Radiology

ORIGINAL RESEARCH • CONTRAST MEDIA

Prevention of Allergic-like Reactions at Repeat CT: Steroid Pretreatment versus Contrast Material Substitution

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Conflicts of interest are listed at the end of this article.

See also the editorial by Davenport and Weinstein in this issue.

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Background: It is unclear whether steroid premedication is an effective means of preventing repeat allergic-like reactions in high-risk patients with a previous allergic-like reaction to iodinated contrast material (ICM).

Purpose: To compare the effectiveness of ICM substitution (ie, using iohexol in a patient with a previous iopromide reaction) with 12- and 2-hour steroid premedication for preventing repeat acute allergic-like reactions in high-risk patients.

Materials and Methods: This retrospective study identified all high-risk (ie, having a previous allergic-like reaction) adult and pediatric patients who underwent a contrast-enhanced CT examination at the institution from June 1, 2009, to May 9, 2017. Prophylactic treatments and repeat reactions were identified using chart review. The effectiveness of prophylactic treatments on repeat reaction rates was examined with multivariable regression models that used generalized estimating equations.

Results: A total of 1973 high-risk patients who underwent 4360 subsequent ICM-enhanced CT examinations were included. Of the 4360 examinations, a total of 280 allergic-like reactions occurred (6%) in 224 of the 1973 patients (11% of patients), with only 19 of 280 reactions (7%) that were more severe than the previous reaction being demonstrated. After adjustment, patients who received a different ICM with and without steroid premedication had a significantly lower rate of repeat reactions than did patients who received steroid premedication and the same ICM (same ICM and steroid premedication: 80 of 423 examinations [19%]; different ICM and no steroid premedication: 10 of 322 examinations [3%]; odds ratio [OR], 0.14 [95% CI: 0.06, 0.33]; $P < .001$; different ICM and steroid premedication: five of 166 patients [3%]; OR, 0.12 [95% CI: 0.04, 0.36]; $P < .001$). When examining the first scan only, patients who received the same ICM had a similar risk of repeat reactions regardless of whether they received steroid premedication (steroid premedication: 44 of 172 patients [26%] vs no premedication: 73 of 298 patients [25%]; OR, 1.00 [95% CI: 0.64, 1.57]; $P = .99$).

Conclusion: In this cohort, using an iodinated contrast material (ICM) substitution was more effective for preventing repeat allergic-like reactions than using steroid premedication and the same ICM that caused the previous reaction.

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Iodinated contrast material (ICM) has dramatically expanded the clinical use of CT examinations. More than 70 million ICM-enhanced CT examinations were performed in the United States in 2019, and more than 1 billion doses of ICM have been administered worldwide to date (1). Acute allergic-like reactions are one of the most clinically significant adverse effects associated with ICM administration, with an aggregate rate of 0.6% (six per 1000 examinations) occurring among ICM-enhanced CT examinations (2). Notwithstanding this low rate, such reactions are observed on a daily basis at large-volume medical centers and affect health care delivery by introducing delays in imaging, adding treatment costs, and, in some cases, causing significant patient harm.

Patients who have had a previous allergic-like reaction to ICM have an increased risk of a repeat reaction (2). The standard of care for these "high-risk" patients is pre-ICM administration of prophylactic corticosteroids, typically oral methylprednisolone at 12 hours and 2 hours or prednisone at 13 hours, 7 hours, and 1 hour before ICM exposure (2,3). However, the efficacy of this pretreatment has been questioned because most previous steroid studies have included high-osmolarity ICMs that are no longer commonly used in clinical practice and had a higher rate of acute reactions than studies using low- and iso-osmolarity ICMs (4–10) and because previous studies have frequently included both high-risk and average-risk (ie, no previous ICM reaction) patients. Furthermore, breakthrough repeat reactions still occur in patients premedicated with a steroid at a rate of 2%–39% (11–13). As such, it is unclear whether steroid premedication remains a useful and effective means of preventing repeat allergic-like reactions in high-risk patients.

Recent retrospective studies have suggested that ICM substitution (ie, using iohexol in a patient with a previous reaction to iopromide) may be more effective than using steroid pretreatment in preventing repeat reactions (14,15). However, these previous studies did not

Abbreviations

ICM = iodinated contrast material, OR = odds ratio

Summary

The study findings do not support the efficacy of steroid premedication (oral methylprednisolone at 12 and 2 hours) for preventing repeat allergic-like reactions in high-risk patients.

