



## Letter

## Hypersensitivity reactions to contrast media injections: a nested case–control study

Hypersensitivity reactions to contrast media (CM) are the third leading cause of all cutaneous drug reactions, after antibiotics and nonsteroidal anti-inflammatory drugs.<sup>1</sup> However, risk factors and the usefulness of skin tests differ from one study to another. In the present study, we examined the incidence and identified new risk factors of hypersensitivity reactions to nonionic iodinated and gadolinium CM. Moreover, we investigated the diagnostic performance of skin testing for the selection of safe alternatives.

From January 2011 through December 2012, all cases of hypersensitivity reactions after intravenous injection of nonionic iodinated contrast (iobitridol, iohexol, iomeprol) during computed tomography, angiography, urography, or paramagnetic contrast (gadoteric acid, gadoteridol, gadobutrol) for magnetic resonance examination in the department of radiology were recorded. All patients were referred to the department of allergy for an allergologic workup at least 4 weeks after the event. The total number of CM-enhanced procedures was estimated using data of contrast solutions administered. Patients reporting nonspecific symptoms, such as a feeling of warmth, dizziness, or headache, were excluded. Skin tests, including skin prick tests, intradermal tests, or patch tests, with CM were performed depending on the type of reaction induced by the CM (eMethods). Controls were matched by age ( $\pm 10$  years), sex, date and procedure, and CM used. Approval was obtained from the institutional review board at La Paz University Hospital (Madrid, Spain).

The case–control statistical method was applied to determine the risk factors. Multivariate Cox proportional hazard regression models were used to analyze the hazard of CM hypersensitivity reactions in relation to the total number of times a patient was exposed to CM. Data analysis was performed using IBM SPSS Statistics 19.0 for Windows (IBM, Armonk, New York).

Among 89 cases reported during the 2-year study and 188 controls, the incidence for CM hypersensitivity reactions was 0.12% (Poisson 95% confidence interval [CI] 0.06%–2.1%). Thirty-two cases were excluded because patients reported nonspecific symptoms. The classification and the severity of the cases are shown in eFigure 1. Patients who had CM reactions had significantly higher levels of creatinine, significantly more comorbid allergic diseases (atopy, rhinoconjunctivitis, asthma, and drug hypersensitivity), more previous exposures to CM, and more frequent co-medication with proton pump inhibitors (PPIs; eTable 1). An allergic reaction was diagnosed in 12 cases (13.5%), 3 of which were delayed reactions. Reactions were mild in 8 cases, moderate in 3 cases, and severe in 2 cases. The tolerability of an alternative (negative skin test reaction) CM or different CM was confirmed in all cases (eTable 2). Prick and intradermal tests with CM were performed in

all but 13 patients. The interval from the last reaction to the study was 1 to 3 months (eTable 3). A new significant risk factor was treatment with PPI (odds ratio 2.8, 95% CI 1.2–7.0; Table 1). In a Cox regression procedure, the hazard of hypersensitivity reaction to CM was increased per administration by 13.1 (95% CI 5.4–31.8) times according to the creatinine value, by 66.8% for allergic reactions, by 65.1% for a history of comorbid allergic conditions, and by 40.8% when a PPI was used (eFig 2).

Recent studies have reported rates of nonionic hypersensitivity reactions of 0.15% to 1.5%. This study showed a relatively low incidence rate of 0.12% (Poisson 95% CI 0.06%–2.1%). This is similar to the 0.15% reported in the largest single series to date of 298,491 patients by Hunt et al<sup>2</sup> but lower than in other large series in the literature.<sup>3</sup> The exclusion of 32 cases owing to nonspecific symptoms may account for the lower radiocontrast-related reaction rate.

Several studies have used skin testing to evaluate patients with CM hypersensitivity reactions. Kim et al<sup>4</sup> prospectively evaluated 1,048 patients with CM hypersensitivity reactions; of these, 56 had immediate reactions. There was only 1 positive immediate hypersensitivity skin test result (0.09%). The incidence of positive results differs depending on the study in question. In a European multicenter study, the percentage of positive skin test results increased from 26% to 50% in patients evaluated within 6 months after the reaction.<sup>5</sup> The interval from the reaction to skin testing has proved relevant for results. We do not believe the time factor is responsible for the small percentage of positive results in this cohort because all testing was performed at least 4 weeks and less than 3 months after reactions occurred. These discrepancies might be due to the larger percentage of patients with severe reactions compared with the present study. However, there is still room for caution on the reliability of skin prick testing for the diagnosis of hypersensitivity reactions to CM and for the choice of safe alternative CM.

