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How to Manage (Treat) Immediate-type Adverse Reactions to GBCA

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Abstract: Acute nonrenal adverse reactions to gadolinium-based contrast agents are infrequent and occur often unexpectedly. Most reactions are self-limiting and do not require treatment. The remaining adverse reactions are either moderate or severe and they require medical treatment. Prompt and effective treatment is very important and requires knowledge, training, and preparation.

Key Words: adverse reactions, gadolinum-based contrast agents, management of reactions

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Acute nonrenal adverse reactions requiring medical treatment after administration of gadolinium-based contrast media are rare.[1] The prevalence after administration of any of the gadolinium-based extracellular contrast agents are lower than after the nonionic iodine-based contrast agents used for radiography and computed tomography (CT).[2] Mild reactions, which are the most frequent, do not need any treatment; some of them (eg, headache, dizziness) are even seen in patients undergoing magnetic resonance (MR)-scanning without a contrast medium questioning whether the adverse reactions are caused by the gadolinium-based contrast agents in all instances.[3] Severe allergic-like reactions to gadolinium-based contrast media have the potential to be life-threatening, but are rare and constitute only a small fraction of all reactions to gadolinium-based contrast agents.[1] The same applies to iodine-based contrast agents.[4] It is important to be aware of the fact that serious reactions may still occur; it remains a source of concern.

The same adverse reactions occur after administration of ultrasound contrast media, gadolinium-based contrast media, and iodine-based contrast media. Thus, it is the same reactions that we must be able to treat all over the department. It makes it easier as the radiologists do not have to participate in different courses; the training courses can be given to all employees at the same time. The crash carts should be the same. The same applies to the instructions for treatment (Tables 1 and 2). It is important to have 1 instruction for adults and 1 for children.

Improvements in the physico-chemical properties of iodine-based contrast medium molecules, particularly the development of lower osmolality agents, were followed by a significant decrease in the frequency of acute adverse reactions.[5,6] Similar changes have not been reported after injection of ionic and nonionic gadolinium-based contrast media despite the fact that their osmolality varies from 600 to 2000 mOsmol/kg.[7] Prospective studies have not shown any significant difference between the 6 extracellular gadolinium-based contrast media with regard to prevalence of acute nonrenal adverse reactions.[1]

RADIOLOGISTS' KNOWLEDGE

Lightfoot et al[8] surveyed American and Canadian radiologists' knowledge about the management of severe contrast material induced allergy-like reactions. No radiologist gave the ideal response, but 41% provided an acceptable drug administration route, concentration, and dose. Only 11% knew which concentration of epinephrine/adrenaline was available in their drug kit and/or crash cart and which equipment would be required to administer it to a patient. Six years earlier, a local audit in Australia demonstrated deficient acute management of anaphylactoid/anaphylactic reactions in radiology departments by both consultants and trainees.[9] Recently, Masch et al[10] showed an unchanged high adrenaline/epinephrine administration error among radiology trainees responding to a surprise mock severe contrast reaction. The problem of insufficient knowledge seems to be universal and to be present among both trainees and radiologists.

KNOWLEDGE ABOUT HOW TO TREAT

Much of the knowledge—if not all—about first-line treatment of acute adverse contrast medium reactions derives from the time when high osmolar iodine-based ionic agents were used. In addition, knowledge about the management of acute adverse reactions to drugs other than contrast media has been obtained. With the current contrast agents, the incidence of acute adverse reactions is sufficiently low that it is difficult to collect study populations of sufficient size to evaluate treatment of reactions in randomized (prospective) trials.

PRINCIPLES FOR FIRST-LINE MANAGEMENT

A poorly managed resuscitation situation and adverse outcome will be costly to practice as well as the individual in terms of financial loss and professional respect. All radiologists should be prepared to give immediate treatment for acute contrast medium reactions. Therefore, first-line management should be simple and suitable for the current era, as acute adverse reactions are rare. The subsequent management of severe adverse reactions including administration of second-line drugs should be handled by the resuscitation team.

