

Comprehensive Allergy Evaluation Is Useful in the Subsequent Care of Patients with Drug Hypersensitivity Reactions During Anesthesia

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What is already known about this topic? Much of what is known about drug hypersensitivity reactions (HSRs) during anesthesia comes from registries developed outside the United States. The rate of HSR to specific general anesthetics varies between countries.

What does this article add to our knowledge? We describe the success of a comprehensive evaluation and management plan for patients with HSRs during anesthesia at a large academic center in Boston.

How does this study impact current management guidelines? This study supports a comprehensive evaluation and management plan for patients with HSR during anesthesia, including skin testing and baseline tryptase level, to minimize the risk of subsequent anesthesia even when the cause is not identified.

BACKGROUND: For patients with a history of drug hypersensitivity reaction (HSR) during anesthesia, strategies to minimize risk with subsequent anesthesia are unclear. Identification of the cause of HSR during anesthesia remains challenging.

OBJECTIVE: To determine the success of a comprehensive allergy evaluation and management plan for patients with HSR during anesthesia, including identification of the causative agent and review of outcomes during subsequent anesthesia exposure.

METHODS: We performed chart reviews of patients referred for the evaluation of HSR during anesthesia between 2003 and 2012. Data collection included patient characteristics, signs/symptoms of HSR during anesthesia, and subsequent outcomes. Patients underwent comprehensive allergy evaluation including skin testing for identifying potential culprit agents, and the results were used to provide recommendations for any subsequent anesthesia.

RESULTS: Over the 10-year study period, 73 patients with HSR during anesthesia were referred for further evaluation. Thirteen patients (18%) had positive skin test results to a drug received during anesthesia. One patient with a positive skin test result was diagnosed with mastocytosis. The causative agents identified in these 13 patients included latex, β -lactam antibiotics, neuromuscular blockers, tetracaine, ondansetron, and fentanyl. On follow-up, 47 of the 73 patients (64%) subsequently underwent procedures requiring anesthesia. Using our recommendations from evaluation and testing, 45 of these 47 patients (96%) successfully tolerated subsequent anesthesia. The 2 patients who developed recurrent HSR during anesthesia were later diagnosed with mast cell disorders.

CONCLUSIONS: Our comprehensive evaluation and management plan minimizes risk with subsequent anesthesia even when the cause of HSR could not be identified. Baseline tryptase levels may be helpful in this patient population to diagnose mast cell disorders. © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;3:94-100)

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Drug hypersensitivity reactions (HSRs) during anesthesia are unpredictable and potentially life-threatening immune-mediated events. These HSRs can be classified as IgE-mediated (defined by positive skin test results or serum specific IgE) or non-IgE-mediated (including cytotoxic, immune complex-mediated, cell-mediated, pseudoallergic, and other immunologic reactions).¹ Although the mechanism may differ, the clinical characteristics of both are often indistinguishable.² The estimated incidence of HSR during anesthesia is between 1:3,500 and

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Abbreviations used

ACE- angiotensin-converting enzyme

ASA- Aspirin

HSR- Hypersensitivity reaction

IQR- Interquartile range

NSAID- Nonsteroidal antiinflammatory drug

1:20,000.³⁻⁶ Most data on the incidence of HSR come from countries with an active reporting policy (ie, Australia, Denmark, France, New Zealand, Norway, and the United Kingdom); the United States does not have such a policy. Mortality associated with HSRs during anesthesia has been estimated to vary between 3% and 6%.⁷

The complete evaluation of patients who develop adverse drug reactions during general anesthesia remains complex. Patients routinely receive multiple medications in a short period of time, which makes it challenging to identify a culprit drug or drugs on the basis of the timing of administration by review of the medical record alone. Previously published guidelines, based on expert opinion, recommend comprehensive skin testing to agents that are listed in the anesthetic record, in addition to latex and other medications given before the HSR.⁸ In the present study, we describe our experience over a 10-year period using a specific evaluation and management plan to identify causative agents and provide recommendations for patients with HSR during anesthesia before subsequent anesthesia.

