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REVIEW

Allergic-like contrast media reaction management in children

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Abstract

The use of contrast materials as part of imaging examinations is common in children of all ages, as these compounds increase image contrast, lesion detection and lesion characterization. Though modern iodinated, gadolinium-based and ultrasound microbubble contrast materials generally are quite safe, acute physiological and allergic-like reactions are possible. The majority of acute contrast reactions in children are mild and self-limited; however, life-threatening reactions can occur. It is our obligation as radiologists to recognize and manage these adverse reactions. The objective of this article is to review the frequency, manifestations and appropriate treatment of acute contrast reactions in the pediatric population.

Keywords Allergic-like reaction · Anaphylactoid reaction · Children · Contrast material · Contrast reaction · Treatment

Introduction

The use of contrast materials is commonplace in pediatric radiology as they improve contrast resolution and diagnostic accuracy. Most often, these materials are administered intravenously (IV) when performing computed tomography (CT) and magnetic resonance imaging (MRI). While the iodinated low-osmolality (LOCM), iodinated iso-osmolality (IOCM), gadolinium-based (GBCM) and ultrasound (US) microbubble contrast materials are generally very safe, they can cause acute adverse reactions that can be potentially life-threatening. The objective of this article is to review the frequency, manifestations and appropriate treatment of acute contrast reactions in the pediatric population.

CME activity This article has been selected as the CME activity for the current month. Please visit the SPR website at www.pedrad.org on the Education page and follow the instructions to complete this CME activity.

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The radiologist's obligation

According to the joint American College of Radiology (ACR)-Society for Pediatric Radiology (SPR) Practice Parameter for the Use of Intravascular Contrast Media, the radiologist or other physician supervising the injection of contrast material must be knowledgeable in the recognition and treatment of adverse events related to contrast material administration, including acute allergic-like reactions [1]. The supervising physician, typically but not always a radiologist, also should be "immediately available" to provide aid should an adverse event occur. The role of the supervising physician is further codified by Centers for Medicare and Medicaid Services rules that require the injection of intravascular contrast material be under the direct supervision of a physician, with non-physician providers and extenders (e.g., a nurse practitioner, physician assistant or radiology assistant) unable to perform this role [1].

Physiological reactions to contrast material

Physiological contrast reactions, which are distinct from allergic-like contrast reactions, can occur following exposure to intravascular (IV or intra-arterial [IA]) or intra-cavitary (e.g., within the gastrointestinal or genitourinary tract) contrast

material. While the mechanisms of these reactions are not fully understood, they are thought to be due to a variety of mechanisms such as direct toxicity and osmotoxicity [2]. Unlike allergic-like reactions, which are generally dose-independent, physiological reactions are partially predictable based on the volume, osmolality and injection rate of administered contrast material. Physiological reactions likely impact structures such as the brainstem, heart and blood vessels and result in transient symptoms such as nausea, emesis, arrhythmia, vasovagal reaction, flushing sensation, coolth, warmth, metallic taste and headaches, among others.

The U.S. Food and Drug Administration-approved package inserts for each contrast material describe physiological reactions that can occur following intravascular administration, with most being mild and short-lived. While the frequencies of these reactions are almost certainly higher than allergic-like reactions, exact frequencies remain unknown in the pediatric population. The treatment of physiological contrast reactions is typically supportive. With few rare exceptions (e.g., arrhythmia, severe vasovagal reaction [hypotension with bradycardia] unresponsive to conservative measures), there is generally no role for medical therapy [3]. Patients presenting with an apparent physiological reaction (excluding minor reactions, such as transient warmth or metallic taste) should be monitored (e.g., 30 min) to ensure that it is not a prodrome for an allergic-like reaction, which may initially present with signs and symptoms typical of a physiological reaction.

Allergic-like reactions to contrast material

Allergic-like contrast reactions are thought to be anaphylactoid, meaning that they manifest similar to true allergic reactions; however, a prior contrast material exposure or antigen-antibody response is not required [4, 5]. While allergic-like reactions can occur after intra-cavitary administration, the overwhelming majority of such reactions follow intravascular injection. For reactions occurring after IV or IA administration, it is suspected that the passage of contrast material through the lungs directly initiates mast cell degranulation with the release of histamine. Additionally, some authors have suggested that other mediators may be involved in these reactions, such as the complement and kinin systems [5]. True allergic reactions to iodinated contrast materials or GBCM are likely rare [6].

