

The changing face of anaphylaxis in adults and adolescents



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ABSTRACT

Background: Our institution has published serial studies of adults and adolescents with anaphylactic events. The first series was published in 1993 and the last was published in 2006. It was our perception that the nature of anaphylactic episodes had changed over the 2 decades since the last review.

Objective: To determine whether the etiologies and presentations of anaphylaxis have changed during the past decade in our population.

Methods: Patient charts were identified based on *International Classification of Diseases, Ninth Revision* codes for anaphylactic shock. Charts identified were analyzed for clinical symptoms reported, comorbidities, etiology, investigative testing, and subsequent treatment. These cases were categorized as definitive, probable, or idiopathic based on history and results from testing, similar to our prior reports.

Results: We identified 281 possible cases, of which 218 met criteria for anaphylaxis. Of these cases, median age was 42 years (range 9–78) and 64% were female. In the review of cases, 85 (39%) were determined to have a definitive etiology, 57 were determined to have a probable etiology (26%), and 76 (35%) were idiopathic. Interestingly, of those with a definitive cause, the most common etiology identified was galactose- α -1,3-galactose, accounting for 28 cases (33%). Foods were the second leading cause, accounting for 24 cases (28%).

Conclusion: In this follow-up report on anaphylaxis etiology from a single center, the most common etiology was galactose- α -1,3-galactose. This differs greatly from prior reports from our center. Interestingly, the percentage of cases attributed to idiopathic anaphylaxis decreased from 59% in our previous report to 35% in the present report, which could largely be explained by the number of galactose- α -1,3-galactose cases.

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Introduction

The incidence of anaphylaxis in adults in America appears to be increasing.^{1,2} In a public survey that included 1,000 unselected adults, 7.7% reported a history of an anaphylactic reaction. After applying more stringent diagnostic criteria, it was estimated that 5.1% of this population had a history of a “probable anaphylaxis” and 1.6% had a history consistent with the existence of a “very likely” anaphylactic event.

The investigators concluded that anaphylaxis is probably far more common than previously recognized, with an estimated prevalence of at least 1.6%. In addition, it is well recognized that anaphylactic events are underdiagnosed and under-reported.³

Anaphylactic events in adults have different clinical characteristics and etiologies than events in children.⁴ Events in adults are often more complicated by the presence of comorbidities, especially cardiovascular disease and the drugs used to treat these diseases.⁵ In addition, events are far more often idiopathic in nature and related to systemic diseases such as mastocytosis.^{6,7} Further, in more recent cohorts, cases also could be related to the relatively new entity caused by specific immunoglobulin E (IgE) to galactose- α -1,3-galactose (α -gal).⁸

Recognizing the unique differences between pediatric and adult cases of anaphylaxis, the allergy and immunology division at our institution began reporting on a series of adolescents and adults who developed anaphylactic events.^{9–13} The first report appeared in 1993 and the most recent report was in 2006.^{9,11} Thus, approximately a decade has passed since we looked at this issue. During that time, as noted earlier, the frequency of anaphylaxis has increased. To obtain a better sense of the magnitude of this increase since 1993 (the date of our first report), we performed a PubMed literature search using the keywords *anaphylaxis in adults*. In 1993, 153 articles were published as detected by

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Table 1
Demographics and Classification of Cohort

	Entire cohort	Definitive cause	Probable cause	Idiopathic
n (%)	218	85 (39.0)	57 (26.1)	76 (34.9)
Female, %	64	61	73.7	60.5
Age (y), median (IQR)	42 (30–56)	42 (27–59)	42 (27–57)	43 (32–56)
Concomitant atopic condition, %	73.4	80.0	78.9	61.8

Abbreviation: IQR, interquartile range.

these keywords. In 2015, 285 such articles were noted, a finding consistent with epidemiologic studies.

