

**MANUAL**

**ON**

**CONTRAST**

**MEDIA**

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## PREFACE

This Seventh 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 General, Small and/or Rural Radiology 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, as well as to the use of iodinated contrast media for gastrointestinal imaging.

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

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## 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 Table 4). 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]. For this reason, each patient should be questioned whether he or she has a history of renal dysfunction. Discussion of contrast-induced nephrotoxicity (CIN) and nephrogenic systemic fibrosis (NSF) can be found in the Chapters on Contrast 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 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 pre-medication.

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. Hyper-osmolality 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<sup>®</sup>) [26,29] and hydrocortisone sodium succinate (Solu-Cortef<sup>®</sup>) [30]. Some have suggested that non-succinate glucocorticoids, such as betamethasone or dexamethasone sodium sulfate (Decadron<sup>®</sup>), 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<sup>®</sup>) – 50 mg intravenously, intramuscularly, or by mouth 1 hour before contrast medium [12]

or

2. Methylprednisolone (Medrol<sup>®</sup>) – 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.

## Emergency Premedication (In Decreasing Order of Desirability)

1. Methylprednisolone sodium succinate (Solu-Medrol<sup>®</sup>) 40 mg or hydrocortisone sodium succinate (Solu-Cortef<sup>®</sup>) 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<sup>®</sup>) 7.5 mg or betamethasone 6.0 mg intravenously q4h until contrast study must be done in patient with known allergy to methylprednisolone, 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.

[Note: For a summary of patient preparation strategies, see the table following the references below.]

## 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 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 cardio-

pulmonary arrest occurs, closed-chest cardiopulmonary resuscitation should be initiated immediately.

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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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## INCIDENCE OF ADVERSE EFFECTS

The actual incidence of adverse effects after the administration of intravascular (IV) contrast media is difficult to determine since similar signs and symptoms may be due to concomitant medications, local anesthetics, needles, catheters, and anxiety, among other things. Underreporting or variation in the categorization or classification of reactions affects statistics regarding incidence. One suggested classification system may help eliminate this variation in future studies [1]. Most adverse effects are mild and do not require treatment. Historically, adverse effects have occurred in 5% to 15% of all patients who receive ionic, high-osmolality contrast media (HOCM). Many patients experience physiologic disturbances (e.g., warmth or heat), and this is often not recorded. The use of HOCM for IV use is now uncommon.

Use of low-osmolality ionic and nonionic contrast media (LOCM) is associated with a lower overall incidence of adverse effects, particularly of non-life-threatening ones. Cochran et al reported an overall incidence of adverse effects of 0.2% for nonionic contrast administered at a single institution [2]. A slightly higher overall incidence of 0.7% was reported from a second institution upon review of 29,508 patients given iopromide over a 2-year period. More recently Wang reported an overall incidence of 0.6% upon review of 84,928 patients who received iohexol, iopromide, or iodixanol [3].

Serious contrast reactions are rare and have occurred in 1 or 2 per 1,000 (0.1% to 0.2%) intravascular injections of HOCM and in 1 or 2 per 10,000 (0.01% to 0.02%) IV injections of LOCM.

The incidence of a fatal outcome from an IV contrast media injection is not known with precision. Older literature from the HOCM era cited rates of fatal outcome from contrast media injections as high as 1 per 40,000 IV

administrations. However, in the large Japanese study [4] of the late 1980s, no fatal reactions were attributed to either HOCM or LOCM despite over 170,000 injections of each. The conservative estimate of 1 fatality per 170,000 contrast media administrations is thus often quoted, but the true incidence is not known. Current low fatality rates likely reflect improvements in treatment of reactions, as well as the now widespread use of LOCM.

Although most serious reactions occur in the immediate postinjection period, delayed reactions have been reported to occur with an incidence of up to 2% (see the following Chapter on Adverse Effects of Iodinated Contrast Media).

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## ADVERSE EFFECTS OF IODINATED CONTRAST MEDIA

The general frequency of adverse events related to the administration of contrast media has decreased considerably with changes in usage from high-osmolality contrast media (HOCM) to low-osmolality contrast media (LOCM). While the incidence of mild and moderate reactions has decreased, severe and life-threatening adverse events continue to occur unpredictably, and appropriate training of, and vigilance by, healthcare workers are necessary in areas where contrast media are administered.

The majority of adverse side effects are mild non-life-threatening events that require only observation, reassurance, and support. Severe adverse side effects, however, may have a mild or moderate prodrome. Nearly all life-threatening reactions occur immediately or within the first 20 minutes after contrast media injection.

The effects of dose, route, 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 reactions and may actually increase it. Any intravascular contrast media administration, regardless of route, may result in an adverse event, ranging from mild discomfort to a severe, life-threatening reaction.

### Pathogenesis Mechanisms

Presentations appear identical to an anaphylactic reaction to a drug or other allergen, but since an antigen-antibody response has not been identified in most reacting patients, such a reaction is classified as “anaphylactoid” or as “non-allergic anaphylactic”. Treatment, however, is identical to that for an allergic anaphylactic reaction.

The precise pathogenesis of most adverse events occurring after the administration of contrast media is unclear. There are multiple potential mechanisms. Some reactions may involve activation, deactivation, or inhibition of a variety of vasoactive substances or mediators. Histamine release must have occurred when patients develop urticaria, but the precise cause and pathway of histamine release are not known.

Physiologic mechanisms may relate to the specific chemical formulation of the contrast media, most notably chemotoxicity and hypertonicity, or to binding of the small contrast media molecule to activators. Patient anxiety may contribute to adverse events. Additives or contaminants such as calcium-chelating substances or substances leached from rubber stoppers in bottles or syringes have been suggested as contributory on some occasions.

In general, accurate prediction of a contrast reaction is not yet possible, although it is clear that certain patients are at increased risk of a reaction.

In some cases, the cause of an adverse event can be identified. The etiology of cardiovascular effects, for example, is complex but to some extent definable. Some effects, such as hypotension and tachycardia, have been thought by some to be related to hypertonicity.

Others, such as the negative inotropy and chronotropy that occur with direct coronary injection, are related to both increased osmolality and ionic concentration. Pulseless electrical activity, with associated cardiac arrest, has been shown to result from a sudden drop in serum-ionized calcium, which in turn may be caused by the specific contrast formulation or an additive.

The incidence and severity of such events seem to decrease with the use of low-osmolality and isotonic contrast media.

Further, cardiovascular effects are more frequent and more significant in patients with underlying cardiac disease. For example, patients with left heart failure are less able to compensate for the osmotic load and the minor negative chronotropic effects of contrast media, because of the high osmolality of some contrast media and because of the volume load. As a result, there is an increased risk of developing acute pulmonary edema. Patients with an acute increase in pulmonary vascular resistance, and thus an acute increase in right heart pressure (e.g., patients with massive pulmonary embolism), have an increased risk of developing right heart failure that may be irreversible.

Vasovagal reactions are relatively common and characterized by hypotension with bradycardia. Pathogenesis is unknown, but the 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. Vasovagal reactions are related to anxiety and can occur while consent is being obtained, with placement of a needle or catheter for injection, or with the administration of contrast media via any route. Such reactions generally present with a feeling of apprehension and accompanying diaphoresis.

Most vagal reactions are mild and self-limited, but should be treated and observed closely until they resolve fully, as they may progress to cardiovascular collapse or be associated with angina or seizure secondary to clinically significant hypotension. (See Table 6 – Management of Acute Reactions in Adults.)

Obtaining a focused patient medical history prior to the administration of contrast media

is critically important. Prior reaction to contrast injection is the best predictor of a recurrent adverse event. It is not an absolute indicator, however, since the incidence of recurrent reactions may range from 8% to perhaps as high as 30%. Pre-existing medical conditions can also foreshadow adverse events. Urticarial reactions are more frequent in patients with a strong history of active allergies. Bronchospasm is a common reaction among patients with active asthma. Hemodynamic changes are more common among patients with significant cardiovascular disease, such as aortic stenosis or severe congestive heart failure.

It is very important that all personnel who administer contrast media be prepared to recognize the variety of adverse events that may occur, monitor the patient, and institute the appropriate measures should treatment of an adverse reaction become necessary. These measures may range from notifying the radiologist, to administering medication, to calling a code. Knowledge about the varying adverse effects of contrast media is important, as it will guide the choice of therapy.

### **Special Circumstances**

Drug package inserts suggest precautions are necessary to avoid adverse events in patients with known or suspected pheochromocytoma, thyrotoxicosis, dysproteinemias, myasthenia gravis, or sickle cell disease. There are scant data, however, to support the need for specific precautions in these patients when low-osmolality contrast media is used. (See the Chapter on Patient Selection and Preparation Strategies.)

### **Types of Reactions**

1. Mild
2. Moderate
3. Severe
4. Organ-specific (see Table 2)

Reactions are most often mild but rarely can be life-threatening. Prediction of occurrence

or severity is impossible, although there are some known risk factors, and anticipation and vigilance are critical. In general, it is not possible to classify the etiology of an adverse event following contrast media administration, but it is possible to clarify and classify severity and begin supportive measures.

### *Mild Reactions*

Some reactions, specifically nausea and vomiting, increase in incidence with increasing osmolality.

The frequency of urticarial reactions was high with the use of HOCM. Urticarial reactions are almost always mild, although it can progress to moderate severity. Mild reactions do not require treatment, but, as noted, they may presage or evolve into a more severe reaction. Any patient with any reaction should, therefore, be observed for 20 to 30 minutes, or as necessary, to ensure clinical stability and recovery.

Pain on injection, particularly with injection into the arteries of the lower extremities or into the external carotid arteries, is largely a function of hypertonicity. It is, therefore, much decreased in both incidence and severity with the use of low-osmolality contrast agents and further decreased with the use of iso-osmolality agents. Similarly, sensations of warmth or flushing are an unpleasant physiologic response of very short duration and not indicative of an adverse event.

### *Moderate Reactions*

Moderate adverse events, by definition, are not immediately life-threatening (although they may progress to be so) but often require treatment. These events include symptomatic urticaria, vasovagal reaction, mild bronchospasm, and tachycardia secondary to transient mild hypotension. Moderate reactions require close monitoring until they resolve completely. Treatment may include diphenhydramine for symptomatic hives,

use of a beta-agonist inhaler for bronchospasm, or leg elevation and/or fluid therapy for hypotension. Vital signs should be obtained in any patient suspected of having a moderate reaction. It is also appropriate to consider securing intravenous (IV) access and providing oxygen.

### *Severe Reactions*

Severe adverse events are potentially or immediately life-threatening. Although they are rare, it is imperative that all personnel who administer contrast media be aware that they occur unpredictably and that they require prompt recognition and treatment. Patients may initially experience a variety of symptoms and signs, ranging from anxiety to respiratory distress, diffuse erythema, or sudden cardiac arrest.

Complete cardiopulmonary collapse requires cardiopulmonary resuscitation and advanced specialized life-support equipment and trained personnel. Cardiopulmonary collapse may occur very rapidly, so all patients receiving IV contrast must be observed closely during the procedure. Since the outcome of cardiopulmonary arrest worsens as the response time increases, prompt recognition of such reactions and rapid institution of treatment are crucial.

Severe adverse events also include profound vasovagal reactions, moderate and severe bronchospasm, laryngeal edema, seizure, and severe hypotension. Pulmonary edema may also occur, particularly, but not exclusively, in patients with underlying congestive heart failure.

### *Organ-Specific Effects*

Some organ-specific adverse effects have been noted above. They include pulseless electrical activity (PEA), pulmonary edema, and seizures. The effect of extravasation of contrast during IV administration is generally mild, particularly if low-osmolality contrast media is used, and specific therapies are dealt with elsewhere.