METHODS

Study design

We performed a chart review of all patients 18 years or older at Massachusetts General Hospital who were referred to the Allergy/Immunology Unit for the evaluation of HSR during anesthesia between January 1, 2003, and December 31, 2012.

Patients were identified using the *International Classification of Diseases, ninth revision* billing codes 995.27 (Other drug allergy), 995.0 (Other anaphylactic reaction), and in-office procedure code 95010 (percutaneous testing to drug, biologic, or venom). Patients who had an HSR during induction or maintenance of anesthesia, or during the immediate postoperative recovery period, were reviewed.

The Wilcoxon rank-sum test was used to calculate the difference in median time to skin testing. The institutional review board approved the study.

Comprehensive allergy evaluation

All patients referred to the Allergy/Immunology Unit underwent comprehensive allergy evaluation, including a detailed review of the HSR obtained from medical records. All anesthesia records, nursing records, operative and procedural reports, and consultation notes of the Allergy/Immunology Unit were reviewed in detail. Patients' demographic characteristics including age, sex, history of atopy, history of drug allergy, medications at the time of the surgery, history of surgery, serum specific IgE to latex, and serum tryptase levels (where available) were recorded. Organ system involvement was also documented with particular attention to cutaneous, oropharyngeal, pulmonary, cardiovascular, gastrointestinal, or other systems. The severity of each reaction was documented using a published grading scale to classify HSR during anesthesia (Table I).⁸

Skin testing was performed at least 4 weeks after the initial HSR as previously described.⁹ Skin prick and intradermal testing were

TABLE I. Severity of hypersensitivity reactions during anesthesia

Grade	Symptoms
I	Cutaneous signs: urticaria, angioedema, generalized erythema
II	Measurable but not life-threatening symptoms: cutaneous signs, hypotension (defined as a decrease of more than 30% in blood pressure with tachycardia), respiratory symptoms (cough, difficulty with mechanical ventilation)
III	Life-threatening symptoms: cardiovascular collapse, tachycardia or bradycardia, arrhythmias, severe bronchospasm
IV	Cardiac and/or respiratory arrest

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TABLE II. Skin testing reagents

Medication	Concentration (mg/mL)	SPT	ID Dilution
Succinylcholine ^{10,11}	50	Undiluted	1:1,000
Cisatracurium ^{10,11}	2	Undiluted	1:1,000 1:100
Rocuronium ^{10,11}	10	Undiluted	1:1,000 1:100
Atracurium ^{10,11}	10	Undiluted	1:1,000
Pancuronium ^{10,11}	2	Undiluted	1:1,000 1:100 1:10
Midazolam ^{10,11}	5	Undiluted	1:20 1:10
Ketamine ^{10,11}	10	Undiluted	1:40
Propofol ¹⁰⁻¹²	10	Undiluted	1:1,000 1:100 1:10
Etomidate ¹¹	2	Undiluted	1:1,000 1:100 1:10
Fentanyl ¹¹	0.05	Undiluted	1:10,000 1:1,000 1:100 1:10
Lidocaine 1% ^{11,13,14}	1%	Undiluted	1:100
Bupivacaine 0.25% ^{11,13,14}	0.25%	Undiluted	1:100
Tetracaine 1% ^{13,14}	1%	Undiluted	1:100
Chlorhexidine gluconate 0.5% ¹⁵	1.2	Undiluted	1:2,500
Odansetron ^{16,17}	2	Undiluted	1:100
Cefazolin ¹⁸	330	1:10	1:100 1:10

ID, Intradermal testing; SPT, skin prick testing.

performed to all available agents listed in the anesthetic record and received immediately before the HSR, with the exception of inhalational agents that have not been previously demonstrated to cause HSR. Previously validated, nonirritating skin testing concentrations were used during allergy evaluation (Table II). Appropriate positive (histamine 6 mg/mL) and negative (saline) controls were also included. A skin prick reaction was considered positive if the maximum diameter of the wheal was at least 3 mm larger than that induced by the negative control. Intradermal skin testing at increasing concentrations was also performed if the skin prick reaction was negative. An intradermal test result was considered