Key Results

- In 1973 patients with a previous allergic-like reaction to iodinated contrast material, patients receiving a different contrast material had a lower reaction rate than those who received steroid premedication and the same contrast material (3% vs 19%, respectively; odds ratio, 0.14; $P < .001$).
- High-risk patients who received the same iodine contrast material had a similar rate of experiencing a repeat reaction regardless of steroid premedication (steroid premedication, 26% vs no premedication, 25%; $P = .99$).

exclusively examine the most common premedication regimen of 12- and 2-hour pre-ICM steroids. The purpose of this single-center retrospective study was to compare the effectiveness of using ICM substitution with using 12- and 2-hour pre-CT steroid premedication for preventing repeat acute allergic-like reactions in patients with a previous allergic-like reaction to ICM. We hypothesized that ICM substitution would be more effective than steroid premedication.

Materials and Methods

Study Design and Clinical Data Retrieval

The study design and implementation of this retrospective study were overseen by our institutional review board and conformed to Health Insurance Portability and Accountability Act guidelines on patient data integrity. The need for informed consent for patients who provided research authorization for retrospective research was waived.

All clinical data were extracted from our institutional electronic medical record system. Clinical data retrievals were grouped into three sections—previous reaction data (ie, previous ICM type, symptoms, and severity), current CT examination data (ie, premedication and ICM type), and repeat reaction data (ie, whether a reaction occurred, symptoms, and severity). Retrieval for each section was independently and separately performed by one author (J.S.M., with 10 years of experience). For each of the three sections, the reviewer was blinded to data from the two other sections while performing the retrieval (ie, the team was blinded to current CT examination data and repeat reaction data while retrieving the previous reaction data). Data were unblinded, patients were assigned to one of the four treatment groups, and analyses were performed only after complete retrieval of all three sections for all patients. Standardized electronic forms were used for all data retrieval. Two authors (R.J.M. and C.H.H., with 13 and 22 years of experience, respectively) not involved in the original chart review performed independent blinded data retrievals of a random selection of 20% of cases. The overall percentages of agreement with the original abstraction were 93% and 95%, indicating excellent agreement among abstractors.

Study Population

The study population consisted of all adult and pediatric patients with a previous allergic-like reaction to ICM who underwent a contrast-enhanced CT examination at our institution from June 1, 2009, to May 9, 2017. Patients who did not provide research authorization were excluded.

Identification and Classification of Previous Allergic-like Reactions

Patients were identified by searching allergy records and retrieving all patients with a documented allergy to any contrast material at the time of their CT examination at our institution. The medical records of these patients were manually reviewed (by J.S.M.) to confirm the type of contrast material (ie, ICM, gadolinium-based contrast material, other contrast material, or unknown), to confirm that the reaction was allergic-like, and to retrieve the symptoms of the previous reaction. Patients were excluded from the study if their previous reaction was caused by a gadolinium-based contrast material or could not be confirmed to have been caused by ICM (ie, allergy to contrast material), the reaction was confirmed to be physiologic (ie, nausea, vomiting, flushing, or vasovagal responses) or not allergic-like, or there was not enough information about their symptoms to confirm that the reaction was allergic-like. The specific ICM that caused the reaction was retrieved when documented. Allergic-like reactions that were dated previous to 1985—the year that the U.S. Food and Drug Administration approved the first low-osmolarity ICMs—were classified as reactions to high-osmolarity contrast materials. Documented reaction symptoms were used to classify the severity of the reaction according to the American College of Radiology criteria as follows: *(a)* a mild reaction was indicated by hives, itching, nasal or eye symptoms, and/or throat itching; *(b)* a moderate reaction was indicated by hives resistant to treatment, diffuse erythema, angioedema without dyspnea, and/or wheezing or shortness of breath; and *(c)* a severe reaction was indicated by angioedema with dyspnea, laryngeal edema, and/or anaphylaxis (2).

Identification and Classification of Repeat Allergic-like Reactions

One author (J.S.M.) performed a manual review of notes from the CT technologist, CT nurse, and radiologist to determine whether the patient received steroid premedication before undergoing CT, to determine whether an ICM different from the ICM that caused the previous reaction was used in this subsequent CT examination, and to identify and classify any repeat allergic-like reactions. Patients were placed in the "steroid-premedicated" group if they had an order for two oral doses of 32 mg of methylprednisolone at 12 and 2 hours before CT (standard institutional protocol), with or without additional antihistamines. Patients who did not take both doses, had an order for a different course of steroids (ie, 2 hours before CT only), received antihistamines only, or received no premedication were placed in the "not-steroid-premedicated" group (Fig 1). For a subset analysis, patients who had an order for the above other or additional treatments were excluded; only patients who had an order for 12- and 2-hour pre-CT methylpred-

nisolone were included in the steroid-premedicated group, and only patients who did not receive any premedication were included in the not-steroid-premedicated group (Fig 1). Acute reactions were classified as mild, moderate, and severe according to the American College of Radiology criteria (2). Physiologic reactions (ie, nausea or vomiting, chills, or vasovagal response) were not included as an outcome.

