

Antibiotics Are an Important Identifiable Cause of Perioperative Anaphylaxis in the United States

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What is already known about this topic? Neuromuscular-blocking agents have previously been reported as the most common etiology of perioperative anaphylaxis.

What does this article add to our knowledge? We found antibiotics as the most common identifiable cause of perioperative anaphylaxis in our cohort.

How does this study impact current management guidelines? Our findings highlight the importance of antibiotics, particularly β -lactams, in the comprehensive evaluation of potential causes of perioperative anaphylaxis.

BACKGROUND: The diagnosis of perioperative anaphylaxis (PA) remains challenging, given its clinical setting, exposure to multiple medications, and rarity. Previous reports have found that PA is most frequently caused by neuromuscular-blocking agents.

OBJECTIVE: To determine characteristics and causes of PA at our center.

METHODS: We performed a retrospective medical record review to identify patients with anaphylaxis. Cases were further categorized by manifestations of anaphylaxis, age, sex, atopy, timing, tryptase level, and previous PA events. Cases with a cause identified by skin or *in vitro* tests were classified as IgE-mediated anaphylaxis.

RESULTS: Thirty cases were identified. Seventeen (57%) had an identifiable cause: antibiotics in 10 (59%)— β -lactams in and metronidazole in 1; latex in 3 (18%); and neuromuscular blockers in 4 (23%). There was no identifiable cause in 13 cases. The most frequent presenting sign of PA was hypotension (97%). Seven patients (23%) presented with cardiac arrest. A minority (17%) exhibited urticaria. Only four had a history of atopy. Most of the reactions occurred during the anesthesia induction phase. Elevated serum tryptase level was found in 10 of 10 (100%) cases of IgE-mediated anaphylaxis compared with 4 of 10 (40%) cases without an identifiable cause.

CONCLUSIONS: We found that antibiotics were the most common identifiable cause of PA. Our findings imply that antibiotic exposure warrants careful attention in the evaluation and management of patients with PA, particularly for those who require repeat and/or future surgeries. © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;3:101-5)

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Perioperative anaphylaxis (PA) is an acute, systemic, potentially life-threatening reaction that occurs during the operative period. Cardiovascular collapse may be the sole manifestation of PA.¹ Diagnostic evaluation using skin or *in vitro* tests for specific IgE to suspected agents is recommended 4 to 6 weeks after the event and should include all the agents administered during anesthesia.² The incidence of PA, according to reports from Europe,³⁻¹⁰ Australia,¹¹ and New Zealand,¹² is estimated between 1:4,000 and 1:20,000, with a mortality rate of 3%-9%.¹³ A recent study from Cleveland Clinic found an incidence of PA of 1:4583.¹⁴ PA is more common in females.¹ IgE-mediated reactions account for 60% of all cases.^{1,13} Previous studies have found that neuromuscular-blocking agents (NMBAs) were the most common identifiable cause of PA.^{8,9,11,15} We sought to identify the patterns and causes for PA in our center.

METHODS

Electronic medical records were searched for all patients with a diagnosis compatible with anaphylaxis from July 1, 2002, to October 31, 2013. The *International Classification of Diseases, Ninth Revision*, codes used included 995.0 (other anaphylactic shock, fish, crustaceans, food additives, milk products, eggs, other specified food), 989.82 (toxic effect of latex), 989.5 (toxic effect of venom), 202.6 (malignant mast cell tumors), 995.20 (adverse effect of medical/biological substance NOS), and 995.27 (other drug allergy). The Cleveland Clinic Foundation Institutional Review Board approved this study. This study is part of a larger ongoing anaphylaxis study.

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Abbreviations used

NMBAs- Neuromuscular-blocking agents

PA- Perioperative anaphylaxis

Definition of atopy

Cases were classified as atopic, nonatopic, or indeterminate. Individuals were classified as atopic on the basis of history with or without confirmatory skin or *in vitro* tests to inhalant allergens. Cases without a compatible history of atopy with or without negative skin or *in vitro* test results were categorized as nonatopic. Individuals with incomplete information were categorized as indeterminate.

