Adverse reactions to contrast media (CM) can be categorized as acute or delayed depending on the timing of the reaction: Acute reactions are defined as those that occur within 1 hour, and delayed reactions are those that occur beyond the 1st hour and mostly within 1 week after CM exposure (5). While acute reactions are either allergic-like HSRs or chemotoxic responses, delayed reactions are thought to be T cell mediated, although the exact pathophysiology remains obscure (6). Because of the rarity of delayed HSRs to GBCAs, current literature mostly focuses on acute HSRs to GBCAs, and studies on delayed HSRs are scarce (1,3,7). A comprehensive analysis of the incidence and risk factors of delayed HSRs is needed to better understand the mechanism behind delayed HSRs to GBCAs.

With the growing incidence of HSRs to GBCAs, identifying possible risk factors and high-risk populations for HSRs is necessary to ensure safer GBCA use. In general, multiple exposures to the same CM in patients with a history of acute HSRs to GBCAs is increasing. Research on the incidence and risk factors for HSRs to GBCAs is needed for their safe use.

**Background:** With the widespread use of gadolinium-based contrast agents (GBCAs), the incidence of allergic-like hypersensitivity reactions (HSRs) to GBCAs is increasing. Research on the incidence and risk factors for HSRs to GBCAs is needed for their safe use.

**Purpose:** To determine the incidence of acute and delayed reactions to GBCAs and to discuss the risk factors and strategies for the prevention of HSRs to GBCAs.

**Materials and Methods:** All cases of HSRs to contrast media that occurred at the Seoul National University Hospital from July 1, 2012, to June 30, 2020, were assessed. Information including age, sex, GBCA type, onset, and severity of HSRs was retrospectively analyzed.

**Results:** Among the 331,070 cases of GBCA exposure in 154,539 patients, 1,304 cases of HSRs (0.4%) were reported. Acute HSRs accounted for 1,178 cases (0.4%), while 126 cases (0.04%) were delayed HSRs. While both premedication (odds ratio [OR] = 0.7, P = .041) and changing the type of GBCA (OR = 0.2, P < .001) showed preventative effects in patients with a history of acute HSRs, only premedication (OR = 0.2, P = .016) significantly reduced the incidence of HSRs in patients with a history of delayed reactions. The risk of an HSR to GBCA was higher in those with a history of an HSR to iodinated contrast media (OR = 4.6, P < .001).

**Conclusion:** The rate of hypersensitivity reactions (HSRs) to gadolinium-based contrast agents (GBCAs) was 0.4%. The absence of premedication, repeated exposures to the culprit GBCA, and a history of HSRs to iodinated contrast media and GBCAs were risk factors for HSRs to GBCAs.

© RSNA, 2022

Online supplemental material is available for this article.
Hypersensitivity Reactions to Gadolinium-based Contrast Agents

**Materials and Methods**

**Study Design, Setting, and Participants**

The study was approved by the institutional review board of the Seoul National University Hospital (approval no. 1911–080–1078). All cases that used GBCAs for MRI and ICM for CT scans at Seoul National University Hospital between July 1, 2012, and June 30, 2020, were reviewed using the electronic medical record–based Contrast Safety Monitoring and Management (CoSM2oS) database.

The reaction type was classified as an acute HSR if it occurred within 1 hour after CM administration and as a delayed HSR if the reaction occurred beyond 1 hour (11). All patients were kept under nurse surveillance for HSRs for 1 hour following CM injection. Symptoms and signs indicating an acute HSR to CM were monitored and recorded in the CoSM2oS database. To determine the incidence rate for delayed HSRs, we educated patients on the symptoms and signs associated with delayed HSRs and instructed them to contact the hospital via telephone if they experienced such symptoms upon discharge. Information about the reaction, including symptom onset and severity, was collected and recorded (12). Data including age, sex, past medical history, history of previous exposures to CM, history of HSRs to CM, types of CM used, premedication, onset and severity of reactions, and treatment of HSRs were collected retrospectively from the CoSM2oS database.