CT Examination Protocol and ICM Administration

Contrast-enhanced CT examinations included in our study were performed with the intravenous materials iohexol (Omnipaque, GE Healthcare), iopromide (Ultravist, Bayer Healthcare), and iodixanol (Visipaque, GE Healthcare). The choice of ICM was protocol specific and patient specific. ICM dosing at our institution is protocol specific and uses a nomogram adjusted for patient weight and baseline renal function. Patients were observed during and after their examination for 30–45 minutes for any acute reactions.

Statistical Analyses

Statistical analyses were performed with JMP software (version 10, SAS Institute) and R software (version 3.6.2, R Foundation for Statistical Computing) (16). Continuous variables are presented as medians and interquartile ranges, and categoric variables are presented as percentages. Differences between the four prophylactic treatment groups were assessed by using the Wilcoxon rank-sum test (continuous) or the Pearson χ^2 test (categoric). $P \leq .05$ indicated a statistically significant difference.

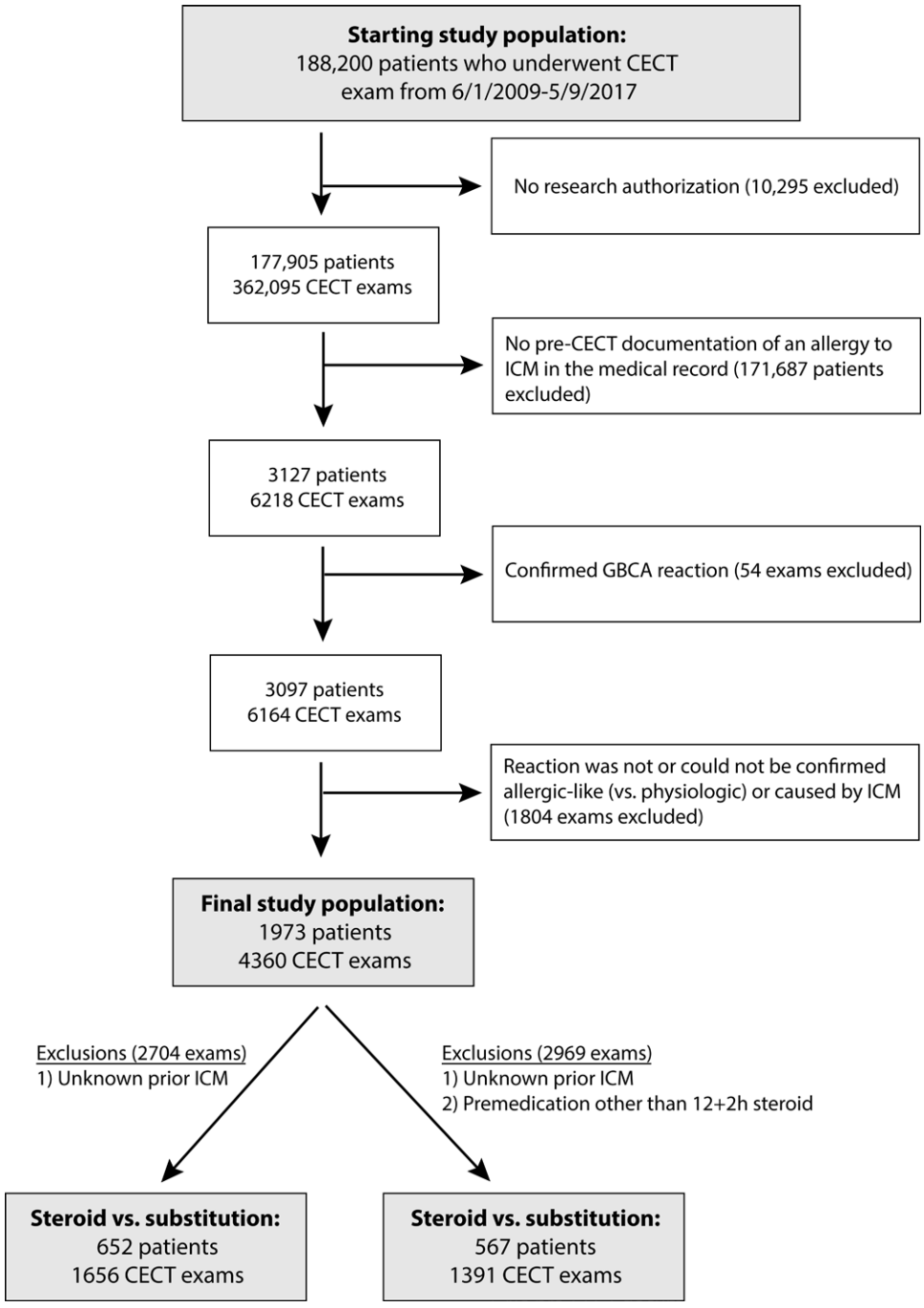

Figure 1: Flowchart of patient study. CECT = contrast-enhanced CT, GBCA = gadolinium-based contrast agent, ICM = iodinated contrast material.