Data collection

Physician investigators reviewed medical records individually. Exclusion criteria included missing data (charts lacking documentation of signs and symptoms of anaphylaxis), absence of clinical criteria of anaphylaxis, or lost to follow-up (skin or *in vitro* tests not performed). Demographic characteristics including age, sex, race, atopic status, and tryptase level were recorded. Details from anesthesia reports were reviewed for clinical manifestations, medication exposures, and treatment administered. The perioperative period was divided into preoperative, intraoperative, and postoperative periods. The intraoperative period was further subdivided into the induction or maintenance phase of anesthesia. The *induction phase* was defined as the start of administration of induction agents until the patient had been deemed ready for surgery by the anesthesiologist. The *maintenance phase* was defined as the end of induction until emergence from anesthesia. All future surgeries after the initial event were also reviewed.

Categorization of cases

The diagnosis of anaphylaxis was based on current World Allergy Organization guidelines.¹⁶ Confirmed cases of PA were further categorized as IgE-mediated if evidence of positive skin test result or serum specific IgE was present or as non-IgE-mediated if there was no cause identified. All cases had clinical evidence of anaphylaxis during the perioperative period.

Protocols (see Table E1 in this article's Online Repository at www.jaci-inpractice.org) for immediate hypersensitivity skin testing to anesthetics agents including NMBAs, analgesics, antibiotics, local anesthetics, povidone iodine, chlorhexidine, and latex were adapted from Anaphylaxis^{1,17} and Diagnostic Testing^{18,19} Practice Parameters. Percutaneous tests were performed on the anterior part of the forearm and included a positive control (histamine; percutaneous: Jubilant HollisterStier LLC, Spokane, Wash, and intracutaneous: ALK, Port Washington, NY) and a negative control (saline; percutaneous: Greer, Lenoir, NC, and intracutaneous: Cleveland Clinic Pharmacy, Cleveland, Ohio). A response of at least 3-mm diameter (with equivalent erythema) more than that of diluent control done simultaneously was considered a positive test result. Intradermal testing was subsequently performed with 0.02 to 0.05 mL of the agents in case of negative skin prick test results. The material for immediate hypersensitivity skin testing for latex was obtained from an industry source. Skin testing was performed at the percutaneous level. Intracutaneous testing to latex was not performed. When the skin test result was negative, provocative latex challenges were performed with the placement of a powdered

latex glove on one of the patient's hands and the placement of a powdered nonlatex glove similar (if not, identical) in appearance and texture on the contralateral hand. Both gloves were left in place for 10 minutes and then removed. Patients were observed for 15 minutes for adverse reaction. If this challenge was negative, patients inflated a powdered latex glove, holding the glove opening in front of their face, and then released the air onto their face. Patients were observed for 15 minutes for adverse reaction.²⁰

Serum specific IgE testing to latex and to penicillin was performed using ImmunoCAP (Phadia, Thermo Fisher Scientific, Uppsala, Sweden). Serum specific IgE testing to NMBAs as has been reported in previous studies was not performed. Values of allergen-specific IgE of more than 0.35 kU/L were considered positive. A serum concentration of tryptase (ImmunoCAP Phadia) greater than or equal to 11 µg/L was considered to be elevated; tryptase levels were repeated after recovery to rule out a systemic mast cell disorder.

All patients with PA were evaluated by an Allergy/Immunology staff physician, who decided to which suspected agents patients should be tested, according to anesthesia records, on the basis of previously published immediate hypersensitivity skin testing protocols.^{1,17-19} (see Table E1 in this article's Online Repository at www.jaciinpractice.org). Skin testing to suspected agents was performed at 2 or more outpatient visits. β-Lactam antibiotic skin testing was usually performed during the first visit, and materials for selected agents (eg, NMBAs) were prepared for subsequent visits. We concluded that 13 cases had no identifiable cause on the basis of negative immediate hypersensitivity (skin and/or serum specific IgE) testing to suspected agents.

