

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.

For more information visit www.intechopen.com



Anaphylactic Shock

*Stephen DeTurk, Shravan Reddy, Anna Ng Pellegrino
and John Wilson*

Abstract

Anaphylaxis is a life threatening hypersensitivity reaction that can cause shock. Epidemiology studies show anaphylaxis and anaphylactic shock is relatively rare, but its incidence is increasing. A review of the pathophysiology of anaphylaxis can provide insight into clinical decisions. Diagnosing anaphylaxis can be difficult as symptoms and history are not always obvious. Diagnostic guidelines provide an objective tool to assess for anaphylaxis. Early intervention during anaphylaxis may prevent development of shock. Management is focused on circulation support with epinephrine and IV fluids, and airway maintenance. Following an acute anaphylactic reaction, patients should be provided with a referral for follow up and educated on avoidance of triggers and use of epinephrine autoinjectors.

Keywords: anaphylaxis, anaphylactic shock, distributive shock, management

1. Introduction

In this chapter, we will learn the differences between anaphylaxis and anaphylactic shock. Epidemiology of anaphylactic shock will be reviewed. We will also discuss the biochemical markers and mediators most noted to triggering an anaphylactic reaction. Lastly, we will provide a review on clinical manifestations and management of an anaphylactic reaction in a nonclinical setting and in a clinical setting.

Throughout this chapter anaphylaxis will be defined according to the World Allergy Organization (WAO) definition 'a severe, life-threatening generalized or systemic hypersensitivity reaction' [1]. This includes Gell-Combs Type I hypersensitivity, as well as anaphylactoid reactions that are immunologically and nonimmunological mediated.

There are few studies on anaphylactic shock, and most recommendations for anaphylactic shock management come from major allergy organizations: WAO, AAAA/ACAAI, and EAACI. The recommendations of these groups for management of anaphylactic shock are presented in this chapter. Recent changes in anaphylaxis definitions require a review of the immunologic and nonimmunologic biochemical pathways of anaphylaxis.

1.1 Definitions

1.1.1 Anaphylactoid reactions

Reactions that occur via mechanisms other than IgE mediated mast cell degranulation have been referred to as *Anaphylactoid reactions*. However, the WAO, AAAA/ACAAI, and EAACI have recommended stoppage of the term [2]. Throughout this chapter reactions that would be included in this term will be referred to as anaphylaxis.

1.1.2 Anaphylaxis

Anaphylaxis is typically taught as Gell-Combs classification type 1 hypersensitivity, that is IgE mediated. However, the World Allergy Organization (WAO) proposed a new expanded definition of anaphylaxis '*a severe, life-threatening generalized or systemic hypersensitivity reaction*' [3]. This new definition of anaphylaxis now includes reactions previously categorized as 'anaphylactoid reactions'.

1.1.3 Anaphylactic shock

End manifestation of anaphylaxis, occurs when there is inadequate tissue perfusion causing end organ damage.

2. Epidemiology

Studies have estimated that the incidence of anaphylaxis is between 0.05 and 2.0% of the population [4], although the actual incidence is not clear. Issues previously identified with epidemiologic studies include variations in definitions, under reporting of anaphylaxis, and unclear use of incidence and prevalence of disease [5].

Although the actual incidence is not clear, there have been multiple studies showing that the incidence of anaphylaxis in the United States has increased in recent years [6–9], although the case fatality rate has decreased [8]. Similar findings are reported in other countries, with UK reporting increasing rates of anaphylaxis [10–12], but no increase in the incidence of fatal anaphylaxis [10]. In Australia the incidence of anaphylaxis [13–15] and fatal anaphylaxis has increased as well [16]. One study on the incidence of anaphylaxis with circulatory symptoms found a rate of approximately 8–9 cases per 100,000 persons per year [17]. Severe anaphylaxis, including respiratory or circulatory symptoms, occurs more frequently at a rate of about 1–3 per 10,000 people [18].

Factors that may affect the incidence of anaphylaxis include geography, seasonal variations, age, and gender [19]. Demographic factors associated with higher incidence include living in northern areas of US [7, 20].

3. Pathophysiology

Anaphylaxis is caused by massive release of biochemical mediators from mast cell and basophils. Mast cells activation occurs mainly via antigen crosslinking of IgE bound to FcεRI receptors on cell membranes. However, other membrane receptors can activate mast cells as well or potentiate IgE activation [21]. The multiple activation pathways allow for immunologic (e.g. IgE mediated) and/or nonimmunologic activation (e.g. drug directly interacting with receptors) (**Figure 1: mechanisms of mast cell degranulation**). Some antigens may mediate effects via several mechanisms simultaneously (e.g. vespid venom, NSAIDs, opiates). In non-IgE mediated anaphylaxis, symptoms can occur on first exposure to an antigen as prior exposure and sensitization is not required.

Reproduced from Spoerl et al. [22] in agreement with publishing under terms of the Creative Commons Attribution (CC BY) license.

3.1 Triggers and cell activation

In IgE mediated anaphylaxis, an immunogen cross links membrane bound IgE in previously sensitized mast cell. Immunogens are typically large foreign proteins