In addition, it was our belief that not only had there been an increase in anaphylaxis in the adult and adolescent populations, but also that the causes of these events had changed. In the approximately 2 decades since our previous publication, it has been recognized that mast cell-activating disorders, including systemic mastocytosis, could account for a significant number of events^{14,15} and, as noted earlier, IgE to α -gal has been found to account for episodes formerly believed to be idiopathic in nature.¹⁶

Because of the increase in frequency of anaphylactic events in adults and adolescents and the difference in causes that have occurred during the past 2 decades, we decided to once again review adult and adolescent patients referred to our clinic during the past 2 decades. Another motivation concerned the limited publications dealing solely with the clinical features of adults and adolescents with anaphylaxis, most of which were published from sites outside the United States.^{17–25} Also, most of these articles did not deal with an eclectic series of patients presenting to an allergy and immunology clinic, but rather focused on specific populations such as those with events related to drugs,²⁵ vaccines,²⁴ or foods^{17,21} or patients requiring hospitalization or treatment in the emergency department. Thus, there was a need for a re-examination of the issue of anaphylaxis in adults and adolescents referred to an outpatient allergy and immunology clinic.

Methods

This is a retrospective study that was conducted in a private university-affiliated allergy and immunology clinic. The patients were seen from 2006 through 2016. The initial diagnosis of anaphylaxis was established by 1 investigator (P.L.). Patients' charts were identified based on *International Classification of Diseases, Ninth Revision* code 995.0 for anaphylactic shock. This was the same coding used in our previous reports from this center and coding that has been used consistently in the clinic since that time. This study was approved by the institutional review board of the University of Tennessee Health Science Center (Memphis, Tennessee).

The charts of individual patients were reviewed by investigators (D.P. and A.K.) and analyzed for demographics, clinical symptoms reported, comorbidities, etiology, investigative testing, and subsequent treatment. The abstractors (D.P. and A.K.) consulted with the investigator (P.L.) who made the initial diagnosis for clarification of diagnosis and etiology of anaphylaxis, if deemed necessary. The diagnosis of anaphylaxis was confirmed using National Institute of Allergy and Infectious Diseases (NIAID) and Food Allergy and Anaphylaxis Network (FAAN) criteria. Cases that satisfied the criteria for anaphylaxis were included in the study. "Investigative testing" was performed based on history and physical examination. Patients with suspected food-related, latex-related, or exercise-induced origins underwent skin prick testing and/or serum specific IgE testing to foods and/or latex. For suspected cases of α -gal anaphylaxis, α -gal IgE levels were obtained after testing for beef, lamb, and pork allergy. For suspected cases of Hymenoptera and fire ant anaphylaxis, skin testing with or without serum specific IgE was done. Patients without any suspected trigger were evaluated for systemic mastocytosis using

serum tryptase and urinary histamine. Bone marrow and skin biopsy examinations were performed as indicated. For select cases, KIT D816 mutational analysis was performed for systemic mastocytosis. We looked further into the etiology of the cases and categorized them as definitive, probable, or idiopathic based on history and results from testing. The etiology is classified as "definitive" when a suspected trigger is confirmed by diagnostic testing⁹ and "probable" when a trigger is not established through clinical examination or diagnostic testing to meet the "definitive" classification. In accord with our previous reporting, cases were classified as "idiopathic anaphylaxis" when they did not fall into any of these categories. We kept these definitions the same as in previous studies to observe trends in etiologies over time.

Descriptive analysis and statistics are displayed. There were no comparisons requiring statistical software or calculations.

Results

Demographics

We identified 281 possible cases, of which 218 met the criteria for anaphylaxis.²⁶ Of these cases, the median age was 42 years (range 9–78) and 64% were female. Only 4 patients were younger than 13 years. Most patients (73.4%) had a diagnosis of a concomitant atopic disease. Demographics of the total cohort and the classification based on etiology are presented in Table 1.

Causes

Of the 218 cases, we classified 85 (39.0%) as having a definitive cause based on history and testing. Of the remaining cases, 57 (26.1%) were classified as having a probable etiology and 76 (34.9%) were idiopathic.

When examining those classified as having a definitive cause, we found that 28 of the 85 cases (32.9%) were attributed to α -gal, whereas foods accounted for 24 (28.2%). Causes for the remainder of the 85 cases were attributed to venom (18.8%), exercise (5.9%), systemic mastocytosis (5.9%), medications (4.7%), and other (3.5%). The various etiologies are presented in Figure 1. Of the food triggers, shellfish was the most common cause, followed by peanuts, tree nuts, fish, and milk.

