Incidence of Intraoperative Hypersensitivity Reactions

A Registry Analysis

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ABSTRACT

Background: Previously reported incidences for intraoperative hypersensitivity reactions vary more than 15-fold. The goal was to determine the incidence of intraoperative hypersensitivity events at a U.S. surgical center.

Methods: With institutional review board (Cleveland, Ohio) approval and waiver of written/informed consent, the anesthesia records of adult patients undergoing noncardiac surgery from 2005 to 2011 at the Cleveland Clinic were queried using a novel electronic search protocol developed to identify potential hypersensitivity reactions: cardiovascular collapse defined as systolic arterial blood pressure less than 50 mmHg; administration of epinephrine; administration of diphenhydramine; physician comments in the anesthesia record suggestive of hypersensitivity reactions; laboratory tests for histamine, tryptase, or immunoglobulin-E within 24 h of surgery; and International Classification of Diseases, Ninth Revision, codes suggestive of hypersensitivity reactions. Each electronically identified candidate chart was evaluated by an adjudication committee. Hypersensitivity reactions were graded on a 5-point severity scale. From these data, the authors determined the proportion of operations having adjudicated hypersensitivity reactions, and calculated the 95% exact binomial CI.

Results: Among 178,746 records, 4,008 charts were identified by the search strategies. After adjudication, 264 hypersensitivity cases were identified. The overall incidence of hypersensitivity reactions was 1:677 surgeries, corresponding to 15 (95% CI, 13 to 17) cases per 10,000 operations. The incidence of severe hypersensitivity reactions (grades 3 to 5) was 1:4,583, corresponding to 2 (95% CI, 2 to 3) cases per 10,000 operations.

Conclusions: The incidence of severe hypersensitivity reactions was similar to previous reports. However, the overall incidence of hypersensitivity reactions was much greater than reported elsewhere, possibly because of a comprehensive search strategy.

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BUILDING upon Emil von Behring's (1854–1917) and Louis Pasteur's (1822–1895) vaccination work, Paul Portier and Charles Richet[1] attempted to immunize dogs with purified sea anemone actinotoxin in 1902. The paradoxical effect was that the animals were sensitized to the toxin—and that subsequent tiny doses proved lethal.[2] This new phenomenon was deemed anaphylaxis.

Anaphylaxis, defined as a severe hypersensitivity reaction, may be mediated by immunoglobulin-E (IgE), termed immunologic, such as with β-lactam antibiotics,[3] but it turns out that this is but one mechanism. Nonimmunologic etiologies, such as with opioids and vancomycin,[3] and idiopathic etiologies[4] also contribute to hypersensitivity reactions. Regardless of the mechanism, the clinical spectrum ranges from benign urticaria to cardiovascular and pulmonary collapse.[5] Hypersensitivity reactions remain concerning because the effects are generally unanticipated, sometimes difficult to diagnose, and can have grave consequences.[6] It is not unusual, for example, for life-threatening hypotension and cardiac arrest to be the first clinical indication of intraoperative anaphylaxis.[6–11]

What We Already Know about This Topic

- The reported incidence of intraoperative hypersensitivity reactions ranges from 1 in 1,480 to 1 in 10,000 anesthetics
- The methodological challenges of identifying, evaluating, and characterizing hypersensitivity reactions need to be addressed to estimate the true incidences accurately

What This Article Tells Us That Is New

- A novel methodology combining electronic search strategies and clinical adjudication was used to identify occurrences of hypersensitivity reactions
- The overall incidence of hypersensitivity reactions identified from the electronic records of 178,746 procedures performed on 120,242 patients was 1 in 677 and that of anaphylaxis was 1 in 4,583
- The incidence of anaphylaxis was similar to that reported in previous studies but that of hypersensitivity reactions was nearly seven times higher

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The estimated incidence of intraoperative hypersensitivity reactions varies widely among studies ranging between approximately 1 in 1,480[12] and 1 in 10,000[9] anesthetics, with severe, life-threatening anaphylaxis ranging between 1 in 6,000[13] and 1 in 20,000[10] anesthetics. Retrospective studies purport fewer incidences[9,10] possibly due to limited data, while prospective studies[12–14] benefit from established testing and reporting protocols. Nonetheless, studies which estimate incidences of voluntary self-reporting are still vulnerable to underreporting.[15] One epidemiological study has attempted to lessen the underestimate by comparing multiple independent reporting systems[16]; however, it too was subject to reporting bias. Accurate estimates of the true incidence will need to address the methodological challenges of identifying, evaluating, and characterizing hypersensitivity reactions.

The Cleveland Clinic possesses a comprehensive searchable electronic database that combines complete intraoperative anesthesia records including hemodynamics and medication administration, inpatient and outpatient laboratory results, diagnoses, and allergies. We developed a novel methodology, combining electronic search strategies and clinical adjudication, to identify occurrences of hypersensitivity reactions.

Our primary goal was to identify potential instances of hypersensitivity reactions, designated by clinical manifestations and interventions, and to determine the incidence and severity of intraoperative hypersensitivity events in a large U.S. surgical population. Secondarily, we assessed patient characteristics associated with hypersensitivity reactions, including the previously identified risk factors of sex,[17,18] muscle relaxants,[17] and antibiotics.[18,19]

Materials and Methods

Search Strategy

With the approval of the Cleveland Clinic Institutional Review Board, Cleveland, Ohio, and waiver of written informed consent, we assessed electronic records from adult patients who had noncardiac surgery between April 2005 and December 2011 using the Cleveland Clinic Perioperative Health Documentation System. This registry contains laboratory data, pharmacy data, discharge International Classification of Diseases, Ninth Revision, codes, and the complete electronic anesthetic records including provider-entered free-text comments. During that period 120,242 patients had 179,621 noncardiac procedures, 28% (n = 33,627) of patients had multiple surgeries and 875 surgeries were excluded from all analyses after retaining the first 10 surgeries per patient. We thus studied 178,746 procedures performed on 120,242 patients.

