

# Incidence and Severity of Acute Allergic-Like Reactions to IV Nonionic Iodinated Contrast Material in Children

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**OBJECTIVE.** The purpose of this study was to evaluate the incidence and severity of acute allergic-like reactions related to IV administration of low-osmolality nonionic iodinated contrast material in children.

**MATERIALS AND METHODS.** Department of radiology contrast material reaction forms involving pediatric (younger than 19 years) imaging examinations performed from January 1, 1999, through June 30, 2006, were retrospectively evaluated for type of acute allergic-like reaction, severity of reaction, and patient outcome. The electronic medical record was reviewed for pertinent medical history related to each acute reaction, including previous contrast material reaction, premedication before administration of IV iodinated contrast material, previous allergic-like reaction to substances other than contrast material, and history of asthma.

**RESULTS.** In our department during the time period specified, 11,306 pediatric IV administrations of low-osmolality nonionic iodinated contrast material were performed. Acute allergic-like reactions to the contrast material were documented in 20 (0.18%) of the patients. Sixteen (80%) of the acute allergic-like reactions were categorized as mild, one (5%) as moderate, and three (15%) as severe. No deaths were attributed to IV nonionic iodinated contrast material. Six (30%) of the patients had a history of allergic-like reaction, including two patients who had a history of reaction to iodinated contrast material. Five (25%) of the patients had a history of asthma.

**CONCLUSION.** Acute allergic-like reactions to IV administration of low-osmolality nonionic iodinated contrast material in children are rare. As in the adult population, most pediatric reactions are mild; however, severe reactions do occur.

In pediatric radiology, nonionic iodinated contrast media (low-osmolality monomers and a single isoosmolality dimer) are used almost exclusively when IV administration is clinically indicated [1]. Although several of these nonionic contrast agents have been in use for nearly 2 decades, few large prospective or retrospective studies have been conducted to evaluate the incidence and severity of acute allergic-like reactions related to IV administration of these agents in children.

It is generally accepted that in adults IV nonionic iodinated contrast material causes fewer acute adverse events than does ionic contrast material [2–4]. Such acute adverse reactions are thought to be related to a combination of hypersensitivity, hypersensitivity-like (anaphylactoid), and chemotoxic reactions [5, 6]. Because the number of pediatric contrast-enhanced imaging examinations performed annually in the United States has increased markedly over the

past decade (an increase of 77% at our institution from 1999 to 2005), it is important that the safety of IV contrast materials in children be established and not simply presumed.

The purpose of this study was to evaluate retrospectively the incidence and severity of acute allergic-like reactions related to the IV administration of low-osmolality nonionic iodinated contrast material in children. We also wanted to identify factors that may be helpful in predicting which pediatric patients are at increased risk of acute allergic-like reactions.

## Materials and Methods

Internal review board approval was obtained before the initiation of this investigation. According to institutional research guidelines, informed consent from patients in this study was not required because of the retrospective nature of the investigation. This study was also conducted in a manner compliant with the Health Insurance Portability and Accountability Act.

**Keywords:** contrast media, contrast reactions, CT, pediatric imaging

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**Fig. 1**—Graph shows annual number of IV administrations of low-osmolality nonionic iodinated contrast material to pediatric patients in department of radiology from January 1, 1999, through March 31, 2006. Results for 2006 are for first and second quarters only (January 1–June 30, 2006).

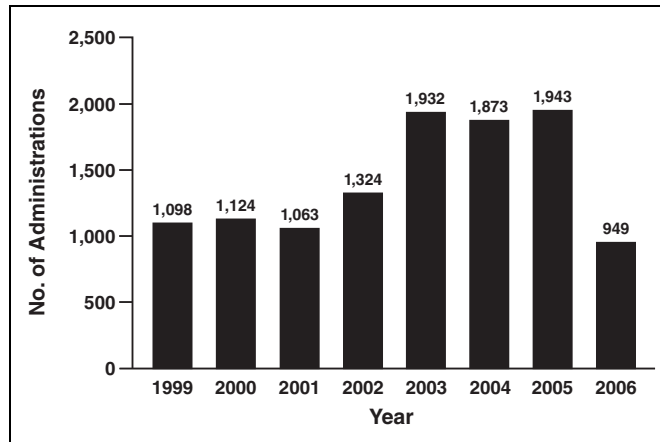


**Fig. 2**—Standardized departmental contrast material allergic-like reaction form. Form is completed by treating radiologist to document reaction, its manifestations, and treatment. Patient's normal (i.e., baseline) blood pressure and pulse rate are documented, if available, to determine clinical significance of heart rate and blood pressure during reaction.