Venous thrombosis can occur in response to an infusion of contrast media. This is related to direct vascular endothelial damage and is more of a problem with HOCM. Contrast media are known to have an effect not only on vascular endothelial function but also on thrombosis and hemostasis. These complex interactions in general are not thought to be major or significant. Contrast media are also known to cause some alteration in red blood cell deformability and in platelet function, but these effects are not thought to be clinically relevant.

Renal effects of contrast media are discussed in the Chapter on Contrast Nephrotoxicity.

In summary, contrast media, acting through various poorly understood mechanisms, can be associated with a variety of adverse events. These events range from trivial to profound and reliable prediction of such reactions is not currently possible. The health care team should be knowledgeable about specific adverse events, risk factors, and signs and symptoms, as well as the need for routine thoughtful patient observation. Personnel must be similarly prepared for expeditious and appropriate treatment when indicated.

### **Delayed Reactions to Contrast Media**

Reactions that are not acute have long been a source of concern with both iodinated and gadolinium-based contrast media. Currently, delayed reactions to gadolinium media in the form of nephrogenic systemic fibrosis (NSF) are a major concern, and are dealt with in detail elsewhere in this manual.

Many different symptoms and signs have been reported as delayed reactions associated with iodinated contrast media. Some relatively common ones are nausea, vomiting, drowsiness, headache, and pruritus without urticaria, all of which are self-limited and usually do not require therapy. Delayed cardiopulmonary arrest has also been reported, but this and other severe

systemic reactions are probably related to etiologies other than the contrast media.

Currently, other than contrast-induced nephropathy, the delayed reactions to contrast media that are of most frequent concern are the cutaneous ones. These are important for several reasons: they occur more often than is generally recognized; they may recur; they may have serious sequelae; and, perhaps most importantly, they are often ascribed to causes other than contrast media.

The incidence of delayed adverse cutaneous reactions has been reported to range from 0.5% to 9%. Some are moderate to severe in distribution and associated symptoms. Delayed cutaneous reactions are more common in patients treated with interleukin-2 (IL-2) therapy.

The onset of delayed cutaneous reactions ranges from 3 hours to 7 days following the administration of a contrast agent. For several reasons (lack of awareness of such adverse events, usual practice patterns, relatively low frequency of serious outcomes), they are often not brought to the attention of the radiologist and are ascribed to other causes because contrast agents have a biologic half-life of less than one hour, are too small to function unbound as antigens, and are minimally protein bound.

Delayed cutaneous reactions present with an exanthem that varies widely in size and distribution. The manifestations are often macular but may be maculopapular or pustular or may resemble angioneurotic edema, and are usually associated with pruritus. They are generally self limited and require only minimal symptomatic therapy. They may, however, progress to severe symptomatology with wide distribution. Cases have been reported that resemble Stevens-Johnson syndrome, toxic epidermal necrolysis, or cutaneous vasculitis, and one fatality has even been described. When the rash is limited, symptomatic therapy such as corticosteroid creams can be used; if it is

progressive or widespread, or if there are significant associated symptoms, consultation with allergy or dermatology services is an appropriate early step.

These adverse events are also unusual in that there is a high rate of recurrence, particularly if the same contrast medium is used but also with a different specific contrast agent. The true recurrence rate is not known, but anecdotally it is greater than 25%. Delayed cutaneous reactions are not, however, associated with other acute adverse events such as bronchospasm or laryngeal edema. The etiology, as with most significant contrast-related complications, is not clear. Because of the tendency to recur and because of the associated symptomatology, these reactions are thought to be T-cell mediated. The effectiveness of prophylaxis, particularly with oral corticosteroids, is unknown.

In summary, delayed cutaneous reactions are relatively frequent and are often mistakenly thought to be caused by another inciting media, in part because of the physiology of contrast media, and in part because many radiologists are (not surprisingly) unaware that such reactions occur. These adverse events appear to be true delayed-hypersensitivity reactions and tend to recur if contrast medium is administered again, particularly if the same agent is used. Their onset ranges from three hours to a week after contrast administration. These reactions should be followed closely, documented thoroughly, and treated symptomatically with the realization that symptoms and signs may occasionally become clinically significant.

### **Other Adverse Effects**

Iodide “mumps” (salivary gland swelling) and a syndrome of acute polyarthropathy are two delayed reactions that can occur with either high-osmolality or low-osmolality contrast media and that may be more frequent in patients with renal dysfunction.

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

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# CONTRAST NEPHROTOXICITY

## Definition

Nephrotoxicity is attributed to radiologic iodinated contrast media when there has been a sudden deterioration in renal status after the administration of a contrast media and no other etiology appears likely from the clinical records. The risk of nephrotoxicity is related to the degree of pre-existing renal disease and hydration. Clinically significant nephrotoxicity after administration of iodinated contrast media is highly unusual in patients with normal renal function.

There is no standard definition for reporting contrast media induced nephrotoxicity (CIN); definitions used have included percent change in the baseline serum creatinine (e.g., a 20% to 50% rise in serum creatinine) and absolute elevation from baseline (increase of 0.5 to 2.0 mg/dl). Studies also vary in the length of time and number of data points over which serum creatinine was obtained following contrast media administration. Few studies have followed patients for more than 72 hours. Porter [1] defined CIN as a serum creatinine increase of: (a) greater than 25% if baseline serum creatinine is less than 1.5 mg/dl, or (b) greater than 1.0 mg/dl if baseline serum creatinine is greater than 1.5 mg/dl, when either occurs within 72 hours after the contrast administration. Solomon et al [2] defined CIN as an acute decrease in renal function manifested by an increase in baseline serum creatinine of at least 0.5 mg/dl (44  $\mu$ mol/l) within 48 hours of injection of contrast. The prevalence of CIN, therefore, varies depending on the definition used.

The clinical significance of these definitions remains open to debate. Even a 50% rise in serum creatinine in a patient with normal renal function may not be clinically significant, because it may not require intervention or affect prognosis if the change is transient, which is usually the case. Two

studies have recently been published which highlight the normal variation in serum creatinine in the absence of contrast administration. In more than 30,000 patients studied by Newhouse et al [3] who did not receive any contrast material, more than half showed a change in serum creatinine of at least 25% and more than a 40% change of at least 0.4 mg/dL. The author's comment that had some of these patients received iodinated contrast, the rise would have undoubtedly been attributed to it, rather than to physiologic variation. Bruce et al [4] showed that a rise in serum creatinine of 0.5 mg/dL or an increase of 25% was similar in a control group of patients who did not receive contrast material as to that found in patients who received either iodixanol or iohexol during contrast-enhanced CT examinations in patients with baseline serum creatinine levels below 1.8 mg/dL.

Serum creatinine has limitations as an accurate measure of renal function because it is influenced greatly by the patient's gender, muscle mass, nutritional status, and age. Normal serum creatinine levels are maintained until the glomerular filtration rate (GFR) — at least as reflected in creatinine clearance — is reduced by nearly 50%; that is, impaired renal function may exist even when serum creatinine levels are "normal." For this reason, it has been suggested that radiologists stratify patients at risk for CIN according to the classification system promulgated by the National Kidney Foundation which is based on the GFR (see Fig 1 at the end of this chapter). Although direct measurement of GFR with insulin or a similar clearance marker would be most accurate in defining renal function before and after contrast administration, this is generally impractical. One alternative is to use a formula to calculate creatinine clearance, (estimated GFR or eGFR) based on age, gender, body weight, and serum creatinine (e.g., Cockcroft-Gault [5] formula or Modification of Diet in Renal Disease [MDRD] formula;

calculators are available on various Web pages). Furthermore, the clinical benefit of using calculated creatinine clearance in assessing CIN risk 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 intravenous hydration, avoidance of contrast material 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 or near normal renal function [6]. A paper published by Herts et al [7] showed when patients were evaluated by eGFR, as 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 media administration had eGFR been used to determine suitability for injection (6.2 % vs 15.3%).

In a recent paper, Thomsen et al [8], however reviewed the relative risk of CIN from two randomized trials using eGFR calculated from serum creatinine by the MDRD formula in patients who received intravenous (IV) contrast media for MDCT examinations. The risk of CIN was found to be 0.6% in patients with an eGFR greater than 40 ml/min and 4.6% in patients with an eGFR less than 40 ml/min but greater than 30 ml/min. In patients with an eGFR < 30 ml/min, the CIN rate was 7.8%.

Another confounding variable in the literature is related to whether contrast media is injected intravenously or intra-arterially. Many of the studies of CIN are obtained from patients undergoing cardiac catheterization. Such patients are more likely to have diabetes and hypertension and are thus at higher risk. Also, many of these

studies investigate contrast media effects in patients who are sick enough to be inpatients long enough to obtain postcontrast creatinine measurements. Additionally, there may be nephrotoxic effects from the angiography procedure itself (e.g., atherosclerotic emboli). Therefore data from cardiac angiography studies may be applicable in that situation but may not predict how the general population of patients undergoing computed tomography (CT) studies will do when the contrast media are injected intravenously.

There is no uniform definition of renal dysfunction. When creatinine clearance is less than 60 ml/min (in a normal young adult equivalent to a serum creatinine of 133 mmol/l or 1.5 mg/dl) the term “renal insufficiency” has been used, and when creatinine clearance is less than 30 ml/min the term “renal failure” is often used.

There is no data on the risk of CIN in children.

## **Pathogenesis**

The exact pathophysiology of CIN is not fully understood. Renal effects are seen with high-osmolality ionic contrast media (HOICM), low-osmolality contrast media (LOICM), and iso-osmolality contrast media (IOICM). Etiologic factors that have been suggested include: 1) renal hemodynamic changes (vasoconstriction), and 2) direct tubular toxicity of the contrast material. Both osmotic and chemotoxic mechanisms may be involved, and some investigations suggest agent-specific chemotoxicity. Regardless, it does appear that the nephrotoxicity of contrast media is related to the dose administered.

## **Risk Factors**

Numerous studies have attempted to isolate risk factors for CIN. The classic review by Byrd and Sherman [9] listed predisposing factors for radiologic contrast media-induced acute renal failure as pre-existing renal insufficiency (serum creatinine level  $\geq 1.5$  mg/dl), diabetes mellitus, dehydration,

cardiovascular disease and the use of diuretics, advanced age ( $\geq 70$  years), multiple myeloma, hypertension, and hyperuricemia. However, studies by Parfrey et al [10] and Schwab et al [11] documented that the patients at highest risk for developing contrast media induced acute renal failure are those with both diabetes *and* pre-existing renal insufficiency. These investigators did not find that, given equal states of hydration, either diabetes alone or renal insufficiency alone (although yielding a somewhat higher risk for renal failure than the normal population) resulted in a statistically greater incidence of renal dysfunction after contrast administration. The age threshold for a high risk of contrast-induced nephrotoxicity is not well established and seems to be changing, as people are becoming healthier at older ages.

One additional risk factor is thought to be the use of multiple contrast examinations within a short time interval. It is known that it takes close to 24 hours for the entire administered dose of contrast media to be excreted by the kidneys, so it has long been a recommendation that intervals of shorter than this be avoided except in urgent situations. There is little hard data to support this recommendation. But a recent paper [12], although criticized by some authorities [13] for methodological issues, seems to support this recommendation. However, despite the recommendation of obtaining a serum creatinine prior to a repeat dose made in this study, we do not believe that there is sufficient evidence to justify this recommendation.