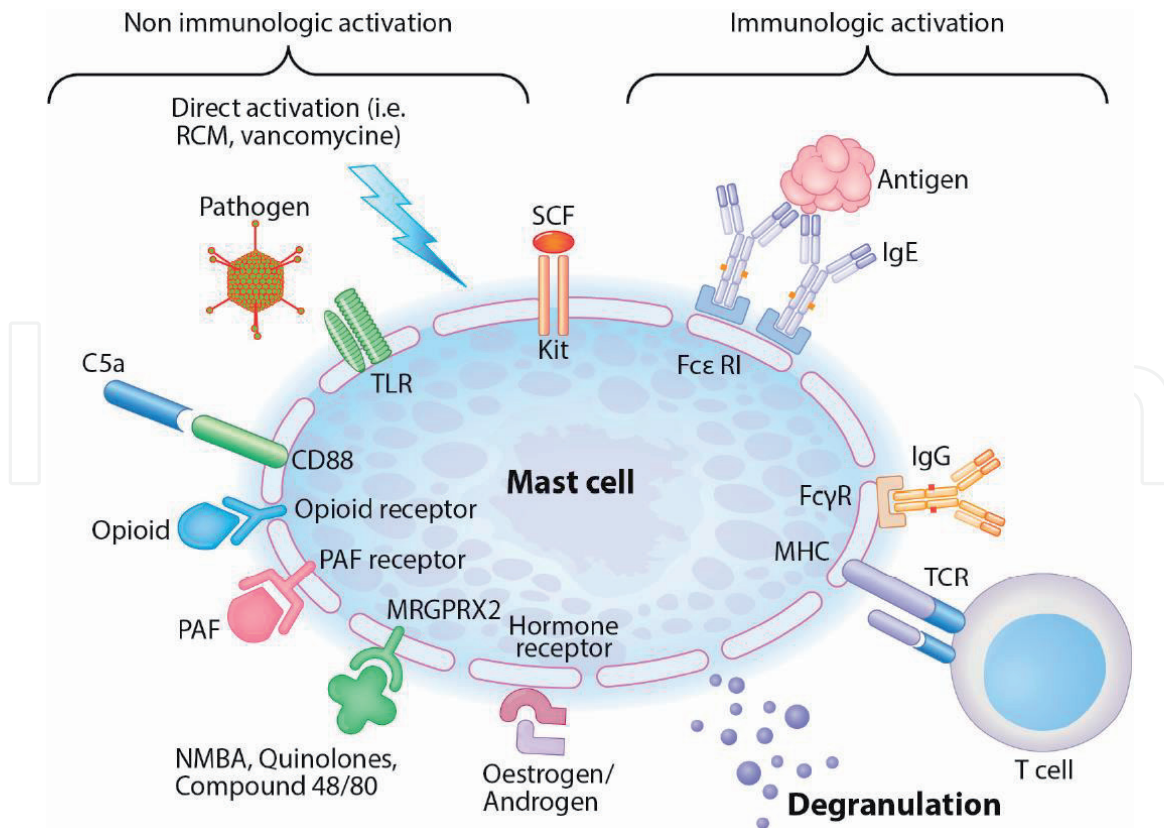


Figure 1. Mechanisms of mast cell degranulation. Abbreviations: RCM, radiocontrast media; TLR, Toll-like receptor; SCF, stem cell factor; FcεRI, high affinity IgE receptor; FcγR, IgG receptor; TCR, T-cell receptor; NMBA, neuromuscular blocking agent; PAF, platelet activating factor; MHC, major histocompatibility complex.

with multiple epitope binding sites (e.g. proteins in insect venom and certain foods) [23]. Antigens that are too small to cross link IgE (e.g. penicillin) must first bind to larger carrier molecules in order to elicit an immune response. Common triggers of IgE-mediated anaphylaxis include various food, venom and medications are summarized in **Table 1**: IgE-dependent triggers and discussed in more detail below.

3.1.1 Food

The most common foods causing anaphylaxis varies by region, in North America the most common food allergies includes milk, egg, peanuts, tree nuts, fish, shellfish, wheat, soy, and sesame [24]. Allergenic proteins have been identified for these common causes as well as in rice, barley, buckwheat, mustard, celery, potato, carrots, and apples [25].

Most cases of anaphylaxis due to food occurs in children or those with known food allergies, and fatal cases are rare [7, 8, 10]. When fatal, the cause of death is more often due to respiratory arrest, although shock can occur as well. Arrest occurs later compared to medication or venom, typically occurring 25–35 min after exposure [26].

3.1.2 Venom

Stinging insects belonging to the order Hymenoptera produce venoms that can cause anaphylaxis. The important insects from this order include bees, vespids (wasps, yellow jackets, hornets) and stinging ants [27]. Vespid venom additionally activates complement in an IgE independent mechanism, which may potentiate anaphylaxis [28]. In addition to hymenoptera venom, bites from rattlesnakes [29],

Foods	Milk Eggs Peanuts Tree nuts Fish Shellfish Soy Wheat Sesame
Bites/venoms	Hymenoptera venom (bee, vespids*, ants) Tick Rattlesnake Hamster
Medications	Antibiotics NSAIDs* Chemotherapy Neuromuscular blocker* Radiocontrast* Opioids*

**Non-IgE mediated mechanisms identified as alternative or additional mechanism.*

Table 1.
IgE-dependent triggers [9, 24, 27, 29–32].

hamsters [30], and ticks [31] have been implicated as causes of anaphylaxis. Fatal cases due stings are more often due to shock than respiratory distress, arrest typically occurs 10–15 min after exposure [26].

3.1.3 Medications

The most common medications causing anaphylaxis are beta-lactam antibiotics, NSAIDs, neuromuscular blocking agents, and chemotherapy [9, 32]. However, nearly any medication has the potential to cause anaphylaxis, some drugs that have been implicated includes intravenous iron [33], gelatin found in a vaccines [34], dextran [35], and human serum albumin [36]. In addition to IgE mediated mechanisms, other mechanisms of inducing anaphylaxis have been identified for multiple drugs [37]. This includes complement or contact activation (e.g. radiocontrast media, pegylated compounds, liposomal drugs [38], and heparin contaminated with oversulfated chondroitin sulfate (OSCS) [39]) and direct mast cell activation (e.g. opiates and neuromuscular blockers [37]). There have been multiple reports of anaphylaxis occurring to biologic agents, where the patient had IgG but no detectable IgE antibody to the therapy [40]. In medication induced anaphylaxis, shock is more common in severe cases than respiratory distress [26, 41]. Arrest occurs can occur rapidly after exposure, most cases in less than 5 min [26].

3.2 Biochemical mediators and clinical pharmacology

Once activated, mast cells and basophils release a cascade of mediators which cause physiologic changes, activate other immunology pathways, and attract other immune cells. Preformed mediators are released immediately upon activation including histamine, tryptase, heparin, and chymase. Over several minutes additional mediators are generated including platelet activating factor, leukotrienes, and prostaglandins (**Table 2**). Various cytokines and chemokines are generated over several hours further propagate the inflammatory response [37, 42].