AN ACUTE ADVERSE REACTION: DEFINITION

An acute adverse reaction is defined as an adverse event that occurs within 60 minutes of an injection of the contrast medium. Most anaphylactic reactions occur within 20 minutes after intravenous injection. Acute adverse reactions may occur despite premedication[11]—the so-called breakthrough reactions. The efficacy of premedication with regard to reduce the risk of acute nonrenal

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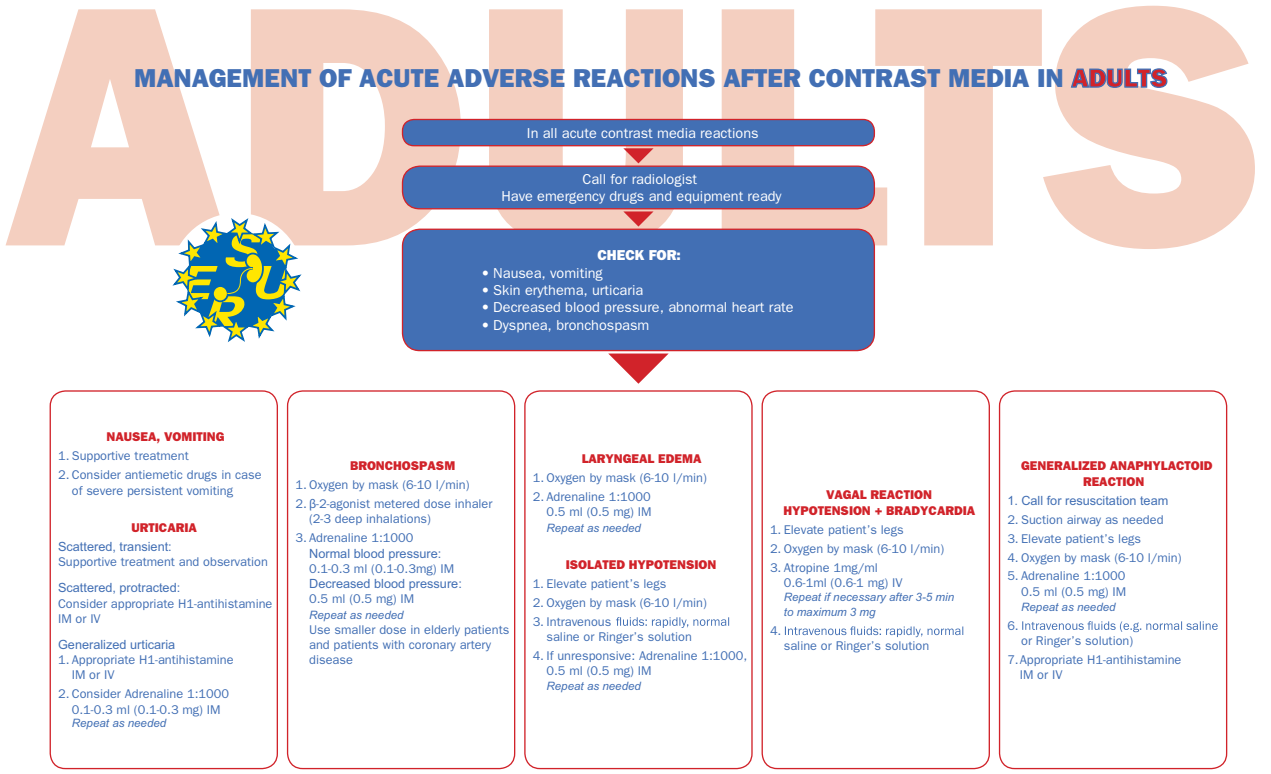
TABLE 1. Management of Acute Adverse Reactions After Contrast Media in Adults According to ESUR Contrast Media Safety Committee. Reprinted with Permission



adverse reactions after exposure to gadolinium-based contrast media has never been studied in a randomized trial. Thus, we do not know whether premedication with corticosteroids and/or histamines has any preventive effect in patients being exposed gadolinium-based contrast medium at all.

MECHANISMS AND PATHOPHYSIOLOGY

Adverse reactions to drugs are generally classified into those that occur only in susceptible subjects and those that may occur in anyone. Reactions occurring in susceptible subjects include drug intolerance (low threshold to the normal pharmacological action of a drug), drug idiosyncrasy (a genetically determined, qualitatively abnormal reaction to a drug related to metabolic or enzyme deficiency), drug allergy (an immunologically mediated reaction, characterized by specificity, prior exposure, transferability by antibodies or lymphocytes, and recurrence on re-exposure), and pseudoallergic reactions that are similar to allergic reactions but lack immunological specificity (nonspecific complement activation and nonspecific histamine release mimicking type 1 allergic reactions).[12]