**Symptoms and Severity of HSRs**

We classified HSRs based on the guidelines outlined in the American College of Radiology Manual on Contrast Media (Table E1 [online]). The manifestations of allergic-like HSRs to GBCAs are similar to those of allergic-like HSRs to ICM, and these reactions are further categorized according to severity as mild, moderate, and severe (8). Mild allergic-like HSRs to GBCAs were defined as limited urticaria or pruritus, cutaneous edema, throat discomfort, nasal congestion, sneezing, and rhinorrhea. Moderate reactions included diffuse urticaria or pruritus, diffuse erythema, facial edema without dyspnea, hoarseness without dyspnea, mild wheezing, and bronchospasms with mild or no hypoxia. Severe reactions were life-threatening symptoms, and these included diffuse edema with dyspnea, diffuse erythema with hypotension, laryngeal edema with stridor or hypoxia, wheezing or bronchospasms with hypoxia, symptomatic arrhythmias, and anaphylactic shock (Table E2 [online]) (8). Patients who experienced physiologic reactions including nausea, flushing, headache, and vasovagal reactions were excluded from the study.

**Premedication Regimens**

When an examination using CM is ordered for a patient with a history of HSRs to CM, CoSM2oS automatically recommends a premedication regimen in accordance with the severity of the previous reaction. The recommended premedication regimens were 4 mg of intravenous chlorpheniramine 30 minutes before CM administration for mild reactions and 40 mg of intravenous methylprednisolone with 4 mg of intravenous chlorpheniramine 1 hour before CM administration for moderate reactions. Patients with a history of severe reactions received a 40-mg dose of intravenous methylprednisolone 4 hours before CM administration and received an additional 40-mg dose of intravenous methylprednisolone with 4 mg of intravenous chlorpheniramine 1 hour before CM administration. The same premedication regimen was used for both GBCAs and ICM (13,14).

**Key Results**

- The recurrence rate for hypersensitivity reactions (HSRs) to gadolinium-based contrast agents (GBCAs) was highest (31% [37 of 118]) in patients who neither received premedication nor switched to a different GBCA.
- Patients who received premedication and switched to a different GBCA showed the lowest rate of recurrence at 5% (21 of 441); in the remainder of the patients who either received premedication or switched to a different GBCA, recurrence rates were 19% (149 of 786) and 6% (six of 100), respectively.
- The risk of HSRs to GBCAs was highest in those with a history of HSRs to iodinated contrast media (odds ratio = 4.6, \( P < .001 \)).

Despite being aware that patients with a history of allergy are at risk for developing adverse reactions to GBCAs, no standardized practices for the prevention of HSRs to GBCA exist. A previous study of 185 patients with mild HSRs to GBCAs demonstrated a higher rate of reactions associated with ionic or cyclic GBCAs (4). Despite being aware that patients with a history of allergy are at risk for developing adverse reactions to GBCAs, no standardized practices for the prevention of HSRs to GBCA exist. A previous study of 185 patients with mild HSRs to GBCAs demonstrated a higher rate of reactions associated with ionic or cyclic GBCAs (4).
Types of GBCA Used
Seven different types of GBCA were used, including gadobutrol (Gadovist, Bayer Schering), gadoterate meglumine (Dotarem, Guerbet), gad oxetate disodium (Primovist, Bayer Schering), gadoteridol (Prohance, Bracco Imaging), gadopentetate dimeglumine (Magnevist, Bayer Schering), gadobenate dimeglumine (Multihance, Bracco Imaging), and gadodiamide (Omniscan, GE Healthcare). The GBCAs were administered intravenously at the standard recommended dosage. No patient received additional doses beyond the recommended dosage. As there are not set protocols that define when a certain type of GBCA should be used, GBCA selection was left to the discretion of the department of radiology.

Retrospective Assessment of Recurrent Reactions
Patients with repeated exposure to GBCAs or ICM were assessed for HSRs each time, and each event was counted as one case. Information regarding the use of premedication and whether certain GBCAs were switched on subsequent exposure was gathered. In addition, the incidence rate of ICM HSRs was obtained by reviewing the data from the CoSMoS database. Retrospective analyses were performed to compare the incidence of HSRs to GBCA in patients with a history of HSRs to ICM to those without such history.