| DEPARTMENT OF RADIOLOGY<br>CONTRAST REACTION REPORT FORM                                                    |                                                                                                              | <b>PEDIATRIC<br/>ONLY</b> |  |
|-------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|---------------------------|--|
| <b>GENERAL<br/>INFORMATION</b>                                                                              | ID NO: _____                                                                                                 |                           |  |
|                                                                                                             | Date/Time of Incident: Date _____ Time _____                                                                 |                           |  |
|                                                                                                             | Inpatient _____ Outpatient _____                                                                             |                           |  |
|                                                                                                             | Previous Incident: Date _____ Type _____                                                                     |                           |  |
| <b>DESCRIPTION OF INCIDENT</b>                                                                              | Date/Time Notified Radiology House Officer _____ Attending Radiologist _____                                 |                           |  |
|                                                                                                             | Attending Physician _____ House Physician _____                                                              |                           |  |
|                                                                                                             | Contrast Agent Administered _____ Dose _____ Route _____ Length of Time _____                                |                           |  |
|                                                                                                             | Procedure Done _____                                                                                         |                           |  |
|                                                                                                             | Patient's Normal Blood Pressure _____ Patient's Normal Pulse _____                                           |                           |  |
|                                                                                                             | Patient's Blood Pressure During Incident _____ Patient's Pulse During Incident _____                         |                           |  |
|                                                                                                             | Pre-Medication Given _____                                                                                   |                           |  |
|                                                                                                             | <b>SYMPTOMS AND SIGNS OF REACTION</b>                                                                        |                           |  |
|                                                                                                             | <b>CARDIOVASCULAR:</b>                                                                                       |                           |  |
|                                                                                                             | <b>RESPIRATORY:</b>                                                                                          |                           |  |
| <b>MEDICAL REPORT</b>                                                                                       | <b>NERVOUS:</b>                                                                                              |                           |  |
|                                                                                                             | <b>SKIN:</b>                                                                                                 |                           |  |
|                                                                                                             | <b>GI TRACT:</b>                                                                                             |                           |  |
|                                                                                                             | <b>OTHER:</b> _____                                                                                          |                           |  |
|                                                                                                             | <b>TREATMENT ADMINISTERED</b>                                                                                |                           |  |
|                                                                                                             | None _____ O <sub>2</sub> _____ IV _____ Epinephrine _____                                                   |                           |  |
|                                                                                                             | Benadryl _____ Atropine _____ Steroids _____ Aminophylline _____                                             |                           |  |
|                                                                                                             | Cardiopulmonary Resuscitation _____ Other _____                                                              |                           |  |
|                                                                                                             | Radiologist Findings _____                                                                                   |                           |  |
|                                                                                                             | Name _____ Date _____ Time _____                                                                             |                           |  |
| <b>O.A.</b>                                                                                                 | Was the contrast reaction kit readily available? _____ Yes _____ No                                          |                           |  |
|                                                                                                             | Were the contents of the reaction kit adequate for this incident? _____ Yes _____ No                         |                           |  |
|                                                                                                             | Was support equipment, e.g., suction equipment, O <sub>2</sub> , etc., readily available? _____ Yes _____ No |                           |  |
|                                                                                                             | Did you have enough support in the management of this contrast reaction? _____ Yes _____ No                  |                           |  |
| <div>RP-2090341/D/S Rev. 10/96</div> <div><b>RADIOLOGY</b></div> <div><b>CONTRAST REACTION REPORT</b></div> |                                                                                                              |                           |  |

Using our institution's computerized radiology information system, we determined that 11,306 IV injections of nonionic iodinated contrast material were administered to pediatric patients (younger than 19 years) at our institution from January 1, 1999, through June 30, 2006 (Fig. 1). Almost all (> 99%) of these injections were for pediatric CT. A small number of IV excretory urograms were obtained during this time period, but the exact number is not known. No pediatric venograms, intraarterial administra-

tions, or examinations performed in other departments (e.g., cardiology) were included in this study.