Of the cases with a probable cause, the most common culprit trigger was foods (35.1%), followed by α -gal (26.3%), medications (22.8%), other (10.5%), and venom (5.3%).

Symptoms

Skin manifestations were the most common, occurring in 96.3% of cases. This was followed by respiratory symptoms (68.3%), neurologic symptoms such as syncope or pre-syncope (53.2%), gastrointestinal symptoms (37.2%), and cardiovascular symptoms (20.2%). By definition, all reactions had to have at least 2 organ systems involved (none of our patients had documented hypotension in the absence of other symptoms). The breakdown of the constellation and frequency of symptom presentations in the entire cohort is presented in Table 2.

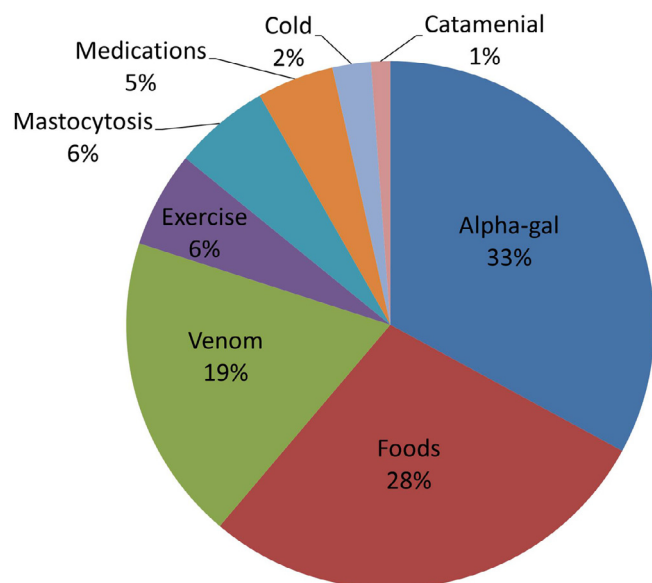


Figure 1. Etiologies of anaphylaxis based on proposed "definitive cause." Alpha-gal, galactose- α -1,3-galactose.

Discussion

The findings presented in this study were obtained by retrospective analysis of medical records of anaphylaxis cases evaluated from 2006 through 2016. These cases included patients 9 to 78 years old who were evaluated at a private university-affiliated allergy and immunology practice. Through this analysis, we identified 218 cases that fulfilled NIAID and FAAN clinical diagnostic criteria for anaphylaxis. Of these 218 anaphylaxis cases, 85 (39%) were determined to have a definite etiology, 57 (26%) were found to have a probable etiology, and 76 (35%) were noted to be idiopathic. Of the cases with a definite etiology, the most common cause was α -gal (33%), followed by

foods (28%), venom (19%), exercise (6%), systemic mastocytosis (6%), and medications (5%). The frequency of anaphylaxis causes in cases of probable etiology was somewhat similar, with the most common cause being foods (35%), followed by α -gal (26%), medications (23%), and venom (5%). Sixty percent of those classified as having a definitive cause had reported more than 1 episode of anaphylaxis to the same agent. This percentage was smaller than for the entire cohort (70% had >1 episode) but was not statistically significant.

Compared with previous reports from our center, idiopathic anaphylaxis cases decreased from 59% of cases reviewed from 1978 through 2003 to 35% of cases in the present report. This decrease in idiopathic anaphylaxis cases likely stems from the discovery of an IgE antibody response to the oligosaccharide α -gal as a cause of anaphylaxis to mammalian meat products. This phenomenon was first described in 2008²⁷ and later described as a possible delayed anaphylaxis to meats and therefore a more common cause of anaphylaxis in 2009.²⁸ Thus, this was unknown during the period of our previous anaphylaxis review. With increased awareness and widely available diagnostic testing for specific IgE to α -gal, α -gal allergy evolved from an unknown entity to the most commonly identified cause of anaphylaxis in our present analysis. When reviewing the specific causative foods for anaphylaxis in our prior study, beef and pork were identified in 9% of cases and could have represented an α -gal allergy that at that time was yet to be discovered. Because α -gal is a delayed anaphylaxis, it likely was classified as idiopathic in most cases, because the history would not have always led to a food as being responsible. An additional factor that could have contributed to the high frequency of identified α -gal allergy in our study population relates to the geographic location of our center. IgE antibodies to α -gal are caused by bites of larval or adult Lone Star ticks, and our center is located in the central area of geographic distribution of Lone Star ticks in the United States.²⁹