Immediate release	Histamine	Vasodilation, edema, bronchoconstriction, mucus secretion, change myocardial contractility
	Tryptase	Vasodilation, edema, bronchoconstriction
	Chymase	Vasodilation, edema, mucus secretion
	Heparin	Initiates formation of bradykinin causing edema
	TNF α	Bronchoconstriction
Rapid generation (min)	PAF	Vasodilation, edema, bronchoconstriction, platelet activation, decrease myocardial contractility
	LTs C4, D4	Potent vasoactive and spasmogenic agents
	Prostaglandin D2	Bronchospasm and increase mucus secretion

Table 2.
Physiologic effects of mediators [42, 49].

Histamine has long been considered the principal mediator of anaphylaxis, and concentrations of histamine correlate with symptom severity [42]. Histamine acts on receptors to cause vasodilation and increased permeability [43, 44], bronchoconstriction, and increase mucus secretion. In the heart H2 receptors have positive chronotropic and inotropic effects and causes coronary vasodilation, while the H1 receptor causes coronary vasoconstriction [45].

Platelet activating factor (PAF) has been increasingly recognized as important in the pathophysiology of anaphylaxis. In PAF receptor knockout mice, symptoms of anaphylaxis are reduced [46]. In humans PAF levels in the serum directly correlates with the severity of anaphylaxis symptoms [47]. In addition to activating platelets, PAF causes vasodilation, increased vascular permeability, decreased myocardial contractility, bronchoconstriction, and initiates allergic response through stimulation of other mediators [48, 49].

4. Signs and Symptoms

Anaphylaxis causes a generalized systemic reaction affecting multiple organ systems, symptoms involving the skin occur in 80–90% of cases, respiratory tract in 70%, GI in 45%, CV in 45%, and CNS involvement in 15% [50, 51]. The cardiovascular and respiratory systems are the principal shock organs in fatal anaphylaxis. Death occurs in most often due to shock or acute respiratory distress, but DIC and epinephrine overdose have also been cited as cause of death [26, 52–55]. Most fatal cases of anaphylaxis due to medication or venoms are a result of shock, in food related anaphylaxis respiratory involvement is the main cause of death although shock is still possible [26, 56].

Anaphylaxis develops rapidly with symptoms developing in minutes. Biphasic reactions, where symptoms resolve and then reappear later occurs around 20% of the time [57]. A systematic review of biphasic reactions found the median time between resolution of initial symptoms and onset of delayed symptoms to be 11 h, with a range of 0.2–72 h [58].

4.1 Cardiovascular changes

Cardiovascular manifestations of anaphylaxis develop due to direct and indirect effects of mediators on the vasculature and heart. Increased vascular permeability causes rapid fluid extravasation, with up to 35% of plasma volume shift occurring

in a matter of minutes [59, 60]. Vascular smooth muscle relaxation causes vasodilation and a rapid decrease in SVR [61, 62]. Rapid drop in measured CVP suggests that venodilation plays a major role as well. The combined effects of extravasation and venodilation cause significant reduction in preload. This can be severe enough to cause Empty ventricle syndrome, has been documented in autopsies of patients who died from anaphylaxis [63].

Arrhythmias and myocardial infarction can also be seen in anaphylaxis. Arrhythmias may develop due to the combined direct effect of mediators, and hemodynamic changes previously described. Myocardial infarctions seen in anaphylaxis may be due to decreased venous return and direct effects of mediators on coronary arteries causing vasospasm or disruption of atherosclerotic plaques [64, 65].

Compensatory response to these changes includes rise in heart rate, ejection fraction, and cardiac index [61, 62]. Although Tachycardia is typical in anaphylaxis, although bradycardia may be seen as well. Bradycardia occurs due to a compensatory *Bezold-Jarisch* reflex, and has been found to have lower mortality rates when compared to cases of anaphylactic shock with tachycardia [66, 67]. Atropine therefore should not be administered, as it would counteract this protective effect and may increase mortality [68].

4.2 Respiratory changes

The entire respiratory tract can be affected in anaphylaxis, involving the upper airway and/or lower airway [69]. Upper airway symptoms develop due to fluid extravasation causing mucosal edema [70]. Some symptoms of upper airway involvement include angioedema, stridor, dysphagia, and rhinorrhea [50, 71]. Lower airway obstruction occurs due to mucosal edema, bronchospasm, and mucous plugging [70]. Oxygen saturation may decrease secondary to respiratory effects of anaphylaxis limiting airflow. When there is diffuse lower respiratory tract involvement, decreased oxygen saturation can persist despite endotracheal intubation [72]. When PaO₂ is adequate, tissue oxygenation can still be compromised causing anaerobic metabolism. In one study on rats, tissue oxygenation of muscle decreased faster in anaphylaxis compared to nicardipine induced hypotension. The anaphylactic group also showed a greater increase in lactate and lactate-pyruvate ratio indicating depletion of intracellular energy storage [73].

4.3 Mucocutaneous, gastrointestinal, and neurologic changes

Mucocutaneous symptoms (e.g. flushing, pruritus, angioedema, and urticaria) are common in anaphylaxis, however in cases of shock cutaneous symptoms are often absent. Vasodilation and increased vasculature permeability leads to flushing and angioedema [74]. In addition to vascular changes, urticaria develops due to inflammatory cell infiltration and neuropeptide release from sensory nerves [75]. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal pain [76]. These symptoms are likely due to intestinal smooth muscle contraction and alterations in water and electrolyte absorption [77, 78]. Neurologic changes are mostly secondary to hypotension and decreased perfusion and may manifest as dizziness, confusion, syncope/presyncope, or headache [50]. More serious effects including seizure and stroke may also be seen but are rare [74, 79].