Statistical Analyses
The incidence of HSRs to CM during the study period was calculated by dividing the number of HSR cases by the total number of cases that received either GBCA or ICM. The prevalence was calculated by dividing the number of patients who experienced HSRs to CM by the total number of patients who underwent contrast-enhanced imaging tests during the study period. The $\chi^2$ test was used to compare the incidence rates between groups. Multivariate logistic regression analyses were performed for re-exposure cases where HSR recurrence was set as the dependent variable and the following were included as covariates: age, sex, previous exposure to GBCAs, and previous history of HSRs to GBCAs. The odds ratios (ORs) for re-exposure cases were obtained through adjusted logistic regression analyses. Generalized estimating equations were used to adjust for clustered cases of

Venn diagram shows hypersensitivity reactions (HSRs) to gadolinium-based contrast agents (GBCAs) and iodinated contrast media (ICM). (A) Number of patients exposed to ICM without HSRs. (B) Number of patients exposed to both ICM and GBCA without HSRs. (C) Number of patients exposed to GBCA without HSRs. (D) Number of patients exposed not to GBCA but to ICM with HSRs. (E) Number of patients exposed to both ICM and GBCA with HSRs to ICM only. (F) Number of patients exposed to both ICM and GBCA with HSRs to both ICM and GBCA. (G) Number of patients exposed to both ICM and GBCA with HSRs to GBCA only. (H) Number of patients exposed not to ICM but to GBCA with HSRs.

Table 1: Incidence of Hypersensitivity Reactions to Gadolinium-based Contrast Agents

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall</th>
<th>Male Patients</th>
<th>Female Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GBCA Use</td>
<td>HSR</td>
<td>GBCA Use</td>
</tr>
<tr>
<td>No. of cases</td>
<td>331 070</td>
<td>1304 (0.4)</td>
<td>153 841</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (y)*</td>
<td>54 ± 21</td>
<td>51 ± 16</td>
<td>55 ± 22</td>
</tr>
<tr>
<td>Median (y)†</td>
<td>59 (43–70)</td>
<td>54 (41–63)</td>
<td>61 (41–72)</td>
</tr>
<tr>
<td>&lt;10 years</td>
<td>10 779</td>
<td>16 (0.2)</td>
<td>5930</td>
</tr>
<tr>
<td>10–19 years</td>
<td>20 518</td>
<td>46 (0.2)</td>
<td>11 083</td>
</tr>
<tr>
<td>20–29 years</td>
<td>19 749</td>
<td>90 (0.5)</td>
<td>10 632</td>
</tr>
<tr>
<td>30–39 years</td>
<td>21 228</td>
<td>149 (0.7)</td>
<td>8836</td>
</tr>
<tr>
<td>40–49 years</td>
<td>36 956</td>
<td>245 (0.7)</td>
<td>13 065</td>
</tr>
<tr>
<td>50–59 years</td>
<td>59 993</td>
<td>322 (0.5)</td>
<td>21 775</td>
</tr>
<tr>
<td>60–69 years</td>
<td>78 654</td>
<td>305 (0.4)</td>
<td>36 601</td>
</tr>
<tr>
<td>70–79 years</td>
<td>58 192</td>
<td>107 (0.2)</td>
<td>31 375</td>
</tr>
<tr>
<td>80–89 years</td>
<td>22 921</td>
<td>23 (0.1)</td>
<td>12 819</td>
</tr>
<tr>
<td>≥90 years</td>
<td>2080</td>
<td>1 (0.05)</td>
<td>1105</td>
</tr>
</tbody>
</table>

Note.—Unless otherwise indicated, data in parentheses are percentages. GBCA = gadolinium-based contrast agent, HSR = hypersensitivity reaction.

* Data are mean ± standard deviation.
† Data are the median, and data in parentheses are the interquartile range.
multiple re-exposures in one patient. \( P < .05 \) indicated a significant difference for all tests. All statistical analyses were performed using SAS software (version 9.4; SAS Institute).

**Results**

**Baseline Characteristics**

Among the 331,070 MRI examinations with GBCAs performed in 154,539 patients during the study period, 1,304 HSRs (0.4%) were reported in 1,104 patients (0.7%) (Figure). During the same study period, a total of 1,202,207 CT scans using ICM were performed in 261,426 patients, and 7,541 of ICM-related HSRs (0.6%) were reported in 6,910 patients (3%). The incidence of HSRs to GBCAs was lower than that to ICM (OR = 0.6; 95% CI: 0.6, 0.7; \( P < .001 \)).

