Media Specifications (continued)

Product	Chemical Structure	Anion	Cation	% Salt Concentration	Iodine+ (mgl/ml)	Viscosity+ 25° C (cps)	Viscosity+ 37° C (cps)	Osmolality (mOsm/kg H_2O)
GASTROINTESTINAL – Oral Contrast								
Gastrografin® (Bracco)	Ionic	Diatrizoate	Meglumine Sodium	66 10	370		8.4	1940
MD-Gastroview™ (Covidien)	Ionic	Diatrizoate	Meglumine Sodium	66 10	367			2000
Omnipaque™ 180 (GE Healthcare)	Iohexol Pediatric Oral Use	Nonionic	Nonionic	None	180	3.1*	2.0	331
Omnipaque™ 240 (GE Heathcare)	Iohexol	Nonionic	Nonionic	None	240	5.8*	3.4	520
Omnipaque™ 300 (GE Healthcare)	Iohexol	Nonionic	Nonionic	None	300	11.8*	6.3	672
Omnipaque™ 350 (GE Healthcare)	Iohexol	Nonionic	Nonionic	None	350	20.4*	10.4	844
URORADIOLOGICAL								
Cystografin® (Bracco)	Ionic	Diatrizoate	Meglumine	30	141	2.0	1.5	556
Cystografin® Dilute (Bracco)	Ionic	Diatrizoate	Meglumine	18	85	1.4	1.1	349
Cysto-Conray™ II (Covidien)	Ionic	Iothalamate	Meglumine	17.2	81	(Instill for retrograde cystography and cystourethrography)		~400
Conray™ 43 (Covidien)	Ionic	Iothalamate	Meglumine	43	202	3	2	1000
Omnipaque™ 240 (GE Healthcare)	Nonionic Iohexol	Nonionic	Nonionic	None	240	5.8*	3.4	520
Omnipaque™ 300 (GE Healthcare)	Nonionic Iohexol	Nonionic	Nonionic	None	300	11.8*	6.3	672
Omnipaque™ 350 (GE Healthcare)	Iohexol	Nonionic	Nonionic	None	350	20.4*	10.4	844
Visipaque™ 270 (GE Heathcare)	Iodixanol	Nonionic	Nonionic	None	270	12.7*	6.3	290
Visipaque™ 320 (GE Healthcare)	Iodixanol	Nonionic	Nonionic	None	320	26.6	11.8	290
INTRATHECAL								
Omnipaque™ 180 (GE Healthcare)	Iohexol	Nonionic	Nonionic	None	180	3.1*	2.0	408
Omnipaque™ 240 (GE Healthcare)	Iohexol	Nonionic	Nonionic	None	240	5.8*	3.4	520
Omnipaque™ 300 (GE Healthcare)	Iohexol	Nonionic	Nonionic	None	300	11.8*	6.3	672
Isovue-M® 200 (Bracco)	Iopamidol	Nonionic	Nonionic	None	200	3.3*	2.0	413
Isovue-M® 300 (Bracco)	Iopamidol	Nonionic	Nonionic	None	300	8.8*	4.7	616
Product	**Chemical Structure**	**Anion**	**Cation**	**% Salt Concentration**	**Iodine+ (mgl/ml)**	**Viscosity+ 25° C (cps)**	**Viscosity+ 37° C (cps)**	**Osmolality (mOsm/kg H_2O)**

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Appendix A continues on next page

Appendix A – Contrast Media Specifications (continued)

Product	Chemical Structure	Anion	Cation	% Salt Concentration	Iodine+ (mgI/ml)	Viscosity+ 25° C (cps)	Viscosity+ 37° C (cps)	Osmolality (mOsm/kg H_2O)
BODY CAVITY								
Onmipaque™ 180 (GE Healthcare)	Iohexol	Nonionic	None	None	180	3.1*	2.0	408
Omnipaque™ 240 (GE Healthcare)	Iohexol	Nonionic	None	None	240	5.8*	3.4	520
Omnipaque™ 300 (GE Healthcare)	Iohexol	Nonionic	None	None	300	11.8*	6.3	672
Omnipaque™ 350 (GE Healthcare)	Iohexol	Nonionic	None	None	350	20.4*	10.4	844
Magnevist® (Bayer Healthcare)	Ionic Linear	Gadopentetate	Dime-glumine			4.9*	2.9	1960
Prohance® (Bracco)	Nonionic GD-HP-DOTA Gadoteridol	Gadoteridol	Calteridol calcium			2.0*	1.3	630
Multihance® (Bracco)	Ionic Linear	Gadobenate	Dime-glumine			9.2*	5.3	1970
Omniscan™ (GE Healthcare)	Gd-DTPA-BMA Linear	Nonionic	Nonionic			2.0	1.4	789
Optimark™ (Covidien)	Nonionic Gd-DTPA-BMEA Gadoversetamide	None	None			2.8**	2.0	1110
EOVIST® (Bayer Healthcare)	Ionic Linear	Gadoxetate	Disodium			n/a	1.19	688
Gastromark™ (Covidien) Oral Suspension	Nonionic Ferrous-ferric oxide ferumoxsil	None	None					
Gadavist™ (Bayer Healthcare)	Macrocyclic						4.96	1603

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