5. Diagnosing

It is often difficult to recognize anaphylaxis, and many cases go undiagnosed [80, 81]. Early intervention in acute anaphylaxis reduces risk of severe reaction and

need for hospitalization [82]. In order to aid in diagnosis of anaphylaxis, diagnostic criteria have been developed (**Table 3**). In the clinic or emergency department, it may be unclear if the patient had been exposed to an allergen. In the ICU or operating room, rapid development of symptoms after administering medication makes recognizing anaphylaxis easier. Following the acute phase of anaphylaxis, serum tryptase and histamine should be measured to aid immunologist in confirming the diagnosis of anaphylaxis during follow-up care [83, 84]. Plasma tryptase remains elevated for 6 h following the onset of symptoms, but histamine levels remain elevated for just 1 h [85, 86]. Urinary histamine metabolites remain elevated for a longer period and may therefore be more useful than plasma histamine for confirming anaphylaxis [86].

5.1 Diagnostic criteria

Anaphylaxis is likely when one of the following criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin and/or mucosal tissue and at least one:
 - a. Respiratory compromise
 - b. Reduced blood pressure or symptoms of end-organ damage
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient
 - a. Involvement of the skin-mucosal tissue
 - b. Respiratory compromise
 - c. Reduced blood pressure or associated symptoms
 - d. Persistent gastrointestinal symptoms
3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours)
 - a. Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline
 - b. Infants and children: low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressure

Table 3.

Clinical criteria for diagnosing anaphylaxis, modified from [3, 87].

5.2 Differential diagnosis

There are several conditions which may mimic certain characteristics of anaphylaxis. Acute anxiety can present as dyspnea and near syncope with hyperventilation. Hypoglycemia can precipitate an altered sensorium and syncope. Vasovagal episodes can involve nausea with vomiting, hypotension, pallor, bradycardia, diaphoresis and syncope. Additional considerations include severe reactive airway disease, vocal cord dysfunction and non-allergy mediated angioedema. Vasovagal episodes can involve nausea with vomiting, hypotension, pallor, bradycardia, diaphoresis and syncope [50, 88].

6. Management

There is a general lack of evidence basis for the treatment of anaphylaxis [89], but multiple expert guidelines highlight the chief treatment as epinephrine, oxygen, and fluids [86, 90, 91].

6.1 Principal treatment

Epinephrine is the first line treatment of anaphylaxis, and delayed administration increases the likelihood of poor outcomes [54, 55, 92]. Despite this, use of

epinephrine in anaphylaxis is infrequent and often delayed [80]. There are no contraindications for use of epinephrine in anaphylaxis, and it should still be administered in patients with history of heart disease [93].

Epinephrine exerts its effects via alpha and beta adrenergic receptors in a dose-dependent response where beta receptors effects are dominant at low doses, but alpha receptors effects are seen at higher doses. The α_1 receptors cause vasoconstriction increasing peripheral vascular resistance and blood pressure and improving coronary and cerebral perfusion. The β_1 receptors exert positive chronotropic and inotropic effects which improves cardiac output and increases blood pressure. In the respiratory system, β_2 receptors stimulation results in bronchodilation, and relief and respiratory symptoms. β receptors also inhibit release of mediators from mast cells and basophils, via increased cAMP production [94].

In most situations intramuscular administration is preferred, but IV epinephrine can be used in the ICU. IM epinephrine should be given in 0.2–0.5 mg doses (1:1000 dilution), and repeated every 5 min depending on the resolution of symptoms [86]. Studies showed that peak epinephrine concentrations were higher when epinephrine was given IM into the thigh, compared to IM administration in the arm or subcutaneous administration [95]. Multiple doses of epinephrine may be required to reverse symptoms [96]. Care should be taken to closely monitor pulse and blood pressure when epinephrine is administered intravenously as there is greater risk of severe adverse effects compared to intramuscular administration including arrhythmias and myocardial infarctions [97].

Following epinephrine administration, patients should continue to be assessed for worsening signs of anaphylaxis. Patients should be placed on pulse oximeter and given high flow oxygen as needed. Patients in anaphylactic shock should be placed in supine or Trendelenburg position to increase blood return to the heart. Patients who are sitting upright can have a significant decrease in preload leading to empty ventricle syndrome and PEA [98].

Due to the intravascular depletion, fluid is often necessary to maintain pressure. Crystalloids or colloids may be used, although physicians should be aware of the anaphylactic potential of some colloid solutions. Normal saline (0.9% saline) should be chosen over other crystalloids as it remains in the intravascular space longer than dextrose solutions [86, 99]. Caution should taken while giving fluids to patients with heart failure to prevent fluid overload.

6.2 Adjunct treatments

Antihistamines are often given as adjunct therapy in anaphylaxis, however there is no evidence to support or advise against their use in anaphylaxis [100]. Steroids may be used to prevent biphasic anaphylaxis [86], although there is no evidence to support the use of steroids in acute treatment of anaphylaxis [101, 102].

Nebulized albuterol or other beta-2 agonists may be useful to treat respiratory distress due to bronchoconstriction. While there is no clinical trial on use of these medications in anaphylaxis, their effectiveness in treating other allergic diseases offers some basis for their use [90].

6.3 Additional consideration

Beta blockers may complicate the treatment of anaphylaxis, as some of the beneficial effects of epinephrine will be diminished [103]. In patients on beta-blockers who do not respond to epinephrine and fluids, other vasopressors should be considered. Glucagon has been reported to be a successful treatment in several case reports of patients on beta blockers who experienced anaphylactic shock [104].

Glucagon mechanism of action is via direct activation of adenylate cyclase, bypassing the blocked adrenergic receptors.

Vasopressin or phenylephrine can be used to increase systemic vascular resistance without further increasing heart rate. Dopamine or norepinephrine can be added in cases of relative bradycardia [105]. Mechanical support with ECMO has been reported to be successful at treating refractory anaphylaxis with profound myocardial dysfunction [106].

Methylene blue has been reported to be an effective treatment in cases of severe anaphylaxis not responding to epinephrine [88], as well as cases of anaphylaxis without hypotension. Methylene blue inhibits NO mediated vasodilation via competitive inhibition of guanylate cyclase decreasing cyclic GMP production and subsequent vasodilation [107]. This mechanism acts independent of adrenergic receptors, and may be effective in patients with refractory anaphylactic shock [108].