Allergic-like contrast reactions, for the most part, are dose (volume of contrast material administered), concentration and injection rate independent. Reaction manifestations can range from mild to severe (Table 1), and symptoms and signs can include pruritis, urticaria, angioedema, laryngeal edema, bronchospasm and anaphylactic shock (hypotension and tachycardia), among others. The management of allergic-like reactions includes supportive measures as well as medical therapy in some instances (see below).

Frequency of allergic-like reactions in the pediatric population

Allergic-like contrast reactions in the pediatric population are rare. Furthermore, the majority of reactions are mild when classified according to the ACR Manual on Contrast Media version 10.3 [3]. Dillman et al. [7] described 20 allergic-like reactions after 11,306 IV injections of iodinated LOCM in a large pediatric cohort with an overall reaction rate of 1.8 reactions per 1,000 injections. In that study, 16 of 20 (80%) reactions were classified as mild. Davenport et al. [8] documented 8 allergic-like reactions after 15,706 IV injections of linear GBCM in pediatric patients with an overall reaction rate of 0.5 reactions per 1,000 injections. In that study, 7 of 8 (88%) reactions were classified as mild. Forbes-Amrhein et al. [9] identified 21 reactions after 32,365 IV injections of GBCM (more than 12,000 of which were of a macrocyclic GBCM) in pediatric patients with an overall reaction rate of 0.6 reactions per 1,000 injections. Ten of 21 (48%) reactions were classified as mild.

It is worth noting that allergic-like contrast reactions are quite rare in very young children and, thus, contrast material administration should not be avoided in such patients if its utilization is appropriate. A study by Callahan et al. [10] demonstrated a significant effect of age on the incidence of contrast reactions related to IV iodinated contrast material administration, with patients younger than 7 years old having a much lower incidence.

Allergic-like reactions also can occur following the intracavitary administration of these contrast materials as well as following the IV administration of US microbubbles [11–13]. The exact frequency of these reactions in the pediatric population is unknown, but they are likely less frequent than reactions following IV iodinated contrast media.

Based on the literature, there does not appear to be a predilection for a specific type of allergic-like reaction for given classes of contrast material. That is to say, while there may be differences in the rate of reactions between various LOCM, IOCM, GBCM and US microbubble contrast materials, the types of reactions that occur are similar.

Recognition of allergic-like contrast reactions

Allergic-like contrast reactions are dynamic events fueled by the large volume of stimulatory agent (the contrast material) that continues to circulate within the patient for hours after administration. The importance of this is that the manifestations of contrast reactions can change over short and

Table 1 Acute contrast reaction manifestations by severity

Severity	Allergic-like	Physiological
Mild	Limited urticaria/pruritis	Limited nausea/vomiting
	Limited cutaneous edema	Transient flushing/warmth/coolth
	Limited "itchy"/"scratchy" throat	Headache
	Nasal congestion/rhinorrhea	Dizziness
	Sneezing	Anxiety
	Conjunctivitis	Altered taste
		Mild hypertension
		Vasovagal reaction that resolves spontaneously
Moderate	Diffuse urticaria/pruritis	Protracted nausea/vomiting
	Diffuse erythema with stable vital signs	Isolated chest pain
	Facial edema without dyspnea	Hypertensive urgency
	Throat tightness or hoarseness with dyspnea	Vasovagal reaction that requires and responds to treatment
	Wheezing/bronchospasm with no or mild hypoxia	
Severe	Facial edema with dyspnea	Hypertensive emergency
	Diffuse edema	Vasovagal reaction resistant to treatment
	Laryngeal edema with stridor and/or hypoxia	Arrhythmia
	Wheezing/bronchospasm with significant hypoxia	Convulsions/seizures
	Anaphylactic shock (hypotension and tachycardia)	Pulmonary edema*
	Pulmonary edema*	

