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Abbreviations:

US: United States

NMBA: Neuromuscular Blocking Agent

ST: Skin Testing

NIC: Non-irritating Concentration

A/I: Allergy/Immunology

MGH: Massachusetts General Hospital

PACU: Post-Anesthesia Care Unit

CPR: Cardiopulmonary Resuscitation

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ABSTRACT

Background: Evidence-based guidelines are needed in the United States to improve evaluation of perioperative allergic reactions including recommendations for subsequent anesthesia.

Objective: Identify causative agent(s) and evaluate patients' tolerability of subsequent anesthesia in patients evaluated by Allergy/Immunology (A/I) at Massachusetts General Hospital.

Methods: We performed a retrospective review of patients referred to the outpatient A/I clinic for perioperative allergic reactions between October 2003 and May 2017. Patient demographics, atopic history and prior adverse drug reactions were reviewed. Patients underwent a comprehensive evaluation with testing including skin testing (ST), drug challenges (when appropriate), tryptase level measurement, and specific IgE to latex measurement. Tolerance of subsequent procedures requiring anesthesia was assessed.

Results: Of 123 patients referred, 74 (60%) were female and mean age was 46 (± 18) years. At least one causative agent was identified in 28 patients (24%, n=28/118). Seventeen of 28 (61%) patients were ST positive to an antibiotic, including 13 (46%) positive to cefazolin; 3 patients (11%) had a positive latex specific IgE. Of 85 patients who had subsequent anesthesia with a known outcome, 78 (91%) did not have another perioperative allergic reaction. Two of five patients with an elevated baseline tryptase level did not tolerate subsequent anesthesia.

Conclusion: The majority of patients safely received subsequent anesthesia after comprehensive A/I evaluation for their perioperative allergic reactions, however improved algorithmic care is needed in the United States. Among ST positive patients (24%), antibiotics (especially cefazolin), were the most common culprits. An elevated baseline tryptase level was associated with an increased risk of recurrent perioperative allergic reactions.

Highlights Box**What is already known about this topic?**

Perioperative allergic reactions are rare but associated with significant morbidity. Identification of the causative agent(s) after a perioperative allergic reaction is challenging.

What does this article add to our knowledge?

A comprehensive evaluation and management plan for perioperative allergic reactions in the US requires testing for a broader group of causative agents than those routinely performed.

How does this study impact current management guidelines?

We devised an updated algorithmic approach to perioperative allergic reactions in the US. Although a culprit was not identified in the majority of our cases, we provide guidance on subsequent management and safety data on subsequent anesthesia.

INTRODUCTION

Perioperative allergic reactions including anaphylaxis are rare but associated with significant morbidity and mortality. There is considerable variability in the incidence and identified causative agents of perioperative allergic reactions between countries.(1-4) The reported incidence ranges from 1:1,380 to 1:20,000 operations, but recent prospective data suggest the incidence may be as high as 1 in 353 operations.(5-7) In the United States (US), antibiotics are the most frequently identified cause of perioperative allergic reactions, accounting for 23% to 59% of identified causative agents.(8-10) Specifically, cefazolin, the guideline-recommended perioperative antibiotic for many operations,(11) is considered the most common cause of perioperative allergic reactions in the US.(12-14) However, in France, neuromuscular blocking agents (NMBA) account for almost 60% of perioperative allergic reactions, with antibiotics are the second most common cause.(15, 16) Perioperative allergic reactions associated with NMBAs are less frequently reported in the US.(4, 8, 9)

Given that multiple drugs are administered simultaneously during anesthesia, identification of the causative agent(s) after a perioperative allergic reaction has posed diagnostic challenges.(12) Allergy practice guidelines recommend comprehensive skin testing (ST) using the non-irritating concentration (NIC) to all perioperative agents listed in the anesthetic record (including disinfectants e.g., ., chlorhexidine) and given prior to the allergic reaction, measuring serum tryptase and evaluating for latex allergy.(7, 17, 18) However, despite this recommended thorough evaluation, US data show that a causative agent is not commonly identified,(8, 9) making subsequent procedures with anesthesia challenging for both the patient and the physician/surgeon.

In the present study, we describe our experience applying a comprehensive evaluation and management plan for perioperative allergic reactions updated using recently published guidelines and used by our

Allergy/Immunology (A/I) group.(7, 10, 14) Data previously published by our group (Dataset I, Dataset II) (10, 14) are combined with new data (Dataset III) to understand the outcomes from the largest cohort of perioperative allergic patients tested in the US. We aimed to improve our diagnostic approach by describing culprit agents causing perioperative allergic reactions, assessing tolerability of subsequent anesthesia using a comprehensive A/I management plan even when no causative agent is identified, and understanding the limitations of our approach when patients developed subsequent perioperative allergic reactions.

METHODS

Study Population

We performed a retrospective review of all patients at Massachusetts General Hospital (MGH) referred to the outpatient A/I clinic for perioperative allergic reactions between October 2003 and May 2017.

Perioperative allergic reactions included those during induction or maintenance of general anesthesia, or during the immediate post-operative recovery period (time period when the patient remains in the post anesthesia care unit). We excluded 16 patients who did not complete the recommended evaluation in the MGH A/I clinic following a perioperative allergic reaction. The study was approved by the MassGeneral Brigham Human Research Committee.

Comprehensive Allergy Evaluation

MGH perioperative allergic reaction recommendations incorporated published guidelines(19) and encourage anesthesia to: (1) send a serum tryptase within 4 hours(20) (ideally <2 hours) for any presumed perioperative allergic reaction and (2) refer the patient to A/I for evaluation between four weeks and six months after the allergic reaction (to minimize false-negative results).(21, 22)

In the A/I clinic, patients were evaluated using a standardized protocol(10) that was internally developed and in accordance with the practice parameters from the American Academy of Allergy, Asthma, and

Immunology(19) and iteratively updated using recently published guidelines.(7) **See Figure 1.** Patient characteristics, including age, sex, atopic history (asthma, allergic rhinitis, eczema), drug allergy history and all perioperative medications were retrospectively reviewed. Evaluation included ST using non-irritating concentrations,(7, 18) drug challenges when appropriate/possible (i.e., oral or intramuscular drugs that were not controlled substances by the Drug Enforcement Agency), baseline tryptase level measurement (reaction tryptase considered elevated when $> (\text{baseline tryptase} \times 1.2) + 2$ whereas >11.4 ng/mL(23) was previously considered elevated), and serum IgE testing to latex (ImmunoCAP system (Upjohn-Pharmacia, Uppsala, Sweden) for patients exposed to latex gloves or equipment. If latex specific IgE was negative (<0.35 kU/L), latex ST was performed .(24, 25)

Skin prick and/or intradermal testing was performed to all agents received prior to perioperative allergic reaction with published NICs. ST was performed with positive (histamine 6mg/mL) and negative (saline) controls. Skin prick or intradermal testing was considered positive if the diameter of the wheal was at least 3 mm larger than that induced by the negative saline control with flare>wheal. Agents without a NIC (e.g., inhalational agents) were not tested. During the study period, additional data on NIC for ST became available and we added more drug testing to our comprehensive evaluation: fentanyl, propofol, midazolam, neostigmine, chlorhexidine (2012), vancomycin and ondansetron (2014), and metronidazole (2016).

Organ system involvement during perioperative allergic reactions were specified as cutaneous, cardiovascular, pulmonary, neurologic, oropharyngeal or gastrointestinal system involvement. Allergic reaction severity was determined following an established grading scale (I-IV).(26) We defined perioperative anaphylaxis as patients with whose reaction included hypotension or was grade III/IV severity.(19)

Following the comprehensive A/I evaluation, explicit recommendations for subsequent use of anesthesia were made.(14) A patient with a positive ST that suggested a mast cell mediated reaction was advised to strictly avoid that specific drug and cross-reactive drugs. If a patient had negative ST and challenge (when appropriate/possible in A/I clinic), then the drug was removed from the allergy list. If ST was negative but challenge not appropriate/possible in A/I clinic, then guidance was given to proceed with close monitoring if these agents were needed again in the operating room. If ST was not available, or if ST was unable to be performed because of use of antihistamines or need for urgent surgery, patients were advised to avoid all potentially implicated agents and A/I made recommendations for safe alternatives. **See Figure 1.** If in the very rare instance there were no reasonable alternatives, a test dose in the perioperative setting was advised under observation only in the operating room or the postanesthesia unit before anesthesia induction(7, 27). This should be performed with adequate cardiovascular and respiratory monitoring and in the presence of experience staff able to manage significant negative events (i.e., hypotension, bradycardia, respiratory depression and anaphylaxis)(7, 27). Test doses at MGH are performed according to a standardized 2-step procedure with specified dosing and timing and collaboration between the allergist and anesthesiologist. Patient monitoring during subsequent anesthesia for signs and symptoms of a perioperative allergic reaction was routinely recommended.

Follow-up: Subsequent Anesthesia

Follow-up information on procedures requiring subsequent anesthesia were collected by two methods: (1) telephone interview and (2) electronic health record review. For the former, we conducted telephone interviews from August 2017 to June 2018. During this structured phone call, patients were asked if they had any procedures requiring anesthesia since their allergy evaluation. Those who responded, “yes,” provided the details of all subsequent procedures and any details of any recurrent allergic reactions. Patients with subsequent procedures requiring general anesthesia outside of our hospital network signed medical record release forms to obtain external procedural and anesthesia records for A/I review. For the

latter, we performed a comprehensive internal electronic health record review, reading all subsequent perioperative notes and anesthesia records for all patients, regardless of whether or not they completed the phone interview. We assumed adequate information in the electronic health records if patients had at least one primary care or specialist visit per year documented through the end of the study period.

Analysis and Statistical Methods

We use descriptive statistics such as numbers with frequencies for categorical variables and means with standard deviations for continuous variables. Although we present the results of the entire population studied (n=123), we indicate throughout the results which dataset the patient belongs to: Dataset I (Guyer et al), Dataset II (Kuhlen et al), or Dataset III (new). All statistical analyses were conducted in SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient Characteristics and Initial Perioperative Hypersensitivity Reaction

Among 123 A/I referrals, 118 patients (96%) completed the comprehensive A/I evaluation. Most patients were female (60%, n=74) with an average age at the time of initial perioperative allergic reaction of 46 (± 18) years. Nearly half of patients were atopic (47%) or had a history of an adverse drug reaction (59%).

See Table 1. The average time from perioperative allergic reaction to initial ST (n=118) was 26 (± 58) months but most patients (65%, 77/118) completed their ST within 6 months of initial perioperative allergic reaction. One patient did not have a documented date for initial perioperative allergic reaction and four patients did not have skin testing performed.

Forty-five (37%) patients had a grade I reaction, 31 (25%) patients had a grade II reaction, 37 (30%) patients had a grade III reaction and 10 (8%) patients had a grade IV reaction. During the initial perioperative allergic reaction, 89 (72%) patients experienced cutaneous symptoms, 54 (44%) patients

developed cardiovascular symptoms, 41 (33%) patients developed pulmonary symptoms, 11 (9%) patients developed neurologic symptoms, seven (6%) developed oropharyngeal symptoms and five (4%) patients developed gastrointestinal symptoms.

Perioperative Anaphylaxis

Sixty (49%) patients met the definition for perioperative anaphylaxis. Of the 10 (8%) patients with grade IV reactions, eight (80%) experienced cardiac arrest and two experienced pulmonary arrest with symptoms of wheezing, bronchospasm and desaturation. These perioperative cardiac arrest patients received cardiopulmonary resuscitation (CPR)/cardioversion (n=6/7) and epinephrine (intramuscular and/or intravenous; n=6/7). The patient who did not receive CPR or cardioversion was given three doses of intravenous epinephrine, intravenous fluids, and dopamine. Allergic reaction treatment information was not available for one patient. Perioperative allergic reaction tryptase levels were obtained in seven patients and elevated in four patients. One of these patients had a reaction tryptase level of 12 ng/mL but no baseline tryptase level.

Comprehensive Allergy/Immunology Evaluation

Ninety-six percent of patients referred to A/I clinic (n=118/123) completed the comprehensive evaluation. At least one causative agent was identified in 28 patients (24%, n=28/118) that completed A/I evaluation. Sixteen of 28 (61%) patients were ST positive to antibiotics: 13 to cefazolin, one to penicillin, one to vancomycin, one to ciprofloxacin, and one to both ciprofloxacin and levofloxacin. The other eleven patients were ST positive to non-antibiotics, including three patients with positive serum latex IgE. **See Figure 2.** Patients with perioperative anaphylaxis were more likely to be ST positive compared to patients with non-anaphylactic perioperative allergic reactions (31% vs 15%, p=0.04).

Subsequent Anesthesia

Follow-up data were available for 111 (93%) patients. **See Figure 3.** Most patients who underwent subsequent procedures requiring general anesthesia tolerated anesthesia (92%, n=78/85). Seven patients (8%, n=7/85) developed a subsequent perioperative allergic reaction during anesthesia. **See Table 2.** In these seven patients, most had a negative ST (n=5), and two patients had positive ST. **See Table 2.**

Tryptase Levels with Initial Hypersensitivity Reaction

A tryptase level was collected in 37 patients (30%) within four hours of the initial perioperative allergic reaction. Average time to tryptase collection was 75.8 (± 52.0) minutes and 22 (79%) were within two hours. Of these 37 patients, reaction tryptase was elevated in 20 (54%) patients using >11.4 ng/mL as criteria(28) Three patients did not have a baseline tryptase level to determine if reaction tryptase was elevated but reaction tryptase was <11.4 ng/mL in these cases.(23) **See Table 3.** No patients with an elevated tryptase experienced a grade I reaction. Four patients with an elevated tryptase experienced a grade II reaction, eleven patients a grade III reaction, and five patients a grade IV reaction. Among five patients with an elevated baseline tryptase level, 40% (n=2) had a subsequent perioperative allergic reaction despite A/I evaluation: two patients were ST negative and three patients were cefazolin ST positive.

DISCUSSION

In this study of perioperative allergic reactions at a large US academic medical center conducted over a decade, our comprehensive A/I evaluation and management strategy provided a valuable algorithmic approach to the clinical management of over 100 patients with perioperative allergic reactions. However, there remains room for improvement. Less than one-third of patients had a culprit identified with this approach and just 9 out of 10 patients tolerated a subsequent procedure requiring anesthesia. Large studies

from several European countries have demonstrated higher identification of culprits and a lower reaction rate during subsequent anesthesia likely related to established guidelines since the early 1990s with continued organization, collaboration, and updating.(29, 30) In our experience, when a causative agent was identified (ST positive), antibiotics, specifically cefazolin, were the most common culprits. However, when evaluation was negative, additional steps are necessary before subsequent anesthesia including consideration of less common causative agents and discussion with anesthesiology to understand other potential diagnoses for the event. (31) Similar to our prior work,(14) an elevated baseline tryptase level was associated with an increased risk of a subsequent perioperative allergic reaction and should prompt evaluation for mastocytosis. These findings support the need to develop formal US guidelines and a network of engaged sites for more widespread implementation of a comprehensive algorithmic approach. Similar large initiatives have been recently developed in other countries with updated guidelines.(7, 17, 31) We must create a more formalized US strategy to improve identification of causative agents and facilitate the safe return to anesthesia in patients with perioperative allergic reactions including anaphylaxis.

Antibiotics have become an increasingly recognized cause of perioperative allergic reactions(7, 32) as there has been coincident increased use of prophylactic antibiotics to prevent postsurgical infections. More than half of patients in our study with an identified culprit developed perioperative allergic reactions due to antibiotics and three-quarters of antibiotic reactions were due to cefazolin, the first-line perioperative antibiotic for a majority of procedures in the US.(11) Beta-lactam antibiotics account for the vast majority of prophylactic antibiotics used in the US and therefore also account for the most perioperative allergic reactions to antibiotics, but the most commonly implicated antibiotics vary with local antibiotic practices.(1, 14, 33) A large prospective study of perioperative anaphylaxis cases in the UK identified teicoplanin (incidence 16.4 per 100,000 administrations) and amoxicillin-clavulanic acid (8.7 per 100,000 administrations) as the most common antibiotic triggers of perioperative

anaphylaxis.(12) Antibiotic allergy assessment using optimal skin testing concentrations(7, 34) remains a critical part of the A/I evaluation of patients with perioperative allergic reactions. If skin testing to the culprit antibiotic cannot be performed, an alternative, unrelated antibiotic should be used for subsequent anesthesia.

Our study identified two patients with positive ST to quinolones. One patient was ST positive to ciprofloxacin and levofloxacin and did not have subsequent anesthesia. The second patient was ST positive to ciprofloxacin and developed a subsequent allergic reaction with anesthesia despite avoidance of ciprofloxacin (although the patient notably tolerated four procedures in the interim). This patient's course could suggest a hidden or unidentified allergen was the cause of the initial and subsequent allergic reaction (and ciprofloxacin ST potentially a false positive as experts still disagree if there is a valuable non-irritating ST concentration(35, 36) or alternatively, the mechanisms of the perioperative allergic reaction was non-IgE (e.g., direct mast cell or IgE-independent mechanism). It is also possible that the patient developed a new drug allergy in addition to ciprofloxacin. Although this patient did not return for additional A/I evaluation after the subsequent perioperative allergic reaction, this case raises an important point about the potential for false positive ST and need for a repeated A/I evaluation after subsequent reactions. Patients are rarely challenged after a positive ST due to the high risk of a potential allergic reaction, but more data on the positive predictive value of ST are needed to improve drug allergy assessments and optimize guidelines for subsequent anesthesia.

In contrast to the US, many countries report NMBAs as the most common perioperative allergic reaction culprit.(3, 37-39) NMBA reactions have been attributed to increased exposure to sensitizing agents containing a substituted ammonium group, which are found in cosmetics, disinfectants, industrial materials, foods and potentially pholcodine containing drugs but pholcodine is rarely present in US products.(39, 40) Our cohort identified one patient with NMBA allergy (cisatracurium). Prior to 2000,

latex was a common perioperative allergic reaction culprit comprising between 15 and 20% of perioperative allergy.(4, 15, 26) However, latex allergy is decreasing as reduction in powdered glove use and latex exposure generally have led to a marked decrease in new sensitizations. Latex is now only the fourth cause of perioperative allergic reactions in France and only a minor cause in the UK and in Germany.(7, 12) In our cohort, all three cases of latex allergy were identified before 2012 with no new perioperative allergic reactions due to latex subsequently. Although we do not confirm a serum latex specific IgE with a positive skin test, and a positive latex specific IgE may be falsely positive in grass/birch allergic patients due to Hev b8 (profilin) , latex skin testing results in the US may be unreliable. Although component resolved testing could be considered(41) to ensure there is no false positive, as it is not uniformly available we suggest latex avoidance for patients with a history of perioperative allergic reaction and positive latex specific IgE

As our diagnostic testing expanded over time with improved data on NIC to anesthetic agents, we notably identified new causative agents. For example, three patients had positive ST to ondansetron and one patient had positive ST to bacitracin with appropriate negative controls.(42) Prior studies have described perioperative anaphylaxis to ondansetron(43) and bacitracin used in wound irrigation.(42, 44) Although we cannot be certain that the positive ST translates to clinical allergy, the temporal association along with other negative STs suggests a strong plausible causal link.(38) In the two cases of bacitracin perioperative allergy, tryptase was elevated at 17.4 ug/L and 74.6 ug/L respectively and normal at baseline, which further supports a mast cell mediated mechanism for the reaction.(42, 44) In addition to the uncommon allergens we identified in our cohort, other data support the emergence of other new potential perioperative allergic reaction culprits, such as vancomycin,(45) sugammadex or the sugammadex-rocuronium inclusion complex,(32, 37, 46) patent blue dye,(39, 47) and chlorhexidine.(7, 48-52) Taken together, these emerging data reinforce the importance of considering all of the agents listed in the anesthesia record prior to perioperative allergic reaction as potential culprits. Additionally,

substances often missing from the anesthesia records, such as disinfectants, sterilizing agents, and excipients, should routinely be considered, particularly if the initial A/I evaluation is unrevealing. Testing all patients with disinfectants was emphasized in recent international recommendations as exposure is common but rarely documented.(7) This could potentially explain the subsequent reactions in our patients and we have accordingly modified our own algorithm (Figure 1).(12)

We found that approximately three-quarters of patients evaluated after perioperative allergic reactions were ST negative which was slightly lower than other US studies that did not find a culprit in 43-52% of patients.(8, 9) Potential reasons for this include use of non-irritating ST concentrations that are not validated and lack of NIC ST data to many agents used during anesthesia (especially a decade ago when we were not routinely testing to fentanyl, propofol, midazolam, neostigmine, chlorhexidine, vancomycin or ondansetron). False negative ST may also occur if time to ST was too early (<4 weeks) or delayed (>6 months) after an allergic reaction.(22, 53) Although we advised patients with perioperative allergic reactions to complete ST within four weeks to six months of the allergic reaction, patients on average were seen for their ST evaluation over 26 months after their allergic reaction. Performing drug challenges would improve the quality of our recommendations,(7, 37, 54) however, challenges to NMBAs, opioids, benzodiazepines, paralytics, and other medications are not possible in our outpatient A/I clinic setting. Despite the limitations of our available diagnostic tools, our management strategy allowed 90% of patients to receive subsequent anesthesia safely.

We strongly recommend obtaining a baseline tryptase level similar to international recommendations.(7, 55) An acute serum tryptase level greater than $\{[\text{baseline tryptase} \times 1.2] + 2\}$ (7, 20, 23) has been recommended to confirm acute mast cell degranulation. When this formula was compared with an acute tryptase level of more than 11.4 mg/L in 85 patients with perioperative anaphylaxis with adequate timing of the samples, the sensitivity, specificity, positive predictive value, and negative predictive value were

75%, 86%, 94%, and 53%, respectively, compared with 53%, 95%, 97%, and 40%, respectively, for acute tryptase value of more than 11.4 ng/L.(20, 23) If reaction tryptase was elevated suggesting a mast cell mediated mechanism a negative evaluation should prompt closer re-examination for any overlooked exposures. An elevated baseline tryptase level $\{[\text{baseline tryptase} \times 1.2] + 2\}$ in the right clinical situation (i.e., perioperative anaphylaxis) should also warrant further evaluation for mastocytosis. Additionally, if patients have subsequent reactions after a negative A/I evaluation, a reconsideration of mast cell disorders is indicated. We continue to educate our anesthesiology colleagues about the clinical value of a reaction tryptase but we are also striving to standardize baseline tryptase collection in all patients referred to A/I clinic for perioperative allergic reactions.

When comprehensive A/I evaluation does not reveal a causative agent, we recommend critical re-evaluation of the case and close collaboration with anesthesiology before proceeding with subsequent anesthesia.(7, 27, 46, 56) It is helpful to consider: (1) the reaction (e.g., were there other potential diagnoses for the event other than allergic reaction, such as an underlying mast cell disorder or hypotension attributable to another cause?), (2) the exposures (e.g., was a potential culprit agent overlooked or not listed in the anesthesia record?), (3) the testing (e.g., was the ST conducted in the appropriate timeframe, of 4 weeks to 6 months after the allergic reaction, with recommended NIC?), and (4) the host (e.g., could the patient have an underlying mast cell disorder?).(14) For example, while hypotension alone may be referred for evaluation of perioperative allergic reaction, hypotension is common during the induction and maintenance of anesthesia.(7)

Our current recommendation, after negative comprehensive evaluation including ST, is to consider use of alternative agents and proceed with close monitoring if these same agents were used again for anesthesia. While it is reasonable to suggest use of alternative agents, it may not always be possible to avoid

NMBAs, propofol, benzodiazepines, and opioids. Further data are needed in the US to optimize recommendations after negative ST, but in addition to critical re-evaluation of the case our current recommendations to A/I practitioners are to: 1) consider pre-medications for subsequent anesthesia; 2) recommend that patients return for repeat A/I evaluation if they develop any subsequent perioperative allergic reactions.

While we report on a relatively small number of patients who developed a perioperative allergic reaction and underwent A/I evaluation, to our knowledge, this is the largest analysis of US patients with perioperative allergic reactions assessed by A/I to date. Although there are no validated ST for drugs other than penicillin, we used the recognized NICs and protocols consistent with EAACI and AAAAI drug allergy practice parameters.(7, 18) Patients in our study did not undergo challenges to drugs when a ST was positive to validate allergy because it is neither ethical nor safe to perform such challenges, especially in outpatient A/I practices. Lastly, we report on a single large academic hospital; our experience may not be generalizable to different patient populations, geographic areas or hospitals/clinics.

In summary, perioperative allergic reactions are rare, but important to evaluate since re-exposure to anesthetics is often necessary. Comprehensive A/I evaluation can be unrevealing for a variety of reasons but considering a broader range of potential causative agents may improve diagnosis. In the US, antibiotics remain the most common culprits identified but many hidden causative agents are emerging as we improve our understanding of culprits and develop improved diagnostic testing tools. While a serum tryptase ideally within two hours of an allergic reaction is helpful, a baseline tryptase is critical to understanding if reaction tryptase is elevated and to prompt evaluation for an underlying mast cell disorder that can increase the risk for a subsequent perioperative allergic reaction. Overall, our revised A/I evaluation and management strategy will provide clear guidance to the anesthesiology team and patient reassurance to facilitate safe return for subsequent surgery requiring anesthesia when indicated.

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Table 1: Patient Characteristics and Initial Perioperative Allergic Reaction. Data are presented as n(%) unless specified.

	Total N=123	Dataset I N=73*	Dataset II N=25*	Dataset III N=25*
Age at the time of the reaction (years) Mean $\pm$ SD**	45.9 $\pm$ 18.0	44.2 $\pm$ 16.9	53.1 $\pm$ 18.4	43.6 $\pm$ 19.8
Female sex	74 (60.2)	46 (63.0)	13 (52.0)	15 (60.0)
Time from reaction to skin testing (months) Mean $\pm$ SD	26.3 $\pm$ 57.9 [†]	31.3 $\pm$ 67.6	8.4 $\pm$ 21.1	30.4 $\pm$ 47.5
Atopic history	58 (47.2)	44 (60.3)	6 (24)	8 (32.0)
Adverse drug reaction history	72 (59.0)	40 (55)	19 (76)	13 (52)
Severity of perioperative reaction				
I	45 (36.6)	28 (38.4)	8 (32.0)	9 (36.0)
II	31 (25.2)	10 (13.7)	10 (40.0)	11 (44.0)
III	37 (30.1)	26 (35.6)	6 (24.0)	5 (20.0)
IV	10 (8.1)	9 (12.3)	1 (4.0)	0 (0)
Organ system involvement				
<i>Cutaneous Symptoms</i>	89 (72.4)	53 (72.6)	16 (64.0)	20 (80.0)
Swelling	34 (38.2)	22 (41.5)	4 (25.0)	8 (40.0)
Rash	36 (40.4)	19 (35.8)	8 (50.0)	9 (45.0)
Erythema/Flushing/Burning	26 (29.2)	16 (30.2)	5 (31.3)	5 (10.0)
Urticaria	25 (28.1)	14 (26.4)	4 (25.0)	7 (35.0)
Itching	16 (18.0)	9 (17.0)	5 (31.3)	2 (10.0)
<i>Cardiovascular Symptoms</i>	54 (43.9)	29 (39.7)	13 (52.0)	12 (48.0)
Hypotension	50 (92.6)	25 (86.2)	13 (100.0)	12 (100.0)
Tachycardia	14 (25.9)	12 (41.4)	0 (0)	2 (16.7)
Bradycardia	10 (18.9)	8 (27.6)	1 (7.7)	1 (8.3)
Cardiac arrest	8 (14.8)	7 (24.1)	1 (7.7)	0 (0)
Arrhythmia	5 (9.3)	5 (17.2)	0 (0)	0 (0)
<i>Pulmonary Symptoms</i>	41 (33.3)	27 (37.0)	6 (24.0)	8 (32.0)
Shortness of breath	16 (40.0)	12 (46.2)	1 (16.7)	3 (37.5)
Wheezing	14 (35.0)	8 (30.8)	3 (50.0)	3 (37.5)
Bronchospasm	13 (31.7)	9 (33.3)	2 (66.7)	2 (25.0)
Desaturation	13 (32.5)	8 (30.8)	2 (66.7)	3 (37.5)
Chest tightness	3 (7.5)	3 (11.5)	0 (0)	0 (0)
Other [‡]	8 (19.5)	6 (22.2)	0 (0)	2 (25.0)
<i>Neurologic Symptoms</i>	11 (9.0)	5 (6.9)	4 (16.0)	2 (8.0)
Agitation/Anxiety	6 (54.5)	3 (60.0)	3 (75.0)	0 (0)
Dizziness/shaking	1 (9.1)	0 (0)	1 (25.0)	0 (0.0)
Other [§]	7 (63.6)	2 (40.0)	3 (75.0)	2 (100.0)
<i>Oropharyngeal Symptoms</i>	7 (5.7)	4 (5.6)	2 (8.0)	1 (4.0)

Throat tightness	3 (42.9)	2 (50.0)	0 (0)	1 (100.0)
Oropharyngeal edema	3 (42.9)	2 (50.0)	0 (0)	1 (100.0)
Tongue swelling	2 (28.6)	0 (0)	2 (100.0)	0 (0)
<i>Gastrointestinal Symptoms</i>	5 (4.1)	1 (1.4)	3 (12.0)	1 (4.0)
Nausea/Vomiting	4 (80.0)	1 (100)	3 (100.0)	0 (0)
Abdominal pain	2 (40.0)	0 (0)	1 (33.3)	1 (100.0)
Incontinence	1 (20.0)	0 (0)	1 (33.3)	0 (0)

*Data are separated into prior publications Dataset I: Guyer et al. (n=73)(10), Dataset II: Kuhlen et al. (n=25)(14), and Dataset III: new data not published previously (n=25)

**Age at time of HSR was only available for 121 of the total 123 patients because one patient did not have a documented date of HSR

†Time from HSR to skin testing was only available for 118 of the total 123 patients because one patient did not have a documented date for HSR and four patients did not have skin testing performed

‡Other pulmonary symptoms include abnormal chest x-ray, increased airway pressures, pneumothorax, cough, pulmonary edema, and pulmonary arrest

§Other neurologic symptoms include hallucinations, diaphoresis, insomnia, loss of consciousness, and headache

Table 2: Clinical History of Patients with Allergic Reactions During Subsequent Anesthesia

<i>ID/ Dataset</i>	<i>Details of Perioperative Allergic Reaction</i>	<i>Grade of Reaction (initial/ subsequent)</i>	<i>Tryptase (reaction/ baseline)</i>	<i>ST +</i>	<i>ST -</i>	<i>Subsequent Reaction Potential Culprits (A/I Evaluation Year)**</i>
34/II	- Initial perioperative allergic reaction with hypotension treated with diphenhydramine and epinephrine - Despite avoidance of ciprofloxacin, a reaction occurred on the patient's fifth subsequent procedure (tolerated four procedures after A/I evaluation without a reaction) - Subsequent reaction was four hours after surgery and three hours after receiving acetaminophen/oxycodone, hydromorphone and fentanyl orally in the post-anesthesia care unit for pain management - There was no tryptase level with subsequent perioperative allergic reaction and no additional follow up A/I evaluation	II/II	25/3	ciprofloxacin	cefazolin, gentamicin, dexamethasone, rocuronium, propofol, midazolam, fentanyl, latex	chlorhexidine, succinylcholine, oxycodone, hydromorphone (2014)
96*/I	- Initial perioperative allergic reaction with hypotension and bradycardia that responded to epinephrine and vasopressin - Developed a subsequent reaction with patches of erythema only during the third of five procedures after AI evaluation. Symptoms resolved within minutes - No reaction occurred during fourth and fifth procedures and cefazolin was avoided with all five subsequent procedures	III/I	247/19	cefazolin	cisatracurium, propofol	chlorhexidine, midazolam, fentanyl, latex, mast cell disorder (2014)
36/II	- Initial perioperative allergic reaction with urticaria and hypotension - Patient developed a subsequent grade I reaction with patches of erythema over trunk immediately after induction of general anesthesia that resolved within minutes	II/I	NA/4.4	0	vancomycin, rocuronium, propofol, midazolam, fentanyl, latex, chlorhexidine	chlorhexidine, clindamycin, ondansetron, phenylephrine, neostigmine, glycopyrrolate (2014)
47*/I	- Initial perioperative allergic reaction about 20 minutes after receiving hydromorphone immediately post-operatively for pain - Underwent 11 subsequent procedures following initial negative A/I evaluation and experienced a subsequent perioperative allergic reaction during the third procedure but tolerated the remaining procedures - During the subsequent reaction, the patient experienced five episodes of apnea, throat tightness, and the sensation of needing to cough in the post-anesthesia care unit	II/IV	NA/NA	0	propofol, bupivacaine, latex	chlorhexidine, laryngospasm ⁺ , mast cell disorder (2006)

	- One episode of apnea required bag/mask ventilation for treatment - Patient tolerated cefazolin in the two procedures before initial perioperative allergic reaction, as well as during fourth subsequent procedure (after subsequent reaction) - Patient anesthesia records incomplete for subsequent reaction, but noted to have received cefazolin during procedure and narcotics/opioids during and after procedure					
58/I	- Initial perioperative allergic reactions (wheezing, bronchospasm, desaturation, hypotension, and tachycardia) was treated with diphenhydramine, ranitidine, and albuterol, but needed cardiopulmonary resuscitation to regain pulse following cardiopulmonary arrest - Experienced a subsequent perioperative allergic reaction during the third of three subsequent procedures similar to the initial reaction - Cefazolin, midazolam, and lidocaine ST was not performed as part of the initial A/I evaluation - Patient did not receive cefazolin (but tolerated midazolam and lidocaine) during the two subsequent procedures after AI evaluation - With third procedure, patient developed a red rash upon cefazolin infusion, followed in quick succession by coughing, wheezing, tachycardia, hypotension, apnea, and cardiac arrest require cardiopulmonary resuscitation along with intubation - Patient was stabilized after epinephrine treatment, regaining pulse, and the procedure was completed	IV/IV	206/27	0	cisatracurium, propofol, fentanyl	chlorhexidine, cefazolin, midazolam, lidocaine, indolent mastocytosis⁺⁺ (2008)
66/I	- Initial perioperative allergic reaction consisted of hypotension, bradycardia, arrhythmia, and urticaria - Underwent five subsequent procedures and experienced a subsequent reaction during his second subsequent procedure - During induction with general anesthesia, and specifically upon propofol administration, the patient became hypotensive with reflex bradycardia prompting treatment with ephedrine and phenylephrine - Tolerated propofol on third and fourth subsequent procedures without any reaction	III/II	NA/NA	0	cisatracurium, propofol	chlorhexidine, gentamicin, midazolam, phenylephrine, neostigmine, glycopyrrolate (2005)
69/I	- Initial perioperative allergic reaction with symptoms of hypotension, bronchospasm, tachycardia and flushing. - During A/I evaluation, ST was negative to cisatracurium and propofol while ST to midazolam was not performed Subsequent perioperative allergic reaction with redness on chest and upper extremities, hypotension and wheezing with exposure to midazolam, propofol, cisatracurium and hydromorphone	III/II	15/9.2	0	cisatracurium, propofol, latex	chlorhexidine, midazolam, phenylephrine, hydromorphone (2007)

Abbreviations: ID = patient study number; ST = skin testing; IV = intravenous; A/I = Allergy/Immunology

*From chart-review only (did not participate in phone interview; **Possible drugs that could have caused subsequent reaction because ST not completed and drug was received with initial

and subsequent procedures; +Discussion with anesthesia documented in chart suggests laryngospasm as a possible etiology for symptoms; **Subsequently diagnosed with indolent

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Sex	Grade of Initial Reaction	Initial tryptase within 4 hours (ng/mL)	Time to initial tryptase (min)	Baseline tryptase (ng/mL)	Dataset	Skin Test Result**	Subsequent Anesthesia
F	I	1.0	30	N/A	III	N/A	Tolerated
M	III	1.6	145	1.3	I	Negative	Tolerated
F	III	2.0	196	N/A	III	Negative	No subsequent anesthesia
F	I	2.0	N/A	N/A	I	Negative	No subsequent anesthesia
M	III	2.2	124	N/A	III	Negative	Tolerated
F	II	2.8	166	N/A	III	Chloroprocaine, Lidocaine	No subsequent anesthesia
M	IV	2.8	N/A	N/A	I	Negative	Tolerated
M	II	2.8	170	N/A	I	Negative	Tolerated
F	I	2.8	105	N/A	III	N/A	Tolerated
M	IV	3.0	25	N/A	I	Latex Specific IgE [†]	Tolerated
F	III	3.4	40	N/A	I	Negative	No subsequent anesthesia
M	II	4.0	55	N/A	II	Negative	No subsequent anesthesia
F	I	5.2	15	6.0	III	Negative	No subsequent anesthesia
F	III	6.0	78	N/A	I	Negative	Tolerated
M	II	7.5 ⁺	76	N/A	III	N/A	No subsequent anesthesia
M	III	7.6 ⁺	N/A	N/A	I	Negative	No subsequent anesthesia
M	IV	8.9 ⁺	N/A	N/A	II	Negative	Tolerated
F	IV	12.0	N/A	N/A	I	Negative	Tolerated
M	III	15.0*	33	9.2	I	Negative	Not tolerated
F	III	15.0*	101	N/A	III	Cefazolin	Tolerated
F	III	19.1*	N/A	3.4	I	Negative	Tolerated

M	III	19.5*	15	N/A	III	cefazolin	Tolerated
M	II	20.7*	102	9.0	II	cefazolin	Tolerated
M	III	23.1*	N/A	3.8	III	Negative	Tolerated
F	II	24.9*	130	3.0	II	Ciprofloxacin	Not tolerated
F	III	35.7*	23	N/A	I	Negative	Tolerated
F	III	38.0*	N/A	N/A	II	Negative	Tolerated
F	III	44.0*	59	4.3	I	Cefazolin	Tolerated
F	IV	44.6*	N/A	5.5	I	Negative	Tolerated
M	III	61.0*	57	4.4	II	Cefazolin	No subsequent anesthesia
M	III	62.0*	21	7.3	II	Negative	Tolerated
F	II	63.1*	13	7.1	III	Negative	Tolerated
F	II	69.0*	45	7.0	I	Vancomycin	No subsequent anesthesia
M	IV	168.0*	73	6.0	I	Cisatracurium	Tolerated
F	IV	182.0*	70	10.1	II	Negative	Tolerated
M	IV	206.0*	159	27.0	I	Negative	Not tolerated
M	III	247.0*	80	19.0	II	Cefazolin	Not tolerated
F	I	N/A	N/A	11.1	III	Negative	Tolerated
M	II	N/A	N/A	13.0	II	Cefazolin	Tolerated
F	II	N/A	N/A	14.3	III	Negative	Tolerated
F	III	N/A	N/A	19.0	I	Cefazolin	Tolerated

Abbreviations: M=Male; F=Female; N/A = Not Applicable

*Baseline tryptase level not available to determine if this represents an elevated reaction tryptase level using $(\text{baseline tryptase} \times 1.2) + 2$; cases from prior to 2015

*Reaction tryptase level remains elevated using $(\text{baseline tryptase} \times 1.2) + 2$

**The name of the medication is listed if a patient was skin test positive; "Negative" is listed if a patient was skin test negative to all agents during Allergy/Immunology evaluation

†Patient was skin test negative to all agents but had positive latex-specific IgE

Figure 1. Algorithm for Allergy/Immunology Evaluation after a Perioperative Allergic Reaction

Figure 1 Legend. This flow chart demonstrates our suggested algorithmic approach to patients with presumed allergic reactions in the perioperative setting. Patients are ideally evaluated by Allergy/Immunology between 4 weeks and 6 months following the reaction. Patients who are skin test positive to or who are unable to undergo skin testing should avoid the suspected agent and consider safe alternatives. Those who are skin test negative should undergo an oral challenge when possible and clinically appropriate. Patients who test positive during the oral challenge should use alternative agents. Those who test negative will have the allergy removed from the electronic health record.

*If elevated, consider evaluation for underlying mast cell disorder

[†] If negative testing, consider (1) skin testing dilutions; (2) hidden culprits (i.e., disinfectants like chlorhexidine, excipients); (3) repeat chart review to determine if any culprits overlooked; (4) evaluation for mast cell disorder (if baseline tryptase was elevated or clinical suspicion) (5) discuss case with anesthesiology to consider alternative etiologies

Figure 2. Results of Skin Testing from Allergy/Immunology Evaluation after Perioperative Allergic Reaction

Figure 2 Legend. This flow chart demonstrates outcomes of Allergy/Immunology (A/I) skin testing (ST) in patients with perioperative allergic reactions. Of 123 patients referred to A/I, 118 patients received ST. Evaluations were not completed by 5 patients. 90 patients tested negative for IgE-mediated hypersensitivity. 28 patients tested positive to both antibiotics (n=17) and non-antibiotics (n=11).

* Two patients were skin test positive to 2 different agents. One patient tested positive to ciprofloxacin and levofloxacin and another patient tested positive to chloroprocaine and lidocaine

† Dataset I Guyer et al., Dataset II Kuhlen et al., Dataset III new data

Figure 3. Outcomes of Subsequent Anesthesia after Allergy/Immunology Evaluation

Figure 3 Legend. This flow chart depicts the outcomes of patients evaluated by Allergy/Immunology (A/I) following subsequent anesthesia. Of 123 patients evaluated, 111 completed follow-up interviews during the study period. 85 patients had subsequent anesthesia. Only 7 patients had reactions with subsequent anesthesia, 5 of which had negative skin testing.

Abbreviations: A/I = Allergy/Immunology

*Dataset I Guyer et al., Dataset II Kuhlen et al., Dataset III new data