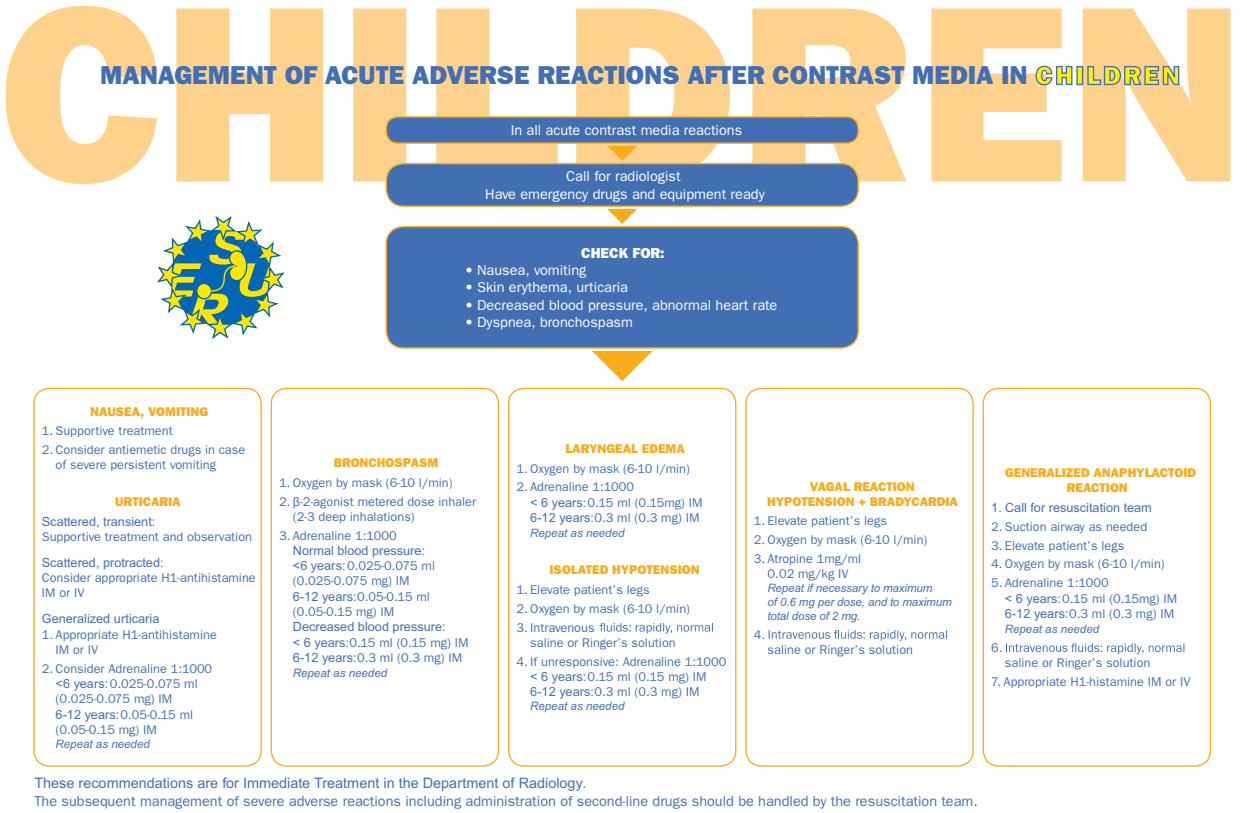
Although some reactions are difficult to categorize, most nonrenal adverse reactions to intravascular contrast media are considered idiosyncratic or pseudo-allergic reactions. They are unpredictable and not dose dependent, and may involve the release of histamine and other active biological mediators such as serotonin, prostaglandins, bradykinin, leukotrienes, adenosine, and endothelin.[13] Activation and inhibition of several enzyme systems have also been implicated. There is no conclusive evidence to indicate that reactions to gadolinium-based contrast media are allergic in nature, as antibodies against contrast media including IgE have only very rarely been demonstrated. Chemotoxic-type effects may also occur and are determined by dose, the molecular toxicity of each agent, and the physiological characteristics of the contrast agents (ie, osmolality, viscosity, hydrophilicity, affinity to proteins, calcium-binding properties, and sodium content). Chemotoxic effects of gadolinium-based contrast media are more likely to occur in patients who are debilitated or medically unstable. Thanks to the small amounts of contrast medium used for magnetic resonance imaging (MRI) high osmolality (osmotoxicity) does not cause shift of fluids from the intracellular to the extracellular space, leading to cell dehydration and an increase in intracellular fluid viscosity precipitating cellular dysfunction like what is seen after exposure to high osmolar iodine-based contrast media.[13,14]