Adapted from the ACR Manual on Contrast Media, version 10.3 (Used with permission [3])

*Pulmonary edema may be an allergic-like manifestation due to anaphylactic shock or may be an isolated non-allergic-like (physiological) reaction occurring in the absence of other allergic-like reaction manifestations

intermediate periods of time, and rebound symptoms and signs can occur after an acute event has initially been treated. Generally speaking, severe symptoms and signs will develop within the first 20 min after contrast material exposure, but they may persist or recur, even after appropriate initial therapy. However, it is worth noting that delayed reactions to contrast material administration, particularly iodixanol, have been described and are predominantly cutaneous in nature [3, 14, 15].

The first step in managing allergic-like contrast reactions of any severity is assessing the patient and the situation to define the severity of current symptoms and to identify available resources and support. In the context of MRI, this generally means removing the patient from the scanner room to limit the threat of inadvertent projectile incidents. Airway, breathing and circulation (the ABCs of basic life support) should be assessed with areas of compromise addressed as needed.

Vital signs (heart rate, respiratory rate, blood pressure and oxygen saturation) should be assessed and generally documented, even if the initial symptoms are mild. Some severe reactions begin with mild symptoms, and obtaining vital signs immediately can allow better detection of a change from baseline. If vital signs cannot be reliably obtained and the patient is severely ill (e.g., losing consciousness, gasping for air, grabbing throat), then the reaction should be assumed to be a severe allergic-like reaction and treated accordingly.

Supportive care for allergic-like contrast reactions

Given that most pediatric allergic-like contrast reactions are mild, supportive care is the mainstay in management. This includes vocally acknowledging the signs and symptoms and their cause, repositioning the patient for comfort (e.g., getting them off the scanner table if possible) and monitoring the patient until symptoms improve or resolve. For patients having difficulty breathing or other respiratory symptoms, oxygen should be administered by face mask at a moderate to high flow rate (>6-8 L/min). For patients experiencing hypotension, elevating the lower extremities and IV administration of isotonic fluid (e.g., 0.9% normal saline or Lactated Ringer's solution) can lead to clinical improvement.

Medications used to treat allergic-like contrast reactions

Several medications may be used to treat pediatric acute allergic-like reactions (Table 2). These include epinephrine (adrenaline), albuterol, diphenhydramine and corticosteroids. These medications have different mechanisms of action and may be appropriate or inappropriate to administer

Table 2 Key medications used in the radiology department to manage acute allergic-like contrast reactions in children

Medication	Indication (s)	Route of administration	Dosage
Diphenhydramine	Moderate to severe pruritis from cutaneous reaction; adjunct treatment in setting of bronchospasm, laryngospasm or anaphylaxis	PO, IM or IV*	1 mg/kg (maximum dose=50 mg)
Albuterol	Bronchospasm	Inhaled**	via MDI: 2 puffs (90 mcg/puff) via nebulizer (maximum dose=10 mg): • <12 years-old, 0.15–0.3 mg/kg • ≥12 years-old 2.5-10 mg
Epinephrine	Laryngeal edema, bronchospasm (moderate-severe), anaphylaxis	IM or IV*	IM (1:1,000 concentration, 1 mg/1 ml): • 10-30 kg, 0.15 mg (0.15 ml) • ≥30 kg, 0.3 mg (0.3 ml) IV (1:10,000 concentration, 1 mg/10 ml): • <10 kg, 0.1 ml/kg • ≥10 kg, 0.1 mg (1 ml)

IM intramuscular, *IV* intravenous, *MDI* metered dose inhaler, *PO* by mouth

*Administer intravenous diphenhydramine and epinephrine slowly (e.g., over 60-120 s) to minimize the risk of side effects

**Either by metered dose inhaler (MDI) or nebulizer

depending on the specific reaction manifestation(s) and the patient's clinical status.

Diphenhydramine

Diphenhydramine is a non-selective antihistamine that blocks (i.e. "antagonizes" or binds, stabilizes and reduces receptor activity by acting as an inverse agonist) a variety of histamine receptors (e.g., H_1, H_2 and H_3 receptors) as well as additional receptors in the body, such as acetylcholine receptors [16, 17]. This medication can be administered either by a peripheral IV catheter, intramuscularly (IM) or by mouth (PO), typically at a dose of 1 mg/kg up to a maximum dose of 50 mg [3]. The IV and IM routes of administration have a more rapid onset compared to the PO route, and may be preferred when treating more severe acute allergic-like reactions.