Statistical analysis

Patient characteristics were described using medians and quartiles for all continuous variables. Counts and percentages were used for all categorical variables. Categorical variables were compared using the Fischer exact test. Continuous variables were compared using the *t* test of the Wilcoxon rank-sum test, as appropriate. All analyses were 2-tailed and were performed at a significance level of .05. SAS 9.3 software (SAS Institute, Cary, NC) was used for all analyses.

RESULTS

We reviewed 4773 cases and identified 717 with anaphylaxis. From the 4773 charts reviewed, 4053 cases were not included in the analysis because of the following reasons: not meeting clinical criteria for anaphylaxis (3414), lost to follow-up (84), and not meeting criteria for PA (555). Thirty of the 717 cases of anaphylaxis were categorized as perioperative. Six hundred and eighty-one cases had other etiologies for anaphylaxis (eg, hymenoptera, drug, and food); 6 cases of periprocedure anaphylaxis (eg, gastrointestinal endoscopy) were excluded.

Table I summarizes demographic characteristics: 63% were women, 83% were white, and the median age was 53.5 years (interquartile range, 46.0-66.0 years). Two thirds were classified as nonatopic. We compared individuals with an IgE-mediated cause identified to those in whom *in vitro* and skin test results were negative. There was no statistically significant difference in these subgroups when compared by either sex or age. An overall difference in IgE status by type of atopic case (atopic, indeterminate, or nonatopy) was found ($P = .040$), but multiple comparisons revealed that there were no statistically significant

TABLE I. Demographic characteristics

Variable	Total (N = 30)	IgE-mediated (N = 17)	Non-IgE-mediated (N = 13)	P
Age (y) (median)	53.5	54.0	53.0	.38
Sex				.710
Female	19 (63.3)	10 (58.8)	9 (69.2)	
Male	11 (36.7)	7 (41.2)	4 (30.8)	
Race				.053
White	25 (83.3)	12 (70.6)	13 (100.0)	
Black	5 (16.7)	5 (29.4)	0 (0.0)	
Atopic status				.040
Atopic	4 (13.3)	0 (0.0)	4 (30.8)	
Nonatopic	20 (66.7)	12 (70.6)	8 (61.5)	
Indeterminate	6 (20.0)	5 (29.4)	1 (7.7)	

Values are n (%) unless indicated otherwise.

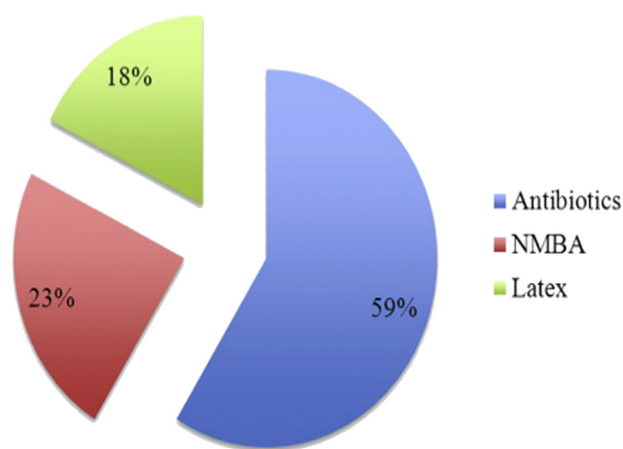


FIGURE 1. IgE-mediated causes of perioperative anaphylaxis (N = 17).

differences when comparing subsets of the types of atopic cases. No white had non-IgE-mediated anaphylaxis ($P = .053$). Two whites were allergic to latex and 3 to antibiotics.