Two low-osmolality nonionic iodinated contrast media were used in pediatric patients during the study period. Iohexol 300 mg I/mL (Omnipaque 300, GE Healthcare/Amersham Health) was used from January 1999 through September 2004, and iopromide 300 mg I/mL (Ultravist 300, Berlex) was used from October 2004 through June 30, 2006. Approximately 7,963 contrast-enhanced pediatric ex-

aminations were performed with iohexol, and 3,343 were performed with iopromide. The volume of IV contrast material administered to each patient was based on standard departmental protocols, primarily related to patient weight. We administered an IV 2-mL/kg dose of contrast material to children weighing 15 kg or more (up to 75 kg). Slightly more contrast material per kilogram was used for children weighing less than 15 kg, and a maximum dose of 150 mL of contrast material was administered to patients weighing 75 kg or more. All IV contrast injections greater than 20 mL were administered with a power injector unless use of this device was specifically contraindicated. Contrast material doses of 20 mL or less typically were hand injected.

It is our departmental policy that all patients, whether pediatric or adult and regardless of time of day, who have an acute allergic-like reaction to IV administration of contrast material be assessed in person by a radiologist (resident, fellow, or attending physician). After assessment and treatment of the patient, the radiologist documents the reaction on a standardized departmental contrast material reaction form (Fig. 2). This system of documentation of allergic-like reactions was in place before January 1, 1999.

All contrast material reaction forms involving examinations of pediatric patients were collected and retrospectively analyzed. Each form was evaluated for the type of acute allergic-like reaction, the IV contrast agent involved, the specific treatment required, and the final disposition of the patient. An allergic-like reaction was defined as acute if the manifestations occurred before the patient left the department of radiology. Delayed allergic-like reactions and chemotoxic reactions (e.g., contrast-induced nephropathy) were not included in this study.

Each documented acute allergic-like reaction was categorized as mild, moderate, or severe according to a departmental classification system (Table 1) similar to that proposed by the American College of Radiology [7]. A reaction was deemed mild if it was self-limited and showed no marked progression. Mild reactions necessitated either no treatment or treatment limited to antihistamine administration for urticaria (hives) or rash. Moderate reactions necessitated immediate medical treatment other than antihistamine administration or eventual transfer to the emergency department if the patient was an outpatient. A reaction was defined as severe if it was life-threatening, necessitated hospital admission of an outpatient or emergency department patient, or was fatal. Reactions with multiple signs and symptoms were classified according to the most severe sign or symptom. Physiologic reactions to contrast media, including nausea, vomiting, altered taste, perspiration, warmth, flushing, and anxiety, are considered side

## Reactions to Contrast Material

**TABLE 1: Institutional Classification of Acute Allergic-Like Reactions to Contrast Media: Reaction Severity and Manifestations**

| Side Effect <sup>a</sup> | Mild Reaction <sup>b</sup> | Moderate Reaction <sup>c</sup> | Severe Reaction <sup>d</sup> |
|--------------------------|----------------------------|--------------------------------|------------------------------|
| Nausea                   | Pruritus                   | Dyspnea                        | Severe respiratory distress  |
| Vomiting                 | Rash                       | Bronchospasm                   | Unresponsiveness             |
| Altered taste            | Urticaria                  | Mild laryngeal edema           | Convulsions                  |
| Perspiration             | Cough                      | Symptomatic tachycardia        | Arrhythmia                   |
| Warmth                   | Nasal stuffiness           | Symptomatic bradycardia        | Cardiopulmonary arrest       |
| Flushing                 | Sneezing                   | Hypotension                    | Progressive angioedema       |
| Anxiety                  | Mild eye swelling          | Hypertension                   |                              |
|                          | Mild facial swelling       |                                |                              |

Note—Adapted with permission from [7]. Patients with multiple signs or symptoms are classified according to the most severe sign or symptom.

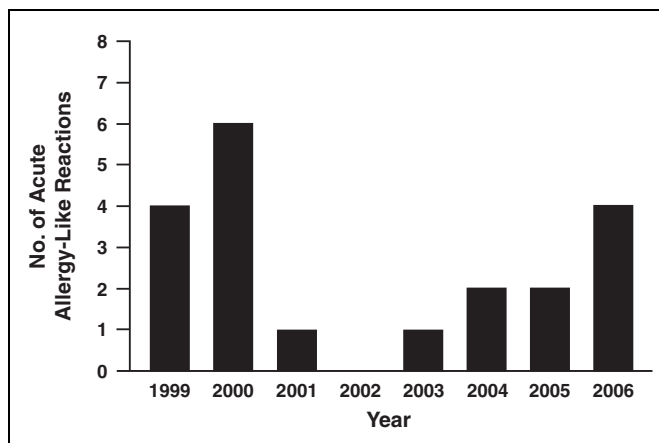
<sup>a</sup>Physiologic responses to contrast agents that are not considered allergic or allergic-like events.