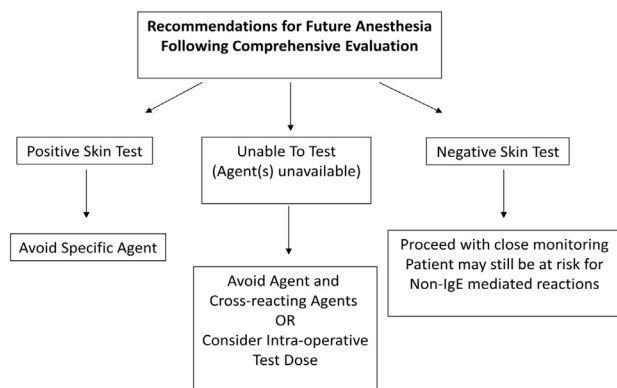


FIGURE 1. Recommendations for future anesthesia after evaluation. Recommendations were provided for subsequent procedures using the results of comprehensive allergy evaluation including skin testing to all available agents received immediately before the HSR and listed in the anesthetic record.

positive if the maximum diameter of the wheal had an increase of more than 3 mm compared with the initial wheal size and had associated erythematous flare. Between 2004 and 2009, the reagents for penicillin skin testing were not available, and so testing was not performed. When possible, these patients returned later for skin testing to penicillin once reagents became available.

Additional laboratory evaluation included measurement of total baseline tryptase level and specific IgE testing for latex using the ImmunoCAP system (Upjohn-Pharmacia, Uppsala, Sweden) if there was latex exposure at the time of the reaction.

Recommendations were made regarding subsequent anesthesia after a comprehensive allergy evaluation. If a patient had a positive skin test result to an agent, suggesting an IgE-mediated HSR, we advised avoidance of that specific agent during subsequent anesthesia. If the skin test result was negative, no specific avoidance of medications was recommended during subsequent anesthesia, although cautious intraoperative monitoring was suggested given the potential risk for a non-IgE-mediated reaction. If antibiotic prophylaxis was necessary, we recommended monitored administration while the patient was awake. If skin testing was not available (as with penicillin antibiotics or nonirritating skin testing concentrations not published), or if skin testing could not be performed because of the use of antihistamine agents or need for urgent surgery, patients were told to avoid these medications and specific recommendations were made for safe alternatives (Figure 1). No specific recommendations for the use of premedications (ie, antihistamines or glucocorticoids) were made for subsequent anesthesia. Close monitoring during subsequent anesthesia for signs and symptoms of an HSR was routinely recommended.

Follow-up data collection

Follow-up information on details of any subsequent procedure or surgery was collected from the electronic medical record. Phone interviews were conducted with patients who did not have follow-up information available in the electronic medical record. A signed medical record release was obtained, and surgical and procedural records were collected and reviewed from outside medical centers. All operative notes and anesthesia records were obtained and reviewed for details of exposure to medications evaluated during

TABLE III. Patients' demographic characteristics

Baseline patient characteristics	N = 73
Age at the time of the reaction (y)	45 ± 17
Sex: female	45 (62)
Median time from HSR to allergy evaluation (mo)	5 (IQR, 2-34)
Patient-reported history of drug allergy	40 (55)
Patient-reported history of severe allergic reaction (includes drug reactions)	11 (15)
Patient-reported history of atopic disorders	
Asthma	23 (32)
Allergic rhinitis	35 (48)
Eczema	3 (4)
Food allergy	6 (8)
Any atopic disorder	44 (60)
Patient-reported history of medication use	
NSAID or ASA	18 (25)
ACE inhibitor	12 (16)
β-Blocker	19 (26)
Any use of the above medications	32 (44)
Severity of adverse drug reaction	
I	29 (40)
II	9 (12)
III	26 (36)
IV	9 (12)
Organ system involvement	
Cutaneous	44 (60)
Oropharyngeal	24 (33)
Pulmonary	29 (40)
Cardiovascular	28 (38)
Gastrointestinal	1 (1)
Other	10 (14)

Values are n (%) unless indicated otherwise.

comprehensive allergy evaluation and development of any subsequent HSR.