6.4 Follow up

Before discharging a patient that experienced anaphylaxis, they should be referred to an immunologist for a thorough evaluation. Labs to assess for anaphylaxis (i.e. tryptase, histamine) should be drawn to assist allergist in making a diagnosis. Patients should also receive a prescription for an epinephrine autoinjector, along with education on how to use it [87].

7. Conclusions

Anaphylaxis is a rapidly acting life-threatening hypersensitivity reaction. Diagnosis of anaphylaxis can be difficult, and early recognition and treatment is essential to prevent development of shock. Shock is more common in cases due to medication compared to food, although shock can occur. The primary treatment in anaphylactic shock is epinephrine, fluids, and oxygen. Additional medications including antihistamines, steroids, and inhaled beta-agonist should be used as needed. In patients who do not respond to epinephrine, other vasopressors or mechanical support can be used.

Abbreviations

AAAAI	American Academy of Allergy, Asthma and Immunology
ACAAI	American College of Allergy, Asthma and Immunology
EAACI	European Academy of Allergy and Clinical Immunology
WAO	World Allergy Organization
Ig	immunoglobulin
Antigen	molecule capable of interacting with Ig, includes immunogens and haptens
Immunogen	molecule that can interact with Ig and cause an immune response
Hapten	molecule that can interact with Ig, but cannot cause immune response on its own

IntechOpen

Author details

Stephen DeTurk^{1*}, Shravan Reddy², Anna Ng Pellegrino³ and John Wilson⁴

1 Research Department, St. Luke's University Health Network, USA

2 Warren Family Medicine Residency, St. Luke's University Health Network, USA

3 Department of Anesthesia, St. Luke's University Health Network, USA

4 Department of Emergency Medicine, St. Luke's University Health Network, USA

*Address all correspondence to: stephen.deturk1@sluhn.org

IntechOpen

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Johansson SGO, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *The Journal of Allergy and Clinical Immunology*. 2004;**113**(5):832-836
- [2] Simons FER, Arduso LRF, Bilo MB, Cardona V, Ebisawa M, El-Gamal YM, et al. International consensus on (ICON) anaphylaxis. *World Allergy Organization Journal*. 2014;**7**:9
- [3] Sampson HA, Munoz-Furlong A, Bock A, Schmitt M, Bass R, Chowdhury BA, et al. Symposium on the definition and management of anaphylaxis: Summary report. *The Journal of Allergy and Clinical Immunology*. 2005;**115**(3):584-591
- [4] Lieberman P, Camargo CA, Bohlke K, Jick H, Miller RL, Sheikh A, et al. Epidemiology of anaphylaxis: Findings of the American College of Allergy, Asthma and Immunology epidemiology of Anaphylaxis Working Group. *Annals of Allergy, Asthma & Immunology*. 2006;**97**(5):596-602
- [5] Tanno LK, Bierrenbach AL, Simons FER, Cardona V, Thong BYH, Molinari N, et al. Critical view of anaphylaxis epidemiology: Open questions and new perspectives. *Allergy, Asthma & Clinical Immunology*. 2018;**14**:11
- [6] Lin RY, Anderson AS, Shah SN, Nurruzzaman F. Increasing anaphylaxis hospitalizations in the first 2 decades of life: New York State, 1990-2006. *Annals of Allergy, Asthma & Immunology*. 2008;**101**(4):387-393
- [7] Jerschow E, Lin RY, Scaperotti MM, McGinn AP. Fatal anaphylaxis in the United States, 1999-2010: Temporal patterns and demographic associations. *Journal of Allergy and Clinical Immunology*. 2014;**134**(6):1318
- [8] Ma L, Danoff TM, Borish L. Case fatality and population mortality associated with anaphylaxis in the United States. *The Journal of Allergy and Clinical Immunology*. 2014;**133**(4):1075-1083
- [9] Graudins LV, Trubiano JA, Zubrinich CM, Elliott AS, Aung AK. Medication-related anaphylaxis treated in hospital: Agents implicated, patient outcomes, and management lessons. *Pharmacoepidemiology and Drug Safety*. 2018;**27**(9):1029-1033
- [10] Turner PJ, Gowland MH, Sharma V, Ierodiakonou D, Harper N, Garcez T, et al. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: An analysis of United Kingdom national anaphylaxis data, 1992-2012. *Journal of Allergy and Clinical Immunology*. 2015;**135**(4):956
- [11] Gupta R, Sheikh A, Strachan D, Anderson HR. Increasing hospital admissions for systemic allergic disorders in England: Analysis of national admissions' data. *British Medical Journal*. 2003;**327**(7424):1142-1143
- [12] Sheikh A, Alves B. Hospital admissions for acute anaphylaxis: Time trend study. *British Medical Journal*. 2000;**320**(7247):1441
- [13] Poulos LM, Waters AM, Correll PK, Loblay RH, Marks GB. Trends in hospitalizations for anaphylaxis, angioedema, and urticaria in Australia, 1993-1994 to 2004-2005. *The Journal of Allergy and Clinical Immunology*. 2007;**120**(4):878-884