As shown in Figure 1, in 57% of the cases, a cause was identified on the basis of results of skin or *in vitro* tests, with these cases categorized as IgE-mediated. Other cases (43%) were labeled as non-IgE-mediated. The most common identifiable cause was antibiotics (59%) followed by NBMA (23%) and latex (18%). Among the antibiotics causing PA, 9 of 10 were β -lactam antibiotics, with the most common being cefazolin.

Clinical manifestations

Table II summarizes clinical manifestations of PA. Virtually all cases manifested hypotension (97%). Only a minority (17%) of the patients exhibited urticaria. Almost half had bronchospasm (43%). Twenty-three percent of the patients presented with cardiac arrest. There were no deaths from PA in this cohort. There were no statistically significant differences in clinical manifestations by IgE-mediated status.

Associated factors and outcomes

As presented in Table III, all patients in whom an IgE-mediated cause was identified had an elevated tryptase level

TABLE II. Clinical manifestations

Variable	Total (N = 30)	IgE-mediated (N = 17)	Non-IgE-mediated (N = 13)	P
Cardiovascular signs				
Hypotension	29 (96.7)	16 (94.1)	13 (100.0)	.99
Median SBP (mm Hg)	60.0	60.0	60.0	.71
Cardiac arrest	7 (23.3)	5 (29.4)	2 (15.4)	.43
Cutaneous signs				
Flushing	10 (33.3)	6 (35.3)	4 (30.8)	.99
Urticaria	5 (16.7)	2 (11.8)	3 (23.1)	.63
Angioedema	5 (16.7)	2 (11.8)	3 (23.1)	.63
Bronchospasm	13 (43.3)	8 (47.1)	5 (38.5)	.72
Median change on PEEP	5.5	5.0	5.5	.68
Diarrhea	1 (3.3)	1 (5.9)	0 (0.0)	.99
Death	0 (0.0)	0 (0.0)	0 (0.0)	

SBP, Systolic blood pressure; PEEP, positive end-expiratory pressure.

Values are n (%) unless indicated otherwise. Hypotension is defined as an SBP of less than 90 mm Hg or more than 30% decrease from that person's baseline.

($P = .011$). There was a borderline significant difference in median tryptase levels according to whether a patient had IgE-mediated anaphylaxis ($P = .096$).

Most cases of anaphylaxis occurred during the induction phase. Those with non-IgE-mediated anaphylaxis had reactions earlier in surgery compared with IgE-mediated cases ($P = .041$). There were no statistically significant differences in the occurrence of clinical outcomes by IgE group ($P = .65$). Of our 30 cases, in 21 the identified agent was avoided during subsequent surgeries, which were performed with no remarkable adverse reactions. Five patients were lost to follow-up, 3 are currently awaiting surgery, and 1 patient died awaiting transplant surgery. The patient's death was not related to any surgical intervention.

DISCUSSION

In our series, antibiotics were the most common identifiable cause of PA (59%), followed by NBMA (23%) and latex (18%). IgE-mediated anaphylactic reactions were more likely to be associated with an elevated tryptase level (mean, 41.3 μ g/L) and occurred later in surgery than did non-IgE-mediated reactions. A cause of IgE-mediated anaphylactic reactions was identified in 57% of all cases, which is comparable to that in previous studies, ranging from 56% to 72%.^{4-6,8-11} Two similar studies evaluating causative agents for PA have been performed in the United States: Moscicki et al²¹ reported barbiturates in 1990 and more recently Gurrieri et al²² also found antibiotics to be the most common identified etiology. Previous reports from outside the United States have described NBMA as the most common agents identified.¹³

A possible explanation for our finding that antibiotics were the most common cause of PA is a higher antibiotic sensitization rate, due to greater antibiotic exposure in the United States than in European countries. However, antibiotic prescription rates in France, Greece, and Italy are higher than in the United States,²³ implying that this is not a likely explanation for our observation.