Different studies have suggested that chemical structures are important for cross-reactivity,<sup>6,7</sup> with the most frequently detected associations involving iodixanol, iohexol, iomeprol, iopentol, and ioversol and specifically the association between iodixanol and its monomer iohexol. In line with our findings, other iodinated CM, such as ioxaglate, iopamidol, iopromide, and iobitridol, have been shown to have limited cross-reactivity. CM cross-reactivity was more common in delayed reactors than in immediate reactors.<sup>8</sup>

To our knowledge, this is the first time that PPIs have been described as a specific factor related to CM hypersensitivity reactions. In a previous study in hospitalized patients, we discovered that PPI treatment quadrupled the risk of a hypersensitivity reaction to a concomitant drug, with a hazard rate of 3.7% per day.<sup>9</sup> In the present study, we observed that the risk also exists for CM, with a hazard of 40.8% per administration. The mechanisms by which PPIs could cause reactions to CM are hypothetical. It has been

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**Table 1**

Logistic regression analysis of risk factors associated with hypersensitivity reactions to CM

| Risk factor                             | OR   | 95% CI     | P value |
|-----------------------------------------|------|------------|---------|
| Comorbid allergic diseases <sup>a</sup> | 3.5  | 1.8–6.7    | <.001   |
| PPI co-medication                       | 2.8  | 1.2–7.0    | .023    |
| Previous exposure to CM                 | 2.1  | 1.4–9.9    | .001    |
| Number of CM received                   | 1.5  | 1.1–1.8    | .001    |
| Creatinine                              | 0.02 | 0.004–0.07 | <.001   |

Abbreviations: CI, confidence interval; CM, contrast media; OR, odds ratio; PPIs, proton pump inhibitors.

<sup>a</sup>Comorbid allergic disease was considered the addition of atopy, rhinoconjunctivitis, asthma, and drug hypersensitivity.

proposed that neutralized gastric acid levels prevent adequate digestion of antigens in the stomach. Although antigens normally degrade into oligopeptides to enter the gastrointestinal tract, undigested antigens can induce a T-helper cell type 2 response and IgE sensitization of the immune system.<sup>10</sup> Such factors increase the risk for developing allergic sensitizations. This allergic status of the patient might be facilitating the reactions to intravenous CM.

In conclusion, the incidence of CM hypersensitivity reactions is low. Twelve cases (13.5%) were confirmed as having an allergic reaction. Current treatment with PPI was identified as a new risk factor.

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### Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2014.07.016>.

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## eMethods

### Study Design and Population

All radiologic staff members involved in CM-enhanced procedures were required to document cases of patients who developed immediate hypersensitivity reactions within 1 hour after receiving an intravenous injection of nonionic iodinated contrast in the department of radiology. Data were collected on age, sex, pre-medication for patients with a history of CM allergy, time of study, and symptoms, signs, and management of adverse reactions. The dose of CM per procedure was estimated at 15 to 150 mL depending on the protocol.

Patients with a history of CM hypersensitivity reactions were included in the study. Hypersensitivity reactions were defined as allergic or nonallergic (formerly referred to as “allergy-like”) reactions that manifest with clinical features, such as urticarial, angioedema, tachycardia, bronchospasm, hypotension, and loss of consciousness. Hypersensitivity reactions were classified further as immediate (onset  $\leq 1$  hour after CM application) or delayed (onset  $> 1$  hour after CM administration).<sup>1</sup> The severity scale of Ring and Messmer<sup>2</sup> was used to classify immediate reactions. Delayed reactions ranged from mild to severe. Mild reactions required no treatment; for moderate reactions, patients responded quickly to treatment and hospitalization was not necessary; and severe reactions were life-threatening or required hospitalization. Suspected allergy was confirmed by a positive skin test reaction. The remaining cases were diagnosed as nonallergic hypersensitivity reactions.