- [14] Liew WK, Williamson E, Tang MLK. Anaphylaxis fatalities and admissions in Australia. *The Journal of Allergy and Clinical Immunology*. 2009;**123**(2):434-442
- [15] Mullins RJ, Dear KBG, Tang MLK. Time trends in Australian hospital anaphylaxis admissions in 1998-1999 to 2011-2012. *The Journal of Allergy and Clinical Immunology*. 2015;**136**(2):367-375
- [16] Mullins RJ, Wainstein BK, Barnes EH, Liew WK, Campbell DE. Increases in anaphylaxis fatalities in Australia from 1997 to 2013. *Clinical and Experimental Allergy*. 2016;**46**(8):1099-1110
- [17] Helbling A, Hurni T, Mueller UR, Pichler WJ. Incidence of anaphylaxis with circulatory symptoms: A study over a 3-year period comprising 940 000 inhabitants of the Swiss Canton Bern. *Clinical and Experimental Allergy*. 2004;**34**(2):285-290
- [18] Moneret-Vautrin DA, Morisset M, Flabbee J, Beaudouin E, Kanny G. Epidemiology of life-threatening and lethal anaphylaxis: A review. *Allergy*. 2005;**60**(4):443-451
- [19] Yu JE, Lin RY. The epidemiology of anaphylaxis. *Clinical Reviews in Allergy and Immunology*. 2018;**54**(3):366-374
- [20] Sheehan WJ, Graham D, Ma L, Baxi S, Phipatanakul W. Higher incidence of pediatric anaphylaxis in northern areas of the United States. *The Journal of Allergy and Clinical Immunology*. 2009;**124**(4):850-852
- [21] Gilfillan AM, Tkaczyk C. Integrated signalling pathways for mast-cell activation. *Nature Reviews Immunology*. 2006;**6**(3):218-230
- [22] Spoerl D, Nigolian H, Czarnetzki C, Harr T. Reclassifying anaphylaxis to neuromuscular blocking agents based on the presumed patho-mechanism: IgE-mediated, pharmacological adverse reaction or "innate hypersensitivity"? *International Journal of Molecular Sciences*. 2017;**18**(6):1223
- [23] Huby RDJ, Dearman RJ, Kimber I. Why are some proteins allergens? *Toxicological Sciences*. 2000;**55**(2):235-246
- [24] Sicherer SH, Sampson HA. Food allergy. *The Journal of Allergy and Clinical Immunology*. 2010;**125**(2):S116-SS25
- [25] Sampson HA. Food allergy. Part 1: Immunopathogenesis and clinical disorders. *The Journal of Allergy and Clinical Immunology*. 1999;**103**(5):717-728
- [26] Pumphrey RS, editor. Fatal anaphylaxis in the UK, 1992-2001. In: *Novartis Found Symp*. Vol. 1999. Chichester; New York: John Wiley; 2004
- [27] Reisman RE. Insect stings. *The New England Journal of Medicine*. 1994;**331**(8):523-527
- [28] Vanderlinden PWG, Hack CE, Kerckhaert JAM, Struyvenberg A, Vanderzwan JC. Preliminary-report—Complement activation in wasp-sting anaphylaxis. *Lancet*. 1990;**336**(8720):904-906
- [29] Hogan DE, Dire DJ. Anaphylactic shock secondary to rattlesnake bite. *Annals of Emergency Medicine*. 1990;**19**(7):814-816
- [30] Lim DL, Chan RME, Wen H, Van Bever HPS, Chua KY. Anaphylaxis after hamster bites—Identification of a novel allergen. *Clinical and Experimental Allergy*. 2004;**34**(7):1122-1123
- [31] Mateos-Hernandez L, Villar M, Moral A, Rodriguez CG, Arias TA, de la Osa V, et al. Tick-host conflict: Immunoglobulin E antibodies

to tick proteins in patients with anaphylaxis to tick bite. *Oncotarget*. 2017;**8**(13):20630-20644

[32] Park HK, Kang MG, Yang MS, Jung JW, Cho SH, Kang HR. Epidemiology of drug-induced anaphylaxis in a tertiary hospital in Korea. *Allergology International*. 2017;**66**(4):557-562

[33] Bailie GR, Clark JA, Lane CE, Lane PL. Hypersensitivity reactions and deaths associated with intravenous iron preparations. *Nephrology Dialysis Transplantation*. 2005;**20**(7):1443-1449

[34] Pool V, Braun MM, Kelso JM, Mootrey G, Chen RT, Yunginger JW, et al. Prevalence of anti-gelatin IgE antibodies in people with anaphylaxis after measles-mumps-rubella vaccine in the United States. *Pediatrics*. 2002;**110**(6):9

[35] Zinderman CE, Landow L, Wise RP. Anaphylactoid reactions to dextran 40 and 70: Reports to the United States Food and Drug Administration, 1969 to 2004. *Journal of Vascular Surgery*. 2006;**43**(5):1004-1009

[36] Stafford CT, Lobel SA, Fruge BC, Moffitt JE, Hoff RG, Fadel HE. Anaphylaxis to human-serum albumin. *Annals of Allergy*. 1988;**61**(2):85-88

[37] Kemp SF, Lockey RF. Anaphylaxis: A review of causes and mechanisms. *The Journal of Allergy and Clinical Immunology*. 2002;**110**(3):341-348

[38] Szebeni J. Complement activation-related pseudoallergy: A stress reaction in blood triggered by nanomedicines and biologicals. *Molecular Immunology*. 2014;**61**(2):163-173

[39] Kishimoto TK, Viswanathan K, Ganguly T, Elankumaran S, Smith S, Pelzer K, et al. Contaminated heparin associated with adverse clinical events and activation of the contact system.

The New England Journal of Medicine. 2008;**358**(23):2457-2467

[40] Finkelman FD, Khodoun MV, Strait R. Human IgE-independent systemic anaphylaxis. *The Journal of Allergy and Clinical Immunology*. 2016;**137**(6):1674-1680

[41] Renaudin JM, Beaudouin E, Ponvert C, Demoly P, Moneret-Vautrin DA. Severe drug-induced anaphylaxis: Analysis of 333 cases recorded by the Allergy Vigilance Network from 2002 to 2010. *Allergy*. 2013;**68**(7):929-937

[42] Stone SF, Brown SGA. Mediators released during human anaphylaxis. *Current Allergy and Asthma Reports*. 2012;**12**(1):33-41

[43] Dale HH, Richards A. The vasodilator action of histamine and of some other substances. *The Journal of Physiology*. 1918;**52**(2-3):110-165

[44] Majno G, Palade G. Studies on inflammation: I. The effect of histamine and serotonin on vascular permeability: An electron microscopic study. *The Journal of Cell Biology*. 1961;**11**(3):571-605

[45] Bristow MR, Ginsburg R, Harrison DC. Histamine and the human-heart—The other receptor system. *The American Journal of Cardiology*. 1982;**49**(1):249-251

[46] Ishii S, Kuwaki T, Nagase T, Maki K, Tashiro F, Sunaga S, et al. Impaired anaphylactic responses with intact sensitivity to endotoxin in mice lacking a platelet-activating factor receptor. *The Journal of Experimental Medicine*. 1998;**187**(11):1779-1788