Delphi Process

Ten senior anesthesiologists participated in a Delphi process using the diagnostic clinical criteria for anaphylaxis proposed by Sampson,[7] the most common treatments, and the most common confirmatory tests as a starting point to develop independent search strategies to identify search criteria that could be used to detect potential hypersensitivity reactions in the electronic database.

Rationale for the Search Strategies

The Sampson criteria (hypotension, skin manifestations, and airway compromise) were designed to identify reactions in the nonoperative setting.[7] The hypotension criterion (systolic blood pressure <100 mmHg) is unsuitable for the intraoperative period because transient hypotensive episodes are not uncommon. Our Delphi team thus felt a lower sustained threshold would be more appropriate.

The most common initial medications given to patients suspected of having hypersensitivity reactions are diphenhydramine and vasopressors depending on the severity. Epinephrine is the preferred vasopressor in suspected anaphylaxis,[11,20] with other vasopressors given as second-line treatments.

Comments are nonstructured fields and must be manually entered in the anesthetic record. An extensive array of terms must be queried to assess the variable documentation of reactions. An expected nonhypersensitivity reaction, such as a patient flushing after atracurium administration, is unlikely to be manually documented. If documented, it would not be deemed a reaction in the subsequent adjudication committee. Conversely, hypersensitivity reactions are unexpected and thus unlikely to be completely unmentioned.

Perioperative immunological laboratory testing indicates a clinician's intention to diagnose a potential allergic reaction. The values of histamine[21] and tryptase[22,23] are time-dependent; therefore, values in the normal ranges do not necessarily negate a hypersensitivity reaction. Conversely, an increased IgE level in patients with asymptomatic sensitization is common.[24] The diagnosis of anaphylaxis based on clinical symptoms is valid regardless laboratory tests.[24]

International Classification of Diseases, Ninth Revision, codes may represent hypersensitivity reactions, but they are not specific to the intraoperative period; therefore, presence and timing of the reaction needs to be assessed in the subsequent adjudication process.

Identification of Episodes

The Delphi committee agreed that the following six responses were reasonable search criteria to identify potential hypersensitivity reactions:

1. Cardiovascular collapse, systolic blood pressure 20 to 50 mmHg for 3 min or more.
2. Intravenous administration of epinephrine.
3. Intravenous administration of diphenhydramine.
4. Physician comments, free-text comments in anesthesia record suggestive of a hypersensitivity reaction. Specifically, we included "Preferred Terms" for indexing anaphylactic reactions from the Medical Dictionary for Regulatory Activity (Northrop Grumman, Los Angeles, CA): allergic, allergy, anaphylactic, anaphylactoid, anaphylaxis, asthma, blood pressure decreased,

bronchospasm, cardiac arrest, cardiorespiratory distress, cardiovascular insufficiency, chest discomfort, choking, circulatory collapse, cough, cardiopulmonary resuscitation, dyspnea, edema, erythema, first use syndrome, fixed eruption, flushing, hives, hypersensitivity, hyperventilation, hypotension, Kounis syndrome, laryngospasm, obstruction, pruritus, rash, reaction, respiratory arrest, respiratory distress, respiratory failure, sensation of foreign body, shock, sneezing, spasm, stridor, swelling, swollen, throat tightness, urticaria, and wheezing.

5. Laboratory tests for histamine, tryptase, or IgE (total or specific) within 24 h of surgery.
6. International Classification of Diseases, Ninth Revision, codes suggestive of hypersensitivity reactions
   - 693.0 Dermatitis medicamentosa, not otherwise specified
   - 782.62 Flushing
   - 995.0 Other anaphylactic shock
   - 995.27 Other drug allergy
   - 995.3 Allergy, unspecified
   - 995.4 Shock (due to) anesthetic.

Case Adjudication

We considered patients identified *via* one or more of the above search criteria as candidates for an intraoperative hypersensitivity reaction. We subsequently compiled all available resources including patient history, anesthesia records, surgical reports, inpatient notes, laboratory data, and outpatient consultations. These records were presented to an adjudication committee consisting of three experienced anesthesiologists.

Hypersensitivity Criteria. Two members of the adjudication committee (L.S. and A.T.) independently evaluated each candidate identified by the electronic search process for the occurrence of a hypersensitivity reaction by clinical symptoms, arguably the principal factor in the evaluation of reactions.[24,25] The adjudicators used the *classical* clinical criteria for anaphylaxis: mucocutaneous signs; airway compromise; or significant reduction of blood pressure without plausible alternative explanation (*i.e.*, brisk blood loss).[7,11]

Treatment of these clinical symptoms by pharmacologic means and confirmation by immunologic testing were used as supporting evidence; treatment alone was insufficient to assess a hypersensitivity reaction, and lack of immunological testing was insufficient to reject a hypersensitivity reaction. We did not consider hypersensitivity reactions as diagnoses of exclusion when we could not find a discernible reason for treatment administrations; we still required at least one classic symptom above. Symptomatic manifestations of preexisting conditions (such as an asthmatic having postinduction bronchospasm) or exaggerated responses to medications (such as an elderly patient) were not deemed hypersensitivity reactions because they could reasonably be attributed to other causes.