### **Consequence**

The clinical course of CIN depends on baseline renal function, coexisting risk factors, degree of hydration, and other factors. Serum creatinine usually begins to rise within the first 24 hours following IV contrast media administration, peaks within 96 hours (4 days), and usually returns to baseline within 7 to 10 days. It is unusual for patients to develop permanent renal failure, and this usually occurs in the setting of multiple risk factors. However, when

chronic renal failure develops it is associated with lifelong morbidity.

Patients who are taking the antihyperglycemic agent metformin are not at increased risk of CIN compared to other similar patients not on metformin. However, there is the risk of metformin-related complications (including lactic acidosis) if such patients were to develop CIN and their renal excretion of metformin was to diminish (see the Chapter on Metformin).

### **Prevention or Amelioration**

#### *Avoidance of Iodinated Contrast Media*

The risk of developing CIN is not an absolute but a relative (and often weak relative) contraindication to the administration of IV iodinated contrast media. With the use of the maneuvers described below to reduce risk, and the usual short clinical course of CIN, the risk of clinically relevant renal dysfunction is very low in many situations. In other cases, the risk may be sufficiently great, and the information that may be obtained by using no contrast media (e.g. noncontrast CT) or by other modalities (e.g., ultrasound or magnetic resonance imaging [MRI]) may be sufficiently useful, that IV iodinated contrast may be avoided. (See the Chapter on Nephrogenic Systemic Fibrosis [NSF] for a discussion on the risk of development of NSF following administration of gadolinium chelates to patients with renal disease). In some clinical situations, the use of iodinated contrast media may be necessary regardless of CIN risk. The use of the minimum dose of radiographic iodinated contrast media that provides sufficient diagnostic information may reduce risk.

#### *Choice of Iodinated Contrast Media*

Barrett and Carlisle [14] reported a meta-analysis of the literature concerning the relative nephrotoxicity of HOCM and LOCM. They concluded that LOCM are, generally, less nephrotoxic than HOCM in patients with underlying renal insufficiency. However, LOCM were *not* shown to confer

a significant benefit in patients with normal renal function where the risk is low. Rudnick et al found similar results in a large prospective study.

Some studies have suggested a benefit for the iso-osmolality contrast agent, iodixanol. Aspelin et al [15] were the first to suggest that iodixanol was associated with a lower risk of CIN than the LOCM, iohexol. This and other studies were initially performed in high-risk diabetic patients undergoing cardiac catheterization. Subsequent reports [16-19] have failed to establish a clear advantage of iodixanol over the other low-osmolality contrast media with regard to CIN, whether administration is IV or intra-arterial. A recent meta-analysis using data pooled from 25 trials failed to demonstrate the superiority of iodixanol compared to LOCM after IV administration [20]. The study was unable to draw a conclusion as to the relative benefit of iodixanol for intra-arterial administration, however.

### *Hydration*

Not all clinical studies have shown dehydration to be a major risk factor for CIN. However, in the dehydrated state, renal blood flow and glomerular filtration rate are decreased, the magnitude of the effects of contrast media on these parameters is accentuated, and there is the theoretical concern of prolonged tubular exposure to contrast media because of low tubular flow rates. Solomon et al [19] studied adult patients with chronic renal insufficiency that underwent cardiac angiography. The incidence of CIN was decreased by hydration with 0.45% saline or 0.9% saline administered at a rate of 100 ml/hr beginning 12 hours before and continuing 12 hours after angiography. In another study, IV 0.9% saline hydration was shown to reduce CIN risk more than 0.45% saline hydration. Hydration with sodium bicarbonate [21] was shown to be more effective than using 0.9% saline in one study, but these results have been challenged and cannot be considered definitive at this time [22-23].

### *Diuretics: Mannitol and Furosemide*

In the study by Solomon et al [2], there were no beneficial effects from the osmotic diuretic mannitol when it was added to saline hydration in patients with or without diabetes. Also, there was an exacerbation of contrast media-induced renal dysfunction when the loop diuretic furosemide was used in addition to saline hydration.

### **Other Agents**

The efficacy of N-acetylcysteine (Mucomyst), an antioxidant, to reduce the incidence of CIN is controversial. A number of individual studies, and a number of meta-analyses, have disagreed as to whether this agent reduces the risk of CIN [24-28]. There is evidence that it reduces serum creatinine in normal volunteers without changing cystatin C (said to be a better marker of GFR than serum creatinine). This raises the possibility that N-acetylcysteine might be simply lowering serum creatinine, so patients do not meet the laboratory criteria for CIN, but not preventing the renal damage. As considerably more investigation is needed, the use of N-acetylcysteine should not be considered as a substitute for close attention to renal function and adequate hydration.

The popular regimen of oral acetylcysteine, 600 mg twice daily on the day before and on the day of administration of iodinated contrast media, is simple, inexpensive, and has few contraindications (although allergic reactions have been rarely reported). However, higher doses may be more effective if the agent is effective at all, and there is controversy over whether solid (not currently available in the USA) or liquid preparations are equally effective. Alternatively, an IV regimen beginning 30 minutes prior to contrast media administration may be considered (150 mg/kg in 200 ml of D<sub>5</sub>W over 30 minutes, followed by 50 mg/kg in 500 ml of D<sub>5</sub>W over 4 hours). However, IV administration may have a higher rate of adverse effects than oral administration [26].

The evidence for other potentially renal-protective medications, such as theophylline, enothelin-1, and IV infusion of fenoldopam, is even less convincing without any provable benefit to date.

### **Recommendations for Prevention of Contrast Induced Nephrotoxicity**

Fortunately, patients with normal renal function are at extremely low risk for CIN. In fact, it may actually not occur if renal function (as opposed to serum creatinine) is truly normal. Indeed, Rao and Newhouse [29] have argued that few properly controlled studies of IV use of iodinated contrast media have been published; in a literature review they found only two properly controlled studies and neither demonstrated renal damage from IV iodinated contrast media. The fear of renal failure should not, therefore, dictate avoidance of diagnostic studies using iodinated contrast media. However, radiologists should be attentive to the possibility of risk factors for renal injury, especially the combination of pre-existing renal insufficiency, diabetes, and dehydration.

There is no universally agreed upon threshold of serum creatinine elevation (or degree of renal dysfunction) beyond which iodinated contrast media should not be administered. In a survey of radiologists by Elicker et al [30] published in 2006, it was clear that policies regarding the cutoff value for serum creatinine varied widely among radiology practices. 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) as a cutoff value in patients with no risk factors other than elevated creatinine; threshold values were slightly lower in diabetics (mean 1.68 mg/dL). Patients in end-stage renal disease who have no remaining natural renal function are no longer at risk for CIN and may receive LOCM or IOCM (but see “Renal Dialysis Patients and the Use of Iodinated Contrast Media” below).

The major preventive action against CIN is to ensure adequate hydration. If the patient cannot be hydrated orally, one could consider IV infusion of 0.9% saline at 100 ml/hr in adults, beginning 6 to 12 hours before and continuing 4 to 12 hours after the administration of contrast media. In healthy outpatients, a state of euhydration should be considered optimal; in any situation where there has been intentional dehydration (i.e. NPO, etc.), an active hydration regimen should be considered prior to contrast media administration.

Addition of a medication that may mitigate the nephrotoxic effect of iodinated contrast media, e.g., N-acetylcysteine, could be considered for patients at risk (i.e., exhibiting renal insufficiency, particularly when associated with diabetes mellitus), but not in lieu of adequate hydration and close surveillance of renal function, especially given its questionable efficacy. A good understanding of the particular patient and communication between radiologist and referring clinician are critically important.

For all patients with suspected renal dysfunction or those considered at risk for contrast nephrotoxicity for other reasons, a baseline serum creatinine level should be obtained before the injection of contrast media. If renal dysfunction is identified, the referring clinician should be advised regarding alternative imaging approaches. Other precautionary recommendations are to increase the interval between contrast media examinations and reduce the contrast dose.

The issue of whether to require *routine* renal function testing prior to contrast administration has also been addressed. Choyke, et al [31] identified six patient survey questions which could exclude patients with abnormal serum creatinine with a high specificity, and suggested that if all of these questions were answered in the negative, 94% would have a normal creatinine and 99% would have a creatinine level under 1.7 mg/dL. These subjects could be reasonably excluded from creatinine screening prior to contrast injection resulting in a significant cost saving. This is

especially applicable to outpatient examinations [32].

In patients with acute renal failure, whatever the etiology, administration of iodinated contrast material should only be undertaken with extreme caution where the benefit to the patient clearly outweighs the risk of permanent renal damage.

### **Suggested Indications for Serum Creatinine Measurement before Intravascular Administration of Iodinated Contrast Media**

- History of “kidney disease” as an adult, including tumor and transplant.
- Family history of kidney failure.
- Diabetes treated with insulin or other medications prescribed by a licensed physician.
- Paraproteinemia syndromes or diseases (e.g., multiple myeloma).
- Collagen vascular disease (e.g., scleroderma, systemic lupus erythematosus)
- Prior renal surgery.
- Certain medications:
  - Metformin or metformin-containing drug combinations.
  - Chronic or high dose use of non-steroidal anti-inflammatory drugs.
  - Regular use of nephrotoxic medications, such as aminoglycosides.
- All inpatients

Although there is little data to support a specific time interval between the date of measurement of the serum creatinine and the proposed contrast administration, in otherwise stable outpatients, many authorities will accept an interval of 30 days as being sufficiently recent to proceed with contrast administration. For inpatients, a much shorter interval seems prudent.

Routine blood urea nitrogen (BUN) testing may be useful as a reflection of hydration but should not be relied on solely in evaluating renal dysfunction.

Other patients who are scheduled for a routine intravascular study do *not* necessarily need a serum creatinine determination before the examination.

### **Renal Dialysis Patients and the Use of Iodinated Contrast Media**

In patients suffering from end-stage renal disease, the question arises as to the emergent need for dialysis after a contrast media examination. Because contrast agents are not protein-bound and have relatively low molecular weights, they are readily cleared by dialysis. The primary concern about patients who are dialysis-dependent is the osmotic load of the contrast media, although direct chemotoxicity on the heart and blood-brain barrier is also of theoretical concern. Unless there is significant underlying cardiac dysfunction, or very large volumes of contrast media are used, there is no need for urgent dialysis [33]. It is important, however, to limit the dose of contrast media used in such patients and to use LOCM or IOCM (rather than HOCM) to reduce the risk of adverse effects related to hypertonicity.

Patients with renal insufficiency who require only intermittent or occasional dialysis are at substantial risk for contrast media-induced nephrotoxicity with further permanent worsening of their renal function. Alternative imaging studies that do not require contrast media should be considered.

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

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**Table 4. National Kidney Foundation Kidney Disease Outcomes Quality Initiative Classification, Prevalence, and Action Plan for Stages of Chronic Kidney Disease\***

Stage†	Description	GFR, mL/min per 1.73 m <sup>2</sup>	Prevalence, n (%)‡	Action§
—	At increased risk	≥60 (with chronic kidney disease risk factors)	—	Screening; chronic kidney disease risk reduction
1	Kidney damage with normal or increased GFR	≥90	5 900 000 (3.3)	Diagnosis and treatment; treatment of comorbid conditions; slowing progression; CVD risk reduction
2	Kidney damage with mild decreased GFR	60–89	5 300 000 (3.0)	Estimating progression
3	Moderately decreased GFR	30–59	7 600 000 (4.3)	Evaluating and treating complications
4	Severely decreased GFR	15–29	400 000 (0.2)	Preparation for kidney replacement therapy
5	Kidney failure	<15 (or dialysis)	300 000 (0.1)	Kidney replacement (if uremia present)

\* CVD = cardiovascular disease; GFR = glomerular filtration rate. Modified and reprinted with permission from reference 7.