The primary outcome was binary (ie, yes or no for repeat allergic-like reaction) and may have been represented multiple times per patient, corresponding to the number of scans obtained in each patient. The primary exposure was prophylactic treatment, with four potential levels being defined by the crossing of two factors as follows: *(a)* same ICM with steroid pretreatment (reference), *(b)* same ICM with no steroid pretreatment, *(c)* different ICM with steroid pretreatment, and *(d)* different ICM with no steroid pretreatment. Examinations for which the previous reaction to ICM was not documented (n = 2704) were excluded from these analyses.

To estimate the unadjusted treatment effects, we initially fit a logistic generalized estimating equation for a repeated binary outcome and assumed an exchangeable correlation structure within each patient. To account for potential confounders, we adjusted for the following variables: age, initial

Table 1: Study Population Characteristics

Characteristic	Value
No. of patients	1973
No. of CT examinations	4360
Demographic information	
Age (y)*	62 (51–72)
No. of women	1141 (58)
Previous reaction	
ICM used	
Iohexol	468 (24)
Iodixanol	24 (1
Iopromide	18 (1)
Iopamidol	10 (0)
Iothalamate meglumine	1 (0)
Ioversol	1 (0)
HOCM	105 (5)
Not provided	1348 (68)
Reaction severity	
Mild	1487 (75)
Moderate	407 (21)
Severe	79 ()
Symptoms†	
Hives, itching, or rash	1459 (74)
Nasal or eye symptoms	130 (7)
Throat symptoms	62 (3)
Wheezing or shortness of breath	207 (10)
Diffuse erythema	60 (3)
Angioedema	148 (8)
Anaphylaxis	68 (3)

Note.—Except where indicated, data are numbers of patients, with percentages in parentheses. HOCM = high-osmolarity contrast material, ICM = iodinated contrast material.

* Numbers are medians, with interquartile ranges in parentheses.

† Some patients had multiple symptoms, so numbers add up to more than 1973.

reaction severity, sex, history of non-ICM allergy and asthma, log (body mass index), CT type, and CT location. Repeat scans in this cohort presented a complication whereby previous treatment selection was highly correlated with the subsequent treatment, invalidating assumptions of exchangeability. To address this, we fit logistic regression models of only the first scan per patient using inverse probability of treatment weighting with a multinomial propensity score for the four interventions to determine how the effects differed. Additional details are provided in Appendix E1 (online).

Results

Study Population and Previous Reactions

We identified a total of 1973 patients with a previous allergic-like reaction to an ICM who underwent a total of 4360 subsequent ICM-enhanced CT examinations at our institution (Fig 1, Table 1). The specific ICM that caused the previous reaction could not be determined in 1348 of the 1973 patients (68%). Hives, itching, or rash were the most common symptoms in previous reactions (1459 of 1973 patients [74%]), which were followed in prevalence by wheezing and shortness of breath (207 of 1973 patients [11%]) and nasal or eye symptoms (130 of 1973 patients [7%]). Most previous reactions were classified as mild (1487 of 1973 patients [75%]). Sixty-eight of the 1973 patients (3%) reported severe previous reactions with symptoms including anaphylaxis.

Prophylactic Treatments for Subsequent CT Examinations

Patients had an order for a 12- and 2-hour steroid premedication regimen for almost half of subsequent CT examinations (Table 2) (1822 of 4360 examinations [42%]). The likelihood of premedication administration increased with the previous reaction severity (Table E1 [online]) (mild reaction: 1202 of 3344 examinations [36%]; moderate reaction: 503 of 865 examinations [58%]; severe reaction: 117 of 151 examinations [77%]). The likelihood of premedication administration was also dependent on specific reaction symptoms during previous examinations, with 1278 of 3250 subsequent examinations (39%) using premedication for patients with previous hives and itching, 108 of 324 of subsequent examinations (33%) using premedication for patients with previous nose or eye symptoms, 59 of 129 subsequent examinations (46%) using premedication for patients with previous throat symptoms, 71 of 124 of subsequent examinations (57%) using premedication for patients with previous diffuse erythema, 241 of 439 subsequent examinations (55%) using premedication for patients with previous dyspnea or wheezing, 198 of 303 of subsequent examinations (65%) using premedication for patients with previous angioedema, and 102 of 132 subsequent examinations (77%) using premedication for patients with previous anaphylaxis.

