

Fatal and Near-fatal Anaphylaxis



Factors That Can Worsen or Contribute to Fatal Outcomes

Paul A. Greenberger, MD

KEYWORDS

- Anaphylaxis • Allergy • Fatalities • Cardiovascular • Histamine • Prostaglandin • Leukotriene

KEY POINTS

- Anaphylaxis implies a risk of death even in patients whose prior episodes have been considered trivial and easily managed.
- Anaphylaxis occurs in all age groups, from infants to the elderly, but most deaths occur in adults.
- Atopy is a risk factor for most types of anaphylaxis.
- There are no absolute contraindications to self-injectable epinephrine, and epinephrine can be administered for anaphylaxis to elderly patients or to those receiving beta-adrenergic blockers.

INTRODUCTION

Anaphylaxis is a medical emergency that implies a risk of death. Most cases of fatal or near-fatal anaphylaxis are characterized by abrupt-onset, progressively more severe symptoms, and short duration of time from exposure to the onset of symptoms. It has been reported that half or more of fatalities occur within 60 minutes of the onset of anaphylaxis.^{1–6} Although full doses of medications, such as penicillins or neuromuscular blocking agents, may have been administered by the time signs or symptoms of anaphylaxis appear, severe symptoms can occur within a minute of administering intravenous medication and a single bite of a food can be associated with fatal or near-fatal anaphylaxis.^{2,7–9} Anaphylactic deaths have occurred even

Supported by the Ernest S. Bazley Trust to Northwestern Memorial Hospital and Northwestern University.

Division of Allergy-Immunology, Department of Medicine, Northwestern University Feinberg School of Medicine, 211 East Ontario Street, #1000, Chicago, IL 60611, USA

E-mail address: p-greenberger@northwestern.edu

Immunol Allergy Clin N Am 35 (2015) 375–386

<http://dx.doi.org/10.1016/j.iac.2015.01.001>

immunology.theclinics.com

0889-8561/15/\$ – see front matter © 2015 Elsevier Inc. All rights reserved.

when the bite of food was spat out and not swallowed or aspirated,⁷ and with just a test dose of 1 to 2 mL of radiographic contrast material.¹⁰ Often, in fatalities, epinephrine was not immediately administered.^{2,7,8}

PATHOPHYSIOLOGY OF FATAL AND NEAR-FATAL ANAPHYLAXIS

The prototype reaction is uniphasic, beginning within minutes or up to 2 to 3 hours after exposure to the cause; some reactions are biphasic, in which the immediate reaction seems to stop for at least 1 hour before returning; and some are protracted, in which the immediate reaction continues for hours or days. Cases of protracted anaphylaxis can last from 3 days to 3 weeks.⁸

Mast cell activation is one mechanism of anaphylaxis, and laboratory evidence of such is shown by an increased total serum tryptase concentration (>11.4 ng/mL) or increased urine histamine or *N*-methylhistamine concentration. Serum histamine measurement is not of practical use because of its short half-life. Preformed mediators within the mast cell include histamine, chymase, tryptase, carboxypeptidase, and cathepsin G. Intravenous infusions of histamine can cause pruritus, flushing, urticaria, chest tightness, and eventually a reduction in blood pressure.¹¹ However, other mediators are thought to contribute to an even greater extent in anaphylaxis. For example, newly synthesized mediators, including prostaglandin D₂, leukotriene D₄, and platelet-activating factor are released, all of which can dilate blood vessels and potentially contract smooth muscle. Kinins, which can cause relaxation of smooth muscle and increased capillary permeability, are also generated during anaphylaxis and likely contribute to acute angioedema, such as massive tongue swelling or hypotensive shock. It remains unclear to what extent tryptase contributes to the pathophysiologic changes of anaphylaxis.

In fatal or near-fatal anaphylaxis, physiologic changes such as the following may be found: (1) hypotensive (distributive) shock from reduced total peripheral resistance and permeable capillaries, with loss of up to 35% of intravascular volume¹²; (2) massive angioedema of the tongue, oropharynx, or larynx; (3) cardiac arrhythmias, such as atrial or ventricular fibrillation with or without myocardial infarction^{6,9,13}; and (4) acute severe bronchoconstriction. It remains uncertain why the shock organ varies in different individuals in fatal and near-fatal anaphylaxis but it seems that, in patients with asthma, the lung is commonly the shock organ^{7,8} and often contributes to death or respiratory failure.