Apart from the increase in identified α -gal allergy, the other important difference that could account for the increase in identifiable causes of anaphylaxis and a decrease in idiopathic anaphylaxis cases is the increased recognition and diagnosis of systemic mastocytosis and other mast cell-related disorders. Symptoms associated with mast cell disorders are widespread and include urticaria, angioedema, flushing, pruritus, respiratory difficulty, hypotension, and gastrointestinal distress.³⁰ Anaphylactic episodes occur in 30% to 40% of patients with mastocytosis and can be recurrent and unpredictable.³¹ Knowledge about mast cells and mastocytosis has increased during the past decade, and consensus classification and diagnostic criteria have been established allowing for improved evaluation and diagnosis.³²

With the exception of α -gal and mastocytosis, the present analysis showed similar frequencies of anaphylactic causes as found previously. After excluding α -gal allergy, foods remained the next most commonly defined cause for anaphylaxis. Among the causative foods, shellfish was the most common, followed by nuts and fish. After foods, causative agents in decreasing frequency were venoms, exercise, and medications. Cases of venom allergy were excluded from review in our prior report, so a comparison cannot be made with the present analysis. Foods, venoms, and medications consistently have been found to be the most common etiologies for anaphylaxis in other recent reviews.^{33–35} Interestingly, if one were to include α -gal cases in foods, then foods would have accounted for most cases (61% of cases considered to have a definitive cause). This would be much higher than in other studies, especially those evaluating patients in the emergency department.^{33–35}

Interestingly, medications accounted for a small percentage (5%) of definitive cases but a larger percentage of probable cases (22%). This finding likely points to the fact that current testing remains lacking for drug allergy, with no test approved by the Food and Drug Administration for drug testing beyond penicillin. In addition, drug challenges were not done in many cases because of the history of

Table 2
Affected Symptoms at Presentation for Entire Cohort

Dermatologic, %	96.3
Respiratory, %	68.3
Neurologic (eg, pre-syncope), %	53.2
Gastrointestinal, %	37.2
Cardiovascular, %	20.2
Symptom constellations, n (%)	
D + R	59 (27.1)
D + R + N	33 (15.1)
D + R + G	20 (9.2)
D + N + G	20 (9.2)
D + N	14 (6.4)
D + R + G	13 (6.0)
D + G	11 (5.0)
D + N + C	9 (4.1)
D + C	8 (3.7)
D + R + N + C	8 (3.7)
D + N + G + C	5 (2.3)
D + R + N + G + C	3 (1.4)
D + R + G + C	3 (1.4)
D + R + C	3 (1.4)
R + G	2 (0.9)
R + C	2 (0.9)
R + N + G + C	1 (0.5)
R + N + G	1 (0.5)
D + G + C	1 (0.5)
N + G + C	1 (0.5)
R + N	1 (0.5)

Abbreviations: C, cardiovascular; D, dermatologic; G, gastrointestinal; N, neurologic; R, respiratory.

anaphylaxis. Thus, it is likely that with better testing for drug allergy, many cases of suspected drug-induced anaphylaxis would be reclassified as “definitive.”

Analysis of clinical manifestations of anaphylaxis in our cohort showed that skin manifestations were the most common (96.3% of cases), followed by respiratory symptoms (68.3%), neurologic symptoms (53.2%), gastrointestinal symptoms (37.2%), and cardiovascular symptoms (20.2%). These frequencies are similar to those found in our previous review⁹ and are consistent with those noted in previous studies.^{33–35} The consistency of these symptoms across multiple studies highlights these key clinical features of anaphylaxis, and these clinical manifestations in turn have been incorporated into the NIAID and FAAN diagnostic criteria for anaphylaxis.