In 488 of 1656 examinations (29%) in which the previous ICM was known, an ICM that differed from the ICM that caused the previous reaction was used in the most recent examination. The likelihood of ICM substitution increased with the previous reaction severity (mild reaction: 310 of 1278 examinations [24%]; moderate reaction: 156 of 348 examinations, [44%]; severe reaction: 22 of 30 examinations [73%]) and was similar between patients who were premedicated with steroids (166 of 589 patients [28%]) and patients who were not premedicated (322 of 1067 patients [30%]). The likelihood of ICM substitution was also dependent on specific reaction symptoms during previous examinations, with 308 of 488 subsequent examinations (63%) using a different ICM for patients with previous hives and itching, 48 of 222 subsequent examinations (22%) using a different ICM for patients with previous nose or eye symptoms, 10 of 80 subsequent examinations (13%) using a different ICM for patients with previous throat symptoms, 11 of 37 of subsequent examinations (30%) using a different ICM for patients with previous diffuse erythema, 93 of 198 subsequent examinations using a different ICM for patients with previous dyspnea or wheezing (47%), 49 of 109 subsequent examinations (45%) using a different ICM for patients with previous angioedema, and 22 of 24 subsequent examinations (92%) using a different ICM for patients with previous anaphylaxis.

Table 2: Subsequent CT Examination and Repeat Reaction Details

Parameter	Value
No. of CT examinations	4360
ICM used	
Iohexol	4071 (93)
Iodixanol	158 (4)
Iopromide	131 (3)
Used ICM different from ICM used at previous examination	
Yes	488 (11)
No	1168 (27)
Unknown previous ICM	2704 (62)
Steroid premedication 12 hours and 2 hours before	1822 (42)
Reaction occurred	280 (6)
Severity of reaction	
Mild	242 (86)
Moderate	37 (13)
Severe	1 (0)
Symptoms*	
Hives, itching, or rash	211 (75)
Nasal or eye symptoms	37 (1)
Throat symptoms	32 (11)
Diffuse erythema	4 (1)
Wheezing or shortness of breath	17 (6)
Angioedema	6 (2)
Anaphylaxis	1 (0)
Severity of repeat vs previous reaction	
Same	243 (87)
Better	18 (6)
Worse	19 (7)

Note.—Except where indicated, data are numbers of patients, with percentages in parentheses. ICM = iodinated contrast material.

* Some patients had multiple symptoms, so numbers add up to more than 280 and percentages add up to more than 100%.

The percentage of patients without an order for steroid premedication increased over the study time frame, whereas the percentage of patients who received a different ICM did not substantially change (same ICM with no premedication: 33% [25 of 75 examinations] in 2009 to 51% [54 of 106 examinations] in 2017; different ICM with no premedication: 13% [10 of 75 examinations] in 2009 to 22% [23 of 106 examinations] in 2017; same ICM with premedication: 44% [33 of 75 examinations] in 2009 to 22% [23 of 106 examinations] in 2017; different ICM with premedication: 9.3% [seven of 75 examinations] in 2009 to 5.7% [six of 106 examinations] in 2017) (Fig 2). Institutional use of iohexol, iodixanol, and iopromide did not change over the study time frame.

Acute Reactions during Subsequent CT Examinations

A total of 280 allergic-like reactions in 4360 examinations (6%) in 224 of the 1973 patients (11%) occurred during subsequent CT examinations in this cohort (Table 2; Table E2 [online]). Repeat reaction rates decreased with the previous reaction severity (mild reaction: 244 of 3344 examinations [7%]; moderate reaction: 34 of 865 [4%]; severe reaction: two of 151 [1%]). Most of these subsequent reactions were mild (242 of 4360 examinations [6%]), with 37 moderate reactions (1% of 4360 examinations) and one severe reaction (0.02% of 4360 examinations) occurring. When compared with patients' previous reactions, the subsequent reactions most often had the same severity (ie, both previous and subsequent reactions were mild) (243 of 280 reactions [87%]), with 18 of the 280 subsequent reactions (6%) that were less severe and 19 of the 280 subsequent reactions (7%) that were more severe compared with the previous reaction occurring. Reaction symptoms were most typically hives, itching, or rash (n = 211), with a smaller subset of reactions involving nasal or eye symptoms (n = 37) or throat symptoms (n = 32). The patient who had a repeat reaction that was severe had reported a previous mild reaction of rash following iodixanol exposure. The patient was premedicated with methylprednisolone and diphenhydramine 2 hours before undergoing CT, received a different ICM (iohexol), and subsequently had an anaphylactic reaction that resolved after emergency department treatment. Among the two patients who had previous severe reactions to ICM and a repeat reaction, one had a mild reaction consisting of itching (resolved without treatment) and the other had a moderate reaction consisting of laryngeal edema (resolved after emergency department treatment).