† Stages 1 to 5 indicate patients with chronic kidney disease; the row without a stage number indicates persons at increased risk for developing chronic kidney disease. Chronic kidney disease is defined as either kidney damage or GFR less than 60 mL/min per 1.73 m<sup>2</sup> for 3 or more months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

‡ Prevalence for stage 5 is from the U.S. Renal Data System (1998); it includes approximately 230 000 patients treated with dialysis and assumes 70 000 additional patients not receiving dialysis. Prevalence for stages 1 to 4 is from the Third National Health and Nutrition Examination Survey (1988 to 1994). Population of 177 million adults age 20 or more years. Glomerular filtration rate is estimated from serum creatinine measurements by using the Modification of Diet in Renal Disease study equation based on age, sex, race, and calibration for serum creatinine. For stages 1 and 2, kidney damage is estimated by using untimed urine samples to determine the albumin-creatinine ratios; greater than 17 mg/g in men or greater than 25 mg/g in women on two measurements indicates kidney damage. The proportion of persons at increased risk for chronic kidney disease has not been estimated accurately.

§ Includes actions from preceding stages.

**Figure 1 Annals of Internal Medicine, Levey et al [34]**

## 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 states 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 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 delaying 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 before instructing the patient to resume metformin after 48 hours.<sup>1</sup>

### *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.<sup>1</sup> 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 reinstatement of metformin can be assured.

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<sup>1</sup>The ACR Committee on Drugs and Contrast Media recognizes that the U.S. Food and Drug Administration (FDA) guidelines for metformin advise that for patients in whom an intravascular contrast study with iodinated materials is planned, metformin should be temporarily discontinued at the time of or before the study, and withheld for 48 hours after the procedure and reinstated only after renal function has been re-evaluated and found to be normal. However, the committee concurs with the prevailing weight of clinical evidence on this matter that deems such measures unnecessary.

## 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\*

<u>Generic Ingredients</u>	<u>Trade names</u>
Metformin	Glucophage Glucophage XR Fortamet Glumetza Riomet
Glyburide/metformin	Glucovance
Glipizide/metformin	Metaglip
Pioglitazone/metformin	ActoPlus Met
Rosiglitazone/metformin	Avandamet

\*As of February, 2007. Additional medications containing metformin may have become available since then.

**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 angi catheters in tiny blood vessels. Contrast medium viscosity and angi catheter size are important factors in determining maximum injection rates. If a rapid injection rate is desired through a small angi catheter 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 mg/ml to 9.4 cps at 370 mg/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 angi catheters, 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 angi catheters (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 angi catheters 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 extravasations 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 0.46% incidence of adverse reactions to ioversol, the majority of which were mild [8]. A smaller study by Fjellidal 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 (Table 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 7). 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/professionals/gfr\\_calculators/gfr\\_children.htm](http://nkdep.nih.gov/professionals/gfr_calculators/gfr_children.htm)):

Currently, the best equation for estimating GFR from serum creatinine in children is the Schwartz equation.

There are several laboratory methods of measuring serum creatinine concentration. These different methods give different results. At this time, it is recommended not to estimate GFR for children when using an alkaline picrate (“Jaffe”) method that has calibration traceable to isotope dilution mass spectrometry (IDMS).

**Equation #1: Original Schwartz Equation** (for use with routine creatinine methods that have not been recalibrated to be traceable to IDMS) [10]

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

- K = constant
  - K = 0.33 in premature infants
  - K = 0.45 in term infants to 1 year of age
  - K = 0.55 in children to 13 years of age
  - K = 0.70 in adolescent males (not females because of the presumed increase in male muscle mass, the constant remains 0.55 for females)

- Height in cm
- Serum creatinine in mg/dL

For this formula, the NKDEP presently recommends reporting estimated GFR values *greater than or equal to 75 mL/min/1.73 m<sup>2</sup>* simply as “≥75 mL/min/1.73 m<sup>2</sup>”, not an exact number.

**Equation #2: Interim IDMS-traceable Schwartz GFR calculator for children** (for use with enzymatic creatinine methods that have been calibrated to be traceable to IDMS) [11]

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

- Height in cm
- Serum creatinine in mg/mL

#### *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<sub>2</sub>O for gadoteridol (Prohance) to 1,970 mosm/kg H<sub>2</sub>O 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 5). 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<sup>2</sup> [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 also 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 Corticosteroid and Antihistamine Premedication Regimen**

	<b>Dosage</b>	<b>Timing</b>
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.

# IODINATED GASTROINTESTINAL CONTRAST MEDIA IN ADULTS: INDICATIONS AND GUIDELINES

## Conventional Fluoroscopy Indications

Barium sulfate contrast media continue to be the preferred agents for opacification of the gastrointestinal tract. They provide greater delineation of mucosal detail, are more resistant to dilution, and are less expensive than water-soluble iodinated contrast media. The current use of iodinated contrast media is primarily limited to those situations in which the administration of barium sulfate is contraindicated: 1) suspected or potential intestinal perforation or leak (including bowel abscess, fistula, or sinus tract); 2) administration before surgical or endoscopic procedures involving the bowel; and 3) confirmation of the position of percutaneously placed bowel catheters.

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 aqueous contrast media in the mediastinum, pleural cavity, or abdomen have been shown. If an initial study with iodinated contrast medium fails to demonstrate a suspected perforation, a repeat study with barium can be performed. Small leaks that are undetected with water-soluble media may be more readily demonstrated by barium sulfate media.

In those patients for whom barium sulfate is contraindicated, guidelines for the use of low-osmolality contrast media (LOCM) rather than high-osmolality contrast media (HOCM) for aqueous contrast media include oral administration to adults who are at risk for aspiration.

When aspirated, LOCM are much less likely to cause pulmonary edema than HOCM

because of their lower osmolality. Iso-osmolality nonionic contrast media may be used in children at risk for aspiration and for evaluation of tracheoesophageal fistula. Water-soluble media are completely absorbed from the lungs, unlike barium which if not completely expectorated, can remain indefinitely and may cause inflammation.

While aspiration of full strength HOCM can cause severe morbidity and mortality, aspiration of LOCM is well tolerated.

## *Therapeutic Uses*

HOCM have been used successfully for the treatment of postoperative adynamic (or paralytic) ileus, barium impaction, and adhesive small-bowel obstruction (see dose in the Administration section below).

## *Contraindications*

Known prior moderate or severe reaction to iodinated contrast media is an at least theoretical contraindication to oral administration of these agents. A small percentage of iodinated contrast media (approximately 1% to 2%) is normally absorbed and excreted in the urine after oral or rectal administration. Mucosal inflammation, mucosal infection, or bowel obstruction increases the amount absorbed by several fold. It is common to see opacification of the urinary tract in such patients.

Because anaphylactoid reactions are not considered to be dose related and can occur with less than 1 ml of intravenous (IV) contrast media, reactions can theoretically occur even from the small amount of contrast medium absorbed from the gastrointestinal tract. There are, however, only very rare reports of moderate or severe

idiosyncratic reactions to orally or rectally administered iodinated contrast media.

HOCM are contraindicated for patients at risk for aspiration. Nonionic LOCM are safer for these patients.

HOCM in hypertonic concentrations should be avoided in patients with fluid and electrolyte imbalances, particularly the very young or elderly patients with hypovolemia or dehydration. The hypertonic HOCM solutions draw fluid into the lumen of the bowel, leading to further hypovolemia. Preparations made from nonionic LOCM are preferable for these patients because for any given required radiographic density, the LOCM version will have lower osmolality. Again, when there is a risk of aspiration, nonionic contrast media is safer than ionic contrast media.

It has been theorized, although not shown, that a small amount of iodine can be absorbed from orally administered iodinated contrast media and may interfere with studies involving protein-bound and radioactive iodine uptake, as well as with spectrophotometric trypsin assay.

#### *Administration*

Ionic and nonionic contrast media concentrations are expressed in milligrams of iodine per milliliter of solution (see Appendix A). A 290 to 367 mgI/ml solution is recommended for fluoroscopic evaluation of the esophagus, stomach, or small bowel in adults.

### **Computed Tomography Indications**

Orally administered contrast media are used for routine gastrointestinal opacification during abdominal computed tomography (CT). In comparison to conventional fluoroscopic imaging, there is no significant difference in the diagnostic quality of CT examinations obtained with HOCM, LOCM, or barium agents, all of which are administered at low concentration. In the

United States, approximately 35% of abdominal CT examinations are currently performed using iodinated gastrointestinal contrast media.

Like conventional fluoroscopic imaging, there are a few specific clinical situations in which water-soluble contrast agents are strongly favored for use in CT over barium agents: suspected gastrointestinal perforation, administration before bowel surgery, and as a bowel marker for percutaneous CT-guided interventional procedures.

#### *Contraindications*

The aqueous contrast solutions used for CT are very dilute and hypotonic (78 mOsm/kg for HOCM). Therefore, aspiration and hypovolemia are not specific contraindications to their use. Idiosyncratic reactions remain a theoretical risk, and are felt to be more relevant to patients with active inflammatory bowel disease.

#### *Administration*

Various iodine concentrations of aqueous contrast media ranging from 4 to 48 mgI/ml have been suggested for bowel opacification with CT. Because the 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 mgI/ml is recommended for oral and rectal administration in adults.

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

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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 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 complication directly related to the IV administration of a GBCM in a sickle cell disease patient. Several small scientific studies [3-5] of sickle patients have employed MR imaging with GBCM without reported adverse effects. In addition, a review [2] of the literature fails to provide evidence for clinically significant hemolysis following the IV administration of GBCM in sickle cell disease patients.

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 nonsickle cell disease 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, 5 and 6). 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 [6] 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

## (Revision performed with input from and approval of the ACR Subcommittee on MR Safety)

### Definition

Nephrogenic systemic fibrosis (NSF) is a fibrosing disease, primarily identified in 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. Death may result in some patients, presumably as a result of visceral organ involvement.

### Associations

#### *Gadolinium-based contrast medium (GBCM) 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. Initially, no other consistent association was identified; however, in 2006 several groups noted a strong association with gadolinium-based contrast media (GBCM) administration to patients with advanced renal disease and the development of NSF [1,2].

Much about NSF is still controversial and/or unknown at least to some extent, including the following: precise quantification of the relative risk of NSF development following administration of the various GBCM; causation; the relative roles of the free gadolinium ion and/or the ligand component of GBCM; requirement for additional risk factors and what they may be (why don't all

at-risk patients develop NSF?); and whether post-GBCM hemodialysis can reduce the risk of subsequent development of NSF.

Regardless of these unresolved issues, empirical data and theoretical lines of reasoning suggest that not all GBCM are associated with an identical risk of NSF in at-risk patients. The majority of studies have reported on the incidence of NSF after gadodiamide exposure. When considering market share data, either gadopentetate dimeglumine or gadoversetamide would be the next most frequently implicated agent. In response, the European Medicines Agency (EMA) classified GBCM into different groups (when considering administration to at-risk patients) [3], as data has suggested that some agents may be less likely to be associated with NSF in high-risk (severe renal failure) patients than others. In a modification of the EMA system, at the present time, the ACR Committee on Drugs and Contrast Media and the ACR Subcommittee on MR Safety prefer to categorize GBCM into the following three groups listed beginning on the following page.

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

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

As of December, 2009, according to data provided by the Food and Drug Administration (FDA) [4], the approximate number of administered doses and the number of NSF cases associated with these three agents were as follows:

<b>Agent</b>	<b>Approximate # of doses (in millions)</b>	<b># of reported NSF cases <i>Single Agent (nonconfounded)</i></b>
<b>Gadodiamide</b>	13	382
<b>Gadopentetate dimeglumine</b>	23	195
<b>Gadoversetamide</b>	4.7	35

While various factors may have influenced the number of cases reported with each of these agents, investigators believe that intrinsic properties of these three agents increase the relative likelihood of NSF developing following exposure in at-risk patients.