There appears to be a geographical difference among studies when reporting etiologic agents of PA.^{3-12,21,22,24} NBMA have been reported more commonly in Europe^{4,8-11,24} than in the

TABLE III. Associated factors and outcomes

Variable	Total (N = 30)	IgE-mediated (N = 17)	Non-IgE-mediated (N = 13)	P
Previous reaction	4 (13.3)	4 (23.5)	0 (0.0)	.11
Elevated tryptase level (>11.5 µg/L)		10 of 10 (100)	4 of 10 (40)	.011
Median (range) tryptase level (µg/L)	21.4 (1.0-120.0)	28.6 (15.5-92.2)	4.8 (1.0-120.0)	.096
Event during anesthesia				.78
Preoperative	1 (3.8)	0 (0.0)	1 (8.3)	
Induction	21 (80.8)	12 (85.7)	9 (75.0)	
Maintenance	4 (15.5)	2 (14.3)	2 (16.7)	
Latency of symptoms*	18.0 (1.0-60.0)	19.5 (10.0-60.0)	10.0 (1.0-32.0)	.041
Clinical outcomes				.53
Uneventful surgeries	21 (70.0)	11 (64.7)	10 (76.9)	
Lost to follow-up	5 (16.7)	4 (23.5)	1 (7.7)	
Awaiting surgery	4 (13.3)	2 (11.8)	2 (15.4)	

Values are n (%) unless indicated otherwise.

*After start of induction in median (range) (min).

United States.^{21,22} Our findings might be explained, at least in part, by differences in immediate hypersensitivity skin testing practices to NMBA. NMBA concentrations for skin testing vary, even within the United States.^{21,22} Both US¹⁸ and European¹⁵ guidelines recommend starting at similar concentrations for intracutaneous testing. However, the guidelines differ on skin prick testing because US guidelines¹ recommend a lower concentration for NMBA testing than do European guidelines.¹⁵ A study²⁵ performed in France found that approximately one half of 30 healthy, anesthesia-naïve adult volunteers had a wheal/flare reaction on percutaneous testing to undiluted rocuronium and vecuronium, suggesting a potential for false-positive skin test results when undiluted NMBA is used for percutaneous testing.

In our study, all NMBA skin testing was performed at diluted concentrations (see Table E1 in this article's Online Repository at www.jaciinpractice.org)— 10^{-2} for percutaneous and 10^{-3} for intracutaneous—compared with the study by Gurrieri et al,²² in which undiluted concentrations were used for percutaneous tests and highly dilute concentrations (10^{-6}) were used for intracutaneous tests. It is important to point out that both studies reported similar results despite using different concentrations of NMBA for skin testing. The sensitivity, specificity, and positive and negative likelihood ratios of skin testing to NMBA at various dilutions have not been determined because it is not possible to challenge patients with positive skin test results because of the risk of inducing paralysis. Further studies are needed to determine appropriate concentrations of NMBA to be used for skin testing.

The higher rate of sensitization to NMBA in Europe^{4,8-11,24} might be due to exposure to other common products containing quaternary ammonium ions,²⁶ such as cosmetic items,²⁷ exposing patients to allergenic epitopes that cross-react with NMBA. An example of this is pholcodine, an oral antitussive agent that is structurally similar to succinylcholine. Pholcodine was previously available in Europe, but not in the United States, and could have sensitized future reactors.²⁸ Seroepidemiological studies comparing Norway, a country in which the population was exposed to pholcodine, with the neighboring country of Sweden showed a geographically asymmetrical distribution of sensitization: in Norway, 6% of blood donors and 11% of those with allergy developed IgE sensitization to pholcodine, whereas in Sweden, no one with IgE to pholcodine was identified.²⁸ Interestingly, the most common identified agents for PA in Denmark were opioids, local anesthetics, and chlorhexidine.⁷