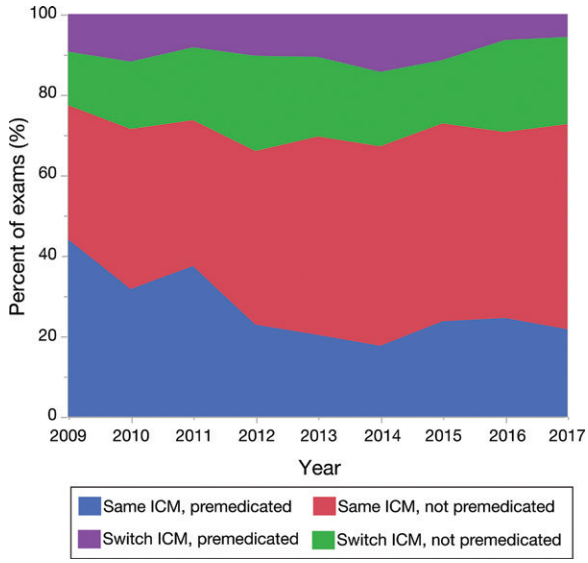

Figure 2: Graph shows percentage of high-risk patients receiving the four prophylactic treatments over time. ICM = iodinated contrast material.

Effect of Prophylactic Treatment on Repeat Allergic-like Reaction Rate

In an unadjusted model, patients who received a different ICM with or without an order for steroid premedication had a significantly lower rate of repeat allergic-like reactions than patients who had an order for steroid premedication and the same ICM (same ICM and steroid premedication: 80 of 423 examinations [19%]; different ICM and no steroid premedication: 10 of 322 examinations [3%], odds ratio [OR], 0.14 [95% CI: 0.07, 0.27]; $P < .001$; different ICM and steroid

Table 3: Effect of Prophylactic Treatment on Repeat Allergic-like Reaction Rate (Other Premedications Included)

Parameter	Reaction Rate	Odds Ratio*	*P* Value
Unadjusted model			
Same ICM, steroid premedication (reference)	80/423 (19)	…	…
Same ICM, no steroid premedication	111/745 (15)	0.75 (0.55, 1.03)	.08
Different ICM, no steroid premedication	10/322 (3)	0.14 (0.07, 0.27)	<.001
Different ICM, steroid premedication	5/166 (3)	0.13 (0.05, 0.34)	<.001
Adjusted model (all CT scans)†			
Same ICM, steroid premedication (reference)	80/423 (19)	…	…
Same ICM, no steroid premedication	111/745 (15)	0.73 (0.48, 1.09)	0.12
Different ICM, no steroid premedication	10/322 (3)	0.14 (0.06, 0.33)	<.001
Different ICM, steroid premedication	5/166 (3)	0.12 (0.04, 0.36)	<.001
Adjusted model (first CT scan only)‡			
Same ICM, steroid premedication (reference)	44/172 (26)	…	…
Same ICM, no steroid premedication	73/298 (25)	1.00 (0.64, 1.57)	.99
Different ICM, no steroid premedication	7/117 (6)	0.26 (0.11, 0.64)	.003
Different ICM, steroid premedication	2/65 (3)	0.16 (0.03, 0.72)	.017

Note.—Except where indicated, data are numbers of examinations, with percentages in parentheses. Patients who had an order for other or additional treatments besides methylprednisolone at 12 hours and 2 hours before CT were included in the analysis (see Materials and Methods). ICM = iodinated contrast material.

* Numbers in parentheses are 95% CIs.

† The adjusted model incorporated age, sex, log (body mass index), CT type and location, history of allergy and asthma, and initial reaction severity. Previous treatment selection for the preceding scan was also incorporated for the adjusted model (all CT scans).

‡ The first CT scan analysis used inverse probability of treatment weighting with a multinomial propensity score for the four interventions.

