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Evaluation of periprocedural hypersensitivity reactions

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ABSTRACT

Background: Identifying the cause of periprocedural hypersensitivity reactions (HSRs) remains challenging because of the multitude of medications involved. Antibiotics are the most common cause in the United States, whereas neuromuscular blocking agents are most common in Europe.

Objective: To identify causative agents for periprocedural HSRs.

Methods: This study was a 7-year retrospective medical record review of patients evaluated between December 2009 and January 2017 at a drug allergy center in Bronx, New York for periprocedural HSRs, defined as occurring soon before, during, or soon after a medical procedure or operation with or without general anesthesia. Demographics, description of historical HSRs, results of testing to potential causative medications, and tolerance of subsequent anesthesia were reviewed.

Results: Thirty-four patients completed a comprehensive evaluation. Skin testing identified an IgE-mediated cause in 22 patients (64.7%). The most common causative class of medications was induction agents ($n = 9$ [36%]), with midazolam being the most frequently implicated ($n = 6$ [3 positive skin test results, 3 equivocal skin test results]). Cefazolin was the most common agent identified ($n = 8$ [32%]) followed by ondansetron ($n = 3$ [12%]). Sixteen of 22 contacted patients were exposed to subsequent anesthesia, including 3 patients with negative evaluations. One patient experienced a mild urticarial HSR.

Conclusion: Induction agents were the most common causative agents in our patients, which differs from other studies. Given the variability in evaluations of periprocedural HSRs across the United States with data published on small sample sizes, there is a need to establish national guidelines to standardize evaluations and to create a national registry to allow for data sharing.

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Introduction

The estimated incidence of perioperative hypersensitivity reactions (HSRs) varies among countries and ranges from 1 in 385 to 1 in 20,000 procedures, with an associated mortality rate of 3% to 9%.^{1–9} A recent study published at a large tertiary care center in the United States noted the occurrence of hemodynamically significant anaphylaxis at a rate of 1 in 8,400 perioperative cases.¹⁰ Identifying the cause of these perioperative HSRs remains challenging because of the multitude of medications administered.¹¹ Comprehensive skin testing to all perioperative agents is recommended along with testing for specific IgE to latex.^{2,11,12} Using this approach, studies have varied in their ability to identify the causative agent, ranging from 18% to 91% of their evaluations.^{3–5,13–22} Recent US studies cited antibiotics as the most common identifiable cause, whereas most European countries identified neuromuscular blocking agents (NMBAs) as the most likely cause.^{3–5,13–21} One Spanish study concluded that antibiotics were the most likely culprit of an

IgE-mediated perioperative HSR in their patient population followed by NMBAs.¹⁶ Although most European studies reported on large patient populations, partly because of diagnosis reporting systems established in many of these countries, most US studies have small sample sizes, ranging from 25 to 73 cases, with culprit agents identified in only 18% to 57% of patients.^{2,4,5,13,22} Therefore, the results of these studies may not be generalizable to different patient populations or geographic locations in the United States. The lack of reporting on the racial and ethnic background of the patient populations in most of these studies may further reduce their generalizability.^{4,5,22} The primary objectives of our study were to characterize patients evaluated at a single tertiary care academic center in the United States for periprocedural HSRs and to compare outcomes in our patients with previously published data.

Methods

We performed a 7-year retrospective electronic medical record review of all patients who underwent evaluation for periprocedural HSRs (defined as HSRs occurring soon before, during, or soon after a medical procedure or operation performed with or without the patient under general anesthesia) at an outpatient drug allergy clinic affiliated with a single tertiary care academic center in Bronx,

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New York, between December 2009 and January 2017. This study was approved by the institutional review board at Montefiore Medical Center/Albert Einstein College of Medicine.

Patients were identified through a database maintained for the drug allergy clinic. A description of the historical periprocedural HSR was obtained through a detailed review of periprocedural medical records, including anesthesia records, nursing records, and operative or procedural reports, when available, and outpatient and inpatient allergy and immunology consultation notes. The severity of the historical periprocedural HSRs was graded on a scale of I to IV adapted from previously published classification systems (eTable 1).^{2,5,23} Medications administered at the time of the procedure were recorded along with serum-specific IgE to latex and serum tryptase, when available. Patient demographics were recorded along with history of prior drug allergy. Results of subsequent outpatient skin prick testing and intradermal testing to potential causative medications administered periprocedurally were reviewed.

All patients underwent individualized testing for potential causative agents using the following standardized panels, as appropriate: NMBAs (succinylcholine, vecuronium, rocuronium, and cisatracurium); induction agents (propofol, etomidate, midazolam, and ketamine); β -lactams (benzylpenicilloyl polylysine, penicillin G, ampicillin, cefazolin, cefoxitin, and ceftriaxone); opiates (morphine and fentanyl); local anesthetics (lidocaine with and without preservative, bupivacaine, mepivacaine, ropivacaine, and chloroprocaine); and ondansetron. At our drug allergy clinic, nonirritating skin testing concentrations are used based on prior studies (Table 1), along with a percutaneous positive histamine control and percutaneous and intradermal negative saline controls.^{2,24–29} A positive intracutaneous reaction, suggestive of an IgE-mediated cause, was defined as a wheal diameter of at least

3 mm larger than the negative control. If the skin prick test result was negative, intradermal testing was performed at defined increasing nonirritating concentrations (Table 1). An intradermal test result was considered positive if the wheal diameter was 3 mm or larger than the wheal of the negative intradermal control and associated with an erythematous flare. Agents were considered causative if they were known to be administered in the periprocedural period and associated with positive skin test results. Patients with positive or equivocal percutaneous and intradermal skin test results were advised to avoid future use of the agent. Patients with negative skin test results to β -lactams and local anesthetics were subsequently challenged to these medications. Because culprit drugs could not be identified in patients who had incomplete anesthesia records, these patients were tested to broad panels of potentially administered drugs and advised to avoid subsequent use of agents with positive or equivocal skin test results. Patients who did not complete a comprehensive evaluation were excluded from analyses. Tolerance of subsequent procedures based on recommendations after completion of the evaluation was obtained through electronic medical record review and telephone calls to patients.

Results

Between December 2009 and January 2017, 42 patients were referred to our drug allergy clinic for evaluation of periprocedural HSRs; 34 patients were included in the analysis. Three patients did not complete a comprehensive evaluation, 1 patient had a history of multiple drug reactions and was referred preoperatively as a precaution, and 2 patients had atypical reactions not consistent with a periprocedural HSR, including acquired methemoglobinemia presumably attributable to benzocaine and a nonimmediate rash 48 hours after a colonoscopy. Two patients who experienced cardiac arrest were deemed unlikely to have had HSRs and were excluded. One patient's arrest was most likely attributable to endotracheal tube malpositioning given complete recovery after repositioning and suctioning of the tube, whereas the other patient likely experienced a known extreme adverse effect of nitroglycerin.

Patient Characteristics

Most patients were female ($n = 25$ [73.5%]), with a median age of 44 years (range, 13–75 years) at the time of their HSR and a median timeframe of 16 weeks (range, 2 weeks to 22 years) between their HSR and evaluation. White ($n = 11$ [32.3%]), Latino ($n = 10$ [29.4%]), and black ($n = 7$ [20.6%]) patients were represented in our patient population. Most patients had no prior drug allergies (median, 0; range, 0–5). Most HSRs were grade III severity and met the criteria for anaphylaxis ($n = 18$ [53%]). Tryptase levels were obtained during periprocedural HSRs for 5 patients and were greater than 11.4 ng/mL (the upper limit of normal in our laboratory) in all cases (median, 29.4 ng/mL; range, 13.6–76 ng/mL). Tryptase levels normalized on repeat in all but one patient, whose level decreased from 37 to 13 ng/mL 6 weeks after his anaphylactic reaction. The etiologic culprits for 4 of the 5 patients with elevated serum tryptase levels were cefazolin ($n = 3$) and rocuronium ($n = 1$). The fifth patient was found to have a positive latex IgE test result (27 kU/L); it is unknown if she was exposed to latex during her procedure. Complete anesthesia records were available for 26 patients (76.5%) (Table 2).

Results of Comprehensive Evaluation

Skin testing to agents administered periprocedurally identified an IgE-mediated cause in 22 patients (64.7%), with a total of 25 positive test results (eTable 2 and Fig 1). The most common causative class of medications was induction agents ($n = 9$ [36%]), of which midazolam was most frequently implicated ($n = 6$ [3 positive skin test results, 3 equivocal skin test results]) followed by

Table 1
Skin Test Reagents

Medication	Concentration	SPT dilution	ID dilution
NMBAs			
Succinylcholine ^{2,22}	50 mg/mL	1:5	1:10,000, 1:1000, 1:500
Vecuronium ^{2,22}	4 mg/mL	Undiluted	1:10,000, 1:1000, 1:100, 1:10
Rocuronium ^{2,22}	10 mg/mL	Undiluted	1:10,000, 1:1000, 1:100
Cisatracurium ^{2,22}	2 mg/mL	Undiluted	1:10,000, 1:1000, 1:100
Anesthetic induction agents			
Propofol ^{2,22}	10 mg/mL	Undiluted	1:1000, 1:100, 1:10
Etomidate ^{2,22}	2 mg/mL	Undiluted	1:1000, 1:100, 1:10
Midazolam ^{2,22}	5 mg/mL	Undiluted	1:1000, 1:100, 1:10
Ketamine ^{2,22}	10 mg/mL	Undiluted	1:1000, 1:100, 1:10
Opiates			
Morphine ^{2,22}	10 mg/mL	1:10	1:10,000, 1:1000
Fentanyl ^{2,22}	0.05 mg/mL	Undiluted	1:1000, 1:100, 1:10
β-Lactams			
Penicillin G ²³	1,000,000 U/mL	6,000 U/mL	100 U/mL, 1000 U/mL, 6000 U/mL
Benzylpenicilloyl polylysine ²⁴	6×10^{-5} mol/L	Undiluted	Undiluted
Ampicillin ^{22,25}	20 mg/mL	Undiluted	Undiluted
Ceftriaxone ^{22,26}	2 mg/mL	Undiluted	Undiluted
Cefoxitin ²²	2 mg/mL	Undiluted	Undiluted
Cefazolin ²²	2 mg/mL	Undiluted	Undiluted
Local anesthetics			
Bupivacaine ²	2.5 mg/mL	Undiluted	1:1000, 1:100, 1:10
Lidocaine ²	10 mg/mL	Undiluted	1:1000, 1:100, 1:10
Lidocaine, preservative free ²	10 mg/mL	Undiluted	1:1000, 1:100, 1:10
Mepivacaine ²	10 mg/mL	Undiluted	1:1000, 1:100, 1:10
Ropivacaine ²	2 mg/mL	Undiluted	1:1000, 1:100, 1:10
Chloroprocaine ²	10 mg/mL	Undiluted	1:1000, 1:100, 1:10
Other agents			
Ondansetron ²⁷	2 mg/mL	Undiluted	1:100, 1:10, 1:1

Abbreviations: ID, intradermal test; NMBA, neuromuscular blocking agent; SPT, skin prick test.

Table 2
Patient Characteristics

Characteristic	Finding ^a (N = 34)
Age at time of HSR, median (range), y	44 (13–75)
Female sex	25 (73.5)
Race/ethnicity	
White	11 (32.3)
Latino	10 (29.4)
Black	7 (20.6)
Multiracial	2 (5.9)
Other or unknown	4 (11.8)
No. of prior drug allergies, median (range)	0 (0–5)
Time between HSR and skin testing, median (range)	16 (2 weeks – 22 years)
Grade of perioperative HSR	
I	8 (23.5)
II	8 (23.5)
III	18 (53)
IV	0 (0)
Tryptase during HSR, median (range), (ng/mL) (n = 5)	29.4 (13.6–76)
Patients with complete anesthesia records	26 (76.5)
Patients with perioperative HSRs	22 (64.7)
Patients with perioperative HSRs	10 (29.4)
Patients with positive skin test results to known administered perioperative agents	22 (64.7)
Patients with at least 1 positive skin test or latex IgE test result	31 (91.2)
Patients sensitized to >1 agent	25 (73.5)

Abbreviation: HSR, hypersensitivity reaction.

^aData are presented as number (percentage) of patients unless otherwise indicated.

etomidate (n = 1), ketamine (n = 1), and propofol (n = 1). Cefazolin was the next most common agent identified (n = 8 [32%]) followed by ondansetron (n = 3 [12%]), NMBAs (n = 2 [8%]), lidocaine (n = 2 [8%]), and fentanyl (n = 1 [4%]). Three patients (patients 1, 9, and 34) were found to have potentially 2 causative agents. Thirty-one patients (91.2%), including 23.5% of patients with incomplete anesthesia records, had positive skin test or in vitro test results. A total of 83 skin test results were positive, including 16 equivocal tests (ketamine [n = 5], midazolam [n = 4],

vecuronium [n = 3], cisatracurium [n = 1], rocuronium [n = 1], morphine [n = 1], and fentanyl [n = 1]) (eTable 2 and Fig 2). Four patients had elevated serum-specific latex IgE (median, 8.45 kU/L; range, 2.7–27 kU/L).

Induction agents (n = 33 [38%]) and NMBAs (n = 23 [26%]) produced the most common positive test results in all patients with perioperative HSRs, including those whose perioperative medications were unknown (Fig 2). Twenty-five patients had more than one positive skin test result and/or elevated latex IgE level. Although fentanyl was administered perioperatively in at least 21 cases, it was identified as a causative agent in only 1 patient. In contrast, ondansetron was only documented to be administered in 6 cases and was identified as the causative agent in 3 (50%) of these patients. Cefazolin was also considered the culprit in 50% of the 16 cases in which it was known to be administered (Fig 3).

Causative agents were identified in most patients with grade I HSRs (62.5%) and grade III HSRs (83.3%) in contrast to 25% of patients with grade II HSRs. Three patients had no positive test results. Chlorhexidine was tested on 2 of these patients, and results were negative in both.

Tolerance of Subsequent Anesthesia

Nineteen of the 31 patients with positive skin test or latex IgE test results were reached for follow-up along with all 3 patients with negative test results (Fig 4). Twelve of 13 patients who required another procedure tolerated subsequent anesthesia based on recommendations to avoid agents with positive or equivocal test results. One female patient developed urticaria localized to her neck during a subsequent surgery that promptly resolved with diphenhydramine, and her surgery was completed. Her initial perioperative reaction was grade III anaphylaxis with diffuse urticaria, increased peak airway pressures, and hypotension after intubation for an aortic valve replacement. Midazolam was found to be the causative agent on skin tests and was subsequently avoided. Chlorhexidine was used preoperatively in both cases, which was not tested. All 3 patients with no identifiable causative agents tolerated subsequent anesthesia.

Discussion

An identifiable IgE-mediated cause of perioperative HSRs was found in 64.7% of our diverse patient population, which had near-equal representation of white, Latino, and black racial and

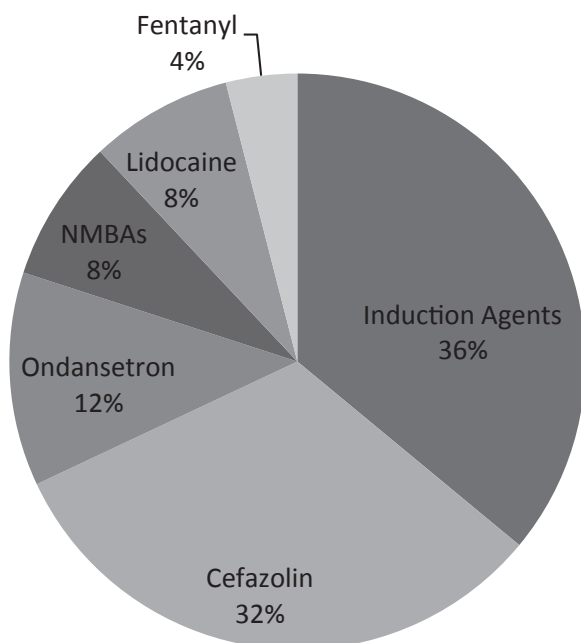


Figure 1. Agents with positive skin test results to administered perioperative agents. A total of 25 skin test results were positive, including 3 equivocal test results, in 22 of 34 patients (64.7%) with identifiable causative agents. NMBAs, neuromuscular blocking agents.

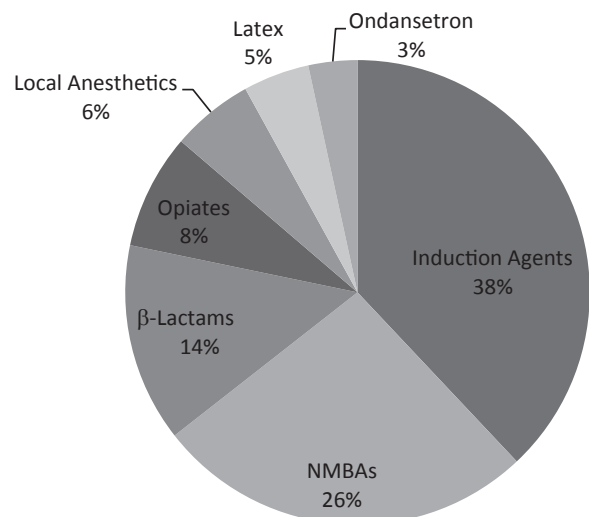


Figure 2. All agents identified by skin or latex IgE testing. A total of 87 skin test or latex IgE assay results were positive, including 16 equivocal test results, in 31 of 34 patients (91.2%).

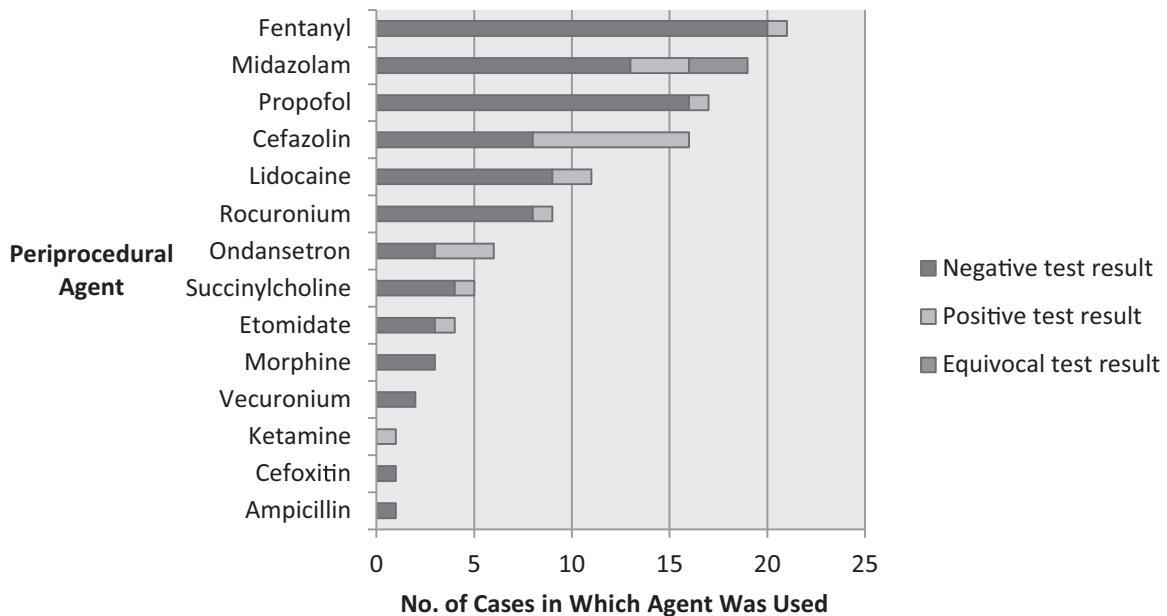


Figure 3. Results of skin tests to administered periprocedural agents. Fentanyl was the most commonly known administered periprocedural agent in at least 21 cases but was identified as a causative agent in only 1 patient. Ondansetron was the causative agent in 50% of the 6 cases it was given. Cefazolin was also considered the culprit in 50% of the 16 cases it was known to be administered. NMBAs, neuromuscular blocking agents.

ethnic groups. Our diagnostic rate is comparable to most US and European studies.^{3–5,13–19,21,22} Induction agents, particularly midazolam, were the most common causative agents in our patients, which differ from US and European studies that most commonly identified antibiotics and NMBAs, respectively.^{3–5,11–15,17–22} Patients with incomplete anesthesia records for whom the causative agent could not be definitively identified were also more likely to have positive skin test results to induction medications. In the 4 most recent US studies, induction agents were implicated in only 2 studies.^{4,5,13,22} Guyer et al²² identified 1 of 73 patients with a positive skin test result

to midazolam, whereas Gurrieri et al⁴ determined propofol to be a causative agent in one patient and both midazolam and propofol in another patient among 38 evaluated patients. Induction agents, including propofol (n = 3), midazolam (n = 2), ketamine (n = 2), and thiopentone (n = 1), were implicated in only 1.1% of 786 patients with an IgE-mediated perioperative anaphylactic event in France.¹⁵ Midazolam was the only induction agent identified as an IgE-mediated culprit in 2 of 103 patients (1.9%) in a study conducted in the United Kingdom, whereas no patients in 2 studies from Spain had positive test results to these medications.^{3,16,17}

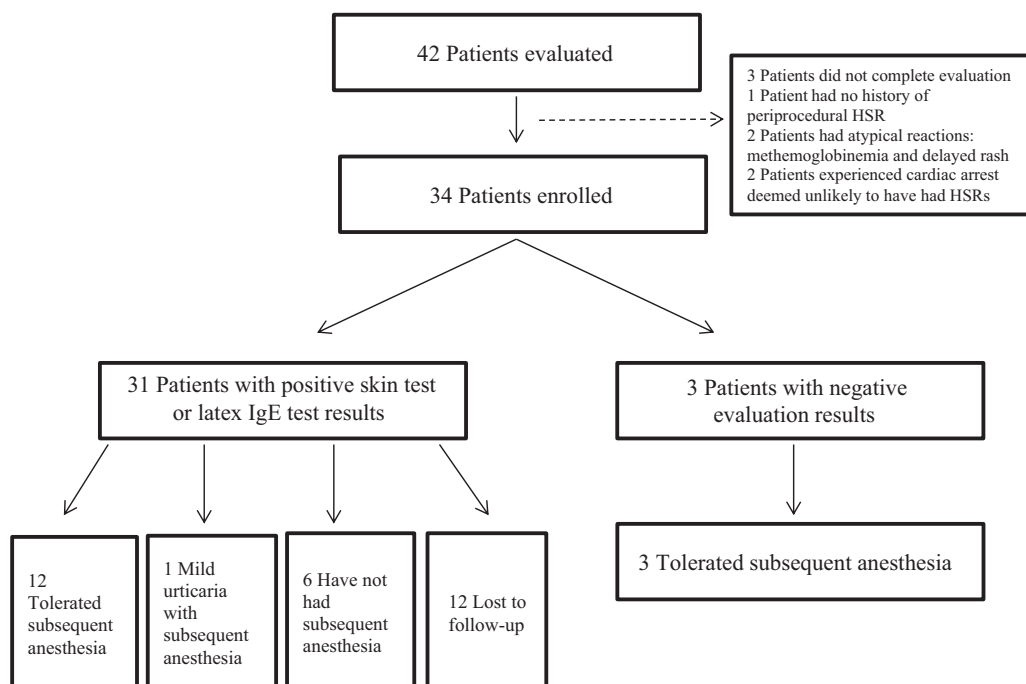


Figure 4. Outcomes after comprehensive evaluation. Of the 16 patients who were exposed to subsequent anesthesia, including 3 patients with negative evaluation results, only 1 patient experienced a mild hypersensitivity reaction (HSR).

Although variations in skin test practices occurred among these studies, they do not fully explain the higher proportion of induction agents identified as culprits in our population. For instance, the concentrations of intradermal preparations for induction agents used in 2 studies at Massachusetts General Hospital were the same as those used in our clinic except for ketamine, and only 1 patient was sensitized to an induction agent in both studies combined.^{5,22} Most European studies use the skin test guidelines jointly published by the European Network for Drug Allergy (ENDA) and the European Academy of Allergy and Clinical Immunology (EAACI) drug allergy interest groups, which specify nonirritating concentrations for NMBAs, induction agents, opiates, and local anesthetics that share the same highest intradermal concentration as our study except for rocuronium.² Given that these studies reported low rates of sensitization to induction agents in their patient populations, these concentrations are likely to be nonirritant and suggestive of true IgE-mediated causes in our patient population. However, given that 3 of 6 skin test results to midazolam were equivocal, skin tests were not performed again, and patients were not challenged to midazolam because of concern for invoking a reaction; it is unknown whether some of the equivocal or positive skin test results were potentially irritating in our patient population. Because the studies conducted at Mayo Clinic and Cleveland Clinic used lower intradermal concentrations for all induction agents and did not test for etomidate and ketamine, respectively, it is possible that some patients with IgE-mediated HSRs to induction agents were not identified.

Cefazolin, which was identified as the leading IgE-mediated cause of perioperative anaphylaxis in other US studies, was the second most common culprit in our patients.^{4,5,13} Because of the small sample sizes in all US studies, fluctuations in leading culprits are possible. Another potential reason for this finding is that intradermal concentrations were higher in 2 of these studies.^{4,5} However, although induction agents as a class were the most common culprits, cefazolin was the most frequently identified single agent. It was also identified as a culprit agent in 50% of the 16 cases in which it was known to be administered. Therefore, it remains an important cause of periprocedural HSRs in the United States.

In all patients evaluated for periprocedural HSRs at our clinic, including patients with incomplete anesthesia records, NMBAs were the second most common agent causing positive skin test result after induction agents. One potential explanation for the higher rate of detection of sensitization to NMBAs was the use of intradermal skin test concentrations on par with the ENDA/EAACI guidelines, which were used for most European studies that found NMBAs to be the most likely culprit.^{2,3,14–21} In recent US studies, skin test concentrations for NMBAs varied greatly and were often lower.^{4,5,13,22} It is not clear whether the use of higher concentrations capture more IgE-mediated reactions or result in irritant reactions.

Our study also noted that ondansetron was the third most common culprit in perioperative HSRs and a causative medication in half of the 6 cases in which it was administered, suggesting this is a potentially underrecognized cause. In a study from the United Kingdom, ondansetron was the cause of 4.9% of 103 perioperative HSRs.¹⁷ Interestingly, it was deemed the culprit in 3 of 13 patients with an IgE-mediated cause in one study at Massachusetts General Hospital in 2014 and none of the cases in a subsequent study at the same hospital published in 2016 using the same skin test concentrations.^{5,22} This discrepancy raises the possibility of the involvement of cofactors in perioperative HSRs. For example, a recent study at the University of Michigan Hospital found protamine was the only drug associated with an increased risk of hemodynamically significant perioperative anaphylaxis.¹⁰ It is unknown how many, if any, patients in our study may have received protamine.

The presence of cofactors during periprocedural HSRs may also explain why some patients with negative evaluations for IgE-mediated allergies are subsequently able to tolerate anesthesia without reactions, which was true for all 3 patients in our study with negative test results. In the study by Guyer et al,²² 37 of 41 patients with negative test results tolerated subsequent anesthesia, including 6 patients for whom the same anesthetic agents were used. Another possibility for the tolerance of subsequent anesthesia is the loss of sensitization through IgE antibodies to culprit drugs, which has been illustrated with β -lactams.³⁰ False-negative results are also possible if a long period has elapsed between the HSR and evaluation. With a median of 16 weeks between HSR and evaluation in our study, false-negative skin test results were possible. It is recommended that skin tests should be performed at least 4 to 6 weeks after an HSR to allow for recovery of allergic mediators from mast cells and basophils and to minimize false-negative results.² One of our patients initially tested 3 weeks after her perioperative HSR had negative skin test results to succinylcholine and positive test results when performed again 6 weeks after her reaction. Only 1 of our patients was tested 2 weeks after his reaction (patient 23), for whom rocuronium was identified as the culprit. All other patients were tested at least 4 weeks after their HSRs. In addition to false-negative results, non-IgE-mediated anaphylaxis, such as IgG-mediated anaphylaxis, direct mast cell activation, and complement-mediated mast cell activation, are possibilities in patients with negative skin test results.^{11,31}

Despite the potential for false-negative results, culprits were identified for most of our patients. However, it is unclear why induction agents, namely midazolam, were the most common culprit in our patients, which differs from all previously published studies. One possibility is the greater diversity of our patient population with the potential for different propensities for sensitization to agents based on exposure and perhaps genetic disposition. Only 1 of the 4 recent US studies specified the race and ethnicity of their patient population, which did not include any patients of Latino ethnicity.^{4,5,13,22} Ethnic differences have been found in drug-metabolizing enzymes, transporters, and pharmacodynamic targets, which can all affect the response to medications. Drug response may be affected not only by genetic differences but also by regional or cultural differences in diet and variations in concomitant medication use.³²

Cross-sensitizing external factors may also play a role in our findings, as previously illustrated by the link between pholcodine exposure and NMBA anaphylaxis. Pholcodine is an opioid cough suppressant with structural similarity to succinylcholine, available in Europe.³³ Pholcodine availability may partly explain the difference in prevalence of perioperative anaphylaxis among European countries and the United States. For instance, NMBA anaphylaxis was 6 times more common in Norway than Sweden. Pholcodine-containing cough mixtures are available in Norway but not in Sweden.^{34,35} One study noted IgE-sensitization to succinylcholine, morphine, and pholcodine in Norwegian patients, whereas no serum was positive in Swedish patients.³⁴ The higher rate of exposure to quaternary ammonium ions, including certain European cosmetics and household products, has also been hypothesized to increase the rate of cross-reactivity with NMBAs in some studies.^{35,36} Patients with quinolone sensitization also have a high prevalence of sensitization to quaternary amines, suggesting another potential path for NMBA sensitization.³⁷ Finally, there was a recent discovery of MRGPRX2, a mast cell receptor capable of causing histamine release in response to drugs that contain tetrahydroisoquinoline motifs, which includes NMBAs, quinolones, and icatibant.³⁸ It is unknown whether this receptor has greater representation in certain racial or ethnic groups and could partially explain the variation in sensitivity to NMBAs.

It is possible that unknown external cross-sensitizing factors may have increased the rate of positive skin test results to induction agents in our study. Midazolam, which yielded the most common positive skin test results among the induction agents, is a benzodiazepine with an imidazole structure that does not have any active metabolites.³⁹ Although cross-reactivity with other imidazole-based compounds is unknown, these compounds have widespread medicinal use in a variety of drugs used to treat cancer, infections, neuropathy, hypertension, and obesity.⁴⁰ Therefore, the possibility of sensitization attributable to one of these drugs is raised. Exposure to unknown cross-reactive agents may also explain why 73.5% of our patients had multiple sensitizations, which differs from most US studies. In the study by Kuhlen et al,⁵ all 9 patients with positive skin test results were sensitized to only one agent, all of which were antibiotics. Patients in the study by Gonzalez-Estrada et al¹³ were also sensitized to only one agent (antibiotics vs NMBAs vs latex). Only 2 of 18 patients (11.1%) in the study by Gurrieri et al⁴ and 1 of 13 patients (7.7%) in the study by Guyer et al²² with IgE-mediated etiologies were sensitized to more than one agent.

There are several limitations to our study. The retrospective nature in conjunction with evaluation of patients from outside institutions led to the absence of complete anesthesia records in 23.5% of our patients, thereby limiting our ability to diagnose a culprit drug in these cases. Three patients were found to have potentially 2 causative agents based on the criteria that these agents were administered periprocedurally and were found to be positive or equivocal on skin testing. In the absence of performing challenges to these medications, it is unknown whether both agents were synergistically causative or if one agent was the prime culprit, which was another limitation of our study. Because patients with positive or equivocal percutaneous and intradermal skin test results were advised to avoid future use of the agent, another potential limitation to our study is the inclusion of equivocal skin test results in our data analysis. This led to the identification of induction agents as the most common causative class of medications, which included 3 equivocal skin test results to midazolam.

Similar to other US studies, our study focused on the evaluation of patients at one center, leading to a small sample size with limited generalizability. Our patients also had the potential for false-negative results, with a median of 16 weeks between HSR and evaluation, which is longer than the recommended 4 to 6 weeks. We also did not routinely evaluate patients for sensitization to chlorhexidine. Of note, the only patient in our study who developed a mild reaction with subsequent anesthesia was exposed to chlorhexidine. Chlorhexidine does not appear to be a common culprit in the United States, with report of 1 positive skin test result in the 4 most recent studies.^{4,5,13,22} Finally, our patient population included a mix of not only patients who had HSRs during operations as in other US studies but also patients who had HSRs during medical procedures that did not require general anesthesia. Therefore, the difference in exposure to various periprocedural agents may account for some of the variation noted in our study and may reduce the ability to compare our results to other studies.^{4,5,13,22}

In conclusion, induction agents were the most common culprits in our patient population, which differs from both US and European studies. Given the variability in skin test concentrations used in different centers across the United States with data published on small sample sizes, there is a need to establish national guidelines and a referral network to standardize the evaluation of periprocedural HSRs and increase the generalizability of results with pooling of nationwide data. National guidelines for the stepwise approach to the management and evaluation of perioperative anaphylaxis have been established in Great Britain and Ireland, with consensus documents jointly published by the Association of Anaesthetists of Great Britain and Ireland and the British Society for Allergy and

Clinical Immunology.^{41,42} In addition to implementing national guidelines in France, there is also a national pharmacovigilance system known as the French Network of Regional Pharmacovigilance Centres.^{2,43,44} This network is composed of 31 regional centers located in teaching hospitals that share a common database to report adverse drug reactions, including perioperative HSRs. Therefore, one potential approach would be to convene drug allergy experts in the United States to formulate and implement national guidelines for the evaluation of perioperative HSRs with subsequent development of a pharmacovigilance system composed of regional academic medical centers to allow for data sharing.

Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2017.07.013>.

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Supplementary Data**eTable 1**

Severity of Periprocedural HSRs

Grade	Symptoms
I	Cutaneous signs only: urticaria, angioedema, and/or erythema
II	Measurable but non–life-threatening symptoms: cutaneous signs, hypotension, tachycardia, and/or respiratory symptoms (cough, bronchospasm, or difficulty ventilating)
III	Life-threatening symptoms: cardiovascular collapse, tachycardia or bradycardia, arrhythmias, or severe bronchospasm
IV	Cardiac and/or respiratory arrest

Abbreviation: HSR, hypersensitivity reaction.

eTable 2Clinical Characteristics of Perioperative HSRs and Identifiable Agents^a

Patient no.	Sex	Race/ethnicity	Procedure performed	Grade of HSR	Time between HSR and skin testing, wk	Perioperative drugs	Agents identified by skin testing or latex IgE
1	Male	White	Aortic valve replacement	I	4	Etomidate, midazolam , cefazolin, fentanyl, lidocaine, rocuronium	Etomidate, midazolam,^b vecuronium^b
2	Female	Latino	Renal transplant	III	8	Cefazolin , ethacrynic acid, fentanyl, midazolam, propofol, rocuronium	Cefazolin
3	Male	White	Ascending aortic aneurysm repair	II	Unknown	Aminocaproic acid, cefazolin, etomidate, fentanyl, lidocaine, midazolam, succinylcholine, vecuronium	Cefoxitin
4	Female	Other	Esophageal dilation and percutaneous endoscopic gastrostomy tube placement	II	8	Etomidate, midazolam, propofol	Negative
5	Female	Black	Colonoscopy	II	12	Midazolam, propofol	Negative
6	Female	Latino	Breast lumpectomy	III	12	Lidocaine with preservative , fentanyl, midazolam	Lidocaine with and without preservative , mepivacaine
7	Female	Black	Unknown	I	1144	Lidocaine , carbocaine, propofol	Lidocaine with and without preservative , chloroprocaine, fentanyl, midazolam, vecuronium
8	Male	Multiracial	Hemodialysis graft expansion	I	52	Fentanyl , midazolam	Fentanyl , etomidate, vecuronium
9	Male	Latino	Dental extractions	I	6	Midazolam, ketamine , lidocaine with epinephrine	Midazolam, ketamine , vecuronium
10	Female	Latino	Endoscopy	I	104	Propofol, unknown agents	Negative
11	Female	Latino	Myomectomy	III	16	Propofol , cefoxitin, fentanyl, midazolam, remifentanyl, rocuronium, succinylcholine?, vasopressin	Propofol , ketamine, ^b vecuronium, ^b latex
12	Female	White	Caesarean delivery	II	416	Cefazolin, ondansetron, unknown local/general anesthetics and opiates	Rocuronium, ^b latex
13	Female	Black	Caesarean delivery	III	6	Cefazolin, dexamethasone, fentanyl, morphine, narcaine, ondansetron, oxytocin, propofol	Ketamine, ^b latex
14	Female	Unknown	Spinal fusion	III	32	Cefazolin , ampicillin, fentanyl, insulin, morphine, omeprazole, vancomycin	Cefazolin , cefoxitin, ceftriaxone, etomidate, ketamine, midazolam, vecuronium
15	Female	Latino	Bariatric surgery	I	260	Unknown	Rocuronium, vecuronium
16	Female	Black	Colonoscopy	II	24	Propofol, unknown agents	Ketamine, ^b fentanyl ^b
17	Female	Black	Spinal surgery	III	572	Meperidine, unknown agents	Ketamine, midazolam, morphine, rocuronium, vecuronium
18	Female	Unknown	Mitral valve repair	III	468	Midazolam? or fentanyl; unknown agents	Midazolam,^b ketamine^b
19	Female	White	Aortic valve replacement	III	4	Midazolam , chlorhexidine, etomidate, fentanyl, rocuronium	Midazolam , ketamine, ^b succinylcholine
20	Female	White	Breast lumpectomy	I	24	Ondansetron , ketorolac, morphine, oxycodone, unknown agents	Ondansetron , midazolam, succinylcholine
21	Female	White	Hip replacement	III	20	Midazolam , fentanyl, ondansetron, propofol, vecuronium	Midazolam , ketamine, succinylcholine
22	Male	Black	Knee surgery	I	52	Fentanyl, lidocaine, midazolam, propofol	Ketamine
23	Male	White	Unknown	III	2	Rocuronium , fentanyl, propofol	Rocuronium , etomidate, ketamine, lidocaine with and without preservative, midazolam, morphine, succinylcholine, vecuronium
24	Male	White	Thoracic surgery	III	4	Cefazolin , chlorhexidine, fentanyl, lidocaine, midazolam, propofol, rocuronium	Cefazolin
25	Female	Multiracial	Thyroidectomy	III	6	Succinylcholine , cefazolin, midazolam	Succinylcholine , benzylpenicilloyl polylysine
26	Male	Latino	Ureteral stent placement	III	4	Cefazolin, propofol, rocuronium	Ketamine, midazolam, ^b vecuronium ^b
27	Female	Latino	Lipoma removal	III	30	Cefazolin , fentanyl, lidocaine, midazolam, propofol, succinylcholine	Cefazolin , ketamine, morphine, vecuronium
28	Female	Other (Indian)	Fertility procedure	II	8	Cefazolin , fentanyl, lidocaine, propofol	Cefazolin , cisatracurium, ^b midazolam
29	Female	Latino	Bladder surgery	II	56	Unknown	Latex
30	Female	Black	Cholecystectomy	III	28	Cefazolin , fentanyl, neostigmine, propofol, rocuronium	Cefazolin , cisatracurium, midazolam
31	Female	White	Microdissection	III	4	Cefazolin , unknown general anesthetics and opiates	Cefazolin , cisatracurium, midazolam
32	Female	White	Esophagogastro-duodenoscopy	II	20	Ondansetron , fentanyl, lidocaine, propofol, succinylcholine	Ondansetron , morphine ^b
33	Male	Latino	Coronary artery bypass	III	6	Cefazolin , fentanyl, lidocaine, midazolam	Cefazolin
34	Female	White	Ectopic pregnancy	III	8	Ondansetron, midazolam , cefazolin, fentanyl, rocuronium	Ondansetron, midazolam^b

Abbreviation: HSR, hypersensitivity reaction.

^aAgents set in bold types were determined to be causative; they were each administered perioperatively and found to be positive or equivocal on skin testing.^bEquivocal skin test results.