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

Gadobenate dimeglumine (MultiHance<sup>®</sup> – Bracco Diagnostics)  
Gadoteridol (ProHance<sup>®</sup> – Bracco Diagnostics)  
Gadoteric acid (Dotarem<sup>®</sup> – Guerbet) - as of this writing not FDA-approved for use in the United States.  
Gadobutrol (Gadovist<sup>®</sup> – Bayer HealthCare Pharmaceuticals) – as of this writing not FDA-approved for use in the United States.

**Group III: Agents which have only recently appeared on the market in the US:**

Gadofosveset (Ablavar<sup>®</sup> – Lantheus Medical Imaging)  
Gadoxetic acid (Eovist<sup>®</sup> – Bayer HealthCare Pharmaceuticals)

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

The differences in frequency among the various GBCM with which NSF has been associated may reflect a combination of factors, including agent toxicity [1,2,4-8], and market share.

NSF is believed to occur more commonly in patients who have received high doses of GBCM as well as in patients who have received higher cumulative lifetime doses of

these agents. Thus, reported frequency may also have been affected if some agents were used at higher doses disproportionately more frequently than others. However, almost half of the patients with biopsy-proven NSF in the International Center for NSF research (ICNSFR) data registry contracted the disease following a single administration, one-third having had magnetic resonance angiography (MRA) [Cowper S,

Presentation at December 8, 2009 Joint Meeting of the Cardiovascular and Renal Drugs and Drug Safety and Risk Management Advisory Committees re: Safety Considerations Related to FDA-Approved Gadolinium-Based Contrast Agents Used with Magnetic Resonance Imaging (MRI) Scans. Hilton Washington DC North/Gaithersburg, Gaithersburg, MD].

If release of free gadolinium ion ultimately proves to be the mechanism for the causation of NSF (see below), it is reasonable to postulate that differences in frequency may, in part, be explained by differences in the chemical properties of the different GBCM. At the same time, no GBCM may be completely free of NSF risk (since all GBCM can release some amount of free gadolinium).

A number of studies have noted that the time between injection of GBCM and the onset of symptoms within days to six months in the vast majority of patients [1,2,8-11]; however, in rare cases, symptoms have appeared years after the last reported exposure [11]

#### *Chronic kidney disease*

Based upon current knowledge it is estimated that patients with severe CKD (CKD4 and CKD5, which corresponds to eGFR values of 15-29 and <15 ml/min/1.73m<sup>2</sup>, respectively) have a 1% to 7% chance of developing NSF after exposure to GBCM [1,2,5,8-11]; however, in some series including selected subgroups of patients, the reported incidence has been as high as 18% [12]. There have been a few isolated reports of biopsy-proven NSF developing in patients with CKD3 (which corresponds to an estimated glomerular filtration rate (eGFR) value between 30 and 59 ml/min/1.73m<sup>2</sup>); however, in most of these cases, the measured eGFR was closer to the lower end of this range [13].

#### *Acute kidney injury*

NSF has also developed in patients with acute kidney injury [14], even if renal function subsequently returned to normal following GBCM administration [15]. In one series, up to 20% of NSF cases were diagnosed in patients who had been in some element of transient acute renal failure (often, but not always, superimposed upon chronic kidney disease) at the time of GBCM administration [16].

#### *High-dose and multiple exposures*

Many of the published series have suggested that renal failure patients are at highest risk when they are exposed to high doses or multiple doses of GBCM. Nonetheless, there are clearly reported instances of NSF occurring in patients who have been exposed to standard (0.1 mmol/kg) single doses of GBCM [11,17] or exceptionally rarely in those who have no known GBCM exposure [18]. Considering that patients may have received GBCM at other institutions without realizing that this was the case, it is certainly quite possible that some of the patients with no known GBCM exposure received GBCM in the past. Conversely, there are also patients with severe CKD, who have received high doses and/or many doses of GBCM, but who have not developed NSF [11]. In one study [19], of 30 patients who had an eGFR of under 30 ml/min/1.73m<sup>2</sup> and who were exposed to high doses of gadodiamide (median dose of 90 ml and range of 40 to 200 ml), only one patient subsequently developed NSF, which calculates to an incidence of only about 3%.

#### *Total cumulative dose of GBCM*

Several articles have suggested that there is a direct relationship between total cumulative dose (over months or years), and the severity [2] and likelihood of NSF [8,20].

### *Other possible risk factors*

A number of other factors have been postulated to explain why some patients with severe CKD who are exposed to GBCM develop NSF and some do not. These include metabolic acidosis or medications that predispose patients to acidosis [1,6], increased iron, calcium, and/or phosphate levels [6,21], high-dose erythropoietin therapy, immunosuppression [8], vasculopathy [22], an acute pro-inflammatory event [10,23], and infection [24], all at the time of GBCM exposure. None of these potential risk factors has been demonstrated consistently to be present in all affected patients in all studies. Therefore, at the present time, none of these risk factors can be considered to have been established as a true co-factor with a high degree of confidence.

### *Hepatic insufficiency / hepatorenal syndrome*

Initially, a number of researchers observed that a disproportionate number of affected patients had severe liver as well as renal dysfunction [10,11], prompting the FDA to warn against the use of GBCM in patients with "...acute renal insufficiency of *any severity* due to the hepatorenal syndrome or in the perioperative transplantation period" [25]. Most of the more recent series have not supported this conclusion. For example, in one study, a review of the literature found that of 291 NSF patients, 34 (12%) had concomitant liver disease [26]; however, all but one of these patients also had known severe renal insufficiency (eGFR of <30 ml/min/1.73m<sup>2</sup>) prior to GBCM administration.

### **Postulated Mechanism**

The exact mechanism of NSF causation is unknown; however, the most widely held theory is that the gadolinium ion dissociates from its chelate in patients with significantly degraded renal function due to the prolonged clearance times of the GBCM in these

patients, as well as to other metabolic factors associated with this level of renal disease. This dissociation occurs by a process known as transmetallation, whereby other cations replace the gadolinium associated with the chelate. Suspected cations include protons (in acidic environments), calcium, iron, zinc, copper, fosrenol, and rare metals. The free gadolinium then binds with other anions (such as phosphate or bicarbonate), and the resulting insoluble precipitate is deposited in the skin and subcutaneous tissues (as well as at other locations) via a process that is still poorly understood [5,27]. A fibrotic reaction ensues, involving the activation of circulating fibrocytes [27,28]. This is supported by the greater presence of gadolinium in affected tissues of NSF patients relative to unaffected tissues [29]. It has not yet been determined whether this deposited gadolinium is free or chemically bound in the initial gadolinium-chelate form or perhaps in the form of a newly-formed other gadolinium-bound moiety. It is noteworthy, however, that the detection of gadolinium in tissue samples may not be required for diagnosis.

Given differences in *in vitro* stability, it is likely that all GBCM are not equally prone to transmetallation *in vivo*. If gadolinium dissociation from its chelate is eventually proved to contribute to, or be primarily responsible for, the development of NSF in many patients, this may help explain why the various GBCM differ in their apparent NSF safety profiles in at-risk patients [30].

### **Recommendations for Identifying High-Risk Groups**

It is important to identify patients who are at increased risk of developing NSF prior to any GBCM injection. Patients at highest risk are those who have severe chronic kidney disease (generally defined as patients who have eGFRs of <30 ml/min/1.73m<sup>2</sup>) [31,32] or acute kidney injury [31,32].

Patients can be screened verbally to identify the presence of a history of renal disease;

however, such screening has been shown to fail to detect many patients with moderate, severe, and end stage chronic kidney disease [33]. Many experts (including the American College of Radiology Subcommittee on MR Safety) have recommended that an eGFR be obtained within six weeks of anticipated GBCM injection in patients who might have reduced renal function. It has been suggested that this would include any patients with a history of renal disease (including a solitary kidney, renal transplant, or renal neoplasm), anyone over the age of 60 years, and patients with history of hypertension or diabetes mellitus [34].

It is recommended for adults that eGFR calculation should be performed using the Modification of Diet in Renal Disease (MDRD) equation. The four-variable MDRD equation takes into account patient age, race, gender, and serum creatinine level. The Schwartz equation should be used for children (also see Chapter on Contrast Media in Children). While a number of Internet sites are now available which can calculate eGFR values in adults and children, the isotope dilution mass spectrometry (IDMS)-traceable MDRD and updated Schwartz equations are also provided here.

*MDRD equation:*

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

*Updated Schwartz equation:*

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

Obviously, decisions concerning the appropriate time interval between the last eGFR determination and GBCM injection will be tempered by any interval change in the patient's clinical condition (which might increase the need for a more recent eGFR).

## **Recommendations for Imaging High-Risk Patients**

Once a high risk patient is identified, a number of additional recommendations can be made [31,32], including considering alternative studies that do not require GBCM injection, informing such patients about the potential risks of GBCM-enhanced magnetic resonance imaging (MRI) studies should such studies be deemed necessary despite the risks, using the lowest possible dose of GBCM required to obtain the needed clinical information, avoiding double or triple dose studies, and avoiding the use of those GBCM that have been most frequently associated with NSF (which, as of June 1, 2010 include gadodiamide [Omniscan<sup>®</sup>], gadopentetate dimeglumine [Magnevist<sup>®</sup>], and gadoversetamide [OptiMARK<sup>®</sup>]). It is also recommended that the referring physician and patient be informed of the risks of GBCM administration and that both the patient and his or her referring physician agree with the decision to proceed after demonstrating an understanding of the potential risks of the procedure and possible alternate imaging/diagnostic options.

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

### **Specific Recommendations**

*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 MR, if such a substitution is deemed feasible.

If a contrast-enhanced MR examination must be performed in a patient with end-stage renal disease on chronic dialysis, avoidance of group I agents (see above) is recommended. Also, use of the lowest possible dose needed to obtain a diagnostic study is suggested, and is recommended as appropriate for all patients regardless of renal status. The ACR Committee on Drugs and Contrast Media and the ACR Subcommittee on MR Safety also recommend that GBCM-enhanced MRI examinations be performed as closely before hemodialysis as is possible, as prompt post-procedural hemodialysis may reduce the likelihood that NSF will develop. However this has not been proved definitively to date. NSF has developed in patients who have received hemodialysis occurring as soon as 9 hours following GBCM administration [36]. Because it may be difficult for a busy 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, and is based entirely on the theory that prolonged retention of gadolinium-chelate may in some way be associated with the ultimate development of NSF. Still, many experts recommend that consideration be given to the performance of several dialysis sessions following GBCM administration, with use of prolonged dialysis times and increased flow rates and volumes to assist in the process of GBCM clearance. Peritoneal dialysis provides much less potential NSF risk reduction compared to hemodialysis and should not be considered protective.

*Patients with CKD 4 or 5 (eGFR <30 ml/min/1.73m<sup>2</sup>) not on chronic dialysis*

The correct course of action in this patient group is problematic, as administration of iodinated contrast media for CT could worsen renal function and lead to the need for dialysis, while administration of GBCM for MRI could lead to NSF.

It is recommended that any contrast media administration be avoided in this group of patients, if feasible. If MRI contrast media administration is deemed essential, judicious use of the lowest possible dose needed to obtain a diagnostic study is recommended. Although there is no absolute proof that any GBCM is completely safe in this patient group, it is recommended that Group 1 agents (see above) be avoided if GBCM is deemed necessary. Further, it may be prudent to avoid re-administration of GBCM 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/1.73m<sup>2</sup>)*

Some investigators have recently suggested that these patients be divided into two subgroups:

CKD 3a (eGFR of 45 - 59 ml/min/1.73m<sup>2</sup>),  
and  
CKD 3b (eGFR of 30 - 44 ml/min/1.73m<sup>2</sup>).