We found that only 18% of the cases were caused by latex, whereas previously reported studies^{8,10} found latex to be a more frequent cause. A lower rate of latex as an etiology for PA likely reflects a decrease in the use of latex products and a corresponding, lower rate of sensitization to latex, particularly among health care workers.²⁹

In our cohort, signs of IgE-mediated anaphylaxis appeared for the most part during induction of anesthesia; this is similar to previously reported findings.¹³ Our data suggest that IgE-mediated reactions occurred later during induction (median, 19.5 minutes) than did non-IgE-mediated reactions (median, 10 minutes). Importantly, 23% of the patients exhibited cardiac arrest as the initial manifestation and there was a relatively low rate (17%) of urticaria compared with previous published studies in which urticaria was more commonly observed.³⁰

Unexpectedly, we observed a difference according to race in the pattern of anaphylaxis, which has not been previously reported. Whites were significantly more likely to have an IgE-mediated reaction; no whites had non-IgE-mediated reactions.

There are several limitations to our study. This was a retrospective medical record review performed at a single center. Other studies from France and Australia with larger sample size have found NMBA as the most common causative agent for PA. A recent review³¹ summarized findings from more than 1800 patients with PA from France and more than 600 patients with PA from Australia. However, these studies included skin testing to additional NMBA to which patients were not exposed in association with PA, skin testing at higher NMBA concentrations, and also *in vitro* tests to NMBA-reactive IgE antibodies, which is currently not recommended by US Practice Parameters.^{1,17-19} During the 11-year period of this study, not all medications used during the perioperative period were tested in some patients (eg, not all patients were tested to piperacillin-tazobactam or cephalosporins, in addition to penicillin, to rule out β -lactam allergy; however, when skin test results were negative, this was typically followed by oral challenge to penicillin or another β -lactam). Referral population bias may affect the generalizability of our findings.

In conclusion, PA is a life-threatening medical emergency that offers an important opportunity for Allergy and Immunology specialists to contribute to improving patient care outcomes. In our review of 30 cases of PA, antibiotics were the most common identifiable cause. Our findings highlight the importance of antibiotics as a critical component of the systematic evaluation of

patients with PA. Because of the low incidence of PA, there is need for multicenter collaborative prospective studies to further clarify etiologies of PA in the United States.

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TABLE E1. Department of Allergy and Clinical Immunology protocol for assessment of intraoperative agents

Medication	Concentration			
	Percutaneous strength	Intracutaneous strength	Intracutaneous strength	Intracutaneous strength
NMBAs				
Rocuronium 10 mg/mL	1:100	1:1,000	1:100	
Pancuronium 2 mg/mL	1:10	1:1,000	1:100	
Atracurium 10 mg/mL	1:100	1:1,000		
Succinylcholine 20 mg/mL	1:10	1:1,000	1:100	
Anesthetic induction agents				
Midazolam 5 mg/mL	Undiluted	1:1,000	1:100	
Propofol 10 mg/mL	Undiluted	1:10,000	1:1,000	
Thiopental 25 mg/mL	1:10	1:100		
Etomidate 2 mg/mL	Undiluted	1:1,000		
Analgesics				
Fentanyl 50 µg/mL	Undiluted	1:1,000		
Antibiotics				
Penicillin G 10,000 U/mL	Undiluted	Undiluted		
Pre-pen 6×10^{-5} mol/L	Undiluted	Undiluted		
Cefazolin 100 mg/mL	Undiluted	1:1,000	1:100	
Cefuroxime 100 mg/mL	Undiluted	1:1,000	1:100	
Metronidazole 2 mg/mL	Undiluted	1:10,000	1:1,000	1:100
Local anesthetics				
Lidocaine 20 mg/mL	Undiluted	1:100		
Others				
Povidone iodine 10 µg/mL	Undiluted			
Chlorhexidine 1%	Undiluted			
Chlorhexidine 4%	1:100			
Latex	Undiluted solid latex/high ammoniated/low ammoniated			

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