The primary indication for this medication in the setting of an allergic-like contrast reaction is the treatment of moderate and severe cutaneous reactions (e.g., widespread urticaria) associated with clinically significant pruritis. Antihistamine medications also can help abate histamine-induced vasodilation and increased capillary permeability [18]. Diphenhydramine does not effectively treat bronchospasm, laryngeal edema or anaphylaxis (i.e. hypotension with tachycardia) in the emergent setting and should not be used as the primary treatment for these reactions. In a small percentage of patients receiving diphenhydramine, clinically significant hypotension may develop that, in theory, could be confused for anaphylaxis. Diphenhydramine also can cause drowsiness, which may be relevant in older pediatric outpatients who are alone and otherwise might have planned to drive following their imaging examination.

Due to the undesirable side effects of diphenhydramine, some have considered using a selective antihistamine instead (e.g., fexofenadine, desloratadine). To our knowledge, those have not been formally tested in the setting of contrast reaction treatment (in adults or children), but they likely would be safe and effective given their efficacy in the treatment of other allergic reactions.

Albuterol

Albuterol is a selective β_2-adrenergic agonist that is administered using either a metered dose inhaler or nebulizer and is used to promote bronchial smooth muscle relaxation that mitigates bronchospasm [19]. The metered dose inhaler route of administration is effective in older, cooperative children, while a nebulizer is preferred in younger, uncooperative patients. Lack of knowledge or cooperation with use of a metered dose inhaler is associated with poor drug delivery and ineffective treatment. A spacer is an inexpensive aerosol chamber that can be used to improve metered dose inhaler drug delivery.

Albuterol is used to treat moderate bronchospasm that manifests with dyspnea and expiratory wheezing and mild or no hypoxia (i.e. asthma-like reactions). Many patients who experience this reaction have a pre-existing diagnosis of asthma and may have a metered dose inhaler with them. When using a metered dose inhaler, 2 puffs (90 μg per puff) are initially administered. This can be repeated if needed. Albuterol dosing using a nebulizer may be weight-based [20]. Albuterol does not effectively treat laryngeal edema or anaphylaxis, and some patients with bronchospasm are not responsive to it; in all such cases, epinephrine is the proper treatment. Albuterol may be associated with transient side effects, such as anxiety and sinus and supraventricular tachycardias [21].

Epinephrine

Epinephrine is an α- and β-adrenergic agonist that causes vasoconstriction, increased systemic peripheral resistance, hypertension, tachycardia, increased cardiac contractility and decreased vascular permeability [22]. Epinephrine is the definitive treatment for all severe acute allergic-like reactions, including moderate-severe bronchospasm, laryngeal edema and anaphylaxis.

Epinephrine is most commonly given IM at a 1:1,000 concentration (1 mg/1 ml) using an autoinjector device at a fixed weight-based dose (15-29 kg dose: 0.15 mg [0.15 mL]; ≥30 kg dose: 0.3 mg [0.3 mL]), or less commonly using a tuberculin syringe at a continuous weight-based dose (dose: 0.01 mg/kg; max [≥30 kg]: 0.3 mg/dose) [3].

Epinephrine can be given by IV (dose: 0.01 mg/kg, max [≥10 kg]: 0.1 mg [1 mL]) at a 1:10,000 concentration (1 mg/10 ml) [3]. IV administration has a quicker onset and can be more easily titrated compared to IM dosing, but clinically significant errors with IV administration are common [23]. The dose administered for anaphylaxis is tenfold lower than the dose administered during cardiopulmonary arrest ("code dose"), and the concentration administered by IV is tenfold less than the concentration administered IM (for all indications). When given IV, epinephrine should be administered slowly to avoid severe complications such as coronary artery vasospasm, myocardial infarction, chest pain and cerebrovascular accident.