The median age of patients with HSRs to GBCAs was 54 years (interquartile range, 41–63 years). The incidence of HSRs was higher in female patients at 0.5% compared with male patients at 0.3% (OR = 1.5; 95% CI: 1.4, 1.7; \( P < .001 \)). In general, the incidence of HSRs to GBCAs was higher in patients aged 30–39 years and was relatively lower in patients younger than 29 years and those older than 70 years (Table 1).

**Acute HSRs to GBCA**

Acute HSRs accounted for 1,178 cases among the total of 331,070 MRI examinations with GBCAs performed during the study period, yielding an incidence rate of 0.4%. Similar to the overall results, the incidence of acute HSRs was slightly higher in female patients at 0.4% (742 of 177,229) than in male patients at 0.3% (436 of 153,841) (OR = 1.5; 95% CI: 1.3, 1.7; \( P < .001 \)). Acute HSRs to GBCA were classified according to symptom severity: 92% (1,080 of 1,178) were mild, 7% (86 of 1,178) were moderate, and 1% (12 of 1,178) were severe reactions (Table 2). A total of 2,154 symptoms were reported among the 1,178 acute HSRs. Itching and limited urticaria were the most frequently reported symptoms at 72% (847 of 1,178) and 72% (843 of 1,178), respectively. (Table E3 [online]). Severe reactions included 12 cases of anaphylaxis, with an incidence rate of 0.004% (12 of 331,070).

**Delayed HSRs to GBCA**

Delayed HSRs accounted for 126 cases among the total of 331,070 MRI examinations performed during the study period, yielding an incidence rate of 0.04% (Table 2). Female patients had higher odds of developing delayed HSRs compared to male patients at 0.05% (90 of 177,229) and 0.02% (36 of 153,841), respectively, and these odds were more pronounced in comparison with acute HSRs (OR = 2; 95% CI: 1.5, 3.2; \( P < .001 \)). Delayed HSRs were classified according to symptom severity: 75% (95 of 126) were mild and 25% (31 of 126) were moderate reactions. A total of 217 symptoms were reported, and the most frequently observed symptoms were itching at 69% (87 of 126), limited urticaria at 49% (62 of 126), and skin rash at 24% (30 of 126) (Table E3 [online]).

**Incidence of HSRs among Different Types of GBCA**

The incidence rate of acute HSRs was compared among the different types of GBCA. (Table 3)

<table>
<thead>
<tr>
<th>Contrast Agent</th>
<th>Total No. of Cases</th>
<th>No. of HSR Cases</th>
<th>No. of Mild HSR Cases</th>
<th>No. of Moderate HSR Cases</th>
<th>No. of Severe HSR Cases</th>
<th>No. of Acute HSR Cases</th>
<th>No. of Delayed HSR Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadobutrol</td>
<td>156,657</td>
<td>614 (0.4)</td>
<td>551 (0.4)</td>
<td>55 (0.04)</td>
<td>8 (0.01)</td>
<td>563 (0.4)</td>
<td>51 (0.03)</td>
</tr>
<tr>
<td>Gadoterate meglumine</td>
<td>117,006</td>
<td>374 (0.3)</td>
<td>338 (0.3)</td>
<td>36 (0.03)</td>
<td>0 (0.0)</td>
<td>316 (0.3)</td>
<td>58 (0.05)</td>
</tr>
<tr>
<td>Gadodextrate disodium</td>
<td>33,918</td>
<td>162 (0.5)</td>
<td>146 (0.4)</td>
<td>15 (0.04)</td>
<td>1 (0.003)</td>
<td>154 (0.5)</td>
<td>8 (0.02)</td>
</tr>
<tr>
<td>Gadoteridol</td>
<td>19,862</td>
<td>151 (0.8)</td>
<td>138 (0.7)</td>
<td>10 (0.05)</td>
<td>3 (0.02)</td>
<td>143 (0.7)</td>
<td>8 (0.04)</td>
</tr>
<tr>
<td>Gadobenate dimeglumine</td>
<td>3435</td>
<td>1 (0.03)</td>
<td>1 (0.03)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.03)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Gadopentetate dimeglumine</td>
<td>192</td>
<td>2 (1.0)</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
<td>1 (0.52)</td>
</tr>
<tr>
<td>Total</td>
<td>331,070</td>
<td>1304 (0.4)</td>
<td>1175 (0.4)</td>
<td>117 (0.04)</td>
<td>12 (0.004)</td>
<td>1178 (0.4)</td>
<td>126 (0.04)</td>
</tr>
</tbody>
</table>