Table 4: Effect of Prophylactic Treatment on Repeat Allergic-like Reaction Rate (12-hour and 2-hour Methylprednisolone Premedication Only)

Parameter	Reaction Rate	Odds Ratio*	*P* Value
Unadjusted model			
Same ICM, steroid premedication (reference)	71/371 (19)	…	…
Same ICM, no steroid premedication	84/591 (14)	0.70 (0.49, 0.99)	.0438
Different ICM, no steroid premedication	6/276 (2)	0.09 (0.04, 0.22)	<.001
Different ICM, steroid premedication	5/153 (3)	0.14 (0.06, 0.36)	<.001
Adjusted model (all CT scans)†			
Same ICM, steroid premedication (reference)	71/371 (19)	…	…
Same ICM, no steroid premedication	84/591 (14)	0.69 (0.44, 1.07)	.10
Different ICM, no steroid premedication	6/276 (2)	0.10 (0.03, 0.31)	<.001
Different ICM, steroid premedication	5/153 (3)	0.14 (0.04, 0.44)	<.001
Adjusted model (first CT scan only)‡			
Same ICM, steroid premedication (reference)	44/164 (27)	…	…
Same ICM, no steroid premedication	60/243 (25)	0.92 (0.57, 1.47)	.92
Different ICM, no steroid premedication	4/97 (4)	0.19 (0.06, 0.55)	.003
Different ICM, steroid premedication	2/63 (3)	0.12 (0.03, 0.53)	.005

Note.— Except where indicated, data are numbers of examinations, with percentages in parentheses. Patients who had an order for other or additional treatments besides methylprednisolone at 12 hours and 2 hours before CT were excluded from the analysis (see Materials and Methods). ICM = iodinated contrast material.

* Numbers in parentheses are 95% CIs.

† Adjusted model incorporated age, sex, log (body mass index), CT type and location, history of allergy and asthma, and initial reaction severity. Previous treatment selection for the preceding scan was also incorporated for the adjusted model (all CT scans).

‡ The first CT scan analysis used inverse probability of treatment weighting with a multinomial propensity score for the four interventions.

premedication: five of 166 patients [3%]; OR, 0.13 [95% CI: 0.05, 0.34]; $P < .001$) (Table 3). This significant difference persisted after adjusting for patient age, sex, body mass index, history of allergies and asthma, and initial reaction severity and the CT type and location (different ICM and no steroid premedication: OR, 0.14 [95% CI: 0.06, 0.33); $P < .001$; different ICM and steroid premedication: OR, 0.12 [95% CI: 0.04, 0.36; $P < .001$).

We observed repeated outcome confounding of the treatment selection in our cohort; once a treatment selection was made for a patient, it appeared to be highly correlated with subsequent treatment selection (Table E3 [online]). To account for this, we performed a sensitivity analysis examining only the first CT scan per patient (Table E4 [online]). Patients who received a different ICM still had a significantly lower rate of repeat reactions than patients who received the same ICM and had an order for steroids (same ICM and steroid premedication: 44 of 172 patients [26%]; different ICM and no steroid premedication: seven of 117 patients [6%]; OR, 0.26 [95% CI: 0.11, 0.64]; $P = .003$; different ICM and steroid premedication: two of 65 patients [3%]; OR, 0.16 [95% CI: 0.03, 0.72]; $P = .017$) (Table 3). The risk of a repeat reaction in patients who received the same ICM did not significantly differ by whether they had an order for steroid premedication (same ICM and no premedication: 73 of 298 patients [25%]; OR, 1.00 [95% CI: 0.64, 1.57]; $P = .99$).

Similar results were observed after excluding all examinations for which patients had an order for other or additional premedication besides 12- and 2-hour pre-CT methylprednisolone (Table 4; Appendix E1 [online]).

Discussion

In our cohort, repeat allergic-like reactions occurred in 224 of 1973 patients (11%) who were considered high risk because of a documented previous allergic-like reaction to iodinated contrast material (ICM). Only 19 of 280 of subsequent reactions (7%) were worse in severity than the previous reaction, and only one severe repeat reaction was observed. Patients who received a different ICM than the one that caused their previous allergic-like reaction had a significantly lower rate of repeat allergic-like reactions than did patients who had an order for steroid premedication and the same ICM (different ICM and no steroid premedication: 10 of 322 examinations [3%] vs same ICM and steroid premedication: 80 of 423 examinations [19%]; odds ratio [OR], 0.14 [95% CI: 0.06, 0.33]; $P < .001$). Furthermore, there was no difference in the rate of repeat reactions between patients who were and were not premedicated with steroids who received the same ICM (steroid premedication: 44 of 172 patients (26%) vs no premedication: 73 of 298 patients [25%]; OR, 1.00 [95% CI: 0.64, 1.57]; $P = .99$). Cumulatively, these findings call into question the efficacy of steroid premedication consisting of oral methylprednisolone at 12 and 2 hours before ICM exposure for preventing repeat allergic-like reactions in these patients.