During intraoperative anaphylaxis occurring in patients with cardiac catheters in place, there was a transient increase of the pulmonary artery pressure, likely from bronchoconstriction, in association with a catastrophic reduction in peripheral resistance.¹² These findings were identified in patients with underlying cardiac disease resulting in greatly reduced blood volume reaching the left ventricle to support the blood pressure or cardiac output. Even in the absence of cardiac disease, patients can present with sudden-onset cardiovascular collapse, myocardial infarction, or ventricular fibrillation.¹³ Cardiac ischemia during anaphylaxis can result from activation of mast cells that are located in the interstitium and adventitia of the larger coronary arteries.¹⁴

Acute severe bronchoconstriction may necessitate ventilatory support because patients can present with respiratory failure with arterial blood gases with pH of 6.95 to 7.05 and P_{CO_2} greater than 90 mm Hg. In this setting, it may be difficult to deliver an effective tidal volume to the patient without using high and potentially dangerous inspiratory pressures. This emergency has led to use of extracorporeal membrane oxygenation.¹⁵

PATHOLOGY AND LABORATORY FINDINGS

The findings from autopsy examinations of fatal anaphylaxis are listed in **Box 1**. Obstructing angioedema of the upper airway can cause death from asphyxiation. Some patients experience acute myocardial infarction from hypotension or cardiac arrest during fatal or near-fatal anaphylaxis. Patients may not present with urticaria, especially if hypotensive. Although infrequent in patients presenting with unexplained shock, the emergence of urticaria as the patient is being resuscitated can raise the possibility that anaphylaxis has occurred. This scenario can be observed in patients who have been stung by an insect or who have idiopathic anaphylaxis.¹³ First responders can help restore the blood pressure and increase cardiac output to peripheral tissues, allowing urticarial lesions to appear.

Results of laboratory investigations in anaphylaxis include:

- The cutoff for serum tryptase concentrations for fatal anaphylaxis is greater than or equal to 44.3 ng/mL.^{16,17} Postmortem serum tryptase concentrations can be greater than 11.4 ng/mL when patients die from nonanaphylactic conditions, including asphyxia (from smothering, suicide, or external compression of the chest), assault, sudden infant death syndrome, sudden cardiac death, acute aortic dissection, heroin injection, and trauma such as from a motor vehicle accident.^{16,17} A concentration greater than or equal to 44.3 ng/mL best differentiates between fatal anaphylaxis and deaths from other causes. There may be some false-negatives in cases of fatal anaphylaxis, such as when the serum tryptase concentration is increased but lower than the cutoff (18 and 37 ng/mL)¹⁶ or in the normal range (such as in food allergy^{8,18}). However, the serum tryptase concentration can be sharply increased and greater than or equal to 44.3 ng/mL in fatalities from food-induced anaphylaxis.¹⁸
- Increased serum immunoglobulin E (IgE) antibodies to foods and stinging or biting insects provide supportive information in exploring causes of fatal anaphylaxis.¹⁸ The results of such determinations can be useful, especially when the serum tryptase concentration is modestly increased (12 ng/mL for fatal soybean-induced anaphylaxis and 17 ng/mL for fatal codfish-induced anaphylaxis).¹⁸ Postmortem serum should be stored frozen at -20°C to preserve IgE antibodies and tryptase. Serum tryptase may still have 50% of its concentration after storage at room temperature for 4 days.¹⁸
- The normal range for histamine in whole blood in living subjects is less than 0.3 ng/mL.¹⁹ In one report, concentrations from cases of fatal anaphylaxis

Box 1

Pathologic findings in fatal anaphylaxis

Angioedema	Massive (obstructing) edema of tongue, lips, larynx, supraglottic area, or epiglottis
Hyperinflation of the lungs	Resembles emphysematous changes
Tracheobronchial secretions	
Mucus plugging of airways	
Congestion	Viscera and lungs (sometimes with pulmonary edema)
Cyanosis	Face and body
Coronary atherosclerosis	Coincidental finding in some patients
Cerebral hypoxia	Global cerebral ischemia
Cutaneous urticaria	
Cutaneous angioedema	
No specific findings	Presumed sudden, severe cardiovascular collapse

were 37.5, 9.0, and 23.2 ng/mL, compared with controls from nonanaphylactic deaths, such as sudden cardiac death, ranging from 5.0 to 22 ng/mL.¹⁹ Thus, there is modest evidence for demonstration of increased blood histamine level in fatal anaphylaxis, but, in terms of utility, all 3 cases of anaphylactic death had serum tryptase concentrations greater than or equal to 45 ng/mL, therefore tryptase concentrations are more feasible with histamine as an adjunct if needed.