TREATMENT

The vast majority of patients with severe anaphylactoid-type reactions recover if they are treated quickly and appropriately. Most patients have reactions while they are still in the radiology department, and 94% to 100% of severe and fatal reactions occur within 20 minutes of the contrast medium injection.[15] The ability to assess and treat the contrast reaction effectively is an essential skill that the radiologist should have and maintain. The first-line drugs and equipment should be readily available in rooms in which either iodine- or gadolinium-based contrast agents are injected. A survey has shown that most departments have these items available.[16]

The radiologist should remain near the patient for at least the first critical minutes following contrast medium injection and should

TABLE 2. Management of Acute Adverse Reactions After Contrast Media in Children According to ESUR Contrast Media Safety Committee. Reprinted with Permission



remain in the immediate vicinity for the next 30 to 45 minutes. If there is an increased risk of an adverse reaction, venous access should be left in place.

Important first-line management includes establishment of an adequate airway, oxygen supplementation, administration of intravascular physiological fluids, and measuring the blood pressure and heart rate. Talking to the patient as you check their pulse rate provides useful initial information: breathing is assessed, the possibility of a vagal reaction (bradycardia) is determined, and a rough estimate of systolic pressure is obtained (a palpable radial artery pulse approximates to a systolic pressure of 80 to 90 mm Hg).

DRUGS

Adrenaline/Epinephrine

Adrenaline/epinephrine is the drug of choice for the management of anaphylaxis, and fatal anaphylaxis is associated with delayed epinephrine/adrenaline administration.[17] Although there are no randomized controlled trials, adrenaline/epinephrine is a logical treatment.[17,18] There is consistent anecdotal evidence supporting its use to ease breathing difficulty and restore adequate cardiac output. The α-agonist effects of adrenaline/epinephrine increase blood pressure and reverse peripheral vasodilatation. The vasoconstriction induced decreases angioedema and urticaria. The β-agonist actions of adrenaline reverse bronchoconstriction, produce positive inotropic and chronotropic cardiac effects (increase in strength and rate of cardiac contractions), and may increase intracellular cyclic adenosine monophosphate (AMP).[19,20] Increments in baseline cyclic AMP levels are generally considered to inhibit mediator release from inflammatory cells. There are β-2 adrenergic receptors on mast cells that inhibit activation.

The use of adrenaline/epinephrine demands careful attention.[21] For example, in individuals with a fragile intracerebral or coronary circulation, the α-agonist effects of a large dose of adrenaline may provoke a hypertensive crisis that could cause a stroke or myocardial ischemia.[22] β-receptor sites usually respond to lower doses of adrenaline/epinephrine than α-sites, but if a patient is on β-blockers, the refractory response that may occur might encourage the radiologist to increase the dose of adrenaline/epinephrine to the point that there are unwanted α-effects. Patients with chronic asthma may simulate patients receiving β-blockers, as they may have a systemic β-adrenergic hypo-responsiveness. When chronic asthmatic individuals develop an anaphylaxis-like reaction with asthmatic symptoms requiring β-receptor stimulation, 1 option is to use isoproterenol as the primary adrenergic drug, combined with more conservative doses of adrenaline/epinephrine.[23,24]

When possible, adrenaline/epinephrine should be avoided for treating a pregnant patient with a severe contrast medium reaction and hypotension.[25] Because uterine vessels are sensitive to the α-effect of adrenaline/epinephrine, the combination of hypotension and adrenaline can cause harmful sequelae to the fetus. Ephedrine is a possible alternative.

Only 1 concentration (1:1000) of adrenaline/epinephrine should be available in the radiology department to avoid confusion under stressful emergency conditions, where ampoules of different concentrations can be misidentified. The 1:1000 preparation should