(From: Proposed Modifications to the CKD classification system from the Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference on Chronic Kidney Disease: Definition, Classification, and Prognosis; London, October, 2009.)

The risk of NSF development in CKD 3a patients is exceedingly small and at this time the only precaution recommended in these patients would be to ensure that the lowest dose of GBCM be administered to obtain a

diagnostic study. In particular, a decision to administer a Group I agent to these patients should be made only following appropriate risk-benefit assessment.

The risk of NSF development in CKD 3b patients is also exceedingly small (as long as a dose of GBCM of 0.1 mmol/kg or less is utilized), albeit not zero. Since eGFR determinations may fluctuate from one day to the next, CKD 3b patients with eGFR levels approaching 30 ml/min/1.73m<sup>2</sup> may actually have similar risks to CKD 4 patients (as they might be classified as having CKD 4 at other times). Thus, similar precautions as those mentioned for CKD 4 and CKD 5 patients, directly above, could be considered in this subset of CKD 3b patients.

#### *Patients with CKD 1 or 2 (eGFR 60 to 119 ml/min/1.73m<sup>2</sup>)*

There is no evidence that patients in these groups are at increased risk of developing NSF. Current consensus is that all GBCM can be administered safely to these patients.

#### *Patients with acute kidney injury (AKI)*

Patients with AKI who have been exposed to GBCM are at risk for developing NSF [15]. Due to the temporal lag between serum creatinine values and actual glomerular filtration rates, it is not possible to determine whether a given patient is in AKI based on a single eGFR determination. Accordingly, caution should be exercised in use of GBCM in patients with known or suspected AKI regardless of measured serum creatinine or calculated eGFR values. GBCM should only be administered to these patients if absolutely necessary. When GBCM administration is required, avoidance of agents associated with the greatest apparent NSF-associated risk (Group I agents) is preferred. Use of the lowest possible dose needed to obtain a diagnostic study is also strongly suggested.

#### *Patients with ascites*

In patients with ascites, GBCM may accumulate within the peritoneal cavity after intravenous administration. Prolonged residence of GBCM in the peritoneal cavity would theoretically increase the risk of NSF. However, there have been no reports of NSF developing in individuals with ascites who do not have underlying severe renal insufficiency. The number of exposures in this population is unknown. The risk of NSF in patients with ascites and normal renal function is not yet defined but is likely to be small. Thus, further investigation is needed to define the risk (if any) of ascites in the absence of renal insufficiency.

#### *Pregnant patients*

GBCM can accumulate in amniotic fluid, which could theoretically increase the risk of maternal and/or fetal NSF. For this reason, GBCM should not be administered in this group unless no alternative imaging study is available and a contrast-enhanced MR scan is absolutely necessary. However, there have been no reports of NSF developing in pregnant women or fetuses/neonates, although the number of exposures in these patients is unknown and likely small.

#### *Children*

At this time (mid 2010), very 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 suggest 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 that eGFR values in certain premies and neonates may be <30 ml/min/1.73m<sup>2</sup> simply due to “immature” renal function (and not due to pathologic renal impairment). In these individuals, we believe that caution should still be used when administering GBCMs, although an

eGFR value <30 ml/min/1.73m<sup>2</sup> should not be considered an absolute contraindication to GBCM administration.

### Caveat

Information on NSF and its relationship to GBCM administration is still evolving, and the summary included here represents only the most recent opinions of the ACR Committee on Drugs and Contrast Media and the ACR Subcommittee on MR Safety (as of June 3, 2010). 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.

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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 staffed and equipped imaging facility. Rapid recognition, assessment, and diagnosis are crucial to the effective implementation of treatment. Training of on-site personnel attending to patients receiving contrast media should include cardiopulmonary resuscitation and/or advanced cardiac life support whenever possible. Ongoing quality assurance and quality improvement programs with in-service training and review sessions are recommended. (See Tables 4, 5, 6, and 7 and the Chapter on Contrast Media in Children.)

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

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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 and gadolinium-based magnetic resonance (MR) 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 MR 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 and the rest eliminated back into the amniotic fluid, the entire cycle being repeated innumerable times.

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 X-Ray Contrast Media (Ionic and Nonionic)**

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.

In conjunction with the existing ACR policy for the use of ionizing radiation in pregnant women, we recommend that all imaging facilities should have policies and procedures to attempt to identify pregnant patients prior to the performance of any examination involving ionizing radiation to determine the medical necessity for the administration of iodinated contrast media. If a patient is known to be pregnant, both the potential radiation risk and the potential added risks of contrast media should be considered before proceeding with the study.

While it is not possible to conclude that iodinated contrast media present a definite risk to the fetus, there is insufficient evidence to conclude that they pose no risk. Consequently, the Committee on Drugs and Contrast Media recommends the following:

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 or via another image modality (e.g., ultrasonography).
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 ionizing radiation and iodinated contrast media provide informed consent to document that they understand the risk and benefits of the procedure to be performed and the alternative diagnostic options available to them (if any), and that they wish to proceed.

### **Gadolinium-Based Contrast Agents**

It is known that gadolinium-based MR contrast media cross the human placenta and into the fetus when given in clinical dose ranges. No adequate and well-controlled teratogenic studies of the effects of these media in pregnant women have been performed. 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.

Gadolinium chelates may accumulate in the amniotic fluid and remain there for an indefinite period of time, with potential dissociation of the toxic free gadolinium ion from the chelate; the significance of this exposure to the fetus is uncertain, and its potential association with nephrogenic systemic fibrosis (NSF) in the child or mother is unknown. Therefore, gadolinium chelates should not be routinely used in pregnant patients.

The ACR Guidance Document for Safe MR Practices [2] also covers use of MR contrast media in pregnant patients, and its recommendations are consistent with those in this Manual. See also the preceding Chapter on NSF.

Because it is unclear how gadolinium-based contrast agents will affect the fetus, these agents should be administered only with extreme caution. Each case should be reviewed carefully and gadolinium-based contrast agent administered only when there is a potential overwhelming benefit to the patient or fetus that outweighs the possible

risk of exposure of the fetus to free gadolinium ions. 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 MR 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 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.

It is recommended that the pregnant patient undergoing an MR examination provide informed consent to document that she understands the risk and benefits of the MR procedure to be performed, and the alternative diagnostic options available to her (if any), and that she wishes to proceed.

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

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## ADMINISTRATION OF CONTRAST MEDIA TO BREAST-FEEDING MOTHERS

Administration of either an iodinated or a gadolinium-based contrast media occasionally is indicated for an imaging study on a woman who is 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 1) less than 1% of the administered maternal dose of contrast medium is excreted into breast milk; and 2) less than 1% of the contrast medium in breast milk ingested by an infant is absorbed from the gastrointestinal tract. Therefore, 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 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]. Because less than 1% of the contrast medium ingested by the infant is absorbed from its gastrointestinal tract [3], the expected 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 undergoing an imaging study, which is 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.

#### *Recommendation*

Mothers who are breast-feeding should be given the opportunity to make an informed decision as to whether to continue or temporarily abstain from breast-feeding after receiving intravascularly administered iodinated contrast media. 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. If the mother remains concerned about any potential ill effects to the infant, she may abstain from breast-feeding for 24 hours with active expression and discarding of 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 study to feed the infant during the 24-hour period following the examination.

### **Gadolinium-Based Contrast Agents**

#### *Background*

Gadolinium compounds are safe and useful as magnetic resonance imaging contrast media. Although free gadolinium is neurotoxic, when complexed to one of a variety of chelates it is safe for use in most adults and children. These hydrophilic gadolinium chelate agents have pharmacokinetic properties very similar to those of iodinated X-ray contrast media. Like iodinated contrast media, gadolinium contrast media have a plasma half-life of approximately 2 hours and are nearly completely cleared from the bloodstream within 24 hours.

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 [7], the expected dose absorbed by the infant from the breast milk is less than 0.0004% of the intravascular dose given to the mother. Even in the extreme circumstance of a mother weighing 150 kg and receiving a dose of 0.2 mmol/kg, the absolute amount of gadolinium excreted in the breast milk in the first 24-hours after administration would be no more than 0.012 mmol. Thus, the dose of gadolinium absorbed from the gastrointestinal tract of a breast-feeding infant weighing 1,500 grams or more would be no more than 0.00008 mmol/kg, or 0.04% (four ten-thousandths) of the permitted adult or pediatric (2 years of age or older) intravenous dose of 0.2 mmol/kg. 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, which are theoretical concerns but have not been reported.

#### *Recommendation*

Review of the literature shows no evidence to suggest that oral ingestion by an infant of the tiny amount of gadolinium contrast medium excreted into breast milk would cause toxic effects [8]. We believe, therefore, that the available data suggest that it is safe for the mother and infant to continue breast-feeding after receiving such an agent.

If the mother remains concerned about any potential ill effects, she should be given the opportunity to make an informed decision as to whether to continue or temporarily abstain from breast-feeding after receiving a gadolinium contrast medium. If the mother so desires, she may abstain from breast-feeding for 24 hours with active expression and discarding of 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 study to feed the infant during the 24-hour period following the examination.

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<p><b>Table 1</b></p> <p><b>Indications for Use of Iodinated Contrast Media</b></p>
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**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

- Angiocardiology
- Computed tomography
- Coronary angiography
- 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)

<p style="text-align: center;"><b>Table 2</b> <b>Organ and System-Specific Adverse Effects from the Administration of Iodine-Based or Gadolinium-Based Contrast Agents</b></p>
--

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 Reactions

### Classification of Severity and Manifestations of Adverse Reactions to Contrast Media

#### Mild

Signs and symptoms appear self-limited without evidence of progression (e.g., limited urticaria with mild pruritis, transient nausea, one episode of emesis) and include

Nausea, vomiting	Altered taste	Sweats
Cough	Itching	Rash, hives
Warmth	Pallor	Nasal stuffiness
Headache	Flushing	Swelling: eyes, face
Dizziness	Chills	Anxiety
Shaking		

Treatment: Requires observation to confirm resolution and/or lack of progression but usually no treatment. Patient reassurance is usually helpful.

#### Moderate

Signs and symptoms are more pronounced. Moderate degree of clinically evident focal or systemic signs or symptoms, including:

Tachycardia/bradycardia	Bronchospasm, wheezing
Hypertension	Laryngeal edema
Generalized or diffuse erythema	Mild hypotension
Dyspnea	

Treatment: Clinical findings in moderate reactions frequently require prompt treatment. These situations require close, careful observation for possible progression to a life-threatening event.

#### Severe

Signs and symptoms are often life-threatening, including:

Laryngeal edema (severe or rapidly progressing)	Convulsions
Unresponsiveness	Profound hypotension
Cardiopulmonary arrest	Clinically manifest arrhythmias

Treatment: Requires *prompt* recognition and aggressive treatment; manifestations and treatment frequently require hospitalization.

**Note:** The above classifications (mild, moderate, severe) do not attempt to distinguish between allergic-like and non-allergic-like reactions. Rather, they encompass the spectrum of adverse events that can be seen following the intravascular injection of contrast media.

