

RADIOCONTRAST MEDIA

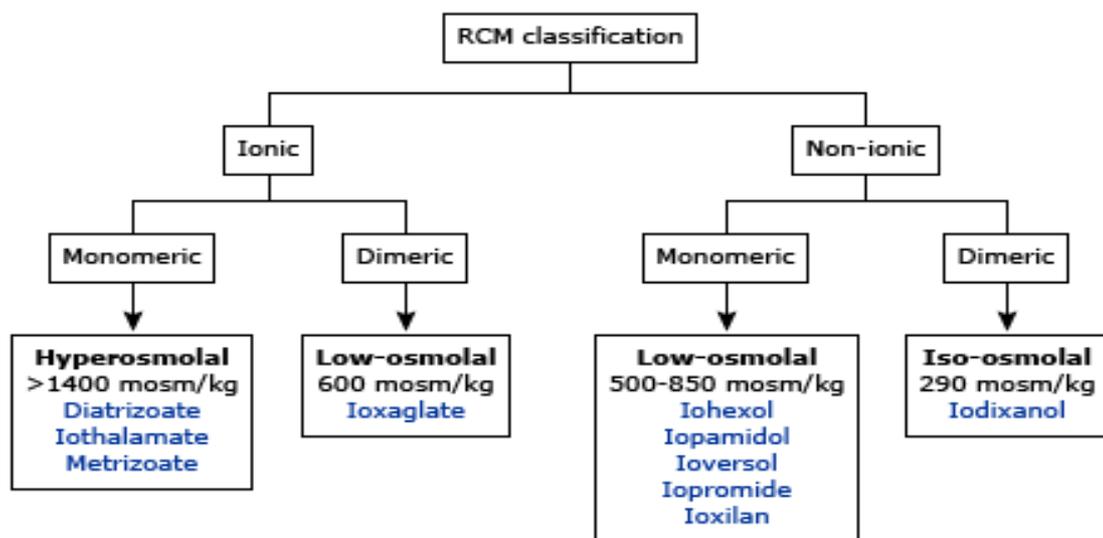


Procedures using RCM include myelography, angiography (including cerebral arteriography), venography, urography, endoscopic retrograde cholangiopancreatography (ERCP), arthrography, and computed tomography (CT). Adverse reactions occur predominantly in association with intravenous administration of RCM.

TYPES OF RADIOCONTRAST MEDIA

The RCM agents currently in use are based upon fully substituted benzoic acid molecules with three atoms of iodine replacing the hydrogen atoms at positions 2, 4, and 6 of the benzene ring. The different agents can be classified based upon three properties :

- The charge of the iodinated molecule (ionic or nonionic)
- The molecular structure (monomeric or dimeric)
- The osmolality of the injected preparation (hyperosmolal, low osmolal, or iso-osmolal relative to normal serum osmolality [275 to 290 mosm/kg])



Categories of agents — the various types of RCM are most commonly categorized by osmolality. High osmolal contrast material (HOCM) agents have osmolalities ≥ 1400 mosm/kg and low osmolal contrast material (LOCM) agents have osmolalities between 500 and 900 mosm/kg. There are also iso-osmolal agents, which are isotonic relative to serum (approximately 290 mosmol/kg). Thus, iso-osmolal agents have a lower osmolality than "low osmolal" agents.

RCM can cause a variety of adverse reactions and the pathophysiology of most of these is poorly understood. As a result, various systems of classifying these reactions exist, based upon severity, timing, signs and symptoms, or presumed pathophysiology.

TYPES OF REACTIONS:

These adverse reactions are divided into two broad categories: chemotoxic reactions and hypersensitivity reactions.

- 1- **Chemotoxic reactions** — Chemotoxic, or physiologic, reactions are related to the chemical properties of radiocontrast agents and are dependent upon dose and infusion rate. These include vasovagal reactions, seizures, arrhythmias, and organ (especially renal) toxicity .
 - **Vasovagal reactions** are considered to be a form of chemotoxic reaction because they may be related to rate of infusion and concentration. These relatively common reactions present with warmth, flushing, nausea, or emesis and are usually transient and self-limited. Severe reactions can involve hypotension or bradycardia. Vasovagal reactions are attributed to fluid shifts caused by the infusion of a hypertonic solution, although the precise mechanism is unknown. These reactions do not preclude further administration of the causative RCM, and slowing the rate of infusion is often sufficient to avoid further symptoms.
 - **Renal toxicity** .
 - **Hyperthyroidism** .