A number of limitations of our study should be noted. The retrospective nature could have limited the number of anaphylaxis cases identified, and the available data reviewed might not have been sufficient to identify etiologies or other clinical features. All patients included for study were evaluated at a private university-affiliated allergy and immunology outpatient practice located in the southeastern United States. Thus, our findings might not be generalizable to other practice settings. However, for primary anaphylaxis etiologies, only the high frequency of α -gal allergy found in our cohort appears to differ from common anaphylaxis etiologies found in other reviews. Moreover, because most patients were not challenged, one could argue that some cases were misclassified. Also, we do not have follow-up data for patients with α -gal allergy to see if their symptoms were alleviated after avoiding mammalian meat.

In summary, we conducted a retrospective analysis of anaphylaxis cases evaluated over a 10-year period at our private university-affiliated allergy and immunology outpatient practice and compared our findings with those noted in our same practice from a previous 25-year period. Allergy to α -gal as the most commonly identified cause of anaphylaxis represented the most striking difference over time. Increased identification of systemic mastocytosis in our present review was another important distinction. Epidemiologic studies of this nature will aid in the evaluation of anaphylaxis to determine a specific etiology and could decrease the number of cases deemed idiopathic.

References

- [1] Altman AM, Camargo Jr CA, Simons FE, et al. Anaphylaxis in America: a national physician survey. *J Allergy Clin Immunol*. 2015;135:830–833.
- [2] Wood RA, Camargo Jr CA, Lieberman P, et al. Anaphylaxis in America: the prevalence and characteristics of anaphylaxis in the United States. *J Allergy Clin Immunol*. 2014;133:461–467.
- [3] Sclar DA, Lieberman PL. Anaphylaxis: underdiagnosed, underreported, and undertreated. *Am J Med*. 2014;127(suppl):S1–S5.
- [4] Braganza SC, Acworth JP, McKinnon DRL, et al. Pediatric emergency department anaphylaxis: different patterns from adults. *Arch Dis Child*. 2006;91:159–163.
- [5] Lieberman P, Simons FE. Anaphylaxis and cardiovascular disease: therapeutic dilemmas. *Clin Exp Allergy*. 2015;45:1288–1295.
- [6] Greenberger PA, Lieberman P. Idiopathic anaphylaxis. *J Allergy Clin Immunol Pract*. 2014;2:243–250.
- [7] Lieberman PL. Idiopathic anaphylaxis. *Allergy Asthma Proc*. 2014;35:17–23.
- [8] Lieberman P, Commins SP. A patient experiencing anaphylaxis and urticaria, in some cases preceded by ingestion of red meat. *J Allergy Clin Immunol Pract*. 2013;1:107–108.
- [9] Kemp S, Lieberman P, Wolf B. Review of 267 cases of anaphylaxis in clinical practice. *J Allergy Clin Immunol*. 1993;91:513.
- [10] Webb L, Green E, Lieberman P. Anaphylaxis: a review of 593 cases. *J Allergy Clin Immunol*. 2004;113:S240.
- [11] Webb LM, Lieberman P. Anaphylaxis: a review of 601 cases. *Ann Allergy Asthma Immunol*. 2006;97:39–43.
- [12] Kemp SF, Lockey RF, Wolf BL, Lieberman P. Anaphylaxis. A review of 266 cases. *Arch Intern Med*. 1995;155:1749–1754.
- [13] Coghan-Johnston M, Lieberman P. Demographic and clinical characteristics of anaphylaxis. *J Allergy Clin Immunol*. 2001;107:S57.. (abstract).
- [14] Schuch A, Brockow K. Mastocytosis and Anaphylaxis. *Immunol Allergy Clin North Am*. 2017;37:153–164.