Severity Grading of Hypersensitivity Reaction. The severity of the hypersensitivity reaction was graded 1 to 5 corresponding to minor, low severity, life-threatening symptoms, cardiac or respiratory arrest, and death.[13,26,27] Severe reactions, grades 3 to 5, were considered and termed anaphylaxis. If there was nonconsensus on hypersensitivity occurrence or grade, a final determination was made by the third adjudicator (A.K.).

Statistical Analysis

Our primary goal was to estimate the incidence of intraoperative hypersensitivity reactions and anaphylaxis. Our secondary goal was to identify baseline and intraoperative factors independently associated with hypersensitivity reactions. In all analyses, the unit of observation was the operation rather than the patient, some of whom had more than one operation.

We determined the proportion of operations having adjudicated hypersensitivity reactions, and calculated its 95% exact binomial CI. We further assessed the relationship between hypersensitivity reactions and all baseline and intraoperative variables using a multivariable generalized estimating equation logistic (*i.e.*, logit link) model and compound symmetry within-subject correlation structure. This included the *a priori* specified interaction between sex and use of a neuromuscular blocking agent, with significance criterion of P value less than 0.10. All factors were forced into the model regardless of statistical significance. Factors were considered significant when P value less than 0.05/34 = 0.0015, using a Bonferroni correction for 34 potential preoperative and intraoperative factors to maintain an overall significance level of 0.05. We *a priori* excluded steroids, diphenhydramine, and vasopressors from our analytical model because they are rarely implicated as causative agents and more likely to be a false association due to their use as treatments for hypersensitivity reactions. We assessed diagnostics for the generalized estimating equation model by assessing the distribution of standardized "dfbeta" statistics for each predictor variable, with the goal of identifying any individual patient clusters (*i.e.*, multiple surgeries on same patient) having undue influence on the results.

SAS statistical software (SAS Institute Inc., Carey, NC) was used for all analyses.

Results

We considered 178,746 surgeries for our analysis. The six electronic search strategies described above yielded 4,008 (2% of the study population) candidate operations, all of which were adjudicated for potential hypersensitivity reactions (fig. 1). Table 1 details the number of candidate patients identified by either 1, 2, 3, or 4 search criteria. The Adjudication Committee determined that 264 (7%) candidate operations were in fact hypersensitivity reactions (table 1). Among the 4,008 cases that were each evaluated by two anesthesiologists, only 27 were referred for adjudication by a third investigator.

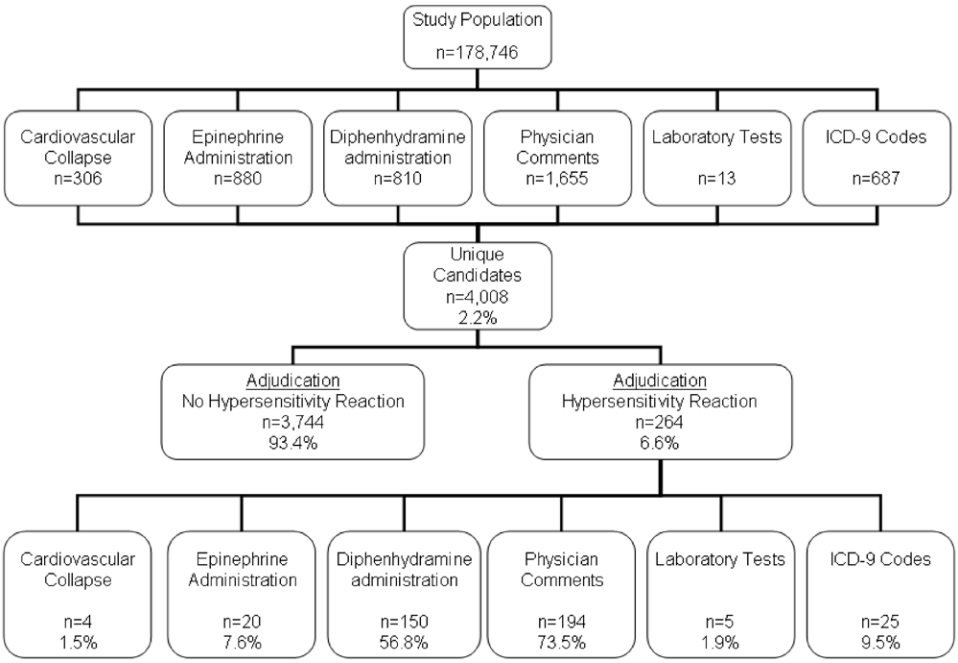

Fig. 1. Study population, identification of candidates, and adjudication results of 178,746 adult patients who had noncardiac surgery at the Cleveland Clinic between April 2005 and December 2011. ICD-9 codes = International Classification of Diseases, Ninth Revision.

Table 1. Unique Candidates Identified by Search Criteria

Number of Categories that Identified Candidate	(n)	Positive Hypersensitivity Reactions
1 search category	3,701	148 (4.0%)
2 search categories	273	99 (36%)
3 search categories	32	16 (50%)
4 search categories	2	1 (50%)
Total of all search categories	4,008	264 (6.6%)

The overall incidence of hypersensitivity reactions was 1:677 surgeries, corresponding to 15 (95% CI, 13 to 17) cases per 10,000 operations. Reaction severity was grade 1, 2, 3, and 4 in 67, 18, 10, and 5% of cases, respectively. No patients died consequent to a hypersensitivity response, and thus none of the reactions was deemed grade 5. The incidence of anaphylaxis, severe hypersensitivity reactions (grades 3 to 5), was 1:4,583, corresponding to 2 (95% CI, 2 to 3) cases per 10,000 operations (table 2).

The mean age ± SD was 56 ± 16 yr and 53% were female in cases without hypersensitivity reactions, while in the hypersensitivity cases, age was 54 ± 16 yr and 63% were female. Patients who demonstrated and did not demonstrate hypersensitivity reactions did not differ strikingly on distributions of American Society of Anesthesiologists physical status classification, body mass index, urgency case, or medical history (table 3).

In our multivariable model (table 3), factors that were significantly associated with experiencing a hypersensitivity reaction after Bonferroni correction were type of surgery ($P = 0.001$ overall), lower body mass index (odds ratio [99.8% CI] of 0.86 [0.75 to 0.99] for a 5-unit increase), having preexisting allergies (1.4 [1.1 to 1.8]) and receiving hetastarch (1.3 [1.0 to 1.6]). Use of neuromuscular-blocking agents was not significantly associated with experiencing hypersensitivity reactions ($P = 0.034$), and the relationship between neuromuscular blocking agents and hypersensitivity reactions did not depend on sex (interaction $P = 0.56$). Our generalized estimating equation model diagnostics looked good and did not identify any influential data points or patient clusters.

Discussion

We identified hypersensitivity reactions in 1:677 patients, and anaphylaxis in 1:4,583 patients. Anaphylaxis is relatively easy to identify because of their impressive clinical presentations. Where we differ is in also identifying a large number of minor-to-low severity cases which appear to have been missed in many previous studies. Both incidences are greater than previously reported,[9,10,13,14,16,28–30] considerably greater in total reactions, possibly due to differences in methodologies such as prospective voluntary reporting, dependence on allergy clinic referrals, and geographic variations.

A systematic review of underreporting of adverse drug reactions concluded that the most important source of underreporting in voluntary systems is the reporting of only severe adverse reactions.[31] For example, a prospective Spanish study reported the incidence of perioperative hypersensitivity reactions to be 1 in 10,263; however, 56% of the 32 reactions were severe.[29] In a 6-yr prospective study in Norway,[32] two thirds of reactions referred to the allergy clinic

Table 2. Severity Grading Scale and Distributions of Reactions

Severity Grade	Definition	(n)	% of Reactions		
1	Cutaneous symptoms; a trivial problem, easily dealt with and not affecting the patient's condition.	176	66.7%	Incidence of ALL hypersensitivity reactions (grades 1–5) 1:677	
2	Measureable but not life-threatening symptoms; a moderate difficulty, with some effect on the patient, but of a low severity.	49	18.5%		
3	Life-threatening symptoms; a serious situation which is either very difficult to manage, or which causes a serious deterioration in the patient's state, and which may or may not have postoperative consequences.	25	9.5%		Incidence of SEVERE hypersensitivity reactions/anaphylaxis (grades 3–5) 1:4,583
4	Cardiac and/or respiratory arrest.	14	5.3%		
5	Death.	0	0%		

were severe; a similar proportions were seen in a prospective study by Malinovsky *et al.*[14] in France which also excluded patients without allergy skin testing.

Retrospective studies are not immune to reporting and documentation limitations. A 17-yr retrospective study in Australia of allergy clinic referrals reported that more than half of reactions were severe.[10] The response rate of a questionnaire-based retrospective study in Japan only yielded a 15% response rate and a mortality rate of almost 5%.[9] Clearly, previous methodologies favored reporting of severe reactions. Our methodology differs markedly in that only 15% of the 264 reactions were severe (grades 3 and 4) and no deaths (grade 5).

Mild reactions, severity grades 1 and 2, are subtle and are obviously least likely to be identified. For example, clinicians may easily overlook isolated minor responses such as cutaneous reactions covered by surgical drapes. The importance of mild reactions is not the initial cutaneous reaction, but the subsequent possibly escalating reaction upon reexposure to the offending agent. Therefore, the mild reactions are not unimportant in context of long-term patient safety, and specific investigations dedicated to these reactions are warranted. We were only able to identify many mild reactions to the extent that clinicians included text comments in the anesthesia records. We surely therefore missed some subtle hypersensitivity reactions (that were presumably also missed clinically); the true incidence is thus likely to be even greater than we report. On the other hand, we are confident that patients designated as having severe hypersensitivity reactions truly did.

Laboratory testing for allergic reactions was rare, except after anaphylaxis. Furthermore, as is usual, most purely laboratory testing proved nondiagnostic. The causative agent was usually nonobvious in our patients, and assigning causality was complicated by the fact that anesthetized patients are usually given many drugs—often more or less simultaneously. That is not to say that follow-up testing is without merit; on the contrary, allergic testing using both laboratory and skin tests is essential for diagnostic evaluation and ultimately for patient safety. Interestingly, if we assume that the patients for whom allergy testing was ordered would also be the same patients reported in a voluntary reporting system, we would have estimated an incidence of 1 in 13,750; strikingly similar to the Perioperative Anaphylactoid Reactions Study Group's reported incidence of 1 in 13,000[30] using postoperative testing criteria.

Physician comments proved to be the most useful search criterion, identifying 74% of the cases eventually deemed to be hypersensitivity reactions. However, it was also the least efficient. A broad array of terms was queried to minimize the number of missed hypersensitivity cases. Several cases of negative statements were encountered (*i.e.*, "no rash noted") along with affirmative statements of past reactions not pertaining to current surgery (*i.e.*, "history of rash with opioids") resulting in 1,461 cases not deemed to be hypersensitivity cases. Newer techniques of natural language processing that consider context and word order in addition to text strings may make queries of physician comments more useful.[33]

The most efficient criterion was laboratory testing with 5 of the 13 tests (38%) adjudicated to be allergic anaphylaxis cases. The negative cases identified by allergy laboratory testing were found to be surgical evaluation of mastocytosis. The lack of allergy testing makes us unable to comment, even broadly, on the distribution of IgE-mediated *versus* non-IgE–mediated reactions.

The restrictive search criterion for cardiovascular collapse (systolic blood pressure 50 to 20 mmHg for ≥3 min) made this strategy independently the least useful being positive in only 4 of the 264 adjudicated hypersensitivity cases. Most cases of hypotension were aggressively treated and lasted less than 3 min. The electronic search criterion for epinephrine boli identified 20 of the 39 severe hypersensitivity reactions, though an additional 12 of the severe hypersensitivity reactions proved through manual chart review of comments and paper code sheets to have been given epinephrine boli. The remaining seven cases were treated with other vasopressors and/or started on epinephrine infusions. Advancement of electronic code charting may make this search strategy more useful in future studies. Interestingly, almost half of severe reactions (46%) were also noted to have cutaneous symptoms, though mild symptoms may fail to be documented during cardiac or pulmonary arrests.

Table 3. Multivariable Associations between Baseline/Intraoperative Factors and Hypersensitivity

Factor	Nonhypersensitivity Cases (n = 178,482)	Hypersensitivity Cases (n = 264)	Multivariable Odds Ratio (99.85% CI)*	*P* Value*
Number of patients	120,128	260		
Age (yr)	56 ± 16	54 ± 16	0.91 (0.79–1.04)†	0.027
Female	53%	63%	1.14 (0.92–1.42)	0.054
Body mass index (kg/m^2)	29 ± 8§	28 ± 6	0.86 (0.75–0.99)†	0.0003‡
ASA class			0.92 (0.67–1.28)	0.44
0	0.6%	0%		
1	5%	4%		
2	39%	42%		
3	47%	45%		
4	8%	8%		
5	0.2%	0%		
6	0.05%	0%		
Urgent case	5%	6%	0.87 (0.55–1.37)	0.32
General anesthesia	86%	96%	1.33 (0.73–2.40)	0.13
Type of surgery				0.0010
General	28%	34%	Ref. = 1	
Vascular	8%	13%	1.38 (0.68–2.77)	0.15
Orthopedic	17%	13%	0.70 (0.34–1.43)	0.12
Neuro	13%	13%	0.94 (0.45–1.96)	0.78
Urology	14%	9%	0.72 (0.31–1.64)	0.20
Plastics	7%	11%	1.12 (0.52–2.39)	0.64
Gynecology	6%	5%	0.68 (0.27–1.74)	0.19
Other	8%	3%	0.34 (0.10–1.20)	0.007
Medical history				
Asthma (pulmonary disease)	8.4%	8.7%	0.98 (0.69–1.41)	0.89
Atopy	0.13%	0.76%	2.35 (0.74–7.52)	0.02
Coronary artery disease	13%	11%	0.95 (0.67–1.34)	0.64
Eczema	1.5%	1.1%	0.84 (0.33–2.15)	0.56
HIV/AIDS	0.25%	0.38%	1.29 (0.26–6.43)	0.62
Hypertension	44%	40%	0.99 (0.79–1.26)	0.94
Preexisting allergies	58%	76%	1.40 (1.10–1.79)	<0.001‡
Intraoperative medication				
Colloids				
Albumin	3%	6%	1.06 (0.70–1.63)	0.64
Hetastarch	33%	50%	1.29 (1.02–1.62)	<0.001‡
Neuromuscular-blocking agents				0.034
None	27%	13%	Ref. = 1	
Depolarizing only	2%	3%	2.60 (0.62–10.9)	0.035
Nondepolarizing only	58%	69%	2.29 (0.80–6.56)	0.012
Depolarizing or nondepolarizing	13%	15%	2.10 (0.67–6.56)	0.039
Opioids	93%	96%	1.14 (0.69–1.91)	0.40
Sedatives				
Propofol	87%	88%	1.00 (0.67–1.50)	0.97
Etomidate	3.9%	5.7%	1.09 (0.64–1.84)	0.61
Midazolam	47%	46%	0.98 (0.80–1.20)	0.77
Thiopental/methohexital	1.7%	3.0%	1.03 (0.54–1.96)	0.89
Local/regional anesthetics				
Lidocaine	70%	74%	0.96 (0.73–1.25)	0.59
Other local anesthetics	8.5%	4.9%	1.05 (0.65–1.68)	0.75
Antibiotics				
Ampicillin/sulbactam	7.7%	6.1%	0.79 (0.50–1.24)	0.096
Cefazolin	43%	33%	0.86 (0.66–1.14)	0.092
Ciprofloxacin	3.6%	7.6%	1.11 (0.68–1.82)	0.49
Clindamycin	2.8%	8.3%	1.49 (0.98–2.26)	0.0026
Gentamycin	1.9%	1.5%	0.93 (0.40–2.19)	0.79
Metronidazole	3.6%	8.3%	1.15 (0.70–1.90)	0.37
Vancomycin	6.0%	14%	1.29 (0.91–1.82)	0.02
Other antibiotics	3.5%	6.4%	1.09 (0.68–1.74)	0.57

(*Continued*)

Table 3. Continued

Factor	Nonhypersensitivity Cases (n = 178,482)	Hypersensitivity Cases (n = 264)	Multivariable Odds Ratio (99.85% CI)*	*P* Value*
Not given neostigmine	62%	65%	1.74 (0.997–3.04)	0.0016
Length of surgery (h)	2.8 [1.7, 4.2]	3.6 [2.3, 5.1]	1.28 (0.96–1.71)†	0.007

Data are presented as mean ± SD, median [25th, 75th quartile], or %.

*Multivariable generalized estimating equation model with logit link. †Odds ratio was calculated for log2-transformed length of surgery (for every twofold increase in hour), for 5-unit increase in body mass index, and 10-yr increase in age, respectively. ‡Significant if $P < 0.0015$ in multivariable model using Bonferroni correction (*i.e.*, 0.05/34 tests). §4.7% missing data points were replaced by the median body mass index in the model.

ASA = American Society of Anesthesiologists; depolarizing = succinylcholine; HIV/AIDS = human immunodeficiency virus/acquired immunodeficiency syndrome; nondepolarizing = atracurium, cisatracurium, pancuronium, rocuronium, or vecuronium; opioids = alfentanil, fentanyl, hydromorphone, morphine, remifentanil, or sufentanil; other anesthetics = bupivacaine, mepivacaine, or ropivacaine; other antibiotics = aztreonam, ceftriaxone, ceftizoxime, cefuroxime, linezolid, oxacillin, piperacillin, or piperacillin/tazobactam.

Though our study was designed to evaluate the incidence of hypersensitivity reactions, it appears to be the first study with sufficient sample size to accurately assess associations with various factors and hypersensitivity reactions.

Higher body mass index was associated with decreased odds of hypersensitivity. It is possible that there were more frail individuals in the hypersensitivity group which may have had more previous exposures to medications leading to an increased incidence of hypersensitivity reactions in this group.

High-molecular-weight hetastarch (6%), the only synthetic colloid used at our institution, was significantly associated with hypersensitivity reactions. Although plasma expanders pose a potential for hypersensitivity reactions, they appear to be rare.[34] It is thus more likely that the volume expander was given to treat hypotension consequent to a hypersensitivity reaction rather than causing the reaction.

Patients with preexisting allergies to medications were more likely to experience an intraoperative hypersensitivity reaction, cross-reactivity surely contributed to the incidence. The structure–activity relationships which confer drug function may also predispose to hypersensitivity reactions.[35] Muscle relaxants show a significant amount of cross-reactivity as indicated by intradermal skin testing.[36]

Muscle relaxants are a commonly reported trigger for hypersensitivity reactions,[10,16,17,30,32,37,38] particularly nondepolarizing muscle relaxants.[16,32,37,38] Although the association was not statistically significant after Bonferroni correction in our study, with an odds ratio of 1.29 (99.85% CI,1.02 to 1.62; $P = 0.006$), previous large studies, such as an 8-yr survey on anaphylaxis in France, found muscle relaxants to be the leading cause of anaphylaxis.[16] Interestingly, pholcodine—an agent implicated in cross-reactively sensitizing patients to nondepolarizing muscle relaxants[39]—is commonly used in France,[40] but is a schedule 1 controlled substance and practically unavailable in the United States.[41]

Our study population was 53% female, and 63% of our adjudicated reactions occurred in women. Sex was not significantly associated with reactions in our patients, but perioperative hypersensitivity reactions have many times been reported to be more common in women,[16,18,29,32,38] possibly related to sex hormones.[42] Furthermore, women are more often reactive to neuromuscular blocking drugs than men,[43] which is consistent with our trend shown in study.

The Cleveland Clinic is a tertiary surgical center; consequently, many of our patients are of high medical acuity and are more likely to have had previous operations and to have been exposed to many drugs. Our patients therefore may be at higher risk for hypersensitivity reactions compared to first-time surgical patients presenting to other surgical environments, leading to higher rates of reactions at our institution. However, the Cleveland Clinic was latex-free throughout the study period; it is thus unlikely that any of the hypersensitivity reactions we observed were triggered by latex. Hospitals that still use latex may thus have an even greater overall risk of intraoperative hypersensitivity reactions given that it is among the most common causes of hypersensitivity reactions.[16] And of course other institutions use somewhat different anesthetic approaches which may influence the incidence of hypersensitivity reactions, including use of different muscle relaxants and antibiotics.

Another limitation of our study is that we cannot interpret associations that we observed in an inferential manner since the exact timing of the hypersensitivity reactions were not known in many cases (*e.g.*, a rash under a garment might be discovered toward the end of the case). Statistically associated intraoperative variables must be interpreted with caution, and causation should not be assumed.

Moreover, our analysis includes many mild cases of hypersensitivity, and the strength of associations with various patient factors would presumably differ if that analysis restricted to anaphylaxis *per se*. With only 39 severe reactions, we could not conduct a multivariable analysis limited to anaphylaxis. Morbidity of the hypersensitivity reactions was beyond the scope of this initial investigation.