<sup>b</sup>Necessitate no medical intervention with the exception of possible antihistamine administration for cutaneous reaction.

<sup>c</sup>Necessitate immediate medical treatment or transfer to the emergency department if patient is undergoing outpatient imaging.

<sup>d</sup>Life-threatening, potentially fatal event typically necessitating hospitalization if patient is undergoing outpatient imaging.

**Fig. 3**—Graph shows annual number of acute allergic-like reactions to IV low-osmolality nonionic iodinated contrast material in pediatric patients in department of radiology from January 1, 1999, through June 30, 2006. Results for 2006 are for first and second quarters only (January 1–June 30, 2006).



effects and not acute allergic-like reactions at our institution and do not necessitate documentation or radiologist intervention. This classification also does not include signs and symptoms related to extravasation of contrast material; such events are managed under separate institutional guidelines.

For all patients who experienced an acute allergic-like reaction, our institutional comprehensive electronic medical record system was searched for any pertinent medical history, including previous contrast material reaction, premedication administered before IV administration of contrast material, previous allergic-like reaction to substances other than contrast material, and history of asthma. The electronic medical record system also was searched for subsequent interventions outside the radiology department and for patient outcome (e.g., discharge to home in usual state of health,

permanent disability related to acute allergic-like reaction, and death).

The rate of acute allergic-like reaction to IV administration of nonionic iodinated contrast materials among pediatric patients was compared with the rate among adult patients at our institution over the same time period. The relative risk was calculated for the pediatric and adult rates. Normal approximation to binomial distribution was used to calculate CI.

### Results

Acute allergic-like reactions related to IV administration of low-osmolality nonionic iodinated contrast material were documented in 20 pediatric patients (0.18% of 11,306 injections) (Fig. 3). The mean age of patients who experienced acute allergic-like reactions was 10.5 years (range, 3 months–16 years). No

patient experienced more than one acute allergic-like reaction over the study period. Fourteen (70%) of the patients who had reactions were girls, and six (30%) were boys. Twelve (60%) of the patients were outpatients, four (20%) were emergency department patients, and four (20%) were hospital inpatients. The rate of acute allergic-like reactions to iohexol was 0.18% (14 acute allergic-like reactions in 7,963 administrations). The rate of reaction to iopromide also was 0.18% (six acute allergic-like reactions in 3,343 administrations). No statistically significant difference in the rate of acute allergic-like reactions was identified between the two nonionic iodinated contrast materials.

Sixteen (80%) of the acute allergic-like reactions were categorized as mild, one (5%) was moderate, and three (15%) were severe. No pediatric deaths during this period were attributed to IV administration of contrast material. Mild acute allergic-like reactions included seven instances of urticaria, four of generalized rash, and two of combined mild facial edema and sneezing. Mild reactions also affected individual patients who experienced new-onset combined sneezing and rhinorrhea, combined generalized rash and asymptomatic tachycardia, and isolated mild facial edema. Four of these patients with cutaneous manifestations were given antihistamine medication before leaving the department of radiology. The only moderate reaction involved a single patient who experienced acute bronchospasm immediately after IV administration of contrast material. This patient had a known history of bronchial asthma and was discharged from the department of radiology after treatment with albuterol.

Three patients had severe acute reactions. A 15-year-old girl in the emergency department needed epinephrine and hospital admission for acute bronchospasm and facial edema after IV administration of nonionic iodinated contrast material. A 10-year-old girl who was an outpatient had progressive facial edema that necessitated hospital admission for observation. Finally, a 15-year-old girl in the emergency department experienced severe bronchospasm, marked hypotension (49/38 mm Hg), tachycardia, and facial edema necessitating treatment with epinephrine. This patient also needed inpatient hospitalization for further management of the acute reaction. All three patients who had severe acute allergic-like reactions were discharged to home in their usual state of health.

Two (10%) of the patients who had acute allergic-like reactions had a history of reaction to IV iodinated contrast material. Both of these previous reactions occurred before January 1, 1999. Both patients had mild acute allergic-like reactions (one urticaria and the other generalized rash) despite receiving appropriate premedication with corticosteroid and antihistamine. Previous pediatric reactions to contrast media are identified at our institution by review of the patient's records in the radiology information system and comprehensive electronic medical record system and by review of reports of previous imaging examinations in which contrast medium was used. Before any contrast-enhanced imaging, all patients or accompanying parents or guardians complete a questionnaire that includes questions about allergy history, including previous contrast reactions, other allergies, and asthma. The questionnaire completion rate is close to 100%. Only in very rare instances, such as the case of an unconscious unidentified emergency department patient who is unaccompanied by family, is completion of the questionnaire not mandatory before CT with IV contrast material.