- 2- **Hypersensitivity reactions** — Hypersensitivity reactions to radiocontrast are idiosyncratic and largely independent of dose and infusion rate. They can occur in response to minute amounts of contrast agent. These reactions can be further subdivided into immediate and delayed :
 - **Immediate hypersensitivity reactions** (IHRs) develop within one hour of administration.

Delayed hypersensitivity reactions develop from one hour to several days after administration. This category includes mild to moderate cutaneous eruptions, urticaria/angioedema and various uncommon reactions, including erythema multiforme minor, fixed drug eruption, Stevens-Johnson syndrome, flexural exanthema, and vasculitis .

Signs and symptoms — immediate hypersensitivity reactions to RCM develop within one hour, and usually within five minutes of RCM administration. Signs and symptoms include :

- Flushing
- Pruritus
- Urticaria
- Angioedema
- Bronchospasm and wheezing
- Laryngeal edema and stridor
- Hypotension and rarely shock
- Loss of consciousness

Risk factors to have adverse reactions:

- **Previous immediate hypersensitivity reaction to RCM** — Patients who have experienced a previous IHR to RCM are at increased risk for another reaction, compared to patients who have tolerated RCM without difficulty.
- **Asthma** — The presence of asthma may increase the risk of IHR, although not all studies have found this.
- **History of allergic disease** — Atopic individuals (ie, those with asthma, allergic rhinitis, atopic dermatitis or food allergies) are three times more likely than nonatopic individuals to have a severe adverse reaction to intravenous iodinated contrast media. However, much of this risk may be borne by the subgroup with asthma since few studies have evaluated those with atopic disease, but without asthma.

Seafood or shellfish allergy is **NOT** an independent risk factor for **IHRs** to RCM, although this is a common misconception. Patients allergic to seafood **are not at increased** risk beyond that of any atopic individual or patients with other food allergies. The epidemiological association between seafood allergy and RCM reactions has been attributed to a common iodine allergy since there is a high iodine content in seafood. However, iodine and iodide are small molecules that do not cause anaphylactic reactions and are structurally unrelated to shellfish allergens (which are tropomyosin proteins). The likely explanation for the association is that seafood is a common cause of food allergy, and individuals with any atopic condition in general are at higher risk for RCM reactions.

Another source of confusion is the patient with contact dermatitis in response to the skin disinfectant povidone-iodine. Patients with this history also do **not** appear to be at higher risk for RCM reactions and vice versa.

- **Possible risk factors** — Treatment with certain medications have been proposed to increase the risk or severity of adverse reactions to RCM, although there is no consensus regarding these effects .These include beta-adrenergic blocking agents (beta-blockers), as well as [aspirin](#) and other nonsteroidal antiinflammatory drugs (NSAIDs).

Prevention of contrast-induced nephropathy:

The administration of radiocontrast media can lead to a usually reversible form of acute kidney injury (formerly called acute renal failure) that begins soon after the contrast is administered. In most cases, there are no permanent sequelae, but there is some evidence that its development is associated with adverse outcomes .

The nephrotoxic properties of contrasts agents appear to vary, with low- and iso-osmolal agents being associated with a relatively decreased incidence of renal injury among high-risk patients.

A variety of preventive measures may reduce the risk of contrast nephropathy :

- The use, if clinically possible, of ultrasonography, magnetic resonance imaging CT scanning without radiocontrast agents, particularly in high-risk patients.
- The use of lower doses of contrast and avoidance of repetitive studies that are closely spaced (within 48 to 72 hours). Very small amounts of contrast (<10 mL) have been safely used in patients with advanced kidney disease for examination of poorly maturing arteriovenous fistula.
- Avoidance of volume depletion or nonsteroidal antiinflammatory drugs, both of which can increase renal vasoconstriction.
- The administration of intravenous saline or possibly [sodium bicarbonate](#).
- The administration of the antioxidant [acetylcysteine](#).
- The use of selected low or iso-osmolal nonionic contrast agents.

transient elevations in the serum creatinine concentration (which are of dubious clinical significance) as end points to now if patient has ARF (eg, ≥ 0.5 mg/dL [44.2 micromol/L] or ≥ 25 to 50 percent above baseline).