RESULTS

We identified 83 patients with HSR during anesthesia over the 10-year study period. Seventy-three patients met inclusion criteria and were included in the analysis. We excluded 10 patients who had any of the following: symptoms of HSR starting more than 24 hours after anesthesia ($n = 1$), patients treated with only local anesthesia ($n = 1$), negative skin test results within 4 weeks after an HSR because of the potential for false-negative skin test results ($n = 4$), and any patient with incomplete or missing records ($n = 4$). Four patients who were younger than 18 years at the time of the HSR were included because their allergy evaluation occurred when they were at least 18 years old. One patient who underwent skin testing 22 days after the HSR was included in the analysis because of identification of the culprit agent by a positive skin test result.

Patient characteristics

Patients were predominantly women (62%), with an average age of 45 ± 17 years at the time of the initial HSR. The median time from initial HSR to comprehensive allergy evaluation was 5 months (interquartile range [IQR], 2-34 months). At the time of the allergy evaluation, patients reported the following

TABLE IV. Causative agents identified by skin testing or latex IgE

Subject ID	Sex	Grade of reaction	Procedure performed	Total tryptase level during HSR (ng/mL)	Positive skin testing
1	F	III	Cholecystectomy	-	Fentanyl
8	F	III	Cesarean section	19	Cefazolin, penicillin G, Pre-Pen, midazolam
11	F	III	ACL repair	44	Cefazolin, penicillin G, Pre-Pen
14	M	IV	Neck reconstruction after burn injury	168	Cisatracurium
18	M	III	Prostatectomy	-	Latex IgE
26	F	I	Sinus surgery	-	Latex IgE
40	F	III	Lumbar discectomy	2	Succinylcholine
41	F	I	Knee arthroscopy	3	Odansetron
42	M	I	Pelvic arterial embolization	-	Odansetron
59	M	III	Incisional hernia repair	-	Tetracaine 1%
62	M	IV	Scalp reconstruction	3	Latex IgE
68	F	I	Hysteroscopic endometrial ablation	-	Odansetron
73	M	III	Laser lithotripsy	86	Cefazolin, penicillin G, Pre-Pen

ACL, Anterior cruciate ligament; F, female; M, male.

comorbidities: 55% reported a history of drug allergy, 48% reported a previous diagnosis of allergic rhinitis, 32% reported a diagnosis of asthma, 15% reported a history of a severe allergic reaction (including previous drug reactions), 8% reported a history of food allergy, and 4% reported a previous diagnosis of eczema. On physical examination performed during the allergy visit, none of the patients had lesions of urticaria pigmentosa. No patient had a history of allergy to any anesthetic agent, and there were no cases of accidental exposure to a previously identified drug allergen during anesthesia (Table III).

HSRs during anesthesia

At the time of the HSR, 44 patients (60%) experienced cutaneous signs and symptoms (urticaria, rash, and flushing), 24 (33%) had oropharyngeal or mucosal signs and symptoms (angioedema and throat tightness), 29 (40%) had pulmonary signs and symptoms (bronchospasm, shortness of breath, and wheezing), and 28 (38%) had cardiovascular signs (bradycardia, tachycardia, hypotension, and arrhythmia). Of the 26 patients with grade III reactions, 18 had hypotension with or without respiratory symptoms. Eight patients with grade III reactions had wheezing or stridor without hypotension. Of the 9 patients with grade IV reactions, 7 had cardiac arrest, with the remaining 2 patients developing respiratory failure. Of the 73 total patients included in the study, 18 patients were routinely using a nonsteroidal antiinflammatory drug (NSAID) or aspirin (ASA), 12 were on an angiotensin-converting enzyme (ACE) inhibitor, and 19 were on a β -blocker before the HSR. Three patients were on a combination of NSAID or ASA, ACE inhibitor, and β -blocker therapy. There was no association between the grade of reaction and the use of NSAID or ASA, ACE inhibitor, or β -blocker individually; however, all 3 patients taking a combination of NSAID or ASA, ACE inhibitor, and β -blocker had grade III reactions (Table III). Serum total tryptase levels were obtained in 27 patients (37%) during HSR and were found to be elevated at more than 11.4 ng/mL in 10 of these 27 patients (37%), with a median of 40 ng/mL (IQR, 19-86 ng/mL).