- The normal range for diamine oxidase, one of 2 enzymes that degrade histamine (the other being histamine-*N*-methyltransferase), is 10 to 30 IU/mL.¹⁹ There was no meaningful difference between concentrations of diamine oxidase in 3 cases of fatal anaphylaxis compared with controls.¹⁹ These preliminary results do not support the notion that there might be a deficiency of diamine oxidase in fatal anaphylaxis.
- Serum concentrations of platelet-activating factor are increased compared with controls and correlate directly with the severity of anaphylaxis.²⁰ There is an inverse correlation between platelet-activating factor acetylhydrolase and severity of anaphylaxis. These findings suggest that there may be insufficient degradation of platelet-activating factor in severe or fatal anaphylaxis.²⁰
- In the setting of non-IgE, non-FcεRI-associated anaphylaxis from oversulfated chondroitin sulfate (OSCS) adulterated heparin, the OSCS caused robust *in vitro* increases in the levels of kallikrein and anaphylatoxins C5a and C3a from plasma.^{21,22}

FACTORS OR CIRCUMSTANCES ASSOCIATED WITH FATAL OR NEAR-FATAL ANAPHYLAXIS

Various factors that can contribute to a fatal or near-fatal anaphylactic reaction have been identified (Box 2). For example, in adults presenting with anaphylaxis, the use of antihypertensive medications (in aggregate) was associated with involvement of 3 or more organ systems and risk of hospitalization.²³ The risk of hospitalization was associated with the severity of anaphylaxis as determined by the presence of at least 1 of the following severity markers: syncope, hypoxia, hypotension, and more than 1 injection of epinephrine.²³

The following discussion considers settings, factors, or circumstances associated with fatal or near-fatal anaphylaxis.

Box 2
Factors or circumstances associated with near-fatal or fatal anaphylaxis
Accidents and mishaps
Adulterated products
Age
Allergens
Atopy
Comorbidities
Munchausen syndrome–contrived anaphylaxis
Patient factors
Route of administration
Treatment-related issues

Accidents and Mishaps

Examples include:

1. Patients confusing medications or nonprescription products. In one case this resulted in ingestion of amoxicillin instead of ascorbic acid.⁹
2. Systems errors. Patients receive a medication to which they are known to be allergic, despite the medical record clearly listing the allergy; or the allergy is listed but the physician or health care professional minimizes the significance of the reaction; or the patient's allergy is not entered into the medical record.
3. Administrative errors in identification of the patient or of the dosage of medication or allergen immunotherapy to be administered.
4. Anaphylaxis in remote areas where first aid is delayed or not likely.
5. Self-injectable epinephrine is not available or not used promptly.
6. Incorrect assumptions about foods, such as assuming that certain peanut-free foods are devoid of allergen, or when the patient or responsible party assumes that the patient is now immune (nonsusceptible) to the risk of anaphylaxis and eats the allergenic food.

Adulterated Products

There may be intentional adulteration of medications (as in the use of OSCS in heparin) or foods (such as hazelnut oil substituted for extravirgin olive oil.) The allergenic risk in the latter example is when there is detectable hazelnut protein in hazelnut oil.^{24,25} In general, refined oils have less protein content than partially refined oils, which have less protein than crude oils. Alternatively, there may be unintentional adulteration of an initially safe food product, such as when a cook adds a tablespoon of peanut butter to a gallon of peanut oil so that, when prepared, the tortillas fold, adhere, and taste better.

Age

Although deaths or nearly fatal anaphylaxis occur in children and adolescents,^{7,8} the literature shows that the preponderance of fatalities occur in adults.^{1-6,12,13,26} Near-fatal anaphylaxis can occur in persons of any age, from infants to the geriatric population. Adolescents may not make safe decisions regarding what to eat. They may not successfully self-inject epinephrine when indicated or may not carry the epinephrine because of negative peer pressure. Alternatively, they may be subject to bullying and having the known food allergen intentionally placed into their lunches at school.^{27,28} Adults may be reluctant to self-inject epinephrine because previous episodes of anaphylaxis have been tolerated after ingestion of 200 mg of diphenhydramine or hydroxyzine.