In studies of patients with moderate renal insufficiency (serum creatinine concentration between 1.4 and 2.4 mg/dL [123 to 211 micromol/L]), some nonionic, low osmolality agents compared to hyperosmolal agents have been associated with a reduced incidence of a mild to moderate decline in renal function .

** **Nonionic iso-osmolal agents** — [Iodixanol](#), the only currently available iso-osmolal nonionic contrast agent (approximately 290 mosmol/kg), may be associated with a lower risk of nephropathy than some low osmolal agents, particularly [iohexol](#),

among diabetic patients with chronic kidney disease (CKD) and a reduced glomerular filtration rate who are given intraarterial contrast, mostly for coronary angiography.

**** Carbon dioxide** — An alternative contrast agent is carbon dioxide, which can be used alone or with small amounts of iodinated contrast. Satisfactory imaging and procedural results are obtained, particularly with modern imaging technology (digital subtraction angiography), with no or little nephrotoxicity .

An important limitation is the risk of neurotoxicity when injected close to the cerebral circulation or if there is a right-to-left intracardiac shunt . Thus, it cannot be used for cerebrovascular imaging, and if to be used, its use should be limited to imaging below the diaphragm .

**** Volume administration, mannitol, and diuretics** — Intravenous volume administration is beneficial, and the type of solution may be important . In comparison, the role of diuretics, [mannitol](#) and other renal vasodilators in this setting is uncertain.

Diuretics — Several small trials have investigated the effect of diuretics. In one trial, 78 patients with stable chronic kidney disease (mean plasma creatinine concentration 2.1 mg/dL [186 micromol/L]) about to undergo coronary angiography were randomly assigned to one of three regimens .

- One-half isotonic (0.45 percent) saline at a rate of 1 mL/kg per hour for 12 hours before and 12 hours after the angiogram
- One-half isotonic saline plus 25 g of [mannitol](#) infused intravenously during the one hour before the procedure
- One-half isotonic saline plus 80 mg of [furosemide](#) infused intravenously during the 30 minutes before angiography

The incidence of acute kidney injury (defined as a rise in the serum creatinine of at least 0.5 mg/dL [44 micromol/L]) was lowest in the group treated with saline alone. [Mannitol](#) was of no added benefit, while there was a suggestion that [furosemide](#) therapy slightly increased the risk. Why this might occur is not known, since volume depletion due to the diuresis was not seen.

- 1- **Intravenous saline** — The optimal intravenous solution (isotonic saline, one-half isotonic saline, or isotonic [sodium bicarbonate](#)) for prevention of contrast nephropathy is unclear.
- 2- **Intravenous bicarbonate** — Since alkalization may protect against free radical injury, the possibility that [sodium bicarbonate](#) may be superior to isotonic saline has been examined in a number of randomized trials and meta-analyses. The results were conflicting as some showed a significantly lower rate of contrast-induced nephropathy with sodium bicarbonate , while others found equivalent rates .

Note : Oral hydration — Given that an increasing number of individuals receive contrast as outpatients, three small trials have evaluated the effectiveness of oral hydration or salt loading in preventing contrast nephropathy. The one trial that included only unrestricted oral fluids (ie, no salt) found a much higher rate of acute kidney injury after contrast than those given isotonic saline.

- 3- **Acetylcysteine** — [Acetylcysteine](#) is a thiol compound with antioxidant and vasodilatory properties. Although not well understood, a possible mechanism of benefit in contrast-induced nephropathy involves minimizing both vasoconstriction and oxygen free radical generation after radiocontrast agent administration.

Dosing (oral) — although data regarding the efficacy of [acetylcysteine](#) are conflicting, if it is to be used, the preferred dose is 1200 mg administered orally twice daily on the day before and the day of the procedure to patients at risk for contrast nephropathy.

Intravenous therapy — Patients requiring emergent coronary angiography or procedures, in whom preventive therapy with oral [acetylcysteine](#) cannot be given the day before, have been treated with intravenous acetylcysteine. The benefit of this approach remains uncertain, and comparison of the various trials is difficult because of differences in patient populations and dosing, or lack of an adequate control group.

