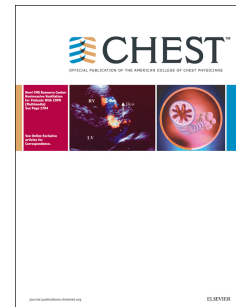


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Daniel LoVerde, DO, MS, Onyinye I. Iweala, MD, PhD, Ariana Eginli, MD, Guha Krishnaswamy, MD, FACP, FCCP, FAAAAI, FAAAAI



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Anaphylaxis

Daniel LoVerde, DO, MS^{1*}, Onyinye I. Iweala, MD, PhD^{2*}, Ariana Eginli, MD³, Guha Krishnaswamy, MD, FACP, FCCP, FAAAI, FACAAI^{1,4,5}

¹Division of Pulmonary, Critical Care, Allergy and Immunology, Department of Medicine, Wake Forest University School of Medicine and Wake Forest Baptist Medical Center, Winston-Salem, NC. ²Division of Rheumatology, Allergy, and Immunology, Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC. ³Department of Medicine, University of Southern California School of Medicine, Los Angeles, CA. ⁴Division of Allergy and Clinical Immunology, Department of Medicine, W.G. (Bill) Hefner VA Medical Center, Salisbury, NC. ⁵Division of Allergy and Clinical Immunology, Department of Medicine, Kernersville Health Care Center, Kernersville, NC.

*Dr. LoVerde and Dr. Iweala contributed equally to the writing and production of this manuscript and are co-first authors.

Name and title of first authors:

Daniel LoVerde, DO, MS^{1*} and Onyinye I. Iweala, MD, PhD^{2*}

Complete contact addresses

Daniel LoVerde, DO, MS:

Department of Medicine
Section on Pulmonary, Critical Care, Allergy and Clinical Immunology
Wake Forest School of Medicine and Wake Baptist Hospital
Medical Center Boulevard Watlington Tower, 2nd Floor, Winston Salem, NC 27157
Email: dloverde@wakehealth.edu

Onyinye I. Iweala, MD, PhD:

University of North Carolina at Chapel Hill
Division of Rheumatology, Allergy, and Immunology
3300 Thurston Building
Campus Box 7280
Chapel Hill, NC 27599-7280
Email: onyinye.iweala@med.unc.edu

Correspondence to: name and email address

Guha Krishnaswamy, MD, FACP, FCCP, FACAAI, FAAAAI

Email: gkrishna@wakehealth.edu

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Abstract

Anaphylaxis is a systemic, life threatening disorder triggered by mediators released by mast cells and basophils activated via allergic (IgE-mediated) or non-allergic (non-IgE-mediated) mechanisms. It is a rapidly evolving, multisystem process involving the integumentary, pulmonary, gastrointestinal and cardiovascular systems. Anaphylaxis and angioedema are serious disorders that can lead to fatal airway obstruction and culminate in cardiorespiratory arrest resulting in hypoxemia and/or shock. Often, these disorders can be appropriately managed in an outpatient setting. However, these conditions can be severe enough to warrant evaluation of the patient in the emergency department and in some cases, hospitalization and management in an intensive care unit (ICU). Recent reports suggest that underdiagnosis and undertreatment of anaphylaxis are common. Several new syndromes have been described recently including bird-egg, pork-cat, delayed allergy to mammalian meat and a diverse group of mast cell activation disorders. Conditions such as postural orthostatic tachycardia syndrome (POTS), Carcinoid syndrome, Munchausen's stridor and factitious anaphylaxis can present similarly and need to be included in the differential diagnosis. Anaphylaxis is a clinical diagnosis but plasma tryptase and urinary histamine levels are often elevated, allowing diagnostic confirmation. However, diagnostic testing should not delay treatment as results may not be immediately available. The sine qua non of treatment is avoidance of any known triggers and epinephrine, which should never be delayed if this disorder is suspected. Secondary treatments include fluids, bronchodilators, antihistamines and glucocorticoids. Patients with cardiopulmonary arrest, airway or vascular compromise require mechanical ventilation, vasopressors and other advanced life support in the ICU.

Introduction

Anaphylaxis and angioedema are serious disorders that can lead to fatