

Frequency and Severity of Acute Allergic-Like Reactions to Intravenously Administered Gadolinium-Based Contrast Media in Children

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Objectives: The purpose of this study is to determine the frequency and severity of acute allergic-like reactions to gadolinium-based contrast media (GBCM) in children before, during, and after the transition from gadopentetate dimeglumine to gadoterate meglumine as our primary clinical GBCM.

Materials and Methods: Institutional review board approval was obtained for this Health Insurance Portability and Accountability Act-compliant retrospective investigation. Allergic-like reactions to GBCM in pediatric patients were retrospectively assessed from January 2009 to January 2017, which included a departmental change of GBCM from gadopentetate dimeglumine to gadoterate meglumine. Allergic-like reactions were identified from departmental and hospital databases. The number of doses of GBCM was obtained from billing data. Allergic-like reaction frequencies for each GBCM were calculated and compared using the chi-squared test.

Results: A total of 32,365 administrations of GBCM occurred during the study period (327 for gadofosveset trisodium; 672 for gadoxetate disodium; 12,012 for gadoterate meglumine; and 19,354 for gadopentetate dimeglumine). Allergic-like reactions occurred after 21 (0.06%) administrations. Reaction frequencies were not significantly different among the GBCM (0.3% gadofosveset trisodium; 0% gadoxetate disodium, 0.06% gadoterate meglumine, 0.08% gadopentetate dimeglumine; $P > 0.05$). Ten (47.6%) reactions were mild, 10 (47.6%) were moderate, and 1 (4.8%) was severe. The overall reaction frequency peaked during the 6-month transition period from gadopentetate dimeglumine to gadoterate meglumine (0.20%), compared with 0.07% pretransition ($P = 0.048$) and 0.04% posttransition ($P = 0.0095$).

Conclusion: Allergic-like reactions to GBCM in children are rare. Gadoterate meglumine has a reaction frequency that does not significantly differ from other GBCMs. During the transition from gadopentetate dimeglumine to gadoterate meglumine, an increase in the frequency of reported allergic-like reactions was observed, likely reflective of the Weber effect.

Key Words: gadolinium-based contrast media, allergic-like reactions, pediatric, reactions

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Gadolinium-based contrast media (GBCM) are used to improve image contrast, lesion visualization, and tissue characterization during magnetic resonance imaging (MRI). The first GBCM was approved for use in humans by the US Food and Drug Administration (FDA) in 1988, and since that time the number of GBCMs on the market and their clinical applications has grown substantially. Currently, there are a total of 9 FDA-approved GBCMs, and it is estimated that 30 million contrast-enhanced MRI examinations are performed annually

worldwide.¹ In selecting a GBCM for clinical use, the risk of adverse events should be taken into consideration, including acute allergic-like reactions,^{2,3} nephrogenic systemic fibrosis,^{4,5} and possibly tissue gadolinium deposition.^{6–9}

Gadoterate meglumine (Dotarem; Guerbet LLC, Cedex, France) is the only ionic macrocyclic GBCM approved for use by the FDA, receiving approval in March 2013.¹⁰ This approval included use in pediatric patients from 2 to 17 years of age. The bulk of clinical safety data used by the FDA during the approval process was obtained in adults, with results being extrapolated to the pediatric population.¹¹ To date, no large study has been conducted in the United States to evaluate the frequency of acute allergic-like reactions in pediatric patients intravenously receiving gadoterate meglumine. Furthermore, no large study in the United States has compared the allergic-like reaction frequency with that of other GBCMs.¹² Because previous studies have suggested that risk of allergic-like reactions may vary among different GBCM,^{13–17} dedicated evaluation of the frequency of allergic-like reaction associated with each new GBCM is important.

The goal of this study was to determine the frequency and severity of acute allergic-like reactions to intravenously administered GBCM in children before, during, and after the transition from gadopentetate dimeglumine to gadoterate meglumine as our primary clinical GBCM.

MATERIALS AND METHODS

Before the initiation of this retrospective study, approval of the institutional review board was obtained. The study complied with the Health Insurance Portability and Accountability Act (United States), and need for informed consent was waived.

Study Population

All intravenous administrations of GBCM carried out on pediatric patients (0–17 years of age) between January 1, 2009, and January 31, 2017, at our institution Cincinnati Children's Hospital Medical Center were identified from a retrospective query of billing records. This time frame was chosen because of the completeness of billing and electronic medical records, and because it included our institutional transition from gadopentetate dimeglumine to gadoterate meglumine as the primary GBCM used for routine clinical MRI (beginning December 2013).

Documentation of Allergic-Like Reactions to GBCM

Allergic-like reactions to GBCM were identified by examining our departmental and institutional voluntary online safety reporting system and all MRI examination reports over the study period. In addition, our electronic medical record system (Epic Systems Corporation, Verona, WI) was queried to find all patients with a documented allergy to “gadolinium” or any of the 9 FDA-approved GBCM. Electronic medical records were then reviewed to find the allergic-like reactions during the study period. All adverse reactions that were not allergic like (defined as per the *American College of Radiology Manual on Contrast Media*, v10.2¹⁸) were excluded from our study.

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Any reaction that occurred in a patient older than 18 years or greater than 24 hours after GBCM administration was excluded from this study.

For each acute allergic-like reaction, the following were documented from available and pertinent records: reaction manifestation (s), contrast medium administered, any medical treatment rendered (including outside the radiology department), and patient disposition (ie, discharged, transferred to the emergency department, admitted to the hospital, or returned to inpatient room). For each patient, any history of atopy (eg, asthma, eczema, and allergic rhinitis) or previous allergic/allergic-like reaction (eg, food/medication allergy, iodinated contrast material allergy, and GBCM allergy) was recorded. Any premedication regimen (eg, corticosteroid and anti-histamine) administered before the acute allergic-like reaction was also documented, as was patient demographic data, including age and sex.

GBCMs Used During the Study Period

The following GBCMs were used at our institution during the study period:

- gadofosveset trisodium (Ablavar; Lantheus Medical Imaging, North Billerica, MA)
- gadoxetate disodium (Eovist; Bayer HealthCare LLC, Whippany, NJ)
- gadoterate meglumine (Dotarem, Guerbet LLC)
- gadopentetate dimeglumine (Magnevist, Bayer HealthCare LLC).

Gadopentetate dimeglumine was the primary GBCM used for clinical MRI between January 2009 and April 2014, with the final administration at our institution occurring in September 2015. Gadoterate meglumine was formally introduced at our institution in December 2013 (although a very small number of doses [<20] were administered between July and November 2013), becoming the primary GBCM for clinical MRI in May 2014. The transition period was defined as this period when gadoterate meglumine was introduced to when it became the primary GBCM (December 2013 through May 2014). The other 2 GBCMs used at our institution during the study period were gadoxetate disodium, a hepatobiliary contrast agent, and gadofosveset trisodium, a blood pool contrast agent.

The dosing of each agent was chosen based on the manufacturer's recommendations. The standard intravenous dose of gadopentetate dimeglumine was 0.4 mL/kg for cardiac studies and 0.2 mL/kg for all other indications. Gadoterate meglumine was administered at a standard dose of 0.2 mL/kg for all indications. Gadofosveset trisodium was administered at a standard dose of 0.12 mL/kg for all indications. Gadoxetate disodium was administered at a standard dose of 0.2 mL/kg for all indications.

Classification of Acute Allergic-Like Reactions

For this study, we classified acute allergic-like reactions, based on the most severe sign/symptom, as mild, moderate, or severe according to the previously published guidelines (Table 1).¹⁸ The severity classification system described above does not specifically define mild versus significant hypoxia; therefore, hypoxia severity was defined as per the guidelines used by the anesthesia department at our institution.¹⁹ An oxygen saturation greater than 75% was characterized as mild, whereas an oxygen saturation less than or equal to 75% was characterized as significant hypoxia.

Physiologic reactions to GBCM administration were considered adverse effects as opposed to allergic-like reactions and were not included in this study. Examples include nausea, vomiting, altered taste, warm sensation, flushing, and anxiety. In addition, any vasovagal and contrast material extravasation events were excluded.

Statistical Analysis

Study data were collected and managed using REDCap (Research Electronic Data Capture) tools.²⁰ Continuous data were summarized using means, standard deviations, and ranges, whereas categorical data were summarized as counts and percentages. Proportions, including acute allergic-like reaction frequencies between GBCMs, were compared using the chi-squared test. A *P* value of less than 0.05 was considered statistically significant for inference testing. Statistical analyses were performed using GraphPad Prism7 (GraphPad Software, Inc, La Jolla, CA).

RESULTS

A total of 32,365 intravenous administrations of GBCM were documented in pediatric patients at our institution between January 1, 2009, and January 31, 2017. This included 327 administrations of gadofosveset trisodium, 12,012 administrations of gadoterate meglumine, 672 administrations of gadoxetate disodium, and 19,354 administrations of gadopentetate dimeglumine. Of the administrations, 53% ($n = 17,156$) occurred in male patients and 47% ($n = 15,209$) in female patients.

Twenty-one acute allergic-like reactions to GBCM were documented during the study period, for an overall reaction frequency of 0.06% (0.3% [1/327] gadofosveset trisodium; 0% [0/672] gadoxetate disodium; 0.04% [5/12,012] gadoterate meglumine; and 0.08% [15/19,345] gadopentetate dimeglumine) (Fig. 1). There was no significant difference in the frequency of reaction between the clinical agents used ($P > 0.05$). Specifically, the reaction frequencies between the primary GBCMs during the study period, gadoterate meglumine and gadopentetate dimeglumine, were not significantly different ($P = 0.26$). The reaction manifestations included limited urticarial/hives ($n = 10$), cutaneous edema ($n = 2$), itch/scratchy throat ($n = 7$),

TABLE 1. Classification of Severity of Acute Allergic-Like Contrast Reactions in Children and Adults

Mild	Moderate	Severe
Limited urticaria/pruritus	Diffuse urticaria/pruritus	Diffuse edema or facial edema with dyspnea
Limited cutaneous edema	Diffuse erythema, stable vital signs	Diffuse erythema with hypotension
Limited "itchy"/"scratchy" throat	Facial edema without dyspnea	Laryngeal edema with stridor and/or hypoxia
Nasal congestion	Throat tightness or hoarseness without dyspnea	Wheezing/bronchospasm, significant* hypoxia (oxygen saturation $\leq 75\%$)
Sneezing/conjunctivitis/rhinorrhea	Wheezing/bronchospasm, mild or no hypoxia (oxygen saturation $>75\%$)	Anaphylactic shock (hypotension + tachycardia)

Adapted from the *American College of Radiology Manual on Contrast Media* Version 10.2.¹⁸

*Significant hypoxia was not defined by the American College of Radiology. We defined this based on oxygen saturation levels per institutional anesthesia criteria.¹⁹

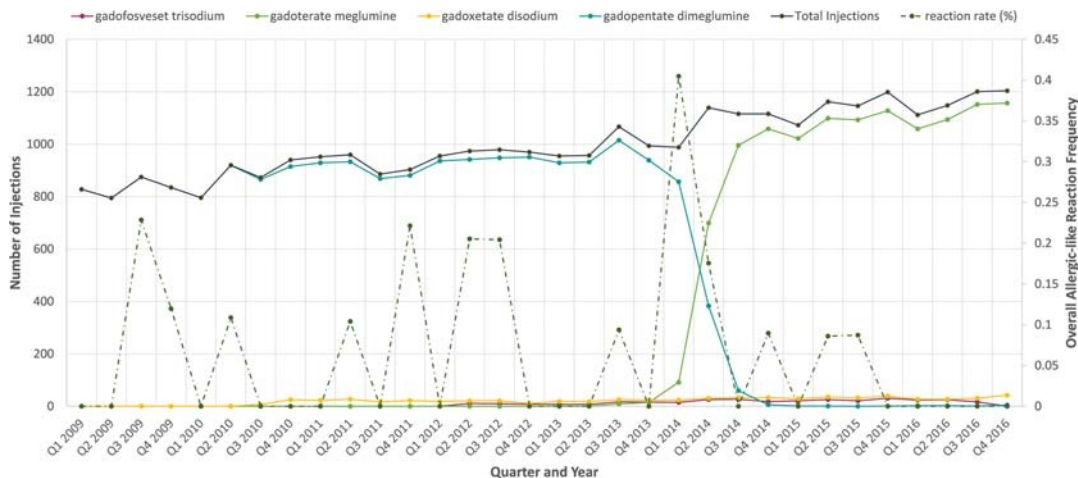


FIGURE 1. Numbers of intravenous administrations of GBCM per quarter and allergic-like reaction frequency for GBCM over the same time frame. Figure 1 can be viewed online in color at www.investigativeradiology.com.

sneezing/rhinorrhea ($n = 2$), diffuse urticarial/pruritus ($n = 2$), diffuse erythema ($n = 3$), facial edema ($n = 2$), throat tightness/hoarseness ($n = 3$), wheezing/bronchospasm ($n = 3$), and hypoxia ($n = 1$); patients could exhibit more than one of the manifestations.

Nine reactions occurred in female patients (0.06% [9/15,209] reaction frequency) and 12 occurred in male patients (0.07% [12/17,156] reaction frequency) ($P = 0.83$). The mean age of patients who experienced acute allergic-like reactions was 11.4 ± 3.8 years (range, 3–18 years). The majority of reactions occurred in the outpatient setting (15/21, or 71%). No reaction involved an emergency department patient, whereas 6 reactions involved hospital inpatients. Outpatients accounted for 68% ($n = 22,092$) of GBCM administrations during the study period.

Acute Allergic-Like Reaction Severity and Treatment

Of the reactions, 47.6% (10/21) were mild, 47.6% (10/21) were moderate, and 4.8% (1/21) were severe. The severe reaction was reported in an outpatient undergoing MRI with gadoterate meglumine and intravenous sedation directed by our anesthesia service. This patient was sedated with both propofol and midazolam and experienced moderate hypoxia before being given GBCM. The patient was stabilized, and GBCM was then intravenously administered to complete the MR examination. This patient then experienced bronchospasm with moderate hypoxia, requiring intubation, but received no documented pharmacologic treatment. The patient was successfully extubated within an hour, was recovered over a several hour period, and was ultimately discharged home the same day.

Medical treatment and disposition for the reported mild and moderate acute allergic-like reactions are presented in Table 2. No patient required treatment with epinephrine, and no GBCM-related death occurred during the study period.

Eleven patients (52% of 21) who experienced an acute allergic-like reaction had never had a previous exposure to GBCM, whereas 9 patients (43% of 21) had an acute allergic-like reaction after having uneventful prior GBCM exposures. Of the 9 patients having prior uneventful GBCM administrations, 7 of the prior exposures were to the same agent associated with the acute allergic-like reaction (5 for gadopentate dimeglumine and 2 for gadoterate meglumine).

A single male patient experienced 2 acute allergic-like reactions during the study period, each reported separately in this study. This patient experienced urticaria and pruritus during his first exposure to gadopentate dimeglumine, was orally treated with 50 mg of diphenhydramine, observed in the Department of Radiology, and eventually discharged home. Before his second GBCM exposure (also gadopentate dimeglumine), which was 21 days after the first exposure, the patient

received an oral pretreatment medication regimen consisting of 30 mg of prednisone 12, 6, and 1 hour before the examination and 50 mg of diphenhydramine 1 hour before the examination. The patient experienced a “breakthrough reaction” of urticaria with pruritus.¹⁸ On this occasion, this patient was transferred to the emergency department, again treated with diphenhydramine, and ultimately discharged home.

Associated Atopic Conditions and Other Allergies

In patients having an acute allergic-like reaction, 38% (8/21) had no documented history of atopy or other allergies, 29% (6/21) had documentation of atopy (4 with asthma and 2 with eczema), and 52% (11/21) had documentation of allergy (allergic rhinitis, food allergy, and/or medication allergy). Four (19%) of 21 patients had history of both atopy and other allergies. The patient that experienced a severe acute allergic-like reaction to GBCM had a documented allergy to amoxicillin manifesting as a skin reaction.

Effect of Transitioning Between GBCMs on Reaction Frequency

During the 6-month period when gadoterate meglumine became the primary GBCM for clinical MRI (December 2013 through May 2014), there were 4 acute allergic-like contrast reactions in 2031 GBCM administrations, a reaction frequency of 0.20%. This compares with 12 acute allergic-like contrast reactions in 18,081 GBCM administrations between January 2009 and November 2013 (reaction frequency of 0.07%) and 5 in 12,227 GBCM administrations between June 2014 and January 2017 (reaction frequency of 0.04%). The frequency of acute allergic-like reactions was significantly higher during the period of GBCM transition compared with both the periods before and after ($P = 0.048$ and $P = 0.0095$, respectively) (Fig. 2).

DISCUSSION

The frequency of acute allergic-like reactions to intravenously administered GBCM in more than 30,000 pediatric patients at our institution was quite low, with a documented frequency of 0.06%. Acute allergic-like reaction frequencies were not significantly different between contrast media used during the study period (eg, 0.04% for gadoterate meglumine, a macrocyclic agent, vs 0.08% for gadopentate dimeglumine, a linear agent).

These reaction frequencies are similar to those reported in other studies that included children. Davenport et al¹⁴ described a 0.05% frequency of acute allergic-like reactions in 15,706 pediatric patients. The majority of patients in the Davenport et al study received gadopentate dimeglumine and gadobenate dimeglumine (MultiHance; Bracco

TABLE 2. Medical Treatment and Disposition for Pediatric Patients Experiencing Mild and Moderate Acute Allergic-Like Reactions to GBCM*

Agent	Reaction Severity†	Disposition		Medical Treatment							Observation Only
		ED Transfer‡	Inpatient Admit§	Oxygen	Intravenous Fluids	Diphenhydramine	Corticosteroid	Albuterol			
Gadofosveset trisodium (Ablavar)	Total	1/21 (5%)	0	0	0	0	1/1 (100%)	0	0		
	Mild	0	0	0	0	0	0	0	0		
	Moderate	1/1 (100%)	0	0	0	0	1/1 (100%)	0	0		
Gadoterate meglumine (Dotarem)	Total	5/21 (24%)	0	0	1/5 (20%)	2/5 (40%)	0	1/5 (20%)	1/5 (20%)		
	Mild	1/5 (20%)	0	0	0	0	0	0	1/5 (20%)		
	Moderate	3/5 (60%)	0	0	1/5 (20%)	2/5 (20%)	0	1/5 (20%)	0		
Gadoxetate disodium (Eovist)	Total	0	0	0	0	0	0	0	0		
	Mild	0	0	0	0	0	0	0	0		
	Moderate	0	0	0	0	0	0	0	0		
Gadopentetate dimeglumine (Magnevist)	Total	15/21 (71%)	2/15 (13%)	1/15 (7%)	0	7/15 (47%)	0	0	7/15 (47%)		
	Mild	9/15 (60%)	1/15 (7%)	0	0	4/15 (27%)	0	0	5/15 (33%)		
	Moderate	6/15 (40%)	1/15 (7%)	1/15 (7%)	0	3/15 (20%)	0	0	2/15 (13%)		
All GBCM	Total	21/21 (100%)	2/21 (10%)	2/21 (10%)	1/21 (5%)	9/21 (43%)	1/21 (5%)	1/21 (5%)	8/21 (38%)		
	Mild	10/21 (48%)	1/21 (5%)	0	0	4/21 (19%)	0	0	6/21 (29%)		
	Moderate	10/21 (48%)	1/21 (5%)	2/21 (10%)	1/21 (5%)	5/21 (24%)	1/21 (5%)	1/21 (5%)	2/21 (10%)		

* Results are presented as the number of reactions (percentage reactions).

†Reaction severity classified as per the *American College of Radiology Manual on Contrast Media*, v10.2.

‡“ED Transfer” refers to outpatients who were referred to the emergency department as a direct result of the allergic-like reaction to GBCM.

§“Inpatient Admit” refers to patients who were admitted to the hospital as a direct result of the allergic-like reaction to GBCM.

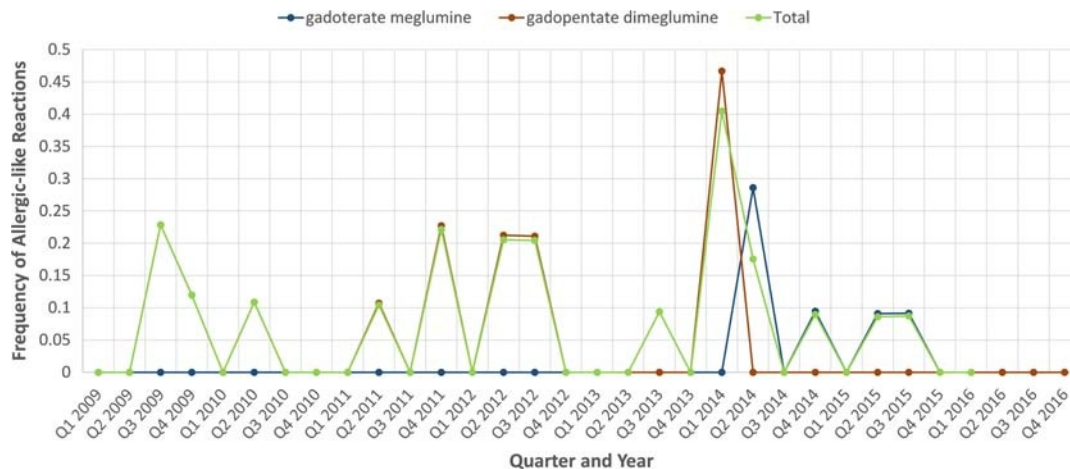


FIGURE 2. Frequency of allergic-like reactions per quarter for gadoterate meglumine, gadopentetate dimeglumine, and overall reaction frequency including all 4 GBCMs used during the study period (gadoterate meglumine, gadopentetate dimeglumine, gadofosveset trisodium, and gadoxetate disodium). Figure 2 can be viewed online in color at www.investigativeradiology.com.

Diagnostics, Inc, Monroe Township, NJ). In another study of 13,344 pediatric patients, the frequency of acute allergic-like reactions was 0.04%, with most receiving gadopentetate dimeglumine.¹⁵ A prospective international study of 1142 pediatric patients receiving gadobutrol, a nonionic macrocyclic agent, demonstrated an acute drug reaction frequency of 0.5%.²¹ Acute drug reactions in this study included physiologic and allergic-like reactions. Other studies report reaction frequencies of 0.06% to 0.32% for GBCMs.^{2,13,16,17,22,23} However, these studies commonly include physiologic reactions in addition to allergic-like reactions as well as both adult and pediatric patients.

There is little published data available regarding adverse events associated with the administration of gadoterate meglumine in children. The reaction frequency for gadoterate meglumine in our study is slightly lower than the frequency of 0.08% reported in a study of 35,580 adult patients by Jung et al.²⁴ Soyer et al.²⁵ found a reaction frequency in pediatric patients of 0%, including physiologic and allergic reactions; however, this study included only 1629 patients, a number likely too small to accurately quantify a reaction frequency. Another small study with 3501 patients, including both pediatric and adult patients as well as both allergic-like and physiologic reactions, reported a reaction frequency of 0.34%.²² To date, and to the best of our knowledge, our study is the largest study assessing the frequency of acute allergic-like reactions to gadoterate meglumine in children.

The 0.08% acute allergic-like reaction frequency to gadopentetate dimeglumine in our study is identical to that established by Davenport et al.¹⁴ in a study that included both adults and children. In a study by Dillman et al, the acute allergic-like reaction frequency for gadopentetate dimeglumine in a combined pediatric and adult population was 0.07%, whereas the frequency was slightly lower with only the pediatric population (0.04%).¹⁵ In a prospective study by Scala et al.²⁶ of 45 patients 2 years or younger who received gadopentetate dimeglumine, 2.2% (1/45) experienced an allergic-like reaction (moderate intensity rash). Based on our study, the reaction frequencies to both gadoxetate disodium and gadofosveset trisodium are also low, with only a single acute allergic-like reaction observed after an injection of gadofosveset trisodium. Given the relatively small number of administrations of these 2 agents, reaction frequencies are likely inadequately assessed and comparisons are of questionable value.

The majority (95%) of acute allergic-like reactions to GBCM in our study was mild or moderate in severity. That said, we observed a greater percentage of moderate reactions in our study compared with prior studies.^{14,15,24} The only GBCM in our study to cause a severe reaction was gadoterate meglumine; however, this reaction is associated

with confounding factors, including contemporaneous administration of intravenous sedation and a hypoxic event before administration of GBCM.²⁷ This single severe reaction accounts for 5% of all observed acute allergic-like reactions, which is slightly less than the frequency found by Jung et al.²⁴ (11%), and comparable with Dillman et al.¹⁵ (7%) and Davenport et al.¹⁴ (3.7%), with all 3 of these studies having a mixed adult and pediatric population. One potential reason for a greater percentage of moderate reactions in our exclusively pediatric population is the smaller caliber of the pediatric airway. Small amounts of edema have a greater effect on the caliber of the pediatric airway compared with the adult airway, resulting in a greater increase in airway resistance, and thus more ready development of throat tightness and/or wheezing.²⁸ Furthermore, it is conceivable that decreased patient reporting of mild symptoms occurs in children compared with adults resulting in inflation of the percentage of more severe reactions. Pediatric patients commonly rely on caregivers or healthcare workers to notice many of the signs and symptoms of acute allergic-like reactions, and thus, mild reactions may go unnoticed and unreported. In addition, mild symptoms in patients undergoing sedation during their examination might not be appreciated.

Prior investigations suggest that history of atopy and other allergies increases the risk for allergic-like reaction to GBCM.^{15,29} Although our data do not address this question, the findings of atopy in 29% of patients with allergic-like reaction, asthma in 19%, and food allergy in 9.5% suggest a higher prevalence of these diseases (vs population frequencies) in the population of patients who experiences acute allergic-like reactions to GBCM. Specifically, according to the Centers for Disease Control, the 2014 prevalence of asthma in children was 9.2% in the United States and 10.4% in the state of Ohio, whereas the prevalence of food allergies in US children was 5.1% between 2009 and 2011.^{30,31}

An interesting finding in our study was the transient increase in acute allergic-like reaction frequency for *both* gadopentetate dimeglumine and gadoterate meglumine as we transitioned our primary clinical GBCM. This observation is consistent with the “Weber effect,” defined as a transient rise in reported adverse drug reactions following the introduction of a new drug to the market, classically peaking within 2 years and declining thereafter.³² Since initial description, the Weber effect has been documented in multiple publications, including when changing MRI contrast agents.^{14,33–35} While the Weber effect has been previously described, this is, to our knowledge, the first description of the Weber effect affecting the long-standing agent (gadopentetate dimeglumine in our case). We believe that this observation supports the hypothesis that

increased awareness to contrast-related adverse events is heightened during a period of transition from one GBCM to another, and that there is increased attention to documenting such reactions.

Our study has limitations. First, it was retrospective and relied on documentation, accuracy, and completeness of the existing medical records. Although the reporting system for contrast reactions at our institution has been in place for many years, it is possible that underreporting of acute allergic-like reactions to GBCM could have occurred. Second, before gadoterate meglumine being on the formulary, a few doses were administered to patients (July to November 2013). These doses were included in the total reaction frequency calculations; however, these were not considered part of the transition period, since an established institutional protocol was not in place. Also, the number of administrations of gadoterate meglumine (12,012) and gadopentetate dimeglumine (19,354) may be underpowered for small, but real differences in rates between these 2 agents. However, such differences are not likely to be clinically important.

Finally, it is possible that a documented acute allergic-like reaction was unrelated to the administration of GBCM. As an example, the one child experiencing a severe reaction was being concurrently exposed to intravenous sedation medications. Such inaccurate reporting could artificially increase the frequency of reactions observed.

In conclusion, acute allergic-like reactions to intravenously administered GBCMs in children are rare, and frequencies of reaction are not significantly different between specific agents, in particular, gadoterate meglumine, a macrocyclic agent, and gadopentetate dimeglumine, a linear agent. As previously shown with other GBCMs, most pediatric allergic-like reactions are mild or moderate in severity, although severe reactions may rarely occur. Furthermore, when transitioning from one GBCM to another in children, there may be a transient increase in the reported frequency of acute allergic-like reactions, likely due to the Weber effect.

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