SUMMARY AND RECOMMENDATIONS

- We recommend NOT using high osmolal agents (1400 to 1800 mosmol/kg)
- We recommend the use of [iodixanol](#) or nonionic low osmolal agents such as [iopamidol](#) or [ioversol](#) rather than [iohexol](#) .
- Avoid volume depletion and nonsteroidal antiinflammatory drugs.
- If there are no contraindications to volume expansion, we recommend isotonic intravenous fluids prior to and continued for several hours after contrast administration . We suggest isotonic bicarbonate rather than isotonic saline.

A suggested regimen is a bolus of 3 mL/kg of isotonic bicarbonate for one hour prior to the procedure, and continued at a rate of 1 mL/kg per hour for six hours after the procedure. This solution can be prepared by adding 150 mEq of [sodium bicarbonate](#) (three 50 mL ampules of 1 mEq/mL sodium bicarbonate) to 850 mL of sterile water.

If isotonic saline is chosen, a suggested regimen is:

- Isotonic saline at a rate of 1 mL/kg per hour, begun at least two and preferably 6 to 12 hours prior to the procedure, and continuing for 6 to 12 hours after contrast administration. The duration of administration of fluid should be directly proportional to the degree of renal impairment (eg, should be longer for individuals with more severe renal impairment).

- If acetylcysteine is administered, we suggest giving 1200 mg orally twice daily rather than 600 mg twice daily the day before and the day of the procedure .
- Based upon the lack of convincing evidence of benefit and the potential risk of anaphylactoid reactions, we suggest not using intravenous [acetylcysteine](#) for the prevention of contrast nephropathy .
- We recommend NOT using [mannitol](#) or other diuretics prophylactically
- Among patients with stage 3 and 4 CKD, we recommend NOT performing prophylactic hemofiltration or hemodialysis after contrast exposure
- Among patients with stage 5 CKD, we suggest prophylactic hemodialysis after contrast exposure if there is already a functioning hemodialysis access .

How to prevent reactions:

A patient who has experienced an immediate hypersensitivity reaction (IHR) to radiocontrast media (RCM) is at increased risk for a recurrent IHR with the next exposure to RCM or patients who have risk factors to develop IHR .

PREVENTATIVE MEASURES — Measures to prevent recurrent reactions in patients with previous IHRs predominantly consist of premedication and use of a different contrast agent. In addition, an allergy evaluation may be considered in patients with severe past IHRs.

Test dosing — the administration of test doses of RCM is NOT recommended in the prediction or prevention of IHRs and should not be considered a substitute for premedication. Severe and fatal reactions to usual doses of RCM have occurred in patients who tolerated test doses of that agent. In addition, fatalities have resulted from the test doses themselves, even amounts as small as 1 to 2 mL (intravenous).

Premedication regimens : Several premedication regimens have demonstrated efficacy in preventing recurrent IHRs in observational series of patients with previous IHRs, although the optimal approach has not been determined . One widely-used approach combines glucocorticoids and H1 antihistamines with the use of a nonionic low osmolal contrast material .

We suggest the following premedication regimen, with administration beginning 13 hours prior to the procedure :

- [Prednisone](#), given orally 13 hours, 7 hours, and 1 hour before (in adults, 50 mg per dose; in children, 0.5 to 0.7 mg/kg per dose, up to 50 mg per dose). If oral administration is not feasible, [methylprednisolone](#) may be administered intravenously at the same time intervals (in adults, 40 mg; in children, 0.5 mg/kg up to a maximum of 40 mg per dose).
- [Diphenhydramine](#), orally or parenterally given 1 hour before (in adults, 50 mg; in children, 1.25 mg/kg , up to 50 mg).

Use of a different radio contrast agent — To avoid a recurrent IHR, an expert committee has suggested that the patient should never again receive the same specific agent that caused the reaction . The utility of this has not been prospectively confirmed. Despite this, we would suggest use of a structurally unrelated radiocontrast agent until more data are available.

Categories of agents — the various types of RCM are most commonly categorized by osmolality .High osmolal contrast material (HOCM) agents have osmolalities ≥ 1400 mosm/kg and low osmolal contrast material (LOCM) agents have osmolalities between 500 and 900 mosm/kg. The lowest osmolality agents are iso-osmolal agents, which are isotonic relative to serum (approximately 290 mosmol/kg).