Note.—Data in parentheses are percentages. HSR = hypersensitivity reaction.
Recurrence Rate: The Effects of Changing GBCA and Using Premedication

The total number of GBCA re-exposure cases was 1445 in 487 patients with a history of HSRs to GBCAs, and the average recurrence rate of HSRs was 15% (213 of 1445). Among the patients with a history of acute HSRs to GBCAs, 16% (206 of 1269) experienced recurrent HSRs, while only 8% (17 of 205) of patients with a history of delayed HSRs experienced recurrent reactions on subsequent exposure. The risk of recurrence was significantly higher in patients with a history of acute HSRs (OR = 2.0; 95% CI: 1.3, 3.6; P = .003).

Both the use of premedication and switching to a different GBCA were effective in preventing HSR recurrence. While the recurrence rate of HSRs was 20% (43 of 218) without premedication, this incidence was reduced to 14% (170 of 1227) with premedication (OR = 0.7; 95% CI: 0.5, 0.95; P = .02 by univariate analysis). Similarly, the recurrence rate of HSRs was significantly lower in patients who switched to a different type of GBCA on subsequent exposure. While HSRs were reported in 21% (186 of 904) of patients when the same GBCA was used, this incidence was reduced to 5% (27 of 541) when the culprit GBCA was changed to a different agent (OR = 0.2; 95% CI: 0.1, 0.3; P < .001 by univariate analysis).

We further divided the patient group into four different categories: patients who neither changed the GBCA nor received premedication, patients who used the same GBCA with premedication, patients who switched to a different GBCA without premedication, and patients who switched to a different GBCA with premedication to analyze the individual and combined effects of the two interventions. While the recurrence rate was highest at 31% (37 of 118) in patients who received neither intervention, patients who both switched to a different GBCA and received premedication showed the lowest rate of recurrence at 5% (21 of 441). In the remainder of the patients who either received premedication or switched to a different GBCA, the recurrence rates were 19% (149 of 786) and 6% (six of 100), respectively (Table 4).

Multivariate logistic regression analyses were performed to identify which measures were effective in the prevention of recurrent HSRs to GBCAs. The use of either premedication or changing the GBCA reduced the recurrence rate. Subgroup analyses according to the type of the initial HSR (ie, acute vs delayed) demonstrated that while both premedication (OR = 0.7; 95% CI: 0.3, 0.98; P = .04) and changing the GBCA (OR = 0.2; 95% CI: 0.1, 0.4; P < .001) had preventative

<table>
<thead>
<tr>
<th>Recurrence and Effect of Intervention</th>
<th>Total Re-exposure</th>
<th>Re-exposure after Acute HSR</th>
<th>Re-exposure after Delayed HSR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence rate</td>
<td>213 of 1445 (15)</td>
<td>206 of 1269 (16)</td>
<td>17 of 205 (8)</td>
</tr>
<tr>
<td>Not premedicated</td>
<td>43 of 218 (20)</td>
<td>40 of 195 (21)</td>
<td>8 of 31 (26)</td>
</tr>
<tr>
<td>Premedicated</td>
<td>170 of 1227 (14)</td>
<td>166 of 1074 (16)</td>
<td>9 of 174 (5)</td>
</tr>
<tr>
<td>GBCA unchanged</td>
<td>186 of 904 (21)</td>
<td>181 of 770 (24)</td>
<td>15 of 162 (9)</td>
</tr>
<tr>
<td>GBCA changed</td>
<td>27 of 541 (5)</td>
<td>25 of 499 (5)</td>
<td>2 of 43 (5)</td>
</tr>
<tr>
<td>Not premedicated, GBCA unchanged</td>
<td>37 of 118 (31)</td>
<td>35 of 108 (32)</td>
<td>7 of 18 (39)</td>
</tr>
<tr>
<td>Premedicated, GBCA unchanged</td>
<td>149 of 786 (19)</td>
<td>146 of 662 (22)</td>
<td>8 of 144 (6)</td>
</tr>
<tr>
<td>Not premedicated, GBCA changed</td>
<td>6 of 100 (6)</td>
<td>5 of 87 (6)</td>
<td>1 of 13 (8)</td>
</tr>
<tr>
<td>Premedicated, GBCA changed</td>
<td>21 of 441 (5)</td>
<td>20 of 412 (5)</td>
<td>1 of 30 (3)</td>
</tr>
</tbody>
</table>