In summary, we developed a novel methodology for evaluating hypersensitivity reactions and anaphylaxis which is suitable for use with dense perioperative registries. We found that the overall incidence of hypersensitivity reactions to be 1:677 among 178,746 surgeries, with the incidence of severe hypersensitivity reactions, anaphylaxis, to be 1:4,583. While the incidence of anaphylaxis was

similar to the total incidence reported in previous studies, the overall incidence of hypersensitivity reactions was about sevenfold greater.

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Competing Interests

Dr. Besson is employed by and receives salary from MSD Pharmaceutical. Drs. Sessler and Saager received honorarium for participation in an MSD Pharmaceutical expert panel. The other authors declare no competing interests.

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References

1. Portier P, Richet C: De l'action anaphylactique de certains venins. C R Soc Biol-Paris 1902; 54:170–2
2. May CD: The ancestry of allergy: Being an account of the original experimental induction of hypersensitivity recognizing the contribution of Paul Portier. J Allergy Clin Immunol 1985; 75:485–95
3. Greenberger PA, Ditto AM: Chapter 24: Anaphylaxis. Allergy Asthma Proc 2012; 33(suppl 1):S80–3
4. Picard M, Giavina-Bianchi P, Mezzano V, Castells M: Expanding spectrum of mast cell activation disorders: Monoclonal and idiopathic mast cell activation syndromes. Clin Ther 2013; 35:548–62
5. Levy JH: Common anaphylactic and anaphylactoid reactions seen by the anesthesiologist, in Anaphylactic Reactions in Anesthesia and Intensive Care, 2nd edition. Boston, Butterworth-Heinemann, 1992, pp 83–120
6. Hepner DL, Castells MC: Anaphylaxis during the perioperative period. Anesth Analg 2003; 97:1381–95
7. Sampson HA, Muñoz-Furlong A, Bock SA, Schmitt C, Bass R, Chowdhury BA, Decker WW, Furlong TJ, Galli SJ, Golden DB, Gruchalla RS, Harlor AD Jr, Hepner DL, Howarth M, Kaplan AP, Levy JH, Lewis LM, Lieberman PL, Metcalfe DD, Murphy R, Pollart SM, Pumphrey RS, Rosenwasser LJ, Simons FE, Wood JP, Camargo CA Jr: Symposium on the definition and management of anaphylaxis: Summary report. J Allergy Clin Immunol 2005; 115:584–91
8. Caimmi S, Caimmi D, Bernardini R, Caffarelli C, Crisafulli G, Pingitore G, Marseglia GL: Perioperative anaphylaxis: Epidemiology. Int J Immunopathol Pharmacol 2011; 24(3 suppl):S21–6
9. Mitsuhata H, Hasegawa J, Matsumoto S, Ogawa R: [The epidemiology and clinical features of anaphylactic and anaphylactoid reactions in the perioperative period in Japan: A survey with a questionnaire of 529 hospitals approved by Japan Society of Anesthesiology]. Masui 1992; 41:1825–31
10. Fisher MM, Baldo BA: The incidence and clinical features of anaphylactic reactions during anesthesia in Australia. Ann Fr Anesth Reanim 1993; 12:97–104
11. Simons FE, Ardusso LR, Bilò MB, Dimov V, Ebisawa M, El-Gamal YM, Ledford DK, Lockey RF, Ring J, Sanchez-Borges M, Senna GE, Sheikh A, Thong BY, Worm M; World Allergy Organization: 2012 Update: World Allergy Organization Guidelines for the assessment and management of anaphylaxis. Curr Opin Allergy Clin Immunol 2012; 12:389–99
12. Lobera T, Audicana MT, Pozo MD, Blasco A, Fernández E, Cañada P, Gastaminza G, Martinez-Albelda I, González-Mahave I, Muñoz D: Study of hypersensitivity reactions and anaphylaxis during anesthesia in Spain. J Investig Allergol Clin Immunol 2008; 18:350–6
13. Fasting S, Gisvold SE: [Serious intraoperative problems—A five-year review of 83,844 anesthetics]. Can J Anaesth 2002; 49:545–53
14. Malinovsky JM, Decagny S, Wessel F, Guilloux L, Mertes PM: Systematic follow-up increases incidence of anaphylaxis during adverse reactions in anesthetized patients. Acta Anaesthesiol Scand 2008; 52:175–81
15. Mertes PM, Guttormsen AB, Harboe T, Johansson SG, Florvaag E, Husum B, Garvey LH, Kroigaard M, Gramstad L, Kvande KT, Trechot P, Malinovsky JM: Can spontaneous adverse event reporting systems really be used to compare rates of adverse events between drugs? Anesth Analg 2007; 104:471–2
16. Mertes PM, Alla F, Tréchot P, Auroy Y, Jougla E; Groupe d'Etudes des Réactions Anaphylactoïdes Peranesthésiques: Anaphylaxis during anesthesia in France: An 8-year national survey. J Allergy Clin Immunol 2011; 128:366–73
17. Galletly DC, Treuren BC: Anaphylactoid reactions during anaesthesia. Seven years' experience of intradermal testing. Anaesthesia 1985; 40:329–33
18. Bigby M, Jick S, Jick H, Arndt K: Drug-induced cutaneous reactions. A report from the Boston Collaborative Drug Surveillance Program on 15,438 consecutive inpatients, 1975 to 1982. JAMA 1986; 256:3358–63
19. Gurrieri C, Weingarten TN, Martin DP, Babovic N, Narr BJ, Sprung J, Volcheck GW: Allergic reactions during anesthesia at a large United States referral center. Anesth Analg 2011; 113:1202–12
20. Garvey LH, Belhage B, Krøigaard M, Husum B, Malling HJ, Mosbech H: Treatment with epinephrine (adrenaline) in suspected anaphylaxis during anesthesia in Denmark. Anesthesiology 2011; 115:111–6
21. Takeda J, Ueda E, Takahashi J, Fukushima K: Plasma N-methylhistamine concentration as an indicator of histamine release by intravenous d-tubocurarine in humans: Preliminary study in five patients by radioimmunoassay kits. Anesth Analg 1995; 80:1015–7
22. Sala-Cunill A, Cardona V, Labrador-Horrillo M, Luengo O, Esteso O, Garriga T, Vicario M, Guilarte M: Usefulness and limitations of sequential serum tryptase for the diagnosis of anaphylaxis in 102 patients. Int Arch Allergy Immunol 2013; 160:192–9
23. Arnold JJ, Williams PM: Anaphylaxis: Recognition and management. Am Fam Physician 2011; 84:1111–8
24. Simons FE: Anaphylaxis. J Allergy Clin Immunol 2010; 125(2 suppl 2):S161–81
25. Dewachter P, Mouton-Faivre C, Castells MC, Hepner DL: Anesthesia in the patient with multiple drug allergies: Are all allergies the same? Curr Opin Anaesthesiol 2011; 24:320–5
26. Mertes PM, Laxenaire MC: Allergy and anaphylaxis in anaesthesia. Minerva Anestesiol 2004; 70:285–91
27. Ring J, Messmer K: Incidence and severity of anaphylactoid reactions to colloid volume substitutes. Lancet 1977; 1:466–9
28. Thienthong S, Hintong T, Pulnitiporn A: The Thai Anesthesia Incidents Study (THAI Study) of perioperative allergic reactions. J Med Assoc Thai 2005; 88(suppl 7):S128–33
29. Escolano F, Valero A, Huguet J, Baxarias P, de Molina M, Castro A, Granel C, Sanosa J, Bartolome B: [Prospective epidemiologic study of perioperative anaphylactoid reactions occurring in Catalonia (1996–7)]. Rev Esp Anestesiol Reanim 2002; 49:286–93

30. Laxenaire MC: [Epidemiology of anesthetic anaphylactoid reactions. Fourth multicenter survey (July 1994–December 1996)]. Ann Fr Anesth Reanim 1999; 18:796–809
31. Lopez-Gonzalez E, Herdeiro MT, Figueiras A: Determinants of under-reporting of adverse drug reactions: A systematic review. Drug Saf 2009; 32:19–31
32. Harboe T, Guttormsen AB, Irgens A, Dybendal T, Florvaag E: Anaphylaxis during anesthesia in Norway: A 6-year single-center follow-up study. Anesthesiology 2005; 102:897–903
33. Ohno-Machado L, Nadkarni P, Johnson K: Natural language processing: Algorithms and tools to extract computable information from EHRs and from the biomedical literature. J Am Med Inform Assoc 2013; 20:805
34. Fisher MM, Brady PW: Adverse reactions to plasma volume expanders. Drug Saf 1990; 5:86–93
35. Hasdenteufel F, Luyasu S, Hougardy N, Fisher M, Boisbrun M, Mertes PM, Kanny G: Structure-activity relationships and drug allergy. Curr Clin Pharmacol 2012; 7:15–27
36. Antunes J, Kochuyt AM, Ceuppens JL: Perioperative allergic reactions: Experience in a Flemish referral centre. Allergol Immunopathol (Madr) 2014; 42:348–54
37. Laxenaire MC, Mertes PM; Groupe d'Etudes des Réactions Anaphylactoïdes Peranesthésiques: Anaphylaxis during anaesthesia. Results of a two-year survey in France. Br J Anaesth 2001; 87:549–58
38. Dong SW, Mertes PM, Petitpain N, Hasdenteufel F, Malinovsky JM; GERAP: Hypersensitivity reactions during anesthesia. Results from the ninth French survey (2005-2007). Minerva Anestesiol 2012; 78:868–78
39. Florvaag E, Johansson SG, Oman H, Venemalm L, Degerbeck F, Dybendal T, Lundberg M: Prevalence of IgE antibodies to morphine. Relation to the high and low incidences of NMBA anaphylaxis in Norway and Sweden, respectively. Acta Anaesthesiol Scand 2005; 49:437–44
40. Johansson SG, Florvaag E, Oman H, Poulsen LK, Mertes PM, Harper NJ, Garvey LH, Gerth van Wijk R, Metso T, Irgens A, Dybendal T, Halsey J, Seneviratne SL, Guttormsen AB: National pholcodine consumption and prevalence of IgE-sensitization: A multicentre study. Allergy 2010; 65:498–502
41. U.S. Department of Justice Drug Enforcement Administration, Office of Diversion Control, Drug & Chemical Evaluation Section: Lists of: Scheduling actions, controlled substances, regulated chemicals, 2012
42. Chen W, Mempel M, Schober W, Behrendt H, Ring J: Gender difference, sex hormones, and immediate type hypersensitivity reactions. Allergy 2008; 63:1418–27
43. Light KP, Lovell AT, Butt H, Fauvel NJ, Holdcroft A: Adverse effects of neuromuscular blocking agents based on yellow card reporting in the U.K.: Are there differences between males and females? Pharmacoepidemiol Drug Saf 2006; 15:151–60