Comprehensive allergy evaluation and management

The median time interval between HSR and subsequent skin testing for all patients was 5 months (IQR, 2-34 months). Median

time to skin testing was not statistically different between patients with positive and negative skin test results (3.1 vs 4.7 months; $P = .09$). Skin testing to agents administered during anesthesia or latex specific IgE testing identified a causative agent in 13 (18%) of the 73 patients. Three patients had positive skin test results to penicillin G, benzylpenicilloyl-polylysine (Pre-Pen, ALK-Abello, Round Rock, Tex), and cefazolin; 2 patients had positive skin test results to neuromuscular blockers; 1 patient was positive to tetracaine; 3 patients were positive to odansetron; and 1 patient was positive to fentanyl. Three patients were found to have a positive latex specific IgE (Table IV). In addition, 1 patient was found to have a persistently elevated tryptase level and was diagnosed with indolent mastocytosis by bone marrow biopsy.

There were 21 patients who received β -lactam antibiotics during anesthesia that were not skin tested to all the available reagents. Six of these patients received cefazolin and had negative penicillin test results but were not tested to cefazolin. Twelve of the patients received cefazolin and had negative skin test results to other medications tested but were not tested for either penicillin or cefazolin. The remaining 3 patients received a penicillin antibiotic but did not undergo penicillin skin testing because of the unavailability of the major determinant, benzylpenicilloyl-polylysine (Pre-Pen), at the time of allergy evaluation. Of these 21 patients, 1 patient had a positive latex IgE, 1 patient had a positive skin test result to succinylcholine, and 19 patients had no causative agent identified after comprehensive evaluation.

Following our management plan as outlined in Figure 1, 45 (96%) of the 47 patients who underwent subsequent anesthesia successfully tolerated operative procedures regardless of the severity of the initial HSR or identification of the causative agent. The severity of the HSR and the rate of identification of the culprit agent did not differ between patients who underwent subsequent anesthesia and those who did not undergo subsequent anesthesia. Six (13%) of the patients had positive skin test results and alternative agents were used during subsequent anesthesia. In the remaining 41 patients with negative skin test results, 31 (75%) had alternative agents used during the operative procedure on the basis of our recommendation and subsequently tolerated anesthesia. Six (15%) of the patients underwent subsequent anesthesia using the same agents and did not develop a reaction. Two (5%) patients underwent subsequent anesthesia

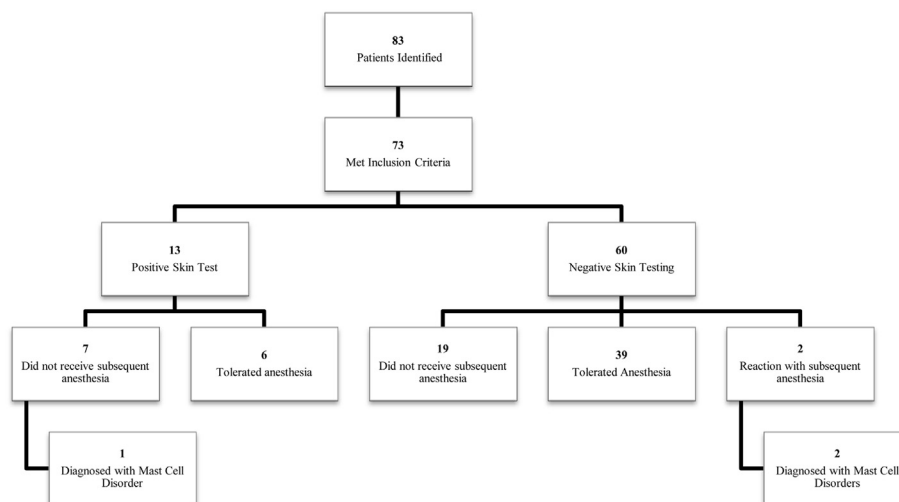


FIGURE 2. Outcomes after comprehensive allergy evaluation.