Effect of intervention

- Premedication1: 0.6 (0.4, 0.9) [0.023] 0.7 (0.3, 0.98) [0.041] 0.2 (0.04, 0.6) [0.16]
- GBCA change2: 0.3 (0.2, 0.5) [<.001] 0.2 (0.1, 0.4) [<.001] 0.4 (0.07, 1.8) [1.03]
- Premedication and GBCA change3: 0.1 (0.06, 0.2) [<.001] 0.1 (0.06, 0.2) [<.001] 0.05 (0.01, 0.5) [0.10]

Note.—Unless otherwise indicated, data are numbers of cases, and data in parentheses are percentages. A total of 29 cases have both acute and delayed hypersensitivity reaction (HSR) history. GBCA = gadolinium-based contrast agent.

1 Multiple logistic regression analysis performed to adjust for age, sex, and severity of previous HSRs, and the generalized estimating equation was used to adjust for clustered cases of multiple re-exposures in one patient. Data are odds ratios, data in parentheses are 95% confidence intervals, and data in brackets are P values.
2 Cases with premedication versus cases without premedication.
3 GBCA changed cases versus GBCA unchanged cases.
4 Cases with premedication and change in GBCA versus cases without premedication and unchanged GBCA.
effects in patients with a history of acute HSRs, only pre-
medication reduced the incidence of HSRs in patients with
a history of delayed reactions (OR = 0.2; 95% CI: 0.04, 0.6;
P = .01) (Table 4).

**GBCA HSRs in Patients with a History of ICM Hypersensitivity**
The prevalence of HSRs to GBCAs was significantly higher in
patients with a history of ICM hypersensitivity at 3% (87 of
2936) compared with patients without such history at 0.7%
(489 of 73614). Similarly, the prevalence of HSRs to ICM
in patients with a history of GBCA hypersensitivity was higher at
15% (87 of 576) compared with patients without such history
at 4% (2849 of 75974). These results show that a history of
hypersensitivity to either GBCA or ICM increases the risk of
developing HSRs to the other (OR = 4.6, 95% CI: 3.6, 5.8;
P < .001) (Table 5).

**Discussion**

Compared with iodinated contrast media, gadolinium-based
contrast agents (GBCAs) are considered to be relatively safe con-
sidering the rarity of adverse reactions associated with their use
(4). However, with the widespread application of GBCAs in the
clinical setting, reports of allergic-like hypersensitivity reactions
(HSRs) to GBCAs are on the rise. Allergic-like HSRs can be
classified according to symptom severity as mild, moderate, or severe
reactions. Most reactions are mild and physiologic, and severe life-threatening reactions are
rare (8). The results of our study also showed that most HSRs
to GBCAs were mild, as severe HSRs accounted for only 0.8%
of all cases. These results were also in agreement with the find-
ings of a meta-analysis of nine studies on acute HSRs caused by
GBCAs, where 81% of the cases were classified as mild, 13% as
moderate, and 6% as severe (3). A different study investigating
the incidence of HSRs to GBCAs also found that 78.7% were
mild cases, while severe cases accounted for only 4.3% (17). The
incidence rate of anaphylactic reactions was 0.004%, and this
rate is similar to that found in previous studies (18). These find-
ings show that although extremely uncommon, severe reactions
including anaphylaxis to GBCA do occur, and we must be pre-
pared to adequately manage these events (15,19).

Compared with acute HSRs, delayed HSRs to GBCA are
relatively rare occurrences, and the existing literature regarding
delayed HSRs is scarce. One of the strengths of this study is
that patients with delayed HSRs were included in the analyses.
Most delayed HSRs manifested as cutaneous reactions, and no
severe reactions were reported among the 331070 cases. These
findings were similar to the results of a previous study where
delayed HSRs to gadobutrol most commonly presented as mild
symptoms, such as urticaria (20). The clinical similarities shared
between delayed reactions to ICM and GBCAs suggest the pos-
sibility that a common underlying mechanism exists (21): Just as
perivascular CD4+ and CD8+ T cell infiltrations are observed in
delayed HSRs to ICM, delayed HSRs to GBCAs are also con-
sidered to be T cell–mediated reactions (6).