Four categories can be distinguished if the agents are further subdivided based upon the charge of the iodinated molecule and the molecular structure . Most agents belong to just two groups: ionic HOCM agents or nonionic LOCM agents.

Low or iso-osmolal contrast agents — LOCM agents cause significantly fewer IHRs compared with HOCM, and nonionic LOCM agents are recommended for any patient with a previous IHR .

In most centers, use of nonionic LOCM agents for all intravascular procedures has become a widespread practice as the cost differential between LOCM and HOCM has decreased, and with the realization that evaluating, observing, and treating even minor reactions has hidden costs . We therefore suggest the following, based upon the type of contrast agent that caused the patient's previous reaction:

- For patients who developed IHRs to HOCM agents in the past, either a nonionic LOCM, an iso-osmolal agent ([iodixanol](#)), or a gadolinium-based agent should be used for future procedures, in combination with premedications.
- For patients who experienced a hypersensitivity reaction to a nonionic LOCM in the past, we suggest either an iso-osmolal agent ([iodixanol](#)) or gadolinium-based agent, in combination with premedications.

Gadolinium-based agents — Gadolinium-based chelates are an alternative for patients with a range of adverse reactions to iodinated contrast agents .Gadolinium-based chelates are widely used in magnetic resonance imaging (MRI). When used with digital subtraction angiography, gadolinium alone or in conjunction with carbon dioxide can be used to produce diagnostic images for angiography and interventional radiologic procedures.

Caution should be used in administering gadolinium to patients with moderate to advanced renal failure, due to the association with nephrogenic systemic fibrosis.

APPROACH FOR EMERGENT PROCEDURES — A rapid pretreatment protocol has been developed for patients with a previous IHR to RCM requiring an emergency procedure (adult doses shown below) :

- [Methylprednisolone](#), 40 mg IV immediately and every four hours until completion of procedure and
- [Diphenhydramine](#), 50 mg PO/IV/IM, one hour before RCM administration and
- Use of the lowest osmolal RCM agent available

Treatment of ANAPHYLAXIS:

Anaphylactic reactions are events initiated when an allergen and IgE combine to induce mast cells to release chemical mediators. Mast cells originate from bone marrow precursors and develop in the organs in which they come to reside. Principal locations are the skin, respiratory tract, GI tract, and blood vessels.

Allergen-specific IgE is bound on the surface of mast cells. The allergen-IgE complex activates the mast cell and induces it to release histamine as well as other mediators.

Histamine binds to specific receptor sites. H1 receptors are found in endothelial and smooth muscle cells and in the central nervous system. H2 receptors are in gastric parietal cells and in inflammatory cells.

The nature of an anaphylactic reaction depends upon the location where it occurs. In the skin, vasodilatation produces urticaria and erythema. In mucosa, vasodilatation produces nasal congestion and laryngeal edema. In the respiratory tract, smooth muscle contraction produces bronchospasm. In peripheral vessels, vasodilatation produces hypotension and shock. Gastrointestinal reactions include nausea, vomiting, diarrhea, and cramps.

Acute management:

The first and most important therapy in anaphylaxis is epinephrine. There are NO absolute contraindications to epinephrine in the setting of anaphylaxis.

Airway: Immediate intubation if evidence of impending airway obstruction from angioedema; delay may lead to complete obstruction; intubation can be difficult and should be performed by the most experienced clinician available; cricothyrotomy may be necessary

It is of importance that medications and equipment be promptly available. An emergency box or cart should be in the immediate vicinity. Preferably it should be sealed (not locked) so that it will be intact when needed, and need to insure that it is fully stocked and that none of its contents have expired. A list of medications, indications, and directions for their use and a list of emergency phone numbers should be prominently displayed.

When summoned to assess a patient who may be having an adverse reaction, you must be able to act quickly, purposefully, and effectively. Ascertain from the

technologist or nurse what the problem is. Speak to the patient to obtain additional information and determine how he/she responds. Consult information on pertinent medical history (this should be obtained before the contrast infusion is started). Immediately stop the contrast infusion, hook up isotonic IV fluids, and open the IV wide. Obtain vital signs. Check the airway and breathing. Listen to the lungs. Check skin color, temperature, and dryness. Do not hesitate to administer oxygen by mask (6–10 liters/min), elevate the patient's legs for hypotension, or start additional IVs as appropriate.