Careful attention to the concentration, dose and administration route of epinephrine is critical to avoid a medication administration error (overdose or underdose). An epinephrine overdose can be associated with permanent morbidity and mortality.

Corticosteroid medications

Corticosteroids, such as hydrocortisone and methylprednisolone, provide no immediate benefit in the acute setting [24]. However, these medications may help prevent rebound signs and symptoms following initial reaction management as well as blunt any delayed manifestations. As mentioned earlier, severe reactions often last longer than the medications used to treat them (e.g., epinephrine), and some reactions may be biphasic with both early and delayed manifestations [24]. Intravenous corticosteroid administration is appropriate after the initial effective treatment of moderate and severe allergic-like reactions. Given their lack of immediate efficacy, corticosteroids are more likely to be administered outside the radiology department (e.g., in the emergency department) by practitioners experienced in their use for managing allergic reactions.

Example contrast reaction scenarios

Scenario 1

A 6-year-old boy undergoes CT with IV iodinated LOCM. Three minutes following contrast material injection, the patient develops abdominal itching. Upon visual inspection, he has three hives. The patient exhibits no respiratory distress, and his blood pressure, heart rate, respiratory rate, and oxygen saturation are normal.

Diagnosis: Mild allergic-like contrast reaction.

Manifestation: Limited urticaria.

Management: Limited (isolated) cutaneous acute allergic-like contrast reactions are generally self-limited and managed with reassurance, and they represent the most common type of allergic-like contrast reaction. The patient should be monitored for a period of time (e.g., 1 h) to ensure that the reaction resolves and does not progress. If the patient is uncomfortable with moderate-to-severe itching, administering an antihistamine can be considered. Supportive oxygen and blood volume expansion with IV fluid are not indicated in this scenario, as the patient is neither dyspneic nor hypotensive.

Scenario 2

A 10-year-old girl undergoes MRI with IV GBCM. Eight minutes following contrast material injection, the patient develops respiratory difficulty. She exhibits tachypnea and mild tachycardia. Her blood pressure is normal, and her peripheral blood oxygen saturation is 89%. Physical examination reveals expiratory wheezing.

Diagnosis: Moderate allergic-like contrast reaction.

Manifestation: Bronchospasm with mild hypoxia.

Management: Bronchospastic contrast reactions are due to constricted small airways and manifest similar to an asthma exacerbation. All bronchospastic contrast reactions are classified as either moderate (mild or no hypoxia) or severe (moderate or severe hypoxia, or no air movement). Oxygen should be administered by face mask (not a nasal cannula) at a flow rate of >6-8 L/min. If the reaction is moderate, albuterol is the first-line therapy. If the patient fails to respond to albuterol therapy or the reaction is severe, then epinephrine should be administered. In this latter situation, it is appropriate to call for assistance based on institutional protocol (e.g., rapid response team, code team, 911). Supportive blood volume expansion with IV fluid is not indicated in this scenario because the patient is not hypotensive.

Scenario 3

A 16-year-old boy undergoes MRI with IV GBCM. Five minutes following contrast material injection, the patient develops respiratory difficulty, tachypnea and mild tachycardia.

His blood pressure is elevated and his peripheral blood oxygen saturation is 84%. Physical examination reveals inspiratory stridor.

Diagnosis: Severe allergic-like contrast reaction.

Manifestation: Laryngeal edema.

Management: Laryngeal edema is due to a capillary leak resulting in upper airway narrowing. All reactions with audible stridor are classified as severe. Oxygen should be administered by face mask (not a nasal cannula) at a flow rate of >6-8 L/min. This should be followed by immediate epinephrine administration. It is appropriate to call for assistance based on institutional protocol (e.g., rapid response team, code team, 911). Supportive blood volume expansion with IV fluid is not indicated in this scenario because the patient is not hypotensive.

Laryngeal edema can cause varying degrees of airway narrowing. Mild laryngeal edema may by asymptomatic or present with subtle signs and symptoms, such as a new cough, subtle voice change or a scratchy throat. By the time stridor is present (i.e. a high-pitched audible noise on inspiration), there is at least moderate or severe airway narrowing. There is controversy whether epinephrine is necessary at the earliest signs of possible laryngeal edema, as many patients with just a scratchy throat will resolve that symptom spontaneously. However, stridor is always an indication for epinephrine.