Skin tests, including skin prick tests, intradermal tests, or patch tests, with CM were performed according to the type of reactions induced by CM. A prick test with undiluted CM (a 100-fold dilution was used in the 2 most severe cases) and latex was followed by an intradermal test with 10-fold dilution of CM. Undiluted iomeprol, iobitridol, and iohexol also were tested. Amidotrizoate and paramagnetic agents were used only in skin prick tests. Histamine and saline were used as positive and negative controls, respectively. Skin tests were read after 15 minutes; results were considered positive if a wheal at least 3 mm in diameter (prick test) or an increase in the diameter of the initial wheal by at least 3 mm surrounded by erythema (intradermal test) was observed. Patch tests were performed with undiluted CM. Patch tests were removed and read at 48 hours with an additional reading at 96 hours and results were considered positive according to the protocol set by the European Society of Contact Dermatitis.<sup>3</sup> The basophil activation test (Baso Flow Ex; EXBIO Praha, a.s., Vestec, Czech Republic) was performed in the most severe case of an immediate hypersensitivity reaction to confirm skin test results. A lymphocyte transformation test was performed in 1 patient who had a delayed hypersensitivity reaction.

Medical records of cases and controls were analyzed retrospectively and data were gathered on prior exposure to CM (from 2007), history of allergies, the Charlson index,<sup>4</sup> the last creatinine value before examination, and co-medication. The sample size was calculated to be 266 patients (margin of error  $\pm 6\%$ , 95% CI), with a variability of 50%. The sample size for logistic regression showed that an  $\alpha$  risk of 0.05 and a  $\beta$  risk of 0.2 for a proportion of 2 controls per case of 240 subjects were needed to recognize an odds ratio greater than or equal to 1.5 as statistically significant.

### Statistical Analysis

The incidence rate was calculated by dividing the number of cases of CM hypersensitivity reactions by the estimated number CM-enhanced procedures performed during the period covered by this study. Uncertainty of the estimation was assessed by the calculation of the 2-sided Poisson 95% CI. A descriptive statistical analysis of the variables was performed. Categorical data were described proportionally and  $\chi^2$  statistics was used to test for a significant association between the CM-reaction group and these categorical exposure variables. To quantify the magnitude of the association, odds ratios and Cornfield 95% confidence limits for odds ratios were calculated. The  $\chi^2$  statistics was corrected for continuity, where appropriate; in that case, Yates-corrected  $\chi^2$  was used. A *P* value of .05 was considered statistically significant. The difference of continuous variables was assessed using the Student *t* test or nonparametric Mann-Whitney *U* test, as appropriate.

The case-control statistical method applied to determine the risk factors was multiple logistic regression modeling. The variables adjusted were age, sex, origin, creatinine, Charlson index, comorbid allergic diseases, procedures, history of hypersensitivity reactions to CM, previous exposure and number of previous exposures to CM, and co-medication. A backward stepwise model was used, with the likelihood ratio criterion of a *P* value less than .10 to retain a variable; the rate of events per variable was at least 10.

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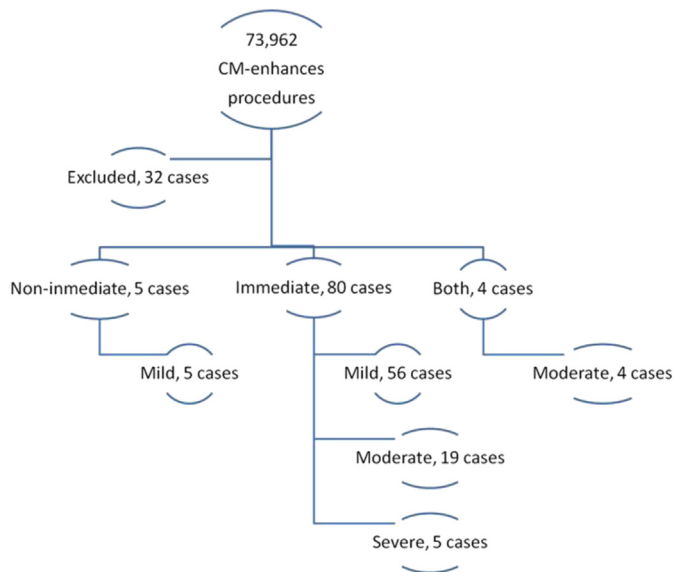