Medications

When injecting medications IV through a needle inserted into a port in the IV tubing, the IV should be running fast enough to promptly carry the medication into the patient. It is also important to be certain that the needle is long enough to extend into the main stream of the IV tubing. The following drugs are stocked on the emergency cart in CT at the University of Wisconsin Hospital and Clinics and defined by adult and pediatric dosage:

Adults

- IM Epinephrine (1 mg/mL preparation): Give epinephrine 0.01 mg per kilogram intramuscularly (maximum per dose: 0.5 mg), preferably in the mid-antrolateral thigh, can repeat every 5 to 15 minutes as needed. If signs of poor perfusion are present or symptoms are not responding to epinephrine injections, prepare IV epinephrine for infusion

Place patient in recumbent position, if tolerated, and elevate lower extremities

- Normal saline rapid bolus: Treat poor perfusion with rapid infusion of 20 mL per kilogram; re-evaluate and repeat fluid boluses (20 mL per kilogram) as needed; massive fluid shifts with severe loss of intravascular volume can occur; monitor urine output
- H1 antihistamine: Consider giving diphenhydramine 1 mg per kilogram (max 40 mg) IV
- H2 antihistamine: Consider giving ranitidine 1 mg per kilogram (max 50 mg) IV
- Glucocorticoid: Consider giving methylprednisolone 1 mg per kilogram (max 125 mg) IV
- Oxygen: Give 6 to 8 liters per minute via face mask, or up to 100 percent oxygen as needed
- Atropine: A parasympatholytic agent used to treat bradycardia that results from a vasovagal reaction (characterized by hypotension and bradycardia).
- The minimum adult dose is 0.6 mg, since a smaller amount can have a paradoxical reverse effect. DOSE: 0.6–1.0 mg IV slowly

Maximum dose = 2 mg

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- Albuterol Inhaler: A Beta-2 agonist that causes bronchodilatation and relieves bronchospasm that may occur with asthma or as a reaction to contrast.

For bronchospasm resistant to IM epinephrine, give albuterol 0.15 mg per kilogram (minimum dose: 2.5 mg) in 3 mL saline inhaled via nebulizer; repeat as needed

- Clonidine: A drug used to treat a hypertensive crisis.
DOSE: 200 mcg (0.2 mg). Bite, chew, and swallow.

- Diazepam: A benzodiazepine used to treat seizures.
DOSE: 5–10 mg IV push
Maximum dose: 30 mg

- Nitroglycerin: A vasodilator used to treat acute angina.

DOSE: 0.4 mg sublingual

May be repeated q 5 minutes for a total of 3 doses.

Monitoring: Continuous non-invasive hemodynamic monitoring and pulse oximetry monitoring should be performed; urine output should be monitored in patients receiving IV fluid resuscitation for severe hypotension or shock.

TREATMENT OF REFRACTORY SYMPTOMS:

Epinephrine infusion^Δ: Patients with inadequate response to IM epinephrine and IV saline, give epinephrine continuous infusion at 0.1 to 1 microgram per kilogram per minute, titrated to effect.

Vasopressors: Patients may require large amounts of IV crystalloid to maintain blood pressure; if response to epinephrine and saline is inadequate, dopamine (5 to 20 micrograms per kilogram per minute) can be given as continuous infusion, titrated to effect.

Glucagon: Patients on beta-blockers may not respond to epinephrine and can be given glucagon 1 to 5 mg IV over 5 minutes, followed by infusion of 5 to 15 micrograms per minute

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 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. 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. However, it should be emphasized that no clinical studies have unequivocally demonstrated prevention of contrast reactions using short-term IV corticosteroid premedication.

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

No randomized controlled clinical trials have demonstrated premedication protection against severe life-threatening adverse reactions. But this may be attributed to the rarity of lifethreatening 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, 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 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

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 intolerance

Pretesting: Preliminary intradermal skin testing with contrast agents is not predictive of adverse reactions, may itself be dangerous, and is not recommended

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

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.



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