Original Article

Antibiotics Are the Most Commonly Identified Cause of Perioperative Hypersensitivity Reactions

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What is already known about this topic? Current knowledge of drug hypersensitivity reactions (HSRs) during anesthesia comes from retrospective studies. The most commonly implicated drugs causing perioperative HSRs vary between countries.

What does this article add to our knowledge? We describe a successful referral and treatment plan for patients with HSRs during anesthesia in a Boston teaching hospital.

How does this study impact current management guidelines? The most commonly identified cause of perioperative HSRs was antibiotics. Allergists should evaluate patients with HSRs during anesthesia to minimize risk with subsequent anesthesia.

BACKGROUND: Hypersensitivity reactions (HSRs) during the perioperative period are unpredictable and can be life threatening. Prospective studies for the evaluation of perioperative HSRs are lacking, and data on causative agents vary between different studies.

OBJECTIVE: The objective of this study was to prospectively determine the success of a comprehensive allergy evaluation plan for patients with HSRs during anesthesia, including identification of a causative agent and outcomes during subsequent anesthesia exposure.

METHODS: All patients referred for a perioperative HSR between November 2013 and March 2015, from a Boston teaching hospital, were evaluated using a standardized protocol with skin testing (ST) within 6 months of HSR. Comprehensive allergy evaluation included collection of patient information, including characteristics of HSR during anesthesia. We reviewed the results of ST and/or test doses for all potential causative medications Event-related tryptase levels were reviewed when available.

RESULTS: Over 17 months, 25 patients completed the comprehensive allergy evaluation. Fifty-two percent (13 of 25) were female with a median age of 52 (interquartile range 43-66) years. The most frequently observed HSR systems were cutaneous (68%), cardiovascular (64%), and pulmonary (24%). A culprit drug, defined as a positive ST, was identified in 36% (9 of 25) of patients. The most common agent identified was cefazolin (6 of 9). After our comprehensive evaluation and management plan, 7 (7 of 8, 88%) patients tolerated subsequent anesthesia.

CONCLUSIONS: Cefazolin was the most commonly identified cause of a perioperative HSR in our study population. Skin testing patients within 6 months of a perioperative HSR may improve the odds of finding a positive result. Tolerance of subsequent anesthesia is generally achieved in patients undergoing our comprehensive evaluation. **© 2016 American Academy of Allergy, Asthma & Immunology** **(J Allergy Clin Immunol Pract 2016;4:697-704)**

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Perioperative hypersensitivity reactions (HSRs) have been estimated to occur in 1:3500 to 1:20,000 procedures, with a mortality rate of up to 9%.[1] However, newer prospective data suggest that this incidence may be as high as 1 in 385

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Abbreviations used
HSR(s)- Hypersensitivity reaction(s)
IgE- Immunoglobulin E
NMBAs- Neuromuscular blocking agents
PCN- Penicillin

operations.[2] Several drugs are often administered simultaneously during general anesthesia, making identification of the causative agent(s) difficult. Identification of the culprit agent of a perioperative HSR is crucial to avoid re-exposure and prevent subsequent untoward outcomes.

Guidelines recommend comprehensive skin testing to chlorhexidine, all preoperative medications listed in the anesthetic record that were given before the HSR, and specific immunoglobulin E (IgE) testing to latex.[3] The literature suggests that there is a geographic difference in the most frequently identified cause of perioperative HSRs. Studies from Europe have implicated neuromuscular blocking agents (NMBAs),[4,5] whereas studies from the United States (US)[6-8] more commonly implicate antibiotics as the cause of perioperative HSRs.

A recent retrospective study described a 10-year period utilizing a specific evaluation and management plan to identify causative agents and provide recommendations for patients with HSRs during anesthesia that require subsequent anesthesia.[6] Limitations of this study were the absence of antibiotic skin testing in some patients due to the lack of skin testing reagents and the prolonged and variable length of time from perioperative HSRs to skin testing, which may have led to a higher rate of false-negative skin testing.[9,10] Decreased availablity of β-lactam testing may explain the low rate of a positive skin test on evaluation (13 of 73 patients, or 18%) and antibiotics as the causal agent (3 of 13 patients, or 23%).

In this study, we describe the application of a comprehensive management plan for perioperative HSRs prospectively over a 17-month period, including skin testing to all possible causative agents within 6 months of HSR, and assessing patients' tolerability of subsequent anesthesia, when indicated.

METHODS

Study design

We performed a prospective cohort study of all patients at Massachusetts General Hospital who were referred to Allergy and/or Immunology for a perioperative HSR between November 2013 and March 2015. These patients were evaluated using a standardized protocol.[6]

Patients were identified based on referral information provided by a central patient scheduler. Patients who had an HSR during induction or maintenance of anesthesia, or during the immediate postoperative recovery period, were included.

Patients were excluded if they were below the age of 18 at the time of evaluation, declined participation in the comprehensive evaluation, or did not complete the recommended comprehensive evaluation. The study was approved by the Partners Healthcare Institutional Review Board.

Comprehensive allergy evaluation

All patients referred to the Allergy and/or Immunology Unit for a perioperative HSR underwent evaluation involving a detailed review of the HSR obtained from the patient's perioperative medical records. The review included anesthesia records, nursing records, operative and procedural reports, and consultation notes of the Allergy and/or Immunology Unit, when applicable. Patient information, including age, sex, atopic history, history of prior drug allergy, medications at the time of the surgery, history of previous surgery, serum-specific IgE to latex, and serum tryptase levels (when available), was recorded. Documentation of perioperative organ system involvement was also recorded and included cutaneous, oropharyngeal, pulmonary, cardiovascular, gastrointestinal, or other system involvement. HSR severity was determined following an established grading scale (I-IV) with a grade of IV representing cardiac and/or respiratory arrest to classify the perioperative HSR (Table I).[3]

TABLE I. Severity of hypersensitivity reactions during anesthesia

Grade	Symptoms
I	Cutaneous signs: urticaria, angioedema, and 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), and respiratory symptoms (cough, difficulty with mechanical ventilation)
III	Life-threatening symptoms: cardiovascular collapse, tachycardia or bradycardia, arrhythmias, and severe bronchospasm
IV	Cardiac and/or respiratory arrest

Adapted from Ring J, Messmer K. Lancet 1977;1:466-9 and Mertes PM, Malinovsky JM, Jouffroy L; Working Group of the SFAR and SFA, Aberer W, Terreehorst I, et al. J Investig Allergol Clin Immunol 2011;21:442-53.

Formal collaboration was established between the Allergy and/or Immunology Unit and the Department of Anesthesia at our institution to capture cases of a perioperative HSR. Initial steps included meetings with the Department of Anesthesia's Quality Assurance Chair and lead nurse coordinator to discuss our cohort project and development of a referral checklist to ensure the best possible patient outcomes. We subsequently arranged a case-based presentation at the Department of Anesthesia's Mortality and Morbidity conference, to discuss commonly encountered drug allergy issues in the perioperative setting including associated HSRs. We encouraged sending serum total tryptase within 4 hours for any suspicion of a perioperative HSR and outpatient referral to Allergy. To ensure the vigilant capture of all possible or probable perioperative HSRs, we maintained weekly communication with the Anesthesia Department's Quality Assurance team during the study period.

Skin testing was performed between 4 weeks and 6 months of the perioperative HSR to minimize false-negative results.[11] Intradermal and/or skin prick testing was performed to all agents received before the HSR with published nonirritating skin testing concentrations. Inhalational agents, which have not been demonstrated to cause HSRs and to which no standardized skin testing exists, were not skin tested. Skin testing during allergy evaluation was performed with nonirritating skin testing concentrations, and appropriately positive (histamine 6 mg/mL) and negative (saline) controls (Table II). A positive skin prick reaction, suggesting an IgE-mediated cause, was considered if the diameter of the wheal was at least 3 mm larger than that induced by the negative control. If the skin prick test was negative, increasing concentrations of intradermal skin testing was performed, when available. A positive intradermal skin test reaction was considered if the diameter of the wheal had an increase of more than 3 mm compared with the saline wheal, and had an associated erythematous flare.

Laboratory evaluation of patients including total baseline tryptase level (if perioperative tryptase value during the HSR was elevated or

TABLE II. Skin testing reagents

Medication	Concentration	SPT	ID dilution
Atracurium[12,13]	10 mg/mL	Undiluted	1:1000
Benzylpenicilloyl polylysine[14]	6.0×10^{-5} M	Undiluted	Undiluted
Bupivacaine 0.25%[13,15,16]	0.25%	Undiluted	1:100
Cefazolin[14,17]	330 mg/mL	Undiluted	1:100 1:10
Ceftriaxone[14,17]	100 mg/mL	Undiluted	1:100 1:10
Cefuroxime[14,17]	100 mg/mL	Undiluted	1:100 1:10
Ciprofloxacin[18]	2 mg/mL	Undiluted	1:1000 1:100
Cisatracurium[12,13]	2 mg/mL	Undiluted	1:1000 1:100
Chlorhexidine gluconate 0.5%[13]	1.2 mg/mL	Undiluted	1:2500
Chloroprocaine 1%[13,15,16]	1%	Undiluted	1:100
Etomidate[13]	2 mg/mL	Undiluted	1:1000 1:100 1:10
Fentanyl[13]	0.05 mg/mL	Undiluted	1:10,000 1:1000 1:100 1:10
Ketamine[12,13]	10 mg/mL	Undiluted	1:40
Latex[12]	Latex fragments soaked in saline	Undiluted Prick through dry glove Prick through wet glove	N/A
Lidocaine 1%[13,15,16]	1%	Undiluted	1:100
Midazolam[12,13]	5 mg/mL	Undiluted	1:20 1:10
NPH insulin[19,20]	100 IU/mL	Undiluted	1:1000 1:100
Odansetron[21,22]	2 mg/mL	Undiluted	1:100
Pancuronium[12,13]	2 mg/mL	Undiluted	1:1000 1:100 1:10
Penicillin G[14]	10,000,000 U/mL	1:100	1:1000 1:100
Propofol[12,13,23]	10 mg/mL	Undiluted	1:1000 1:100 1:10
Protamine sulfate[24]	10 mg/mL	1:10 Undiluted	1:100 1:10 Undiluted
Rocuronium[12,13]	10 mg/mL	Undiluted	1:1000 1:100
Succinylcholine[12]	20 mg/mL	Undiluted	1:1000
Tetracaine 1%[15,16]	1%	Undiluted	1:100
Vancomycin[17]	50 mg/mL	Undiluted	1:10,000
Vecuronium[12,13]	10 mg/mL	Undiluted	1:1000 1:100

ID, Intradermal testing; *IU*, international units; *mg*, milligrams; *ml*, milliliters; *SPT*, skin prick testing.

absent) and specific IgE testing for latex if there was evidence of perioperative latex exposure was obtained. Latex-specific IgE testing was performed using an ImmunoCAP system (Upjohn-Pharmacia, Uppsala, Sweden), and, if negative, latex skin testing was performed (Table II).

Following this comprehensive allergy evaluation, the allergy team made recommendations for subsequent use of anesthesia. A patient with a positive skin test, suggesting an IgE-mediated HSR, was advised to strictly avoid that specific agent. If a patient had negative skin testing, no specific medication avoidance was recommended. If skin testing was not available, or if skin testing was unable to be performed because of the use of antihistamine agents or need for urgent surgery, patients were advised 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. Patient monitoring during subsequent anesthesia for signs and symptoms of an HSR was recommended.

Follow-up data collection

Follow-up information on subsequent procedures was collected via standardized telephone interview for all patients who completed the comprehensive assessment. Patients who did not have follow-up information available in the electronic medical record were asked to sign medical record release to obtain their surgical and procedural records. All subsequent perioperative notes and anesthesia records were obtained and reviewed for details of exposure to medications evaluated during comprehensive allergy evaluation and development of HSRs.

RESULTS

Over the 17-month period, 30 patients with an HSR during anesthesia were referred to the allergy practice; 25 were included in the analysis. Five patients were excluded because of the following: below the age of 18 at the time of evaluation (n = 1), declined participation in the comprehensive evaluation (n = 2), or did not complete comprehensive allergy evaluation (n = 2).

Patient characteristics

Fifty-two percent (n = 13) of patients were female, with a median age of 52 (interquartile range [IQR] 43-66) years at the time of the initial HSR. The median time from the HSR to the initial allergy evaluation and skin testing was 32 (IQR 3-89) days and 61 (IQR 49-146) days, respectively (Table III). At the time of the allergy evaluation, 56% (n = 14) of patients reported a prior history of drug allergy, 20% (n = 5) reported a previous diagnosis of allergic rhinitis, 20% (n = 5) reported a diagnosis of asthma, 12% (n = 3) reported a history of food allergy, and no patients reported a previous diagnosis of eczema. No patients reported a previous history of allergy to any anesthetic agent.

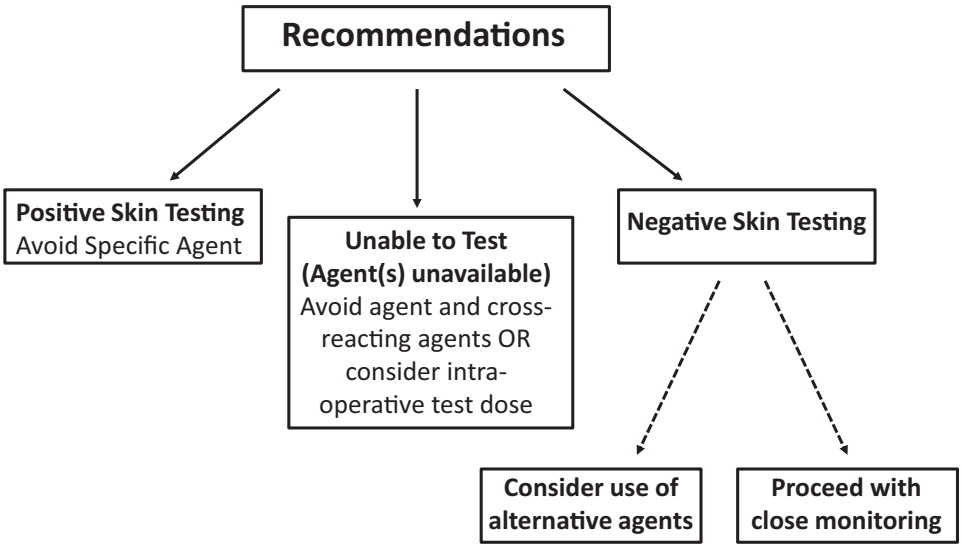

FIGURE 1. Recommendations for future anesthesia following evaluation. Recommendations were provided for subsequent procedures using the results of comprehensive allergy evaluation including skin testing to all available agents received immediately before the HSR and listed in the anesthetic record.

HSRs during anesthesia

Seven patients (28%) had a grade I HSR, whereas 10 (40%) patients had a grade II HSR. All the 6 patients with a grade III HSR had hypotension with or without respiratory symptoms. The 2 patients with a grade IV HSR had cardiac arrest and neither developed respiratory failure. During the HSR, 17 patients (68%) experienced cutaneous signs and symptoms (urticaria, rash, and flushing), 5 (20%) had oropharyngeal or mucosal symptoms (angioedema and throat tightness), 6 (24%) had pulmonary symptoms (bronchospasm, shortness of breath, and wheezing), and 16 (64%) had cardiovascular signs (bradycardia, tachycardia, hypotension, and arrhythmia). Serum total tryptase levels were obtained in 11 patients (44%) during their HSR; levels were elevated at greater than 11.4 ng/mL in 8 (73%) of these patients (Table IV). Ten tryptase values were obtained within 4 hours of the onset of the HSR and 8 were elevated (Table IV). One additional patient had a tryptase checked at 8 hours, which was not elevated (6 ng/mL).

Comprehensive allergy evaluation and management

Skin testing to agents administered perioperatively or latex-specific IgE testing identified a causative agent in 9 of the 25 patients (36%) who completed the comprehensive evaluation. All of the 9 patients with positive skin testing were positive to antibiotics. Of these patients, 6 had positive skin testing to cefazolin, 1 patient had positive skin testing to penicillin (PCN) G, 1 patient had positive skin testing to ciprofloxacin, and 1 patient had positive skin testing to vancomycin (Table V). In addition, 2 patients were found to have a persistently elevated tryptase levels. Both of these patients underwent evaluation for possible mastocytosis, with negative bone marrow biopsy results. There were no positive skin tests to any other agents administered perioperatively.

Following our management plan (Figure 2),[6] 8 patients underwent subsequent anesthesia with 7 (88%) tolerating operative procedures regardless of the severity of the initial HSR (Figure 2).

TABLE III. Patient characteristics

Demographic and clinical features of HSRs	n = 25
Age at the time of the HSR median (IQR)	52 (43-66)
Sex: female no. (%)	13 (52)
Time from HSR to allergy evaluation (days) median (IQR)	32 (3-89)
Time from HSR to skin testing (days) median (IQR)	61 (49-146)
Patient-reported history of drug allergy	14 (56)
Patient-reported history of atopic disorders	
Asthma	5 (20)
Allergic rhinitis	5 (20)
Eczema	0 (0)
Food allergy	3 (12)
Any atopic disorder*	6 (24)
Severity of perioperative HSR	
I	7 (28)
II	10 (40)
III	6 (24)
IV	2 (8)
Organ system involvement	
Cutaneous	17 (68)
Oropharyngeal	5 (20)
Pulmonary	6 (24)
Cardiovascular	16 (64)
Gastrointestinal	3 (12)
Other	3 (12)

HSR, Hypersensitivity reaction; *IQR*, interquartile range.
*Defined as history of asthma, allergic rhinitis, eczema, or food allergy. Values are n (%) unless indicated otherwise.

Only one of these patients had an elevated baseline tryptase value, but tolerated subsequent anesthesia without incident. Five (63%) of the patients had positive skin test results and alternative antibiotic agents were used during subsequent anesthesia without development of a perioperative HSR. Premedication or the use of

TABLE IV. Perioperative HSR-associated tryptase values*

Subject ID	Sex	Grade of reaction	Total tryptase (ng/mL)†	Time to tryptase (min)
1	M	III	62	30
2	M	III	61	80
7	M	II	4	55
10	M	III	247	80
12	F	III	38	45
17	F	II	69	45
19	M	II	21	102
24	F	IV	182	70
26	F	II	25	160
27	M	II	3	170
Median* (IQR)			50 (22-67)	75 (48-97)

IQR, Interquartile range; *min*, minutes; *ng/mL*, nanograms per milliliter.
*All listed values were obtained within 4 h of the HSR onset.
†Tryptase reference range is <11.5 ng/mL.

TABLE V. Causative antibiotic agents identified by skin testing

Subject ID	Sex	Grade of reaction	Procedure performed	Total tryptase during the HSR (ng/mL)*	Positive skin test
2	M	III	Muscle biopsy	61	Cefazolin
6	F	II	Lumpectomy	–	Cefazolin
8	F	I	Total knee replacement	–	Cefazolin
10	M	III	Renal transplantation	243	Cefazolin
17	F	II	Atrial fibrillation ablation	69	Vancomycin
18	M	III	Endoscopy with biopsy	–	PCN
19	M	II	Brachial plexus block	21	Cefazolin
26	F	II	Bilateral mastectomy	25	Ciprofloxacin
29	M	II	Rotator cuff repair	–	Cefazolin

F, Female; *HSR*, hypersensitivity reaction; *M*, male; *ng/mL*, nanograms per milliliter; *PCN*, penicillin.
*Tryptase reference range is <11.5 ng/mL.

alternative agents with the exception of antibiotics was not recommended for patients undergoing subsequent anesthesia. In the remaining 3 patients with negative skin testing results, 1 (33%) developed a perioperative HSR after undergoing subsequent anesthesia. The perioperative HSR experienced by this patient was a mild cutaneous reaction (erythematous patches only) that spontaneously resolved without intervention. Two (67%) of the patients underwent subsequent anesthesia using the same agents and did not develop an HSR. One (13%) patient underwent subsequent anesthesia without reaction; however, detailed anesthesia reports were not available.

DISCUSSION

Twenty-five patients completed a prospective comprehensive evaluation after the perioperative HSR, and a suspected IgE-mediated cause, with positive skin testing, was found in 36%, higher than 18% in a previously published study.[6] We identified antibiotics as the most commonly identified cause of perioperative HSRs by skin testing, with cefazolin having the most frequently observed positive skin testing. Tryptase levels, obtained during HSRs, aid in the evaluation of perioperative anaphylaxis. Nearly all patients who completed this evaluation and followed recommendations tolerated subsequent anesthesia, suggesting the value of allergy evaluation and management to both the patient and the anesthesiologist.

Causative agents have varied between studies. Dong et al[4] from France evaluated 1253 patients with an HSR during anesthesia, and were able to establish a diagnosis of an IgE-mediated HSR in 786 cases (63%), whereas 467 cases (37%) were considered non–immune-mediated. The French investigators found that NMBAs were the most frequent cause of anaphylaxis (47%), followed by latex (20%), antibiotics (18%), opioids (2%), colloids (2%), hypnotics (1%), and other substances including dyes (9%). Investigators from Spain reported a much higher incidence of antibiotics causing anaphylaxis (44%).[25] Protamine, cisatracurium, amoxicillin-clavulanate, atracurium, and dipyrone (in order of most to least likely) were recently found in a prospective cohort from Spain as causes of an IgE-mediated perioperative HSR.[2] A case series of 38 patients with a perioperative HSR from the United States found an IgE-mediated cause in 18 (47%), with 9 of these patients having positive skin testing to an antibiotic.[8] Overall, cefazolin (7 patients) was the most common agent identified. In this same series, 6 of these patients had elevated tryptase levels, but negative skin testing, and a non–IgE-mediated reaction was suspected in the remaining cases. A more recent case series of 30 patients with a perioperative HSR from the United States by Gonzalez-Estrada et al found an IgE-mediated cause in 17 (57%). Ten of these patients had positive skin testing to an antibiotic.[7] The observed differences between these studies have several possible explanations including population level rates of sensitization and nonstandard timing and methods of skin testing.

Similar to the recently published Spanish[25] and US[6,7] studies, we also found that antibiotics were the most frequently identified cause of perioperative HSRs. Compared with our institution's prior study,[6] our higher rate of skin test positivity (36% vs 18%) may be due to the availability of antibiotic skin testing and the reduced time interval to testing. It is unclear why our rates of skin test positivity are not as high as other recent studies, but may be explained by a less severe perioperative HSR in our study compared with others (64% vs 97% of patients with hypotension) or selection and/or referral bias present in the retrospective studies compared with our more inclusive cohort study. Cefazolin, a first generation cephalosporin, is the recommended first-line prophylactic agent for most procedures, including hip and knee surgeries, and in combination with metronidazole for colorectal surgery.[26] Cefazolin does not share side chains with other cephalosporins or β-lactam antibiotics. In patients with cefazolin allergy in the perioperative setting, other cephalosporins such as cefoxitin would be tolerated based on its different side chain.[27] Data supporting cefazolin tolerance in PCN-allergic patients come from only retrospective reviews that are subject to selection bias. In one review of 300 patients with a documented PCN allergy, only one had an adverse reaction to cefazolin.[28] To date, we know of no specific reports of patients' tolerance of PCNs given the IgE-mediated HSR to cefazolin. Previous perioperative HSR evaluation-related studies, including

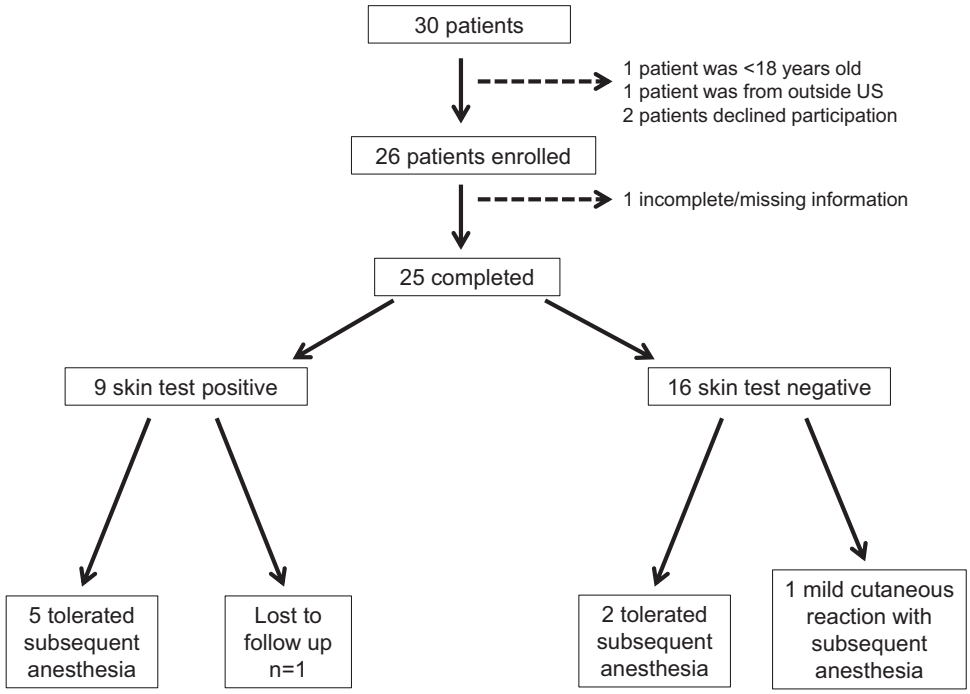

FIGURE 2. Outcomes after comprehensive evaluation. Of the 30 patients consecutively referred to our center, 4 were excluded (1 patient <18 years old, 1 patient lived outside the United States, 2 patients declined participation), 26 patients were enrolled, and 25 patients completed our comprehensive evaluation. Of these 25 patients, 8 underwent subsequent anesthesia and 1 was lost to follow-up. All 5 patients with a positive skin test tolerated the subsequent anesthesia. One of 3 patients that had negative skin testing had a mild reaction with subsequent anesthesia.

one from our institution,[6] may have had a lower rate of antibiotic skin test positivity due to the lack of antibiotic skin testing reagents. Of the 9 patients, 6 identified with positive skin testing in our study were positive only to cefazolin. Given the findings of our study, we suggest that anesthesiologists and proceduralists follow guidelines[3] that recommend that antibiotic prophylaxis be administered preoperatively to a monitored, awake patient before anesthesia induction.

Generally, we were able to evaluate patients with a perioperative HSR within 1 month after the HSR, and skin test patients within 2 months. This likely helped us to find a higher rate of positive skin tests, because previously published data report a decline over time in IgE antibodies in patients with drug allergy.[6,9,10,29,30] In 2013, Lafuente et al[30] found 25 patients (57%) with positive skin testing when performed at 0-4 days (stage 1) and again at 4-8 weeks (stage 2) after the perioperative HSR. Interestingly, a higher rate of skin test positivity was found in stage 1 (60%) compared with stage 2 (40%) with 3 patients having positive skin testing only in stage 1. This may be a consequence of false-negative results when testing is delayed. In one study, the mean time to evaluation after the HSR in skin test positive subjects was 12 months, compared with 36 months in those who were skin test negative.[29] Avoidance of false-negative skin testing can be achieved if performed at least 4 weeks after the HSR.[9,10] Therefore, a patient with an HSR during anesthesia should be referred for evaluation, with HSR-specific skin testing completed within 6 weeks to 6 months of the reaction.

Our recommendation, after negative skin testing, was no specific medication avoidance. We certainly recognize the concern for false-negative skin testing because our testing is not standardized with an established negative predictive value. Concern for false-negative testing may be even higher when the timing of skin testing is not optimal. In our study, we identified only 3 patients with negative skin testing and all of these patients had mild-to-moderate HSRs. If a patient experiences a severe HSR and has negative skin testing, there are no data to inform our best practices. It may be appropriate to suggest the use of alternative agents in these cases. Further data are needed to optimize recommendations after negative skin testing.

Elevated or increased perioperative tryptase levels are seen in IgE-mediated and non−IgE-mediated perioperative HSRs. Similar to a recent study[7] that found elevated tryptase levels in 100% (10 of 10) of cases of IgE-mediated anaphylaxis, our study showed 67% (6 of 9) of patients with an elevated tryptase having an IgE-mediated cause, compared with 0% (0 of 2) with a nonelevated tryptase level. An increase in serum tryptase compared with the baseline value is an indicator of mast cell activation even if the serum tryptase level is below the upper normal value of 11.4 ng/mL.[31] Although an elevated tryptase level is helpful in determining whether or not a perioperative HSR is IgE mediated, it is certainly not diagnostic. Dong et al[4] reported in 2012 on 599 cases of perioperative HSRs in which serum tryptase was measured and found a mean tryptase level of 13 ng/mL in 10.6% of cases labeled as non-IgE HSR. However, the information gained through obtaining a tryptase level during a potential perioperative HSR likely outweighs cost involved in conducting the test. Given the importance of this test in helping the allergist evaluate patients with perioperative HSRs, we

frequently engage the Department of Anesthesia with case-based educational events that demonstrate its utility. Performing perioperative tryptase testing in cases of suspected HSR has become a quality improvement goal shared by both departments.

In our study population, 2 patients had persistently elevated tryptase levels during the HSR and after the event in follow-up. Both of these patients underwent evaluation for possible systemic mastocytosis. Although uncommon, mast cell disorders were identified in 3 (4%) patients of our institutions' prior perioperative HSR study.[6] Further support of this statement comes from a previous study of mast cell disease in patients with drug HSRs, where 7 of 86 (8%; 95% confidence interval 3.8%-16.1%) patients with drug hypersensitivity had increased serum tryptase levels (>11.4 ng/mL), although only 1 patient was diagnosed with systemic mastocytosis after bone marrow biopsy.[32] Although incidence rates remain unknown, general anesthetics have been listed as risk factors for anaphylaxis in patients with mastocytosis,[33-36] and guidelines have been published to minimize the risks of anesthesia in adult patients with systemic mastocytosis.[37,38] It is therefore important to repeat a total tryptase measurement at least 24 hours after all signs and symptoms of an HSR have resolved for patients who develop a perioperative HSR.

This study has several limitations, including its low number of subjects. Indeed, we had only 9 patients with subsequent anesthesia, which is far too low to draw firm conclusions on the safety of subsequent anesthesia following our recommendations. However, this analysis provides a unique look at the clinical findings and recommendations made by allergists, and supports the utility and safety of our approach. The creation of a system for referral of all intraoperative anaphylaxis cases helped reduce selection bias, but when compared with the other prospective perioperative HSR study,[2] we may have been referred the more severe reactions and may have missed more mild reactions. In select cases, we were limited by the delayed timing of skin testing or the patient's preference not to pursue a comprehensive evaluation. This delay in skin testing could have led to false-negative results given the waning of skin test positivity over time.[39] We are also limited by the lack of validated skin testing for most drugs, except for PCN, used in skin testing. For instance, a nonirritating concentration for ciprofloxacin remains a point of controversy in the literature and results should be interpreted with caution.[17,40,41] It is possible that we identified antibiotics as the most common cause of an IgE-mediated perioperative HSR because antibiotic testing is superior to testing for other agents. However, our protocols use the nonirritating concentrations informed by the best data currently available and consistent with the testing standards in the Drug Allergy Practice Parameters. Additionally, because anesthetic drugs require expert administration, patients in our study with negative skin tests did not undergo drug challenges to confirm the lack of drug hypersensitivity. Lastly, we report on only 1 Boston teaching hospital, so our experience here may not be generalizable to different patient populations, geographic areas, or hospitals and/or clinics with different practices and resources.

In summary, we identified antibiotics—specifically, cefazolin—as the most likely cause of a perioperative HSR in our patient cohort. Additionally, a serum tryptase test may be helpful in evaluating a perioperative HSR. Furthermore, by prospectively enrolling patients in our institution's comprehensive evaluation and management plan, they were able to tolerate subsequent anesthesia.

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