**Figure 1.** Flowchart of hypersensitivity reactions to procedures using contrast media and their severity.

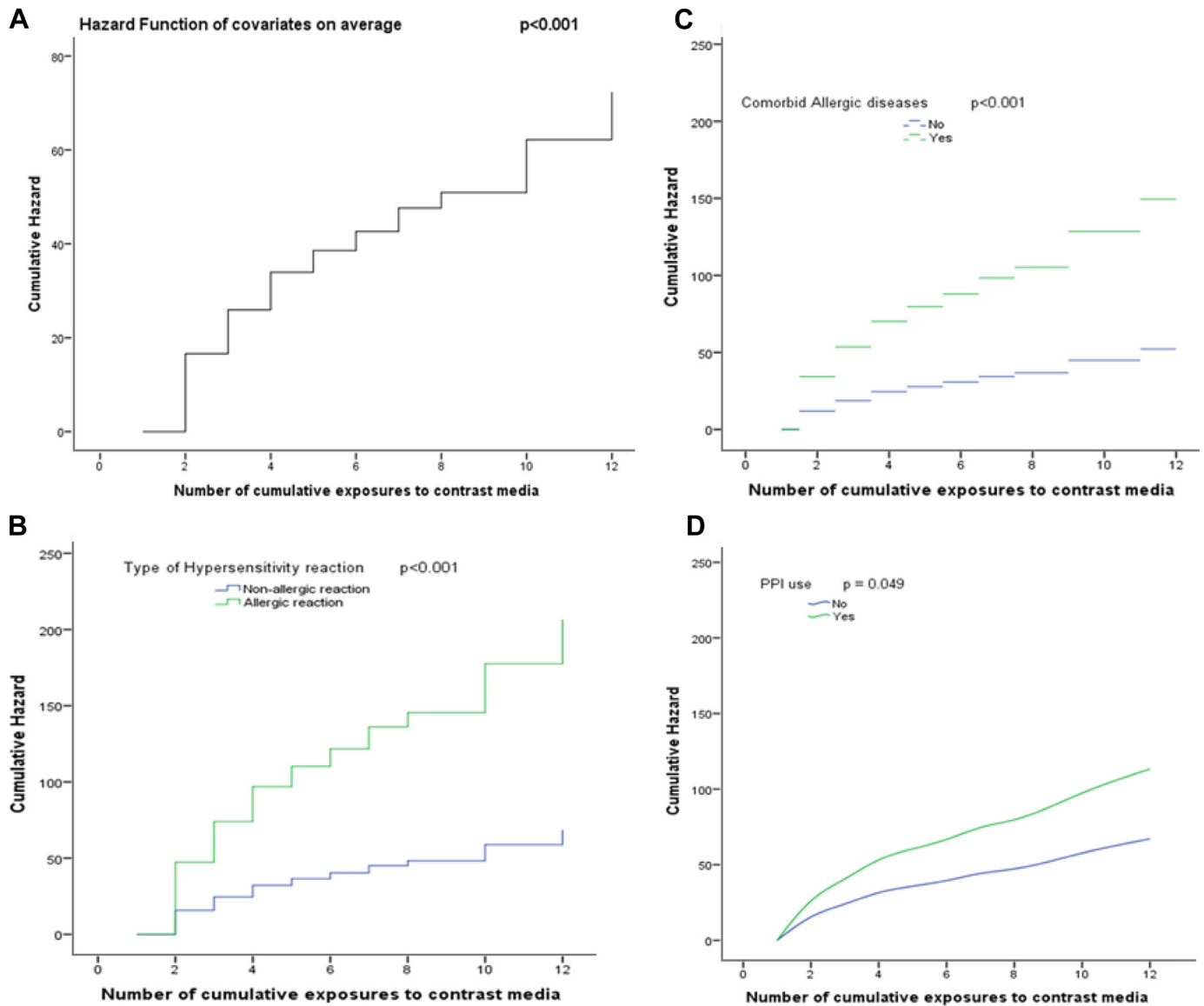


**Figure 2.** Cox survival analysis. Graphs illustrate (A) the cumulative hazard to contrast media, equal to the negative logarithm of the survival probability overall, (B) type of hypersensitivity reactions to contrast media, (C) comorbid allergic disease, and (D) proton pump inhibitor use.