without reaction; however, detailed anesthesia reports were not available for review. Two (5%) of the patients developed HSR during subsequent anesthesia despite following our recommendations to use alternative agents and were found to have elevated baseline total tryptase levels (Figure 2). In total, 3 (4%; 95% CI, 0.9%-11.8%) patients with HSR during anesthesia in this study were diagnosed with mast cell disorders.

DISCUSSION

We identified 73 patients with HSR during anesthesia referred for evaluation to the Allergy/Immunology Unit over a 10-year period. A comprehensive evaluation and management strategy was created and used for patients with HSR to anesthesia. The skin test result was positive, suggesting IgE-mediated allergy, in a minority of patients (18%). Although our rate of identification of culprit drugs was lower than that of other publications,¹⁹⁻²¹ a thorough evaluation allowed us to make informed recommendations and 45 patients (6 with a positive skin test result and 39 in whom no causative agent was identified) successfully tolerated subsequent anesthesia without complication. This demonstrates that most patients who followed our recommendations tolerated anesthesia using information from their evaluation, including the use of medications with negative skin test results, underscoring the value of our evaluation and management strategy after HSR during anesthesia—both to the patient and to the anesthesiologist.

The published literature indicates large differences in the frequency of identification of causative agents responsible for HSR during anesthesia and large variability in the rank order of agents responsible. In a French study evaluating 1253 patients with HSR during anesthesia, a diagnosis of IgE-mediated HSR was established in 786 cases (63%) while 467 cases (37%) were considered non-immune-mediated.¹⁹ Neuromuscular-blocking agents were the most frequent cause of anaphylaxis (47%), followed by latex (20%), antibiotics (18%), opioids (2%), colloids (2%), hypnotics (1%), colloids (2%), and other substances including dyes (9%). A study from Spain reported a much higher incidence of antibiotics causing anaphylaxis, approximately 44%

of the total cases.²⁰ In a US case series of 38 patients who experienced an anaphylactic reaction during anesthesia, 18 (47%) were IgE-mediated, with the likely causative agent identified by a skin test. Six of these patients had elevated tryptase levels but negative skin test results; a non-IgE-mediated reaction was suspected in the remaining cases.²¹ Antibiotics were the most common causative agent associated with an IgE-mediated reaction and seen in 9 patients (50%), with cefazolin being the most common agent identified (7 patients). The observed differences between studies have several possible explanations, including different populations with different rates of sensitization and different methods of skin testing and evaluation.

Similar to the previously published US series,²¹ we found that antibiotics were the most frequent cause of HSR during anesthesia. Unfortunately, because of the lack of penicillin skin testing reagents from 2004 to 2009, we were unable to complete skin testing in 21 patients who had received β -lactam antibiotics before the HSR. Eighteen (86%) of these patients received cefazolin perioperatively. Complete skin testing to penicillin skin testing reagent and cefazolin would have likely identified additional culprits, and it remains possible that cefazolin was the most common cause of IgE-mediated HSR in our series. A follow-up study to evaluate this hypothesis is being conducted. Therefore, similar to published guidelines,⁸ we also recommend that antibiotic prophylaxis, especially cefazolin, be administered preoperatively to a monitored awake patient so that symptoms of a reaction can be easily detected and prompt treatment can be initiated.