[47] Vadas P, Gold M, Perelman B, Liss GM, Lack G, Blyth T, et al. Platelet-activating factor, PAF acetylhydrolase, and severe anaphylaxis. *The New England Journal of Medicine*. 2008;**358**(1):28-35

- [48] Cuss F, Dixon CS, Barnes P. Effects of inhaled platelet activating factor on pulmonary function and bronchial responsiveness in man. *The Lancet*. 1986;**328**(8500):189-192
- [49] Montrucchio G, Alloatti G, Camussi G. Role of platelet-activating factor in cardiovascular pathophysiology. *Physiological Reviews*. 2000;**80**(4):1669-1699
- [50] Simons FER. Anaphylaxis. *The Journal of Allergy and Clinical Immunology*. 2010;**125**(2):S161-SS81
- [51] Brown SGA. Clinical features and severity grading of anaphylaxis. *The Journal of Allergy and Clinical Immunology*. 2004;**114**(2):371-376
- [52] Pumphrey RSH. Lessons for management of anaphylaxis from a study of fatal reactions. *Clinical and Experimental Allergy*. 2000;**30**(8):1144-1150
- [53] Pumphrey RSH, Gowland MH. Further fatal allergic reactions to food in the United Kingdom, 1999-2006. *The Journal of Allergy and Clinical Immunology*. 2007;**119**(4):1018-1019
- [54] Bock SA, Munoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2006. *The Journal of Allergy and Clinical Immunology*. 2007;**119**(4):1016-1018
- [55] Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *The Journal of Allergy and Clinical Immunology*. 2001;**107**(1):191-193
- [56] Pumphrey RSH, Roberts ISD. Postmortem findings after fatal anaphylactic reactions. *Journal of Clinical Pathology*. 2000;**53**(4):273-276
- [57] Tole JW, Lieberman P. Biphasic anaphylaxis: Review of incidence, clinical predictors, and observation recommendations. *Immunology and Allergy Clinics of North America*. 2007;**27**(2):309
- [58] Lee S, Bellolio MF, Hess EP, Erwin P, Murad MH, Campbell RL. Time of onset and predictors of biphasic anaphylactic reactions: A systematic review and meta-analysis. *The Journal of Allergy and Clinical Immunology: In Practice*. 2015;**3**(3):408
- [59] Fisher M. Blood-volume replacement in acute anaphylactic cardiovascular collapse related to anesthesia. *British Journal of Anaesthesia*. 1977;**49**(10):1023-1026
- [60] Fisher MM. Clinical observations on the pathophysiology and treatment of anaphylactic cardiovascular collapse. *Anaesthesia and Intensive Care*. 1986;**14**(1):17-21
- [61] Nicolas F, Villers D, Blanloeil Y. Hemodynamic pattern in anaphylactic shock with cardiac-arrest. *Critical Care Medicine*. 1984;**12**(2):144-145
- [62] Beaupre PN, Roizen MF, Cahalan MK, Alpert RA, Cassorla L, Schiller NB. Hemodynamic and two-dimensional trans-esophageal echocardiographic analysis of an anaphylactic reaction in a human. *Anesthesiology*. 1984;**60**(5):482-484
- [63] Brown SGA. The pathophysiology of shock in anaphylaxis. *Immunology and Allergy Clinics of North America*. 2007;**27**(2):165
- [64] Brown AFT. Anaphylactic shock—Mechanisms and treatment. *Journal of Accident & Emergency Medicine*. 1995;**12**(2):89-100
- [65] Kounis NG. Kounis syndrome (allergic angina and allergic myocardial infarction): A natural paradigm? *International Journal of Cardiology*. 2006;**110**(1):7-14

- [66] Campagna JA, Carter C. Clinical relevance of the Bezold-Jarisch reflex. *Anesthesiology*. 2003;**98**(5):1250-1260
- [67] Demetriades D, Chan LS, Bhasin P, Berne TV, Ramicone E, Huicochea F, et al. Relative bradycardia in patients with traumatic hypotension. *The Journal of Trauma*. 1998;**45**(3):534-539
- [68] Dewachter P, Mouton-Faivre C, Emala CW. Anaphylaxis and anesthesia: Controversies and new insights. *Anesthesiology*. 2009;**111**(5):1141-1150
- [69] Kemp SF, Lockey RF. In: Castells MC, editor. *Pathophysiology and Organ Damage in Anaphylaxis*. Totowa: Humana Press Inc; 2011. 33-46 p
- [70] Brown SG. Anaphylaxis: Clinical concepts and research priorities. *Emergency Medicine Australasia*. 2006;**18**(2):155-169
- [71] Lieberman P, Kemp SF, Oppenheimer J, Lang DM, Bernstein IL, Nicklas RA, et al. The diagnosis and management of anaphylaxis: An updated practice parameter. *The Journal of Allergy and Clinical Immunology*. 2005;**115**(3):S483-S523
- [72] Smith PL, Kageysobotka A, Bleecker ER, Traystman R, Kaplan AP, Gralnick H, et al. Physiologic manifestations of human anaphylaxis. *The Journal of Clinical Investigation*. 1980;**66**(5):1072-1080
- [73] Dewachter P, Jouan-Hureaux V, Franck P, Menu P, de Talance N, Zannad F, et al. Anaphylactic shock—A form of distributive shock without inhibition of oxygen consumption. *Anesthesiology*. 2005;**103**(1):40-49
- [74] Lieberman P. Anaphylaxis. *Medical Clinics of North America*. 2006;**90**(1):77
- [75] Tharp M. Chronic urticaria: Pathophysiology and treatment approaches. *The Journal of Allergy and Clinical Immunology*. 1996;**98** (6 Pt 3):S325
- [76] Vighi G, Marcucci F, Sensi L, Di Cara G, Frati F. Allergy and the gastrointestinal system. *Clinical and Experimental Immunology*. 2008;**153**(s1):3-6
- [77] Scott R, Diamant S, Gall D. Motility effects of intestinal anaphylaxis in the rat. *American Journal of Physiology-Gastrointestinal and Liver Physiology*. 1988;**255**(4):G505-GG11
- [78] Perdue M, Chung M, Gall D. Effect of intestinal anaphylaxis on gut function in the rat. *Gastroenterology*. 1984;**86**(3):391
- [79] Jain J, Banait S, Srivastava AK, Lodhe R. Stroke intracerebral multiple infarcts: Rare neurological presentation of honey bee bite. *Annals of Indian Academy of Neurology*. 2012;**15**(2):163-166
- [80] Sclar DA, Lieberman PL. Anaphylaxis: Underdiagnosed, underreported, and undertreated. *The American Journal of Medicine*. 2014;**127**(1):S1-S5
- [81] Aun MV, Kalil J, Giavina-Bianchi P. Adults and children with anaphylaxis in the emergency room: Why it is not recognized? *Current Opinion in Allergy and Clinical Immunology*. 2018;**18**(5):377-381
- [82] Fleming JT, Clark S, Camargo CA, Rudders SA. Early treatment of food-induced anaphylaxis with epinephrine is associated with a lower risk of hospitalization. *Journal of Allergy and Clinical Immunology-in Practice*. 2015;**3**(1):57-62
- [83] Laroche D, Gomis P, Gallimidi E, Malinovsky JM, Mertes PM. Diagnostic value of histamine and tryptase concentrations in severe anaphylaxis