- [15] Yu JE, Akin C. Mast cell disorders. *J Allergy Clin Immunol Pract*. 2016;4:557–558.
- [16] Commins SP, Jerath MR, Cox K, et al. Delayed anaphylaxis to alpha-gal, an oligosaccharide in mammalian meat. *Allergol Int*. 2016;65:16–20.
- [17] Kool B, Chandra D, Fitzharris P. Adult food-induced anaphylaxis hospital presentations in New Zealand [published online ahead of print April 6, 2016]. *Postgrad Med J*. doi:10.1136/postgradmedj-2015-133530.
- [18] Hananashvili I, Givon-Lavi N, Bartal C, Broides A. Anaphylactic reactions in adult patients in Southern Israel. *Asian Pac J Allergy Immunol*. 2016;34:44–50.
- [19] Thong BYH, Cheng YK, Leong KP, et al. Anaphylaxis in adults referred to a clinical immunology/allergy center in Singapore. *Singapore Med J*. 2005;46:529.
- [20] Koh YI, Choi IS, Chung SU, Cho S. Clinical features of adult patients with anaphylaxis associated with food in Gwangju and Chonnam area. *Korean J Asthma Allergy Clin Immunol*. 2004;24:217–223.
- [21] Asero R, Antonicelli L, Arena A, et al. Causes of food-induced anaphylaxis in Italian adults: a multi-centre study. *Int Arch Allergy Immunol*. 2009;150:271–277.
- [22] Ye YM, Kim MK, Kang HR, et al. Predictors of the severity and serious outcomes of anaphylaxis in Korean adults: a multicenter retrospective case study. *Allergy Asthma Immunol Res*. 2015;7:22–29.
- [23] Treudler R, Kozovska Y, Simon JC. Severe immediate type hypersensitivity reactions in 105 German adults: when to diagnose anaphylaxis. *J Invest Allergol Clin Immunol*. 2008;18:52–58.
- [24] Seitz CS, Bröcker EB, Trautmann A. Vaccination-associated anaphylaxis in adults: diagnostic testing ruling out IgE-mediated vaccine allergy. *Vaccine*. 2009;27:3885–3889.
- [25] Moneret-Vautrin DA, Latache C. Drugs as risk factors of food anaphylaxis in adults: a case-control study. *Bull Acad Natl Med*. 2009;193:351–362.
- [26] Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. *J Allergy Clin Immunol*. 2006;117:391–397.
- [27] Chung CH, Mirakhor B, Chan E, et al. Cetuximab-induced anaphylaxis and IgE specific for galactose- α -1,3-galactose. *N Engl J Med*. 2008;358:1109–1117.
- [28] Commins SP, Satinover SM, Hosen J, et al. Delayed anaphylaxis, angioedema, or urticaria after consumption of red meat in patients with IgE antibodies specific for galactose- α -1,3-galactose. *J Allergy Clin Immunol*. 2009;123:426–433.
- [29] Steinke JW, Platts-Mills TAE, Commins SP. The alpha-gal story: lessons learned from connecting the dots. *J Allergy Clin Immunol*. 2015;135:589–596.
- [30] Theoharides TC, Valent P, Akin C. Mast cells, mastocytosis, and related disorders. *N Engl J Med*. 2015;373:163–172.
- [31] Siebenhaar F, Akin C, Bindslev-Jensen C, et al. Treatment strategies in mastocytosis. *Immunol Allergy Clin North Am*. 2014;34:433–447.
- [32] Pardanani A. Systemic mastocytosis in adults: 2017 update on diagnosis, risk stratification and management. *Am J Hematol*. 2016;91:1147–1159.
- [33] Gonzalez-Estrada A, Silvers SK, Klein A, et al. Epidemiology of anaphylaxis at a tertiary care center. *Ann Allergy Asthma Immunol*. 2017;118:80–85.
- [34] Lee S, Hess EP, Lohse C, et al. Trends, characteristics, and incidence of anaphylaxis in 2001–2010: a population-based study. *J Allergy Clin Immunol*. 2017;139:182–188.
- [35] Motosue MS, Bellolio F, Van Houten HK, et al. Increasing emergency department visits for anaphylaxis, 2005–2014. *J Allergy Clin Immunol Pract*. 2017;5:171–175.