Scenario 4

A 13-year-old boy undergoes CT with IV iodinated LOCM. Immediately following contrast material injection, the patient develops tachycardia and hypotension. His respiratory rate and oxygen saturation are normal. The patient's skin shows extensive erythema. He exhibits decreased responsiveness and his breath sounds are normal.

Diagnosis: Severe allergic-like contrast reaction.

Manifestation: Anaphylaxis (hypotension with tachycardia).

Management: Hypotension with tachycardia immediately following the administration of contrast material is consistent with anaphylaxis, which is a severe allergic-like contrast reaction. In this setting, cutaneous abnormalities (e.g., urticaria or diffuse erythema), changes in mentation and responsiveness, airway narrowing and facial edema can occur. Oxygen should be administered by face mask (not a nasal cannula) at a flow rate of >6-8 L/min because hypoxia may be impending. This should be followed by epinephrine administration as well as blood volume expansion via IV fluid administration of either isotonic saline (0.9%) or Lactated Ringer's solution. Elevating the patient's legs helps return blood to the central venous circulation and also may help increase blood pressure. It is appropriate to call for assistance based on institutional protocol (e.g., rapid response team, code team, 911).

Anaphylactic shock (severe allergic-like reaction presenting with hypotension and tachycardia) must be distinguished from vasovagal reaction (physiological reaction of varying severity presenting with hypotension and bradycardia). Both may result in diminished consciousness and both present with hypotension. The differentiating factor is the heart rate. Anaphylactic shock should be managed with epinephrine, while vasovagal reaction usually responds to non-pharmacological supportive measures or may uncommonly require atropine. Vasovagal reactions may occur at any time during the imaging study, including before contrast material administration, such as at the time of IV catheter placement.

Detailed algorithms for treating the above scenarios as well as other adverse reactions to contrast material exposure that may occur in children can be found in Table 2 (Treatment of Acute Reactions to Contrast Media in Children) of the ACR Manual on Contrast Media version 10.3 [3].

Patient and family education

An allergic-like contrast reaction becomes an opportunity to educate patients and families about what has occurred, their future risk of reaction and available options for prophylaxis. The key point to convey is one of awareness so that if the patient is to undergo an examination at the same or another institution utilizing the same class of contrast material, the patient and family can advocate for themselves and appropriate precautions can be taken. It also is important to convey that while precautions should be taken, a history of allergic-like contrast reaction should not preclude future examinations that are clinically indicated. Premedication is an option but is not always effective at preventing another contrast reaction [25]. Data suggest that switching to a different agent within the same class also may reduce the reaction recurrence rate.

Contrast reaction documentation and referring provider communication

All allergic-like contrast reactions should be documented following appropriate management. The reaction manifestations (specific signs and symptoms), treatment(s) offered and patient disposition should be recorded somewhere in the institutional medical record system, in the radiology report or both. The contrast material also should be added to the patient's known allergy list. In addition to documenting the reaction in the medical record or radiology report and updating the patient's history, consider communicating the nature of the reaction to the referring provider (e.g., by phone or approved electronic messaging).

Conclusion

The majority of acute pediatric allergic-like contrast reactions are mild and self-limited. However, life-threatening contrast reactions do occur. Physiological reactions are more common than allergic-like reactions, are usually transient and generally require only supportive care. It is our obligation as radiologists supervising the administration of contrast material to be capable of both recognizing and treating such contrast reactions. It is important to be familiar with the basic treatment-related medications and contrast reaction scenarios, as immediate treatment of severe allergic-like reactions has the potential to be life-saving. Ultimately, when a contrast reaction is suspected, we are of greatest value if we keep calm, respond promptly, assess the patient swiftly, and initiate appropriate supportive and medical therapy as indicated.

Compliance with ethical standards

Conflicts of interest Drs. Dillman and Trout receive funding from Guerbet regarding clinical trial design. Dr. Dillman also receives funding from Bracco Diagnostics related to contrast-enhanced ultrasound. Dr. Davenport has no disclosures.

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