with shock or cardiac arrest during anesthesia. *Anesthesiology*. 2014;**121**(2):272-279

[84] Schwartz LB. Diagnostic value of tryptase in anaphylaxis and mastocytosis. *Immunology and Allergy Clinics of North America*. 2006;**26**(3):451

[85] Laroche D, Vergnaud MC, Sillard B, Soufarapis H, Bricard H. Biochemical markers of anaphylactoid reactions to drugs—Comparison of plasma histamine and tryptase. *Anesthesiology*. 1991;**75**(6):945-949

[86] Lieberman P, Nicklas RA, Oppenheimer J, Kemp SF, Lang DM, Bernstein DI, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *The Journal of Allergy and Clinical Immunology*. 2010;**126**(3):477-480

[87] Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, 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. *The Journal of Allergy and Clinical Immunology*. 2006;**117**(2):391-397

[88] Lee JK, Vadas P. Anaphylaxis: Mechanisms and management. *Clinical and Experimental Allergy*. 2011;**41**(7):923-938

[89] Simons FER. Pharmacologic treatment of anaphylaxis: Can the evidence base be strengthened? *Current Opinion in Allergy and Clinical Immunology*. 2010;**10**(4):384-393

[90] Simons FER, Arduzzo LRF, Bilo MB, El-Gamal YM, Ledford DK, Ring J, et al. World Allergy Organization anaphylaxis guidelines: Summary. *The Journal of Allergy and Clinical Immunology*. 2011;**127**(3):587-593

[91] Muraro A, Roberts G, Worm M, Bilo MB, Brockow K, Rivas MF, et al. Anaphylaxis: Guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy*. 2014;**69**(8):1026-1045

[92] Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *The New England Journal of Medicine*. 1992;**327**(6):380-384

[93] Kemp SF, Lockey RF, Simons FER. World allergy org ad hoc C. epinephrine: The drug of choice for anaphylaxis. A statement of the World Allergy Organization. 2008;**63**(8):1061-1070

[94] Brown AFT. Therapeutic controversies in the management of acute anaphylaxis. *Journal of Accident & Emergency Medicine*. 1998;**15**(2):89-95

[95] Estelle F, Simons R, Gu XC, Simons KJ. Epinephrine absorption in adults: Intramuscular versus subcutaneous injection. *The Journal of Allergy and Clinical Immunology*. 2001;**108**(5):871-873

[96] Korenblat P, Lundie MJ, Dankner RE, Day JH. A retrospective study of epinephrine administration for anaphylaxis: How many doses are needed? *Allergy and Asthma Proceedings*. 1999;**20**(6):383-386

[97] McLean-Tooke A, Goulding M, Bundell C, White J, Hollingsworth P. Postmortem serum tryptase levels in anaphylactic and non-anaphylactic deaths. *Journal of Clinical Pathology*. 2014;**67**(2):134-138

[98] Pumphrey RSH. Fatal posture in anaphylactic shock. *The Journal of Allergy and Clinical Immunology*. 2003;**112**(2):451-452

[99] Simons FER, Arduzzo LRF, Bilo MB, El-Gamal YM, Ledford DK, Ring J, et al. World allergy organization guidelines for the assessment and Management of Anaphylaxis. *The Journal of Allergy and Clinical Immunology*. 2011;**127**(3):22

[100] Sheikh A, Ten Broek V, Brown SG, Simons FE. H1-antihistamines for the treatment of anaphylaxis: Cochrane systematic review. *Allergy*. 2007;**62**(8):830-837

[101] Choo KJL, Simons FER, Sheikh A. Glucocorticoids for the treatment of anaphylaxis. *Cochrane Database of Systematic Reviews*. 2012;**4**:CD007596

[102] Choo KJL, Simons E, Sheikh A. Glucocorticoids for the treatment of anaphylaxis: Cochrane systematic review. *Allergy*. 2010;**65**(10):1205-1211

[103] Toogood JH. Beta-blocker therapy and the risk of anaphylaxis. *Canadian Medical Association Journal*. 1987;**136**(9):929-933

[104] Thomas M, Crawford I. Glucagon infusion in refractory anaphylactic shock in patients on beta-blockers. *Emergency Medicine Journal*. 2005;**22**(4):272-273

[105] LoVerde D, Iweala OI, Eginli A, Krishnaswamy G. Anaphylaxis. *Chest*. 2018;**153**(2):528-543

[106] Raper RF, Fisher MM. Profound reversible myocardial depression after anaphylaxis. *Lancet*. 1988;**1**(8582):386-388

[107] Bauer CS, Vadas P, Kelly KJ. Methylene blue for the treatment of refractory anaphylaxis without hypotension. *The American Journal of Emergency Medicine*. 2013;**31**(1):3

[108] Lo JCY, Darracq MA, Clark RF. A review of methylene blue treatment for cardiovascular collapse. *The Journal of Emergency Medicine*. 2014;**46**(5):670-679