Another aspect of age is the intrinsic reactivity from allergic reactions that can increase with age. In a review of children and adolescents who were known to have had positive double-blind, placebo-controlled food challenges, the eliciting dose of the food declined as children aged.²⁹ Regarding peanut allergy, the median dose for a positive challenge was 790 mg in children less than 5 years of age, 310 mg in children 5 to 10 years of age, and just 70 mg in children 11 years and older.²⁹ These findings were unaffected by the presence of asthma.

Allergens

The potency of allergens is variable, and attempts have been made to determine the lowest dose of allergens that cause an observable adverse effect. If the highest dose tolerated is known, this could affect product manufacturing and labeling. This

information would be valuable for policy making because fatalities or near-fatal anaphylaxis have occurred after single bites of peanuts, tree nuts, seeds, and other foods.⁷⁻⁹

Roasted peanuts are more allergenic than boiled peanuts.³⁰⁻³² There are 11 well-characterized allergens in peanut, and heating increases the binding of *Ara h 1* and *Ara h 2* to IgE antibodies.³⁰ Furthermore, heated *Ara h 2* adsorbed to human intestinal epithelial cells to a greater extent, which could result in enhanced signaling and subsequent immunoreactivity.³⁰

The use of component-resolved immunoassays for diagnosis of food allergies may help elucidate the differential susceptibilities of allergic patients to various foods. For example, shrimp tropomyosin (*Pen a 1*) is considered the major allergen in patients with shrimp allergy, but other allergens are being recognized.³³ In sera from 15 patients with shrimp-induced anaphylaxis, just 7 showed anti-*Pen a 1* IgE antibodies. As experience is gained with component-resolved immunoassays, it is hoped that risk assessment will be improved, ideally into true anaphylaxis-prone, urticaria-prone, and oral allergy syndrome-prone categories.

The allergen may not be a food but a contaminant in the food, such as wheat flour contaminated by dust or storage mite ingested by a person allergic to dust mites.^{34,35} Contamination of foods such as pancakes, beignets, grits, polenta, pizza dough, and mackerel or bonito covered in flour has been described.³⁴ There are heat-resistant and heat-labile allergens in mites, but it is the heat-resistant allergens that seem to cause anaphylaxis, and can be near fatal (acute respiratory failure) or fatal.^{34,35} This form of anaphylaxis is preventable with proper storage of flour.

There is a single case report of fatal anaphylaxis after consumption of presumably 2 mold-contaminated pancakes.³⁶ A 19-year-old man with asthma and allergies, who was not apparently allergic to dust or eggs, died after eating pancakes that had been prepared with flour that had been opened previously and had a use-by date that had expired 2 years earlier. A variety of fungi were identified in the pancake mix, including *Aspergillus flavus* and *Aspergillus niger*, *Penicillium* species, *Fusarium* species, and *Mucor*.³⁶ Two friends of the deceased stopped eating the pancakes because the pancakes tasted like rubbing alcohol.³⁶ It is not known whether the anaphylaxis was attributable to mites instead of fungi, and mites were not tested for in the report.

Atopy

Atopy is a risk factor for most, but not all, causes of anaphylaxis. This information is presented in [Table 1](#).

Comorbidities

Comorbidities can contribute to the risk of an unfavorable outcome from anaphylaxis and have been identified in 22 of 25 fatal cases in which the mean age of patients was 59 years.² Postmortem findings often include coexisting evidence of asthma, emphysema, or preexisting cardiovascular disease, such as coronary or aortic atherosclerosis, myocardial ischemia, or valvular heart disease.

Asthma, especially if severe, has been recognized as a risk factor for anaphylaxis.^{37,38} After controlling for age, sex, race/ethnicity, co morbidities, and allergen immunotherapy, there was a 5.2-fold increased incidence of anaphylactic shock in patients with asthma.³⁸

Patients with indolent systemic mastocytosis are known to be susceptible to systemic reactions from Hymenoptera stings. The finding of an increased serum tryptase concentration or lesions of urticaria pigmentosa in a patient with venom

Table 1
Effect of atopy on types of anaphylaxis

Atopy Is a Risk Factor	Atopy Is Not a Risk Factor
Asthma (especially if persistent severe)	Penicillin
Exercise-induced anaphylaxis	Neuromuscular blocking agents
Food	Insulin
Idiopathic anaphylaxis	
Hymenoptera	
Latex	
Radiographic contrast media	

anaphylaxis may lead to the diagnosis of indolent systemic mastocytosis in previously undiagnosed patients.

By definition, idiopathic anaphylaxis (IA) implies a risk of death or severe anaphylaxis.^{13,39–41} Use of empiric prednisone compared with H1 antihistamines alone has been associated with favorable outcomes, including reduced frequency of episodes and severity of this condition.^{40,41} IA-Frequent means that there have been 6 episodes of anaphylaxis in the past 12 months or 2 within the past 2 months. IA-Infrequent means that there have been 5 or fewer episodes of anaphylaxis in the past 12 months.

As noted earlier, patients receiving antihypertensive medications (taken in aggregate) are at increased risk of anaphylaxis.²³ β -Blockers, angiotensin-converting enzyme inhibitors, and diuretics analyzed individually did not correlate with syncope, hypotension, or hypoxia.²³ Bradykinin, which causes vasodilatation and angioedema, is degraded primarily by angiotensin-converting enzyme. It has been reported that patients with peanut and tree allergy who had lower concentrations of serum angiotensin-converting enzyme had more severe pharyngeal edema.⁴²

Beta-adrenergic blocking agents may or may not potentiate the severity or increase the incidence of anaphylaxis. For example, in a prospective study of patients undergoing cardiac angiography, there was not an increased risk of anaphylaxis during radiographic contrast material infusions in patients receiving beta-adrenergic blockers,⁴³ although this has been reported from a retrospective, case control study.⁴⁴ Nor was there an increased risk of anaphylaxis in patients undergoing allergen immunotherapy.⁴⁵ Nevertheless, the use of beta-adrenergic blockers may identify patients with underlying cardiovascular disease (but it should be remembered that epinephrine is not contraindicated in patients taking these medications because of the potential for coronary ischemia or hypertension). Although there have been concerns that systemically administered epinephrine might cause exaggerated alpha-adrenergic effects when administered to patients receiving beta-adrenergic blockers during treatment of anaphylaxis, it is more likely that the anaphylactic shock will be difficult to reverse and that additional doses of epinephrine may be required along with other measures of resuscitation.

The concomitant use of moderate to high doses of tricyclic antidepressants may potentiate the effects of epinephrine, but any such drug-drug interactions are expected to be more severe in the setting of a monoamine oxidase inhibitor or cocaine.

Munchausen Syndrome–contrived Anaphylaxis

Munchausen stridor is nonorganic laryngeal obstruction in which the perpetrator produces loud, frightening, stridorous sounds, often resulting in emergency intubation.^{46,47} Some nonintubated patients are treated with intravenous epinephrine for

ongoing stridor that perplexes inexperienced physicians. In contrast, Munchausen anaphylaxis is true anaphylaxis.^{48,49} For example, a patient with purported Hymenoptera anaphylaxis provoked anaphylactic signs and symptoms from her established aspirin hypersensitivity by surreptitious ingestion of aspirin to convince others that Hymenoptera stings were the cause.⁴⁸ Patients with Munchausen syndrome can provoke severe or potentially fatal factitious disease, including anaphylaxis, and are often resistant to professional advice or psychiatric treatment because the underlying disorder results in secondary gain.

Patient Factors

Patients who have experienced anaphylaxis can have impaired quality of life for multiple reasons, including:

1. Anxiety, panic, hypochondriasis, or depression about future episodes and loss of control of their health.
2. Uncertainty as to the cause of the anaphylaxis or how to prevent future episodes.
3. Lack of a management plan, including whether, when, and how to self-administer epinephrine.
4. Therapeutic nihilism that meaningful interventions from health care professionals are available. In patients with IA, in addition to concurrent pharmacotherapy directed at IA, psychiatric consultation and therapy can be effective in patients who become depressed about anaphylaxis, as has been shown in patients with IA-F. Fatalities have been described in patients with IA when empiric treatment has not been undertaken by patients.³⁹

When patients minimize or deny the potential severity of future episodes of anaphylaxis, life-threatening conditions can occur. For example, a 19-year-old college student with peanut allergy while in a bar accepted a dare to eat 1 peanut. Shortly thereafter, he experienced life-threatening respiratory distress and required intubation, with a P_{CO_2} of more than 90 mm Hg and pH less than 7.0. The patient survived but did not want to accept responsibility for his unwise and dangerous intentional ingestion of a peanut.

Another example is that of patients who minimize or deny the risks of future anaphylactic episodes from Hymenoptera stings or are unaware of an immunomodulatory treatment, and do not receive the salutary protective benefits of venom immunotherapy.

Route of Administration

Fatal and severe to near-fatal anaphylaxis can occur with any route of administration (intravenous, intra-arterial, intra-articular, oral, contact, inhalational, kissing, and penile-vaginal sexual intercourse). The median time to shock, respiratory arrest, or cardiac arrest from a series of 20 fatal episodes of anaphylaxis was as follows: iatrogenic (systemically administered) reactions, 5 minutes; venom stings, 15 minutes; and foods, 30 minutes.²⁶ In a series of 25 cases of fatal anaphylaxis, the anaphylactic event started within 30 minutes of exposure in 20 of 25 cases, with death in 60 minutes in 13 of 25 cases.² These findings support the belief that the more rapid the reaction following exposure to the antigen, the worse the anaphylaxis may be.

Treatment-related Issues

In addition to delays in the diagnosis of anaphylactic shock and initiation of treatment with epinephrine and, when feasible, intravenous fluids, the attempted first aid of patients while in the sitting and upright positions has been reported as being associated with sudden demise.⁵⁰ Specifically, the abrupt change in posture (from seated or lying down to standing, or from lying in bed to sitting in a chair) has been associated with

sudden death from anaphylaxis.⁵⁰ The loss of intravascular volume resulting in little filling pressure into the right ventricle with reduced cardiac output has led to the term empty ventricle syndrome.⁵⁰ The recommendation is that, when patients are in anaphylactic shock, they should be treated in the supine position (as tolerated, depending on level of dyspnea), with legs elevated to try to make the inferior vena cava the most dependent vessel. Also, antishock trousers can be used for this purpose.⁵⁰

SUMMARY

Most episodes of anaphylaxis do not result in a fatality and the goal of treatment must be to prevent deaths and future reactions. A high-risk situation may be one in which mitigating factors are not recognized or opportunities for improvement are overlooked, and this applies to anaphylaxis. Therefore, in any patient with anaphylaxis, an allergy-immunology consultation is indicated to help confirm or rule out allergens, to teach about avoidance as well as risks, to possibly reduce risk (IA, venom allergy), and for optimal treatment of anaphylaxis.⁵¹ For patients who have experienced anaphylaxis from Hymenoptera stings or fire ant bites, immunotherapy is highly effective to reduce the risk of future stings or bites. Empiric treatment of patients with frequent episodes of idiopathic anaphylaxis with prednisone and H1 antihistamines can help modify the natural history of this condition by reducing the frequency and severity of episodes, and empiric treatment with H1 antihistamines and on-demand epinephrine is ineffective for acute episodes in most patients with IA-I. Self-injectable epinephrine remains indicated, and patients should be taught whether, when, and how to administer it as part of an individualized action plan.^{51,52}

REFERENCES

1. Delage C, Irely NS. Anaphylactic deaths: a clinicopathologic study of 43 cases. *J Forensic Sci* 1972;17:525–40.
2. Pumphrey RS, Roberts IS. Postmortem findings after fatal anaphylactic reactions. *J Clin Pathol* 2000;53:273–6.
3. Greenberger PA, Rotskoff BD, Lifschultz B. Fatal anaphylaxis: postmortem findings and associated comorbid diseases. *Ann Allergy Asthma Immunol* 2007;98:252–7.
4. Riches KJ, Gillis D, James JA. An autopsy approach to bee sting-related deaths. *Pathology* 2002;34:257–62.
5. Low I, Stables S. Anaphylactic deaths in Auckland, New Zealand: a review of coronial autopsies from 1985 to 2005. *Pathology* 2006;38:328–32.
6. James LP, Austen KF. Fatal systemic anaphylaxis in man. *N Engl J Med* 1964;270:597–603.
7. Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol* 2001;107:191–3.
8. Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to foods in children and adolescents. *N Engl J Med* 1992;327:380–4.
9. Golbert TM, Patterson R, Pruzansky JJ. Systemic allergic reactions to ingested antigens. *J Allergy* 1969;44:96–107.
10. Yamaguchi K, Katayama H, Takashima T, et al. Prediction of severe adverse reactions to ionic and nonionic contrast media in Japan: evaluation of pretesting. A report from the Japanese Committee on the Safety of Contrast Media. *Radiology* 1991;178:363–7.

11. Kaliner M, Sigler R, Summers R, et al. Effects of infused histamine: analysis of the effects of H-1 and H-2 histamine receptor antagonists on cardiovascular and pulmonary responses. *J Allergy Clin Immunol* 1981;68:365–71.
12. Fisher MM. Clinical observations on the pathophysiology and treatment of anaphylactic cardiovascular collapse. *Anaesth Intensive Care* 1986; 14:17–21.
13. Wong S, Greenberger PA, Patterson R. Nearly fatal idiopathic anaphylactic reaction resulting in cardiovascular collapse and myocardial infarction. *Chest* 1990;98:501–3.
14. Perskvist N, Edston E. Differential accumulation of pulmonary and cardiac mast cell-subsets and eosinophils between fatal anaphylaxis and asthma death: a postmortem comparative study. *Forensic Sci Int* 2007;169:43–9.
15. Lafforgue E, Sleth JC, Pluskwa F, et al. Successful extracorporeal resuscitation of a probable perioperative anaphylactic shock due to atracurium. *Ann Fr Anesth Reanim* 2005;24:551–5.
16. Edston E, Eriksson O, Van Hage M. Mast cell tryptase in postmortem serum—reference values and confounders. *Int J Legal Med* 2007;121:275–80.
17. Edston E, van Hage-Hamsten M. β -Tryptase measurements post-mortem in anaphylactic deaths and in controls. *Forensic Sci Int* 1998;93:135–42.
18. Yunginger JW, Nelson DR, Squillace DL, et al. Laboratory investigation of deaths due to anaphylaxis. *J Forensic Sci* 1991;36:857–65.
19. Mayer DE, Krauskopf A, Hemmer W, et al. Usefulness of post mortem determination of serum tryptase, histamine and diamine oxidase in the diagnosis of fatal anaphylaxis. *Forensic Sci Int* 2011;212:96–101.
20. Vadas P, Gold M, Perelman B, et al. Platelet-activating factor, PAF acetylhydrolase, and severe anaphylaxis. *N Engl J Med* 2008;358:28–35.
21. Blossum DB, Kallen AJ, Patel PR, et al. Outbreak of adverse reactions associated with contaminated heparin. *N Engl J Med* 2008;359:2674–84.
22. Kishimoto TK, Viswanathan K, Ganguly T, et al. Contaminated heparin associated with adverse clinical events and activation of the contact system. *N Engl J Med* 2008;358:2457–67.
23. Lee S, Hess EP, Nestler DM, et al. Antihypertensive medication use is associated with increased organ system involvement and hospitalization in emergency department patients with anaphylaxis. *J Allergy Clin Immunol* 2013;131:1103–8.
24. De Ceglie C, Calvano CD, Zamboni CG. Determination of hidden hazelnut oil proteins in extra virgin olive oil by cold acetone precipitation followed by in-solution tryptic digestion and MALDI-TOF-MS analysis. *J Agric Food Chem* 2014;62:9401–9.
25. Teuber SS, Brown RL, Haapanen LA. Allergenicity of gourmet nut oils processed by different methods. *J Allergy Clin Immunol* 1997;99:502–7.
26. Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy* 2000;30:1144–50.
27. Lieberman JA, Weiss C, Furlong TJ, et al. Bullying among pediatric patients with food allergy. *Ann Allergy Asthma Immunol* 2010;105:282–6.
28. Shemesh E, Annunziato RA, Ambrose MA, et al. Child and parental reports of bullying in a consecutive sample of children with food allergy. *Pediatrics* 2013; 131(1):e10–7.
29. van der Zee T, Dubois A, Kerkhof M, et al. The eliciting dose of peanut in double-blind, placebo-controlled food challenges decreases with increasing age and specific IgE level in children and young adults. *J Allergy Clin Immunol* 2011; 128:1031–6.

30. Starkl P, Krishnamurthy D, Szalai K, et al. Heating affects structure, enterocyte adsorption and signalling, as well as immunogenicity of the peanut allergen Ara h 2. *Open Allergy J* 2011;4:24–34.
31. Verma AK, Kumar S, Das M, et al. Impact of thermal processing on legume allergens. *Plant Foods Hum Nutr* 2012;67:430–41.
32. Vissers YM, Iwan M, Adel-Patient K, et al. Effect of roasting on the allergenicity of major peanut allergens Ara h 1 and Ara h 2/6: the necessity of degranulation assays. *Clin Exp Allergy* 2011;41:1631–42.
33. Asero R, Mistrello G, Amato S, et al. Shrimp allergy in Italian adults: a multicenter study showing a high prevalence of sensitivity to novel high molecular weight allergens. *Int Arch Allergy Immunol* 2012;157:3–10.
34. Sanchez-Borges M, Chacon RS, Capriles-Hulett A, et al. Anaphylaxis from ingestion of mites: pancake anaphylaxis. *J Allergy Clin Immunol* 2013; 131:31–5.
35. Edston E, van Hage-Hamstem M. Death in anaphylaxis in a man with house dust mite allergy. *Int J Legal Med* 2003;117:299–301.
36. Bennett AT, Collins KA. An unusual case of anaphylaxis: mold in pancake mix. *Am J Forensic Med Pathol* 2001;22:292–5.
37. Gonzalez-Perez A, Aponte Z, Vidaurre C, et al. Anaphylaxis epidemiology in patients with and patients without asthma: a United Kingdom database review. *J Allergy Clin Immunol* 2010;125:1098–104.
38. Iribarren C, Tolstikh IV, Miller MK, et al. Asthma and the prospective risk of anaphylactic shock and other allergy diagnoses in a large integrated health care delivery system. *Ann Allergy Asthma Immunol* 2010;104:371–7.
39. Patterson R, Clayton DE, Booth BH, et al. Fatal and near fatal idiopathic anaphylaxis. *Allergy Proc* 1995;16:103–8.
40. Ditto AM, Harris KE, Krasnick J, et al. Idiopathic anaphylaxis: a series of 335 cases. *Ann Allergy Asthma Immunol* 1996;77:285–91.
41. Wong S, Yarnold PR, Yango C, et al. Outcome of prophylactic therapy for idiopathic anaphylaxis. *Ann Intern Med* 1991;114:133–6.
42. Summers CW, Pumphrey RS, Woods CN, et al. Factors predicting anaphylaxis to peanuts and tree nuts in patients referred to a specialist center. *J Allergy Clin Immunol* 2008;121:632–8.
43. Greenberger PA, Meyers SN, Kramer BL, et al. Effects of beta-adrenergic and calcium antagonists on the development of anaphylactoid reactions from radiographic contrast media during cardiac angiography. *J Allergy Clin Immunol* 1987;80:698–702.
44. Lang DM, Alpern MB, Visintainer PF, et al. Elevated risk of anaphylactoid reaction from radiographic contrast media is associated with both beta-blocker exposure and cardiovascular disorders. *Arch Intern Med* 1993; 153:2033–40.
45. Hepner MJ, Ownby DR, Anderson JA, et al. Risk of systemic reactions in patients taking beta-blocker drugs receiving allergen immunotherapy injections. *J Allergy Clin Immunol* 1990;86:407–11.
46. Bahna SL, Oldham JL. Munchausen stridor—A strong false alarm of anaphylaxis. *Allergy Asthma Immunol Res* 2014;6(6):577–9.
47. Patterson R, Schatz M, Horton M. Munchausen's stridor: non-organic laryngeal obstruction. *Clin Allergy* 1974;4:307–10.
48. Hendrix S, Sale S, Zeiss CR, et al. Factitious Hymenoptera allergic emergency: a report of a new variant of Munchausen's syndrome. *J Allergy Clin Immunol* 1981; 67:8–13.

49. Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol* 2010; 126:477–80.
50. Pumphrey RS. Fatal posture in anaphylactic shock. *J Allergy Clin Immunol* 2003; 112:451–2.
51. Lieberman PL. Recognition and first-line treatment of anaphylaxis. *Am J Med* 2014;127:S6–11.
52. Simons FE, Arduoso LR, Bilò MB, et al. International consensus on (ICON) anaphylaxis. *World Allergy Organ J* 2014;7(1):9 eCollection 2014.