We investigated re-exposure rates and recurrent reactions over
a relatively long study period of 8 years. A total of 213 cases of
HSRs to GBCAs observed in our study was significantly lower, at 0.4%, and these
findings are in agreement with the re-

| Table 5: Prevalence of HSR to ICM and GBCA according to a History of HSRs to One
| or the Other |
|------------------|------------------|------------------|------------------|
| Comparison       | Population       | HSR (%)          | Odds Ratio   | P Value   |
| HSR to GBCA      | 1104 of 154539   | 0.7              | 0.3 (0.25, 0.28) | <.001* |
| HSR to GBCA in ICM users | 576 of 76550   | 0.8              | 0.2 (0.17, 0.2)  | <.001† |
| Without HSR to ICM | 489 of 73614   | 0.7              | 1             | ...     |
| With HSR to ICM  | 87 of 2936      | 3                | 4.6 (3.6, 5.8)  | <.001   |
| HSR to ICM       | 6910 of 261426  | 3                | 3.8 (3.5, 4.0)  | <.001‡ |
| HSR to ICM in GBCA users | 2936 of 76550 | 4                | 5.3 (4.8, 5.8)  | <.001§ |
| Without HSR to GBCA | 2849 of 75974  | 4                | 1              | ...     |
| With HSR to GBCA | 87 of 576       | 15               | 4.6 (3.6, 5.8)  | <.001   |

Note.—Data in parentheses are 95% confidence intervals. Odds ratio was obtained with
the χ² test. GBCA = gadolinium-based contrast agent, HSR = hypersensitivity reaction,
ICM = iodinated contrast media.

* Compared with the risk of HSR to ICM.
† Compared with the risk of HSR to ICM in GBCA users.
‡ Compared with the risk of HSR to GBCA.
§ Compared with the risk of HSR to GBCA in ICM users.
yielding an average recurrence rate of 15%; this number is lower than that reported in previous studies. In a study that retrospectively analyzed the acute HSRs caused by GBCAs in 84,367 patients, the recurrence rate was reported to be as high as 30% (eight of 27) (15). In another study investigating the preventive effect of changing GBCAs in 185 patients with a history of acute HSRs to GBCAs, the recurrence rate was 19.6% (78 of 397) (10). Perhaps the longer follow-up period and larger number of re-exposure cases may explain the relatively lower recurrence rate observed in our study.

The frequency of adverse reactions to GBCAs has been reported to be eight times higher in patients with a history of GBCA hypersensitivity (8). Although results of a study conducted by Ryoo et al indicate that changing the CM to one of a different molecular structure class may reduce the chance of HSR recurrence (10), no official recommendations can be made, as there are no published large-scale randomized clinical trials to confirm the effectiveness of this approach. To identify which interventions were efficacious in reducing the likelihood of repeat reactions, we investigated both the individual and the