Six (30%) of the patients who had reactions, including one of the patients who had a previous acute allergic-like reaction to iodinated contrast medium, had a history of allergic-like reaction to substances other than contrast media. Five (25%) of the patients had a history of bronchial asthma, including three of the four patients who experienced moderate or severe acute allergic-like reactions.

## Discussion

The 0.18% incidence of acute allergic-like reactions to pediatric IV administration of nonionic iodinated contrast material established in this retrospective study is lower than that in several earlier pediatric studies in which either ionic or nonionic contrast material was used. Gooding et al. [8] in 1975 reported results of a study of IV administration of ionic contrast material to 12,419 pediatric patients undergoing excretory urography. The investigators found an adverse reaction rate of 3.4%. Approximately 13% of the reactions were allergy like, resulting in a rate of approximately 0.4% for allergic-like reactions and a rate of approximately 3% for other adverse events, such as physiologic side effects.

Three studies [9–11] with smaller numbers of pediatric patients receiving IV nonionic iodinated contrast media for pediatric CT and excretory urography showed adverse reaction

rates ranging from 0.9% to 36%. In a large study of administration of nonionic iodinated contrast material (including iohexol, iopamidol, and metrizamide but not iopromide) to 13,461 patients 19 years old and younger, Katayama et al. [2] found an adverse reaction rate of 3.49%. This high reaction rate compared with our finding may be due in part to the classification of side effects (e.g., nausea, vomiting, flushing) as adverse reactions in the study by Katayama et al.

The incidence of acute reactions related to IV administration nonionic iodinated contrast material to children in this study is lower than the rates frequently reported for the adult population. Katayama et al. [2] reported an adverse reaction rate of 3.14% for 153,961 adult patients receiving strictly nonionic contrast media for CT. A more recent study by Mortelé et al. [12] showed an adverse event rate of 0.7% (of which at least 88% of the reactions were allergic-like) among 29,508 patients who underwent contrast-enhanced CT with iopromide. Cochran et al. [4], however, reported an adverse event rate of 0.23% ( $\approx 90\%$  of the reactions were allergic-like) during 9 years in which nonionic contrast material was used exclusively. Thus the allergic-like reaction rate among adults in their study was approximately 0.21%, similar to our pediatric rate.

The incidence of acute allergic-like reactions related to IV administration of contrast material in the adult population at our institution over the same time period in which the pediatric study was conducted and with the same contrast agents was approximately 0.7% (668 allergic-like reactions in approximately 96,927 IV administrations) (unpublished data). The difference between our institutional observed pediatric and adult allergic-like reaction rates was statistically significant, with a relative risk of reaction among adults compared with children of 3.9 (95% CI, 2.5–6.1). The reason for a lower reaction rate in the pediatric population is unknown; however, age appears to be a risk factor for contrast reaction. When the data in the study by Katayama et al. [2] are stratified by age, pediatric and elderly patients have lower rates of reactions than patients between these extremes of age.

As with adults [2, 4, 12], most pediatric acute allergic-like reactions related to IV administration of nonionic iodinated contrast material are mild. Severe acute allergic-like reactions in children, although rare overall in our population ( $< 0.03\%$  of administrations), represented 15% of all acute reactions. Be-

cause severe reactions can occur after administration of contrast material to children, institutions and radiologists performing IV contrast-enhanced examinations of pediatric patients should be prepared to effectively manage these occurrences.

Possible risk factors for acute allergic-like reactions related to IV administration of nonionic iodinated contrast media to pediatric patients appear to be similar to those observed in adults [2, 10, 12]. Apparent risk factors among the 20 pediatric patients who experienced acute allergic-like reactions in our study included a history of reaction to iodinated contrast material, bronchial asthma, and previous allergic-like reaction to substances other than contrast material. It should be noted, however, that the prevalence of these conditions in our entire pediatric patient population is unknown.

Two patients in our study experienced acute allergic-like reactions to low-osmolality nonionic iodinated contrast media despite appropriate prophylactic premedication, the so-called breakthrough reaction [13]. We do not, however, have data on the number of patients who received premedication and did not experience a reaction to contrast administration.