be given intramuscularly only. Intravenous administration of adrenaline by inexperienced staff can be dangerous. A recent study by Campbell et al[17] supports the current guidelines that recommend the initial use of intramuscular epinephrine/adrenaline and avoidance of intravenous bolus. Lack of intravenous access is associated with a faster epinephrine administration time.[26] The intramuscular route has several benefits: (1) there is a greater margin of safety; (2) it does not require intravenous access; and (3) the intramuscular route is easier to learn. The best site for intramuscular injection is the antero-lateral aspect of the middle third of the thigh. The needle used for injection needs to be sufficiently long to ensure that the adrenaline is injected into the muscle.[18] Dilution of adrenaline for intravenous use is time-consuming and delays treatment. Only 43% of the participants in an Australian audit knew the recommended dose of adrenaline .[9] Masch et al[26] found an unchanged high epinephrine/adrenaline administration error rate among radiology trainees responding to a surprise mock severe contrast medium reaction. This reinforces the need for a standard dose such as 0.5 mg in adults and 0.3 mg in children between 6 and 12 years old. Below 6 years of age, the Resuscitation Council in UK[18] recommends 0.15 mg. If there is no improvement in the patient's condition, the intramuscular adrenaline dose can be repeated at about 5-minute intervals by non-specialists if the specialist resuscitation team has not arrived.

Oxygen

Oxygen by mask at a relatively high rate (6 to 10 l/min) is very important in the initial treatment of all severe reactions to intravascular contrast media and for other emergencies unrelated to contrast media that occur in the radiology department or angiography suite (eg, vagal reaction, hypotension, cardiac ischemia). Hypoxia can be a major complicating factor in all these situations, and can be induced by drugs such as adrenaline used for treating reactions. A ''non-rebreather'' mask is optimal; nasal ''prongs'' are much less effective and should be avoided in an acute situation for preventing hypoxemia. Oxygen should be used for all patients; a history of chronic obstructive pulmonary disease or emphysema is not a contraindication to starting oxygen therapy for an acute reaction.

Antihistamines and H2 Receptor Blockers

H2 antihistamines and H2 receptor blockers have a limited role in treating contrast media reactions. They are used primarily to reduce symptoms from skin reactions.

Corticosteroids

High-dose intravenous corticosteroids do not play a role in the first-line treatment of the acute adverse reaction. However, very high doses of corticosteroids may have an immediate stabilizing effect on cell membranes and may be used in the second-line treatment. Standard doses can be effective in reducing delayed recurrent symptoms, which can be observed for as long as 48 hours after an initial reaction. It takes 6 hours before corticosteroids are fully active.[27,28]

Inhaled β-2 Adrenergic Agonists

Inhaled β-2 adrenergic agonists such as albuterol, metaproterenol, and terbutaline deliver large doses of bronchodilating β-2 agonist drugs directly to the airways with minimal systemic absorption and, therefore, minimal cardiovascular effects.

Atropine

Atropine blocks vagal stimulation of the cardiac conduction system. Large doses of atropine (0.6 to 1.0 mg) are indicated, as low doses (eg, less than 0.5 mg) of atropine can be detrimental for treating bradycardia associated with contrast media induced vagal reactions.[21,29–32]

FLUID

Intravascular Fluid Administration

Intravascular fluid administration is very important, and it alone has been reported to be the most effective treatment for hypotension.[33] Starting intravenous fluid early before drug treatment is the highest priority in treating hypotension. There is no evidence to support the use of colloids over crystalloids in this setting. For initial resuscitation, 0.9% saline is a suitable fluid.

Treatment of Specific Reactions

Detailed protocols for treatment of nonrenal acute adverse reactions are summarized in Tables 1 (adults) and 2 (children). The recommendations are for immediate treatment in the Department of Radiology. Subsequent management of severe adverse reactions including administration of second-line drugs should be handled by the resuscitation team.

Nausea and Vomiting

Nausea and vomiting, though usually self-limited, may be the first signs of a more severe reaction. With urography using ionic, high-osmolar iodine-based contrast agents, 15% to 20% of fatal reactions began with nausea and vomiting.[34] For this reason, the patient should be observed closely for systemic symptoms, while intravenous access is maintained. The injection should be slowed or stopped. In severe, protracted cases, injection of an anti-emetic may be used.

Cutaneous Reactions

Treatment is usually not necessary if there are only a few scattered hives or pruritus. However, the patient should be observed closely for other systemic symptoms that may develop, and intravenous access should be maintained. Treatment should be given only if the urticaria is extensive or bothersome to the patient.

Bronchospasm

Bronchospasm without coexisting cardiovascular problems should be treated with oxygen and inhaled bronchodilators. Using a metered dose inhaler, treatment typically involves 2 to 3 deep inhalations. Adrenaline may be used if bronchospasm is not relieved by the inhaled bronchodilators.