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Cases</th>
<th>Types of GBCA</th>
<th>Reaction Rate (%)*</th>
<th>Frequently Observed Symptoms by Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granata et al (1)</td>
<td>10,608</td>
<td>Gadobenate dimeglumine, gadobutrol, gadopentate dimeglumine, gadoxetic acid disodium</td>
<td>Overall: 0.3 (32/10,608)</td>
<td>Mild: skin rash, urticaria Moderate: bronchospasm, mild laryngeal edema, symptomatic tachycardia Severe: respiratory distress, progressive angioedema, arrhythmia</td>
</tr>
<tr>
<td>Li et al (2)</td>
<td>9,528</td>
<td>Gadodiamide, gadopentate dimeglumine, gadoteratate meglumine</td>
<td>Overall: 0.48 (45/9,528)</td>
<td>Mild: nausea and/or vomiting, rash, urticaria Moderate: dyspnea, bronchospasm Severe: anaphylactic shock</td>
</tr>
<tr>
<td>Dillman et al (3)</td>
<td>78,353</td>
<td>Gadobenate dimeglumine, gadodiamide, gadopentetate dimeglumine</td>
<td>Overall: 0.07 (54/78,353)</td>
<td>Mild: urticaria, itchy throat, rash, mild dyspnea, nasal congestion, mild periorbital and/or facial edema Moderate: dyspnea, facial angioedema, bronchospasm, bronchospasm, hypotension Severe: respiratory distress, hypoxia, laryngeal edema</td>
</tr>
<tr>
<td>Behzadi et al (4)</td>
<td>716,978</td>
<td>Gadobenate, gadobutrol, gadodilamide, gadofosveset, gadopentetate dimeglumine, gadoxetate</td>
<td>Overall: 0.14 (662/716,978)</td>
<td>Mild: urticaria, pruritus, cutaneous edema, itchy throat, nasal congestion, sneezing, conjunctivitis, rhinorrhea Moderate: diffuse urticaria, erythema, facial edema, hoarseness, wheezing Severe: hypotension, laryngeal edema with hypoxia, bronchospasm, anaphylactic shock</td>
</tr>
<tr>
<td>Jung et al (15)</td>
<td>141,623</td>
<td>Gadobenate, gadobutrol, gadodilamide, gadopentate dimeglumine, gadoxetate</td>
<td>Overall: 0.079 (112/141,623)</td>
<td>Mild: urticaria, skin rash, coughing, facial and/or orbital edema Moderate: bronchospasm, laryngeal edema, generalized erythema Severe: laryngeal edema, hypotension, arrhythmia, cardiopulmonary arrest</td>
</tr>
<tr>
<td>Sodagari et al (16)</td>
<td>147,624</td>
<td>Gadobenate dimeglumine, gadobutrol, gadofosveset trisodium, gadopentetate dimeglumine, gadoxetate disodium</td>
<td>Overall: 0.17 (254/147,624)</td>
<td>Mild: skin rash, urticaria, coughing, facial edema Moderate: bronchospasm, laryngeal edema, generalized erythema Severe: laryngeal edema, convulsions, hypotension, arrhythmia, cardiopulmonary arrest</td>
</tr>
</tbody>
</table>

*Note.—GBCA = gadolinium-based contrast agent.

* Data in parentheses were used to calculate rates.
combined effects of premedication and switching to a different type of GBCA. While the recurrence rate was highest at 31% (37 of 118) in patients who received neither intervention, patients who had premedication and switched to a different type of GBCA showed the lowest rate of recurrence at 5% (21 of 441). In patients with a history of acute HSRs, both interventions were effective; however, in patients whose initial reaction was a delayed HSR, only premedication was effective in preventing repeat reactions. These findings suggest that acute and delayed HSRs have different underlying mechanisms: The process of antigen recognition is different for immunoglobulin E-mediated reactions and T cell receptor-mediated responses (22). Further studies are needed to elucidate these processes.

This study had several limitations. First, certain results of our study conflict with results from multi-institutional samples and meta-analyses. For example, our study shows a lower rate of HSRs to gadobenate compared with gadoteridol, which conflicts with results from a previous meta-analysis conducted by Behzadi et al (4). This may be due to smaller agent-specific sample sizes compared with past analyses. A multicenter study with a larger sample size involving a spectrum of GBCAs is needed to validate the findings of our study. Second, the incidence of delayed HSRs is likely to have been underestimated, as these events were recorded on a self-reporting basis. Third, as our study included only a limited number of cases with delayed HSRs to GBCAs, we were unable to identify an effective preventive strategy for delayed reactions to GBCAs.

In conclusion, acute and delayed hypersensitivity reactions (HSRs) were observed in 0.4% and 0.04% of patients exposed to gadolinium-based contrast agents (GBCAs), respectively. In all patients undergoing MRI with GBCA exposure, a detailed history of previous HSRs should be conducted, and when necessary, appropriate prevention measures such as using premedication and switching to a different type of GBCA should be implemented.

Author contributions: Guarantors of integrity of entire study, Y.H.A., D.Y.K., S.B.P., H.R.K.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research. Y.H.A., D.Y.K., S.B.P., H.R.K.; clinical studies. S.B.P., G.Y.P., S.H.K., Y.H.C., S.Y.L., H.R.K.; statistical analysis, D.Y.K., S.B.P.; and manuscript editing, Y.H.A., D.Y.K., S.B.P.


References