The use of prophylactic premedication to reduce the risk of acute allergic-like reactions in patients at risk is influenced by our departmental guidelines on the subject. The guidelines suggest premedication when a patient (outpatient, inpatient, or emergency department patient) has had a previous allergic-like reaction to iodinated contrast material; has multiple (usually four or more) allergies or a severe allergy to another substance; or has asthma with frequent, recent, or severe attacks. These risk factors are identified through the questionnaire described earlier, the electronic medical record, the radiology information system, or review of reports from previous contrast-enhanced imaging examinations. The recommended premedication regimens are given in Table 2. Patients at risk usually are identified sufficiently far ahead of time to allow administration of the first dose of corticosteroid 13 hours before IV administration of contrast material. Not infrequently, contrast-enhanced examinations are rescheduled to allow the full 13-hour premedication regimen. Emergency studies can be performed without IV contrast material, with IV contrast material without premedication, or with a shortened premedication regimen. In such situations at our institution, departmental guidelines leave the final decision on premedication and IV contrast ma-

## Reactions to Contrast Material

**TABLE 2: Institutional Pediatric and Adult Oral Premedication Regimens Before Administration of IV Contrast Media**

| Drug            | Timing                                          | Pediatric Dosage                   | Adult Dosage |
|-----------------|-------------------------------------------------|------------------------------------|--------------|
| Prednisone      | 13, 7, and 1 h before contrast-enhanced imaging | 0.5–0.7 mg/kg orally (up to 50 mg) | 50 mg orally |
| Diphenhydramine | 1 h before contrast-enhanced imaging            | 1.25 mg/kg orally (up to 50 mg)    | 50 mg orally |

Note—Adapted with permission from [7]. Regimens are for patients at increased risk of acute allergic-like reaction to contrast media. IV administration (substituting an equivalent dose of hydrocortisone for prednisone) can be used for patients who cannot ingest oral medication.

terial administration to the discretion of the radiologist to accommodate the variety of clinical situations that occur. A discussion of risks and benefits of prophylactic premedication is beyond the scope of this article.

To our knowledge, no evidence exists to determine whether the isoosmolar nonionic iodinated agent iodixanol has a lower, similar, or higher rate of acute allergic-like reactions in the pediatric population compared with low-osmolality nonionic iodinated contrast agents. Given the low rate of reaction to iodinated contrast media in the pediatric population, it would take a study with a very large, possibly prohibitively large, number of patients to have sufficient statistical power to find a significant difference between agents. There also may be a theoretic role for use of iodixanol in imaging of patients with a previous reaction to low-osmolality contrast material (i.e., changing contrast agents with the intention of reducing reaction risk). To our knowledge, this theory has not been studied, and a prospective study to test the hypothesis would require a large series of subjects. In a study comparing iodixanol with iohexol that was conducted with a small number of subjects, the investigators [14] concluded that both agents are well tolerated in the pediatric population with low rates of adverse events. To our knowledge, no randomized trial with a large number of subjects has been performed to compare the various low-osmolality nonionic agents with one another in the pediatric population.

There were a few limitations associated with this retrospective investigation. We assumed that all acute allergic-like reactions were appropriately documented. Appropriate documentation of acute allergic-like contrast reactions is emphasized repeatedly

in resident and departmental meetings, including a yearly in-service session dedicated to contrast material. However, if a contrast material reaction form was not completed according to departmental policy or was completed and lost, we did not include the reaction in this study. Such occurrences would have led to underestimation of the incidence of acute allergic-like reactions. Second, it is possible that certain events reported as acute reactions were not truly events directly attributable to IV administration of contrast material and might have occurred in the absence of IV contrast material administration. Such occurrences would have led to overestimation of the incidence of acute allergic-like reactions. Finally, additional patients may have experienced breakthrough reactions that were not identifiable with the information in the available medical records.

In conclusion, the use of IV low-osmolality nonionic iodinated contrast material for imaging of pediatric patients is quite safe. The incidence of acute allergic-like reactions related to such contrast media is lower in the pediatric population than in the adult population. Pediatric acute allergic-like reactions are infrequent and typically are mild in intensity. Severe acute allergic-like reactions, however, do occasionally occur in the pediatric population. Death related to the IV administration of contrast material is very rare; no contrast material-related pediatric death occurred at our institution during the period of review. As with adults, there are apparent risk factors that predispose some patients to acute contrast reactions, including a history of contrast reaction, previous allergic-like reaction to other substances, and bronchial asthma.

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