Previous studies by Abe et al (14) and Park et al (15) also found that using an ICM substitution without premedication was more effective than using premedication and the same contrast material. However, there were several limitations with these studies. First, these results may have been affected by selection bias, by which patients viewed as being at a higher risk of experiencing a repeat reaction may have been more likely to receive premedication than patients viewed as being at a lower risk. Second, premedicated patients in these studies included both patients who received 12- and 2-hour pre-CT steroid protocols, typically considered the standard for prophylactic treatment, and patients who received 1- to 2-hour pre-CT steroid protocols or antihistamine-only protocols that are considered less effective (17). Third, patients with previous physiologic reactions (ie, nausea and/or vomiting, flushing) were included in these studies, potentially confounding the results. A history of physiologic reactions does not increase the risk of a repeat allergic-like reaction, and steroid pretreatment is not recommended to prevent physiologic reactions (2).

Our study expanded on these previous studies in several ways. First, our study minimized potential selection bias by incorporating variables, including the initial reaction severity; the patient age, sex, and history of allergies and asthma; and the CT type and location in our adjusted generalized estimating equation model. Second, only patients with a confirmed previous allergic-like reaction to ICM were included in the study, and only allergic-like reactions were included as outcomes. Third, only patients who had an order for 12- and 2-hour pre-CT methylprednisolone were included in the premedicated group. Finally, our study examined a larger number of patients.

Current practice guidelines and recommendations have questioned the efficacy of steroid premedication in high-risk patients (2,3,18), and various studies have documented the risks associated with steroids, including the potentially increased risk of infection and transient leukocytosis and hyperglycemia (18–22), longer hospitalizations and higher rates of hospital-acquired infections (23), and the potential for a delay in diagnosis because of the multihour premedication protocol. The European Society of Urogenital Radiology states that "Clinical evidence of the effectiveness of premedication [for patients at increased risk of reaction] is limited" (3). In 2020, the Joint Task Force on Practice Parameters of the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology concluded that "Evidence is lacking to support the role of…glucocorticoid routine premed in patients receiving low-osmolar or iso-osmolar ICMs to prevent recurrent radiocontrast media anaphylaxis" (24). Both the American College of Radiology and the European Society of Urogenital Radiology guidelines note that substituting contrast materials may help to reduce the risk of repeat reactions in high-risk patients but acknowledge that current data are limited (2,3). Our findings provide additional evidence to strengthen these guidelines and recommendations.

We observed that the percentage of high-risk patients who were premedicated decreased over the study time frame (54% [57 of 105 patients] to 35% [108 of 311 patients]). This decrease was primarily driven by relaxed steroid premedication guidelines, particularly in patients with mild previous reactions. A previous study at our institution (18) found that most patients with a history of hives who were not premedicated did not have a repeat reaction following ICM exposure and that any repeat reactions that occurred were similar in severity to the previous reaction. These findings prompted a departmental practice change in 2012 that removed the premedication requirement for these patients. Our current study illustrates this practice change; steroid premedication decreased in patients with a previous reaction of hives from 50% to 55% in 2009–2011 to 30%–35% in

2012–2017, whereas steroid premedication remained relatively unchanged in patients with previous reactions with other symptoms (45%–50% from 2009 to 2017).

We could not retrospectively determine the specific ICM that caused the previous reaction in the majority of examinations (1348 of 1973 patients [68%]) in our cohort. Deng et al (25) examined the records of more than 36 000 high-risk patients and reported that only 12% of cases documented the specific ICM. These findings illustrate the major challenge in effectively implementing ICM substitution in the clinic. Standardized prospective collection of these data, along with improved and accessible medical record systems, will be critical for ICM substitution to even have a chance of replacing steroid premedication in these high-risk patients (26).

Our study had several other limitations. First, we relied on medical record documentation and patient recollection to determine which ICM caused the previous reaction and the symptoms and severity of the previous reactions, which may have introduced error into the study. Second, we are unable to assess potential patient noncompliance with the steroid premedication protocol. Third, some of the previous or current acute reactions in this study may have been attributable to non-ICM causes. Finally, although we attempted to adjust for clinical differences among treatment groups, our results may have still been affected by selection bias. Additional retrospective studies and prospective randomized controlled trials are needed to further assess the efficacy of ICM substitution for preventing repeat allergic-like reactions.

In our cohort of high-risk patients, substituting iodinated contrast materials (ICMs) without using steroid premedication was more effective for preventing repeat allergic-like reactions than using 12- and 2-hour pre-CT steroid premedication and using the same ICM that caused the previous reaction.

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