<p style="text-align: center;"><b>Table 4</b> <b>ABCD Approach for Patient Evaluation and Treatment</b></p>
---

**A**

Airway, oxygen

Assessment (severity and category of reaction); blood pressure and pulse (necessary);  
electrocardiogram monitor may be necessary for evaluation of cardiac rhythm

Assistance (call for it)

Access (venous)-secure/improve intravenous line(s) – peripheral or central

**B**

Breathing (begin cardiopulmonary resuscitation [CPR] if necessary); use mouth  
protective barrier

Bag-valve-mask (e.g., “Ambu” bag) or mouth-mask

Begin full resuscitation efforts (CPR) if necessary; call cardiopulmonary arrest response  
team

Beware of atypical manifestation (e.g., beta-blockers may prevent tachycardic response)

**C**

Circulatory assistance: as appropriate, administer isotonic fluid (e.g., Ringer’s lactate,  
normal saline), infuse rapidly, and may use pressure bag or forceful infusion

Categorize reaction and patient status

Call cardiopulmonary arrest response team if necessary; CPR; continue to monitor

Common denominators: assess cardiac output; capillary leak (third spacing); decreased  
venous return, decreased peripheral vascular resistance; pulmonary edema

**D**

Drug therapies (Tables 5 and 6)

Do: monitor, assess, and reassure the patient; use correct dose (concentration) and route  
for drugs; push intravenous fluids and oxygen

Don’t delay (call for help, if you need it); don’t use incorrect dose(s) and drugs

<p style="text-align: center;"><b>Table 5</b> <b>Management of Acute Reactions in Children</b></p>
--

**Urticaria**

1. No treatment needed in most cases.
2. For moderate itching, consider H<sub>1</sub>-receptor blocker: Diphenhydramine (Benadryl<sup>®</sup>) PO/IM or slow IV push 1 to 2 mg/kg, up to 50 mg.
3. If severe itching or widely disseminated, consider alpha agonist: epinephrine IV (1:10,000) 0.1 mL/kg slow push over 2 to 5 minutes, up to 3 mL.

**Facial Edema**

1. Secure airway and give O<sub>2</sub> 6 to 10 liters/min (via mask, face tent, or blow-by stream). Monitor: electrocardiogram, O<sub>2</sub> saturation (pulse oximeter), and blood pressure.
2. Give alpha agonist: epinephrine IV (1:10,000) 0.1 mL/kg slow push over 2 to 5 minutes, up to 3 mL/dose. Repeat in 5 to 30 minutes as needed.
3. Consider H<sub>1</sub>-receptor blocker: Diphenhydramine (Benadryl<sup>®</sup>) IM or slow IV push 1 to 2 mg/kg, up to 50 mg.
4. Note, if facial edema is mild and there is no reaction progression, observation alone may be appropriate.

If not responsive to therapy, call for assistance (e.g., cardiopulmonary arrest response team, call 911, etc.).

**Bronchospasm**

1. Secure airway and give O<sub>2</sub> 6 to 10 liters/min (via mask, face tent, or blow-by stream). Monitor: electrocardiogram, O<sub>2</sub> saturation (pulse oximeter), and blood pressure.
2. Give inhaled beta-agonist [bronchiolar dilator, such as albuterol (Proventil<sup>®</sup> or Ventolin<sup>®</sup>)], 2 to 3 puffs from metered dose inhaler. Repeat as necessary.
3. If bronchospasm progresses, give epinephrine (1:10,000) IV 0.1 mL/kg slow push over 2 to 5 minutes, maximum 3mL/dose. Repeat in 5 to 30 minutes as needed.

If not responsive to therapy, call for assistance (e.g., cardiopulmonary arrest response team, call 911, etc.) for severe bronchospasm or if O<sub>2</sub> saturation < 88% persists.

**Laryngeal Edema**

1. Secure airway and give O<sub>2</sub> 6 to 10 liters/min (via mask, face tent, or blow-by stream). Monitor: electrocardiogram, O<sub>2</sub> saturation (pulse oximeter), and blood pressure.
2. Give epinephrine (1:10,000) IV 0.1 mL/kg slow push over 2-5 minutes, maximum 3mL/dose. Repeat in 5 to 30 minutes as needed.

If not promptly responsive to initial therapy, call for assistance (e.g., cardiopulmonary arrest response team, call 911, etc.).

**Pulmonary Edema**

1. Secure airway and give O<sub>2</sub> 6 to 10 liters/min (via mask, face tent, or blow-by stream).  
Monitor: electrocardiogram, O<sub>2</sub> saturation (pulse oximeter), and blood pressure.
2. Give diuretic: furosemide (Lasix<sup>®</sup>) IV 1 to 2 mg/kg.

If not responsive to therapy, call for assistance (e.g., cardiopulmonary arrest response team, call 911, etc.).

**Hypotension with Tachycardia (Anaphylactic Shock)**

1. Secure airway and give O<sub>2</sub> 6 to 10 liters/min (via mask). Monitor: electrocardiogram, O<sub>2</sub> saturation (pulse oximeter), and blood pressure.
2. Legs elevated 60° or more (preferred) or Trendelenburg position.
3. Keep patient warm.
4. Give rapid infusion of IV or IO normal saline or Ringer's lactate.
5. If severe, give alpha agonist: epinephrine IV (1:10,000) 0.1 mL/kg slow push over 2-5 minutes, up to 3 mL/dose. Repeat in 5 to 30 minutes as needed.

If not responsive to therapy, call for assistance (e.g., cardiopulmonary arrest response team, call 911, etc.).

**Hypotension with Bradycardia (Vagal Reaction)**

1. Secure airway and give O<sub>2</sub> 6-10 liters/min (via mask). Monitor: electrocardiogram, O<sub>2</sub> saturation (pulse oximeter), and blood pressure.
2. Legs elevated 60° or more (preferred) or Trendelenburg position.
3. Keep patient warm.
4. Give rapid infusion of IV or IO normal saline or Ringer's lactate. Caution should be used to avoid hypervolemia in children with myocardial dysfunction.
5. Give atropine IV 0.02 mg/kg if patient does not respond quickly to steps 2, 3, and 4. Minimum initial dose of 0.1 mg. Maximum initial dose of 0.5 mg (infant/child), 1.0 mg (adolescent). May repeat every 3-5 minutes up to maximum dose up to 1.0 mg (infant/child), 2.0 mg (adolescent).

If not responsive to therapy, call for assistance (e.g., cardiopulmonary arrest response team, call 911, etc.).

Abbreviations: IM= intramuscular  
IO= intraosseous  
IV=intravenous  
PO=orally

## Table 6 Management of Acute Reactions in Adults

### Urticaria

1. Discontinue injection if not completed
2. No treatment needed in most cases
3. Give H<sub>1</sub>-receptor blocker: diphenhydramine (Benadryl<sup>®</sup>) PO/IM/IV 25 to 50 mg.

If severe or widely disseminated: give alpha agonist (arteriolar and venous constriction): epinephrine SC (1:1,000) 0.1 to 0.3 ml (=0.1 to 0.3 mg) (if no cardiac contraindications).

### Facial or Laryngeal Edema

1. Give O<sub>2</sub> 6 to 10 liters/min (via mask).
2. Give alpha agonist (arteriolar and venous constriction): epinephrine SC or IM (1:1,000) 0.1 to 0.3 ml (=0.1 to 0.3 mg) or, especially if hypotension evident, epinephrine (1:10,000) slowly IV 1 to 3 ml (=0.1 to 0.3 mg).  
Repeat as needed up to a maximum of 1 mg.

If not responsive to therapy or if there is obvious acute laryngeal edema, seek appropriate assistance (e.g., cardiopulmonary arrest response team).

### Bronchospasm

1. Give O<sub>2</sub> 6 to 10 liters/min (via mask).  
Monitor: electrocardiogram, O<sub>2</sub> saturation (pulse oximeter), and blood pressure.
2. Give beta-agonist inhalers (bronchiolar dilators, such as metaproterenol [Alupent<sup>®</sup>], terbutaline [Brethaire<sup>®</sup>], or albuterol [Proventil<sup>®</sup> or Ventolin<sup>®</sup>]) 2 to 3 puffs; repeat as necessary. If unresponsive to inhalers, use SC, IM, or IV epinephrine.
3. Give epinephrine SC or IM (1:1,000) 0.1 to 0.3 ml (=0.1 to 0.3 mg) or, especially if hypotension evident, epinephrine (1:10,000) slowly IV 1 to 3 ml (=0.1 to 0.3 mg).  
Repeat as needed up to a maximum of 1 mg.

Call for assistance (e.g., cardiopulmonary arrest response team) for severe bronchospasm or if O<sub>2</sub> saturation < 88% persists.

### Hypotension with Tachycardia

1. Legs elevated 60 degrees or more (preferred) or Trendelenburg position.
2. Monitor: electrocardiogram, pulse oximeter, blood pressure.
3. Give O<sub>2</sub> 6 to 10 liters/min (via mask).
4. Rapid intravenous administration of large volumes of Ringer's lactate or normal saline.

*If poorly responsive:* epinephrine (1:10,000) slowly IV 1 ml (=0.1 mg)  
Repeat as needed up to a maximum of 1 mg

If still poorly responsive seek appropriate assistance (e.g., cardiopulmonary arrest response team).

**Hypotension with Bradycardia (Vagal Reaction)**

1. Secure airway: give O<sub>2</sub> 6 to 10 liters/min (via mask)
2. Monitor vital signs.
3. Legs elevated 60 degrees or more (preferred) or Trendelenburg position.
4. Secure IV access: rapid administration of Ringer's lactate or normal saline.
5. Give atropine 0.6 to 1 mg IV slowly if patient does not respond quickly to steps 2 to 4.
6. Repeat atropine up to a total dose of 0.04 mg/kg (2 to 3 mg) in adult.
7. Ensure complete resolution of hypotension and bradycardia prior to discharge.

**Hypertension, Severe**

1. Give O<sub>2</sub> 6 to 10 liters/min (via mask).
2. Monitor electrocardiogram, pulse oximeter, blood pressure.
3. Give nitroglycerine 0.4 mg tablet, sublingual (may repeat x 3); *or*, topical 2% ointment, apply 1 inch strip.
4. If no response, consider labetalol 20 mg IV, then 20 to 80 mg IV every 10 minutes up to 300 mg.
5. Transfer to intensive care unit or emergency department.
6. For pheochromocytoma: phentolamine 5 mg IV. (may use labetalol if phentolamine is not available)

**Seizures or Convulsions**

1. Give O<sub>2</sub> 6 to 10 liters/min (via mask).
2. Consider diazepam (Valium<sup>®</sup>) 5 mg IV (or more, as appropriate) or midazolam (Versed<sup>®</sup>) 0.5 to 1 mg IV.
3. If longer effect needed, obtain consultation; consider phenytoin (Dilantin<sup>®</sup>) infusion – 15 to 18 mg/kg at 50 mg/min.
4. Careful monitoring of vital signs required, particularly of pO<sub>2</sub> because of risk to respiratory depression with benzodiazepine administration.
5. Consider using cardiopulmonary arrest response team for intubation if needed.

**Pulmonary Edema**

1. Give O<sub>2</sub> 6 to 10 liters/min (via mask).
2. Elevate torso.
3. Give diuretics: furosemide (Lasix<sup>®</sup>) 20 to 40 mg IV, slow push.
4. Consider giving morphine (1 to 3 mg IV).
5. Transfer to intensive care unit or emergency department.

Abbreviations: IM= intramuscular  
IV=intravenous  
SC=subcutaneous  
PO=orally

## Table 7

### Equipment for Emergency Carts\*

The contact number of the cardiopulmonary arrest response team phone should be clearly posted.