Laryngeal Edema

Laryngeal edema does not respond well to inhaled β-2 agonists; they may actually worsen it. Therefore, careful clinical evaluation of the patient before beginning treatment is extremely important to differentiate laryngeal edema from bronchospasm. Adrenaline is the primary treatment for laryngeal edema. Oxygen administration is also important in the management of this condition.

Hypotension

Profound hypotension may occur without respiratory symptoms. Normal sinus rhythm and tachycardia differentiate this reaction from the so-called vagal reaction (hypotension and sinus bradycardia). Initially, the patient's legs should be elevated, as this returns about 700 mL of blood to the central circulation.[33] Isolated hypotension is best treated first by rapid intravenous fluid replacement rather than vasopressor drugs. A total volume of up to 3000 mL may be required to reverse the hypotension.

Vagal Reaction

Vagal reactions are characterized by the combination of prominent sinus bradycardia (pulse rate <60 beats/min) and hypotension (systolic pressure <80 mm Hg). Although their exact cause is

unknown, vagal reactions seem to be elicited or accentuated by anxiety. Proper recognition of this reaction and the associated bradycardia is vital so that the correct treatment of increasing intravascular fluid volume and reversing the vagal stimulation is used. Elevation of the patient's legs and rapid infusion of intravenous fluids treat the vasodilatation and expanded vascular space. The bradycardia is treated by intravenous administration of atropine to block vagal stimulation of the cardiac conduction system.

Generalized Anaphylactoid Reactions

These are acute, rapidly progressing, systemic reactions characterized by multi-system involvement with pruritus, urticaria, angioedema, respiratory distress (bronchospasm and/or laryngeal edema), and profound hypotension that require prompt response. Anaphylaxis is likely when of the following 3 criteria are met: (1) sudden onset and rapid progression of symptoms, (2) life-threatening airway and/or breathing and/or circulation problems, and (3) skin and/or mucosal changes (flushing, urticaria, angioedema).[18] Recent exposure to a contrast agent supports the diagnosis. Initial treatment includes maintenance of the airway, administration of oxygen, rapid infusion of intravenous fluids, and administration of adrenergic drugs. Adrenaline is the drug of choice.[17] Intramuscular injection of 0.5 mL of 1:1000 adrenaline preparation is recommended in preference to intravenous administration, which requires careful electrocardiogram (ECG) monitoring and slow administration, ideally by people experienced in its use. According to the Project Team of the Resuscitation Council in the United Kingdom, adrenaline 1:1000 should never be used intravenously because of the risk of arrhythmia, and subcutaneous administration is not helpful in acute life-threatening situations.[18,35,36]

Hypoxia increases the risk of severe cardiac arrhythmias. Also, the amount of adrenaline should be limited in patients who are receiving noncardioselective β-blocking medications (eg, propranolol) as discussed above. Adrenaline should be avoided, if possible, in a pregnant patient experiencing an anaphylactoid reaction with hypotension. When adrenaline is contraindicated, bronchospasm can be treated with a β-2 agonist inhaler (β-2 with no α-effects).

Serum Tryptase Measurement After Acute Reactions to Contrast Agents

During anaphylaxis, tryptase is released from the mast cells into the blood. Blood tryptase levels peak at 1 to 2 hours, and decline rapidly with a 2-hour half-life. Whether or not collapse after contrast medium represented an anaphylactoid reaction may be important to future care of the patient. The UK Resuscitation Council[18] recommends that blood samples for tryptase are taken following suspected anaphylaxis, so that the diagnosis can be established. The minimum re-commendation is 1 sample 1 to 2 hours after the reaction. Ideally, 2 samples should be obtained—the first once resuscitation is underway, the second at 1 to 2 hours after the reaction, and the third at 24 hours or during convalescence .[18]

Be Prepared

Prompt recognition and treatment can be invaluable in blunting an adverse response of a patient to gadolinium-based contrast agents and may prevent a reaction from becoming severe or even life-threatening. Radiologists and their staff should review treatment protocols regularly (eg, at 6 to 12 monthly intervals) so that each can accomplish his or her role efficiently.[9,21,28,32,37–39] Recently, Masch et al[26] reported that annual hands-on training appears to have a little effect on epinephrine/adrenaline administration error rates or long-term practical knowledge retention. If confirmed by others, training might take place at least quarterly. As a matter of fact, knowledge, training, and preparation are crucial for guaranteeing appropriate and effective treatment if there is an adverse contrast-related event.

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