**eTable 1**

Characteristics of patients with and without CM-induced hypersensitivity reactions

| Total                                              | Cases (n = 89) | Controls (n = 188) | OR <sup>a</sup> (95% CI) | P value |
|----------------------------------------------------|----------------|--------------------|--------------------------|---------|
| Male patients, n (%)                               | 45 (50.6)      | 92 (48.9)          | 1.07 (0.6–1.8)           | .628    |
| Origin, n (%)                                      |                |                    |                          |         |
| Spanish                                            | 77 (86.5)      | 169 (89.9)         | 0.72 (0.3–1.7)           | .405    |
| Other European                                     | 5 (5.7)        | 5 (2.7)            | 2.2 (0.5–8.9)            | .218    |
| South American                                     | 3 (3.4)        | 11 (5.9)           | 0.6 (0.1–2.2)            | .558    |
| African                                            | 2 (2.3)        | 3 (1.6)            | 1.4 (0.2–10.2)           | 1.000   |
| Asian                                              | 1 (1.1)        | 0 (0)              | Inf (0.1–Inf)            | .701    |
| Age in years, mean (SD)                            | 54.9 (16.6)    | 55.5 (14.8)        |                          | .753    |
| Creatinine (mg/dL), mean (SD)                      | 0.98 (0.26)    | 0.64 (0.24)        |                          | <.001   |
| Days since last creatinine measurement, mean (SD)  | 125.2 (204.34) | 79.82 (156.8)      |                          | .060    |
| Charlson index, mean (SD)                          | 1.96 (2.16)    | 2.7 (2.1)          |                          | .382    |
| Comorbid allergic diseases, n (%)                  | 43 (48.3)      | 42 (22.3)          | 3.25 (1.8–5.8)           | <.001   |
| Atopy                                              | 27 (30.3)      | 10 (5.3)           | 7.8 (3.4–18.3)           | <.001   |
| Rhinoconjunctivitis                                | 19 (21.3)      | 7 (4.3)            | 7.0 (2.4–14.7)           | <.001   |
| Asthma                                             | 8 (9.0)        | 6 (3.7)            | 3.0 (0.9–10.1)           | .040    |
| Drug hypersensitivity                              | 7 (8.0)        | 3 (1.6)            | 5.3 (1.2–26.4)           | .024    |
| Antibiotics                                        | 4              | 2                  |                          |         |
| NSAID                                              | 2              | 1                  |                          |         |
| Carboplatin                                        | 1              | 0                  |                          |         |
| Procedure, n (%)                                   |                |                    |                          |         |
| CT                                                 | 55 (61.8)      | 117 (62.2)         | 1.0 (0.6–1.7)            | .944    |
| Urography                                          | 20 (22.5)      | 43 (22.9)          | 1.0 (0.5–1.9)            | .941    |
| Magnetic resonance                                 | 13 (14.6)      | 26 (13.8)          | 1.1 (0.5–2.1)            | .862    |
| Angiography                                        | 1 (1.1)        | 2 (1.1)            | 1.1 (0.0–15.1)           | 1.000   |
| History of hypersensitivity reactions to CM, n (%) | 4 (4.5)        | 1 (1.1)            | 8.8 (0.9–210)            | .066    |
| CM received (n), mean (SD) <sup>b</sup>            | 2.8 (2.2)      | 3.6 (3.7)          |                          | .024    |
| Previous exposure to CM, n (%)                     | 65 (73)        | 99 (52.7)          | 2.4 (1.4–4.4)            | .001    |
| Co-medication, n (%)                               |                |                    |                          |         |
| ≥1 drug                                            | 68 (76.4)      | 147 (78.2)         | 0.9 (0.5–1.7)            | .739    |
| PPI                                                | 22 (24.7)      | 22 (11.7)          | 2.5 (1.2–5.0)            | .006    |
| Statins                                            | 21 (23.6)      | 47 (25.0)          | 0.9 (0.5–1.7)            | .800    |
| Antihypertensive treatments <sup>c</sup>           | 23 (23.6)      | 60 (31.9)          | 0.7 (0.4–1.4)            | .303    |
| ARA II                                             | 8 (9.0)        | 21 (11.2)          | 0.8 (0.3–2.0)            | .580    |
| β Blockers                                         | 6 (6.7)        | 18 (9.6)           | 0.7 (0.2–1.9)            | .434    |
| ACEI                                               | 5 (5.6)        | 20 (10.6)          | 0.5 (0.2–1.5)            | .255    |
| ASA                                                | 12 (13.5)      | 22 (11.7)          | 1.2 (0.5–2.6)            | .673    |
| Metformin                                          | 6 (6.7)        | 22 (11.7)          | 0.6 (0.2–1.5)            | .201    |
| Allopurinol                                        | 5 (5.6)        | 8 (4.3)            | 1.4 (0.4–4.7)            | .844    |
| Antineoplastic agents                              | 2 (2.2)        | 18 (9.6)           | 0.2 (0.0–1.0)            | .051    |

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARA II, angiotensin II receptor antagonist; ASA, acetylsalicylic acid; CI, confidence interval; CM, contrast media; CT, computed tomography; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; PPI, proton pump inhibitor.

<sup>a</sup>P value significant.

<sup>b</sup>The largest number of procedures with contrast media was 12 for the case group and 22 for the control group.

<sup>c</sup>Antihypertensive treatments included diuretics and calcium antagonists.

**eTable 2**

Characteristics of hypersensitivity reactions to CM

|                                                                                                   | n (%)       |
|---------------------------------------------------------------------------------------------------|-------------|
| Clinical manifestations                                                                           |             |
| Urticaria                                                                                         | 51 (57.3)   |
| Erythema–exanthema                                                                                | 17 (19.1)   |
| Anaphylaxis                                                                                       | 21 (23.6)   |
| Type of CM and severity of reaction                                                               |             |
| Nonionic iodinated CM                                                                             | 76 (85.4)   |
| Mild                                                                                              | 52 (68.4)   |
| Moderate                                                                                          | 20 (26.3)   |
| Severe                                                                                            | 4 (5.3)     |
| Gadolinium CM                                                                                     | 13 (14.6)   |
| Mild                                                                                              | 9 (69.2)    |
| Moderate                                                                                          | 3 (23.1)    |
| Severe                                                                                            | 1 (7.7)     |
| Treatment for reaction                                                                            |             |
| Anti-H <sub>1</sub>                                                                               | 77 (86.1)   |
| Corticosteroids                                                                                   | 72 (80.9)   |
| Metoclopramide or H2RA                                                                            | 7 (7.9)     |
| CPR                                                                                               | 1 (1.1)     |
| Drugs received                                                                                    |             |
| 0                                                                                                 | 7 (7.9)     |
| 1                                                                                                 | 27 (30.3)   |
| 2                                                                                                 | 35 (39.3)   |
| 3                                                                                                 | 17 (19.1)   |
| 4                                                                                                 | 3 (3.4)     |
| Outcome                                                                                           |             |
| Observed clinically in emergency department                                                       | 6 (6.7)     |
| Resolved after hospitalization in ICU                                                             | 2 (2.2)     |
| Resolved after hospitalization                                                                    | 1 (1.1)     |
| Observed clinically and discharged                                                                | 80 (89.9)   |
| Allergic reaction and severity <sup>a</sup>                                                       |             |
| Immediate reaction                                                                                | 9 (10.1)    |
| Mild                                                                                              | 3 (3.4)     |
| Moderate                                                                                          | 3 (3.4)     |
| Severe                                                                                            | 3 (3.4)     |
| Delayed mild reaction                                                                             | 3 (3.4)     |
| Subsequent administration of CM                                                                   |             |
| No                                                                                                | 64 (71.9)   |
| Yes                                                                                               | 22 (24.7)   |
| Unknown                                                                                           | 3 (3.4)     |
| Premedication before readministration                                                             |             |
| No                                                                                                | 1 (1.13)    |
| Yes                                                                                               | 4 (4.6)     |
| Unknown                                                                                           | 17 (19.1)   |
| Hypersensitivity after subsequent exposure to CM with premedication <sup>b</sup>                  | 1 (25)      |
| Successful if negative skin test reaction to CM and/or different CM after subsequent exposure (%) |             |
| Allergic reaction                                                                                 | 4/4 (100)   |
| Nonallergic reaction                                                                              | 16/16 (100) |

Abbreviations: CM, contrast media; CPR, cardiopulmonary resuscitation; H2RA, H<sub>2</sub> receptor antagonist; HR, hypersensitivity reaction; ICU, intensive care unit.

<sup>a</sup>All allergic reactions were to nonionic iodinated CM, but 13 patients were not studied.

<sup>b</sup>This patient had a mild delayed allergic reaction; skin test reactions were positive for all nonionic iodinated CM.

**eTable 3**Allergy study<sup>a</sup>

|                                              | Test reaction              | Results                            | Immediate | Late     |
|----------------------------------------------|----------------------------|------------------------------------|-----------|----------|
| Iomeprol                                     |                            |                                    |           |          |
| Prick or intradermal test                    | positive<br>negative<br>NP | 9 (12.0)<br>55 (73.3)<br>11 (14.7) | 7 (77.8)  | 2 (22.2) |
| Patch test                                   | positive<br>negative<br>NP | 1 (1.3)<br>5 (6.7)<br>69 (92)      |           |          |
| Iobitridol                                   |                            |                                    |           |          |
| Prick or intradermal test                    | positive<br>negative<br>NP | 2 (2.7)<br>61 (81.3)<br>12 (16)    | 2 (100)   |          |
| Patch test                                   | positive<br>negative<br>NP | 1 (1.3)<br>5 (6.7)<br>69 (92)      |           |          |
| Iohexol                                      |                            |                                    |           |          |
| Prick or intradermal test                    | positive<br>negative<br>NP | 5 (6.7)<br>57 (76)<br>13 (17.3)    | 3 (60.0)  | 2 (40.0) |
| Patch test                                   | positive<br>negative<br>NP | 1 (1.3)<br>4 (5.3)<br>70 (93.3)    |           |          |
| Iodioxanol                                   |                            |                                    |           |          |
| Prick or intradermal test                    | positive<br>negative<br>NP | 3 (4.0)<br>60 (80.0)<br>12 (16.0)  |           | 3 (100)  |
| Patch test                                   | positive<br>negative<br>NP | 1 (1.33)<br>4 (5.3)<br>70 (93.33)  |           |          |
| Diatrizoate meglumine and diatrizoate sodium |                            |                                    |           |          |
| Prick or intradermal test                    | positive<br>negative<br>NP | 63 (84)<br>12 (16)                 |           |          |
| Patch test                                   | positive<br>negative<br>NP | 6 (8.0)<br>69 (92.0)               |           |          |
| Gadoteric acid                               |                            |                                    |           |          |
| Prick or intradermal test                    | positive<br>negative<br>NP | 10 (13.3)<br>65 (86.7)             |           |          |
| Patch test                                   | positive<br>negative<br>NP | 75 (100)                           |           |          |
| Gadobutrol                                   |                            |                                    |           |          |
| Prick or intradermal test                    | positive<br>negative<br>NP | 10 (13.3)<br>65 (86.7)             |           |          |
| Patch test                                   | positive<br>negative<br>NP | 75 (100)                           |           |          |
| Gadoteridol                                  |                            |                                    |           |          |
| Prick or intradermal test                    | positive<br>negative<br>NP | 9 (12.0)<br>66 (88.0)              |           |          |
| Patch test                                   | positive<br>negative<br>NP | 75 (100)                           |           |          |
| Others <sup>b</sup>                          |                            |                                    |           |          |
| Prick or intradermal test                    | positive<br>negative<br>NP | 2 (2.7)<br>2 (2.7)<br>70 (93.3)    | 1 (50)    | 1 (50)   |
| Patch test                                   | positive<br>negative<br>NP | 1 (1.2)<br>73 (98.9)               |           |          |
| Latex                                        |                            |                                    |           |          |
| Prick or intradermal test                    | positive<br>negative<br>NP | 27 (36.0)<br>48 (64.0)             |           |          |

Abbreviations: LTT, lymphocyte transformation test; NP, not performed.

<sup>a</sup>Thirteen cases were not studied. The basophil activation test reaction was positive for iomeprol and iohexol and negative for the other contrast media tested in the 2 severe cases tested, which confirmed the positive results of the intradermal tests. An LTT was performed in 1 patient who had had a delayed hypersensitivity reaction; the LTT resulted in a toxic reaction in this patient.

<sup>b</sup>Ioxaglate positive prick test reaction in 2 patients tested and negative mangafodipir trisodium prick test reaction in 2 patients tested.