- Oxygen cylinders, flow valve, nasal prongs, tubing, partial non-rebreather oxygen masks\*\* (adult and pediatric sizes).
- Suction: wall-mounted or portable; tubing and catheters.
- Oral airways: rubber/plastic; and/or protective breathing barriers.
- “Ambu® - type” bag – valve mask and mouth mask (adult and pediatric sizes) with protective barrier.
- Endotracheal tubes: laryngoscopes (adult and pediatric sizes).
- Stethoscope; sphygmomanometer, tourniquets, tongue depressor.
- Intravenous solutions and tubing.
- Normal saline, Ringer's lactate.
- Syringes: variety of sizes.
- Needles: variety of sizes, including cardiac needle.
- Tracheostomy set, cut-down trays with sterile instruments.
- Necessary drugs and medication.

The following items should be on the emergency cart or immediately available:

- Defibrillator.
- Electrocardiogram.
- Blood pressure/pulse monitor.
- Pulse oximeter (optional).

Medications:

- Epinephrine 1:10,000, 10 ml preloaded syringe (for IV injection).
- Epinephrine 1:1000, 1 ml (for SC/IM injection) – optional, or
- Epinephrine IM auto-injector (injects 0.15 mg or 0.3 ml of 1:2000 [EpiPen Jr®\*\*\*] or 0.3 mg or 0.3 ml of 1:1000 [EpiPen®\*\*\*] - optional
- Atropine 1 mg in 10 ml preloaded syringe.
- Beta-agonist inhaler.
- Diphenhydramine for IM/IV injection.
- Nitroglycerin (NTG) – 0.4 mg tabs, sublingual.
- Aspirin 325 mg.

\* If in a hospital or clinic, the emergency cart should conform with hospital or departmental policies and procedures but usually includes these listed items.

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

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

## Appendix A - Contrast Media Specifications

Product	Chemical Structure	Anion	Cation	% Salt Concentration	% Iodine Concentration	Iodine+ (mg/ml)	Viscosity+ 25° C (cps)	Viscosity+ 37° C (cps)	Osmolality (mOsm/kg H <sub>2</sub> O)
<b>INTRAVASCULAR</b>									
Omnipaque <sup>®</sup> 140 (GE Healthcare)	Iohexol	Nonionic	Nonionic	None	14	140	2.3*	1.5	322
Conray <sup>™</sup> 30 (Covidien)	Ionic	Iothalamate	Meglumine	30	14.1	141	2	1.5	600
Ultravist <sup>®</sup> 150 (Bayer HealthCare)	Iopromide	Nonionic	Nonionic	<0.1	15	150	2.3*	1.5	328
Optiray <sup>™</sup> 160 (Covidien)	Ioversol 34%	Nonionic	Nonionic	None	16	160	2.7	1.9	355
Isovue <sup>®</sup> -200 (Bracco)	Iopamidol 40.8%	Nonionic	Nonionic	None	20	200	3.3*	2.0	413
Conray <sup>™</sup> 43 (Covidien)	Ionic	Iothalamate	Meglumine	43	20.2	202	3	2	1000
Omnipaque <sup>®</sup> 240 (GE Healthcare)	Iohexol 51.8%	Nonionic	Nonionic	None	24	240	5.8*	3.4	520
Optiray <sup>™</sup> 240 (Covidien)	Ioversol 51%	Nonionic	Nonionic	None	24	240	4.6	3.0	502
Ultravist <sup>®</sup> 240 (Bayer Healthcare)	Iopromide	Nonionic	Nonionic	<0.1	24	240	4.9*	2.8	483
Isovue <sup>®</sup> -250 (Bracco)	Iopamidol 51%	Nonionic	Nonionic	None	25	250	5.1*	3.0	524
Visipaque <sup>®</sup> 270 (GE Healthcare)	Iodixanol	Nonionic	Nonionic	None	27	270	12.7*	6.3	290
Conray <sup>™</sup> (Covidien)	Ionic	Iothalamate	Meglumine	60	28.2	282	6	4	1400
Isovue <sup>®</sup> -300 (Bracco)	Iopamidol 61.2%	Nonionic	Nonionic	None	30	300	8.8*	4.7	616
Omnipaque <sup>®</sup> -300 (GE Healthcare)	Iohexol 64.7%	Nonionic	Nonionic	None	30	300	11.8*	6.3	672
Optiray <sup>™</sup> 300 (Covidien)	Ioversol 64%	Nonionic	Nonionic	None	30	300	8.2	5.5	651
Oxilan <sup>®</sup> 300 (Guerbet)	Ioxilan 62.3%	Nonionic	Nonionic	None	30	300	9.4*	5.1	585
Ultravist <sup>®</sup> 300 (Bayer Healthcare)	Iopromide	Nonionic	Nonionic	<0.1	30	300	9.2*	4.9	607
Hexabrix <sup>™</sup> (Covidien)	Ionic	Ioxaglate	Meglumine Sodium	39.3 19.6	32	320	15.7*	7.5	≈600
Optiray <sup>™</sup> 320 (Covidien)	Ioversol 68%	Nonionic	Nonionic	None	32	320	9.9	5.8	702
Visipaque <sup>®</sup> -320 (GE Healthcare)	Iodixanol	Nonionic	Nonionic	None	32	320	26.6	11.8	290
Optiray <sup>™</sup> 350 (Covidien)	Ioversol 74%	Nonionic	Nonionic	None	35	350	14.3	9.0	792

Product	Chemical Structure	Anion	Cation	% Salt Concentration	% Iodine Concentration	Iodine+ (mg/ml)	Viscosity+ 25° C (cps)	Viscosity+ 37° C (cps)	Osmolality (mOsm/kg H <sub>2</sub> O)
<b>INTRAVASCULAR</b>									
Omnipaque <sup>®</sup> -350 (GE Healthcare)	Iohexol 75.5%	Nonionic	Nonionic	None	35	350	20.4*	10.4	844
Oxilan <sup>®</sup> 350 (Guerbet)	Ioxilan 72.7%	Nonionic	Nonionic	None	35	350	16.3*	8.1	695
Isovue <sup>®</sup> -370 (Bracco)	Iopamidol 75.5%	Nonionic	Nonionic	None	37	370	20.9*	9.4	796
MD-76 <sup>™</sup> R (Covidien)	Ionic	Diatrizoate	Meglumine Sodium	66 10	37	370	16.4	10.5	1551
Ultravist <sup>®</sup> 370 (Bayer Healthcare)	Iopromide	Nonionic	Nonionic	<0.1	37	370	22.0*	10.0	774
Cholografin <sup>®</sup> (Bracco)	Ionic	Iodipamide	Meglumine	52	25.7	257	6.6	5.6	664
<b>GASTROINTESTINAL – Oral Contrast</b>									
Gastrografin <sup>®</sup> (Bracco)	Ionic	Diatrizoate	Meglumine Sodium	66 10	37	370		8.4	1940
MD-Gastroview <sup>™</sup> (Covidien)	Ionic	Diatrizoate	Meglumine Sodium	66 10	37	370			2000
Omnipaque <sup>®</sup> 180 (GE Healthcare)	Iohexol	Nonionic	None	18	18	180	3.1*	2.0	331
Omnipaque <sup>®</sup> 240 (GE Healthcare)	Iohexol	Nonionic	None	24	24	240	5.8*	3.4	520
Omnipaque <sup>®</sup> 300 (GE Healthcare)	Iohexol	Nonionic	None	30	30	300	11.8*	6.3	672
Omnipaque <sup>®</sup> 350 (GE Healthcare)	Iohexol	Nonionic	None	35	35	350	20.4*	10.4	844
<b>URORADIOLOGICAL</b>									
Cystografin <sup>®</sup> (Bracco)	Ionic	Diatrizoate	Meglumine	30	14.1	141	2.0	1.5	556
Cystografin <sup>®</sup> Dilute (Bracco)	Ionic	Diatrizoate	Meglumine	18	8.5	85	1.4	1.1	349
Cysto-Conray <sup>™</sup> II (Covidien)	Ionic	Iothalamate	Meglumine	17.2	8.1	81	(Instill for retrograde cystography and cystourethrography)		
Conray <sup>™</sup> 43 (Covidien)	Ionic	Iothalamate	Meglumine	43	20.2	202	3	2	1000
Omnipaque <sup>®</sup> 240 (GE Healthcare)	Nonionic	Nonionic	None	24	240		5.8*	3.4	520
Omnipaque <sup>®</sup> 300 (GE Healthcare)	Iohexol	Nonionic	None	30	30	300	11.8*	6.3	672

Product	Chemical Structure	Anion	Cation	% Salt Concentration	% Iodine Concentration	Iodine+ (mg/ml)	Viscosity+ 25° C (cps)	Viscosity+ 37° C (cps)	Osmolality (mOsm/kg H <sub>2</sub> O)
Omnipaque <sup>®</sup> 350 (GE Healthcare)	Iohexol	Nonionic	None	35	35	350	20.4*	10.4	844
Visipaque <sup>®</sup> 270 (GE Healthcare)	Iodixanol	Nonionic	None	27	27	270	12.7*	6.3	290
<b>URORADIOLOGICAL</b>									
Visipaque 320 (GE Healthcare)	Iodixanol	Nonionic	None	32	32	320	26.6	11.8	290
<b>INTRATHECAL</b>									
Omnipaque* 180 (GE Healthcare)	Iohexol	Nonionic	Nonionic	None	18	180	3.1*	2.0	408
Omnipaque <sup>®</sup> 240 (GE Healthcare)	Iohexol	Nonionic	None	24	24	240	5.8*	3.4	520
Omnipaque <sup>®</sup> 300 (GE Healthcare)	Iohexol	Nonionic	None	30	30	300	11.8*	6.3	672
Isovue-M <sup>®</sup> 200 (Bracco)	Iopamidol	Nonionic	Nonionic	None	20	200	3.3*	2.0	413
Isovue-M <sup>®</sup> 300	Iopamidol	Nonionic	Nonionic	None	30	300	8.8*	4.7	616
<b>BODY CAVITY</b>									
Omnipaque* 180 (GE Healthcare)	Iohexol	Nonionic	None	None	18	180	3.1*	2.0	408
Omnipaque <sup>®</sup> 240 (GE Healthcare)	Iohexol	Nonionic	None	24	24	240	5.8*	3.4	520
Omnipaque <sup>®</sup> 300 (GE Healthcare)	Iohexol	Nonionic	None	30	30	300	11.8*	6.3	672
Omnipaque <sup>®</sup> 350 (GE Healthcare)	Iohexol	Nonionic	None	35	35	350	20.4*	10.4	844
<b>MR CONTRAST MEDIA</b>									
Product	Chemical Structure	Anion	Cation	Viscosity + 25° C (cps)	Viscosity+ 37° C (cps)	Osmolality (mOsm/kg H <sub>2</sub> O)			
Magnevist <sup>®</sup> (Bayer Healthcare)	Ionic Linear	Gadopentetate	Dimeglumine	4.9*	2.9	1960			
Prohance <sup>®</sup> (Bracco)	Nonionic GD-HP-DOTA Gadoteridol			2.0*	1.3	630			
Multihance <sup>®</sup> (Bracco)	Ionic Linear	Gadobenate	Dimeglumine	9.2*	5.3	1970			
Omniscan <sup>®</sup> (GE Healthcare)	Gd-DTPA-BMA Linear	Nonionic		2.0	1.4	789			

Product	Chemical Structure	Anion	Cation	Viscosity + 25° C (cps)	Viscosity+ 37° C (cps)	Osmolality (mOsm/kg H <sub>2</sub> O)		
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					

+ Data from product package inserts, product brochures, or technical information services.

\* Measured at 20° C.

\*\* Data on file with Covidien \*\*\* Hexabrix is licensed by a registered trademark of Guerbet, S.A. and sold by Covidien in the U.S.

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