The median time interval between HSR and subsequent skin testing for all patients was 5 months (IQR, 2-34 months). Previously published data reported a decline over time in the identification of IgE antibodies in patients with penicillin allergy and this is likely true for other drugs as well.²² It has been reported that the longer the time lapse between the event and evaluation, the more difficult it appears to identify the causative allergen correctly. The mean time to evaluation after HSR in subjects with positive skin test results was 12 months compared with 36 months in those with negative skin test results.²³ It is generally recommended that skin testing should be performed at

least 4 to 6 weeks after the HSR to prevent false-negative skin test results. In a recent study, early skin testing was performed 0 to 4 days after an initial HSR and identified 3 patients with positive skin test results (N = 25; 6.8%). Later skin testing was repeated to all of the same agents 4 to 8 weeks after HSR and all 3 patients had negative skin test results. In addition, 10 patients had positive skin test results only at the later skin testing visit. Although the optimal time to perform skin testing after HSR has not been validated, this study suggests that early skin testing performed immediately after HSR may complement later skin testing performed 4 to 8 weeks after HSR.²⁴

Taken together, the above information suggests that any patient with HSR during anesthesia should be referred for evaluation by an allergist as soon as possible after the HSR and at least within 12 months to avoid false-negative results.^{23,25}

The combination of NSAID or ASA, ACE inhibitor, and β -blocker seems to contribute to the severity of HSR during anesthesia, but more data are needed to understand the contributing factor of these medications. In addition, the 2 patients who developed recurrent HSR during anesthesia were subsequently diagnosed with mast cell disorders. In total, there were 3 patients with HSRs during anesthesia diagnosed with mast cell disorders: 1 patient was identified at the time of the initial HSR evaluation, and 2 patients were identified after recurrent HSRs. Although a rare disease, mast cell disorders comprised 4% (95% CI, 0.9%-11.8%) of our patients with HSR during anesthesia. In a previous study of mast cell disease in patients with drug HSR, 7 out of 86 (8%; 95% CI, 3.8%-16.1%) patients with drug HSR had increased serum tryptase levels (>11.4 ng/mL) although only 1 patient was diagnosed with systemic mastocytosis after bone marrow biopsy.²⁶ Exposure to general anesthetics has been listed as a risk factor for HSR in patients with mastocytosis²⁷⁻³¹; however, the incidence specifically for general anesthetics is not known. There are general guidelines that have been published to minimize the risks of anesthesia in adult patients with systemic mastocytosis.³² Although serum tryptase is a valuable laboratory marker of anaphylaxis, we recommend that the total tryptase level during HSR³³ be compared with a baseline total tryptase level in all patients with HSR during anesthesia. The baseline tryptase level should be obtained at least 24 hours after all signs and symptoms have resolved if a baseline level before HSR is not available. The formula for a clinically meaningful elevated serum tryptase level has been previously published.³⁰ It is important to note that a normal tryptase result does not exclude the diagnosis because the reported sensitivity is 64% and the specificity is 89% in patients presenting with suspected anaphylaxis during anesthesia.³⁴

This study has several potential limitations including the retrospective design. There may have been additional cases of HSR during anesthesia that were not captured by our identification methods. In addition, the study cohort may have been subject to selection or referral bias. At the time of the study, we did not have a system for referral of all intraoperative anaphylaxis cases and this may have biased our cohort to include the more severe HSRs. If this were the case, however, our conclusions about the safety of subsequent anesthesia would likely be strengthened. Last, we were limited by both the delayed timing of skin testing and, in some cases, the lack of availability of penicillin skin testing reagents for several years. Our skin testing results could have been false-negative results given the waning of skin test positivity over time.³⁵ In addition, as mentioned earlier,

from 2004 through 2009, reagents for penicillin skin testing were unavailable. Thus, we are unable to fully discern the true impact of penicillin or cefazolin on intraoperative anaphylaxis.

In summary, we identified 3 groups of patients who developed HSR to anesthesia: those who had positive skin test results to agents they received during anesthesia, those who had negative skin test results to all the agents received during anesthesia, and a subset of 3 patients who were subsequently diagnosed with mast cell disorders. Although this is a retrospective review with associated limitations, our results demonstrate that a comprehensive allergy evaluation and management plan minimizes the risk of subsequent anesthesia even among patients in whom the cause of HSR during anesthesia was not identified. Furthermore, mast cell disorders should be considered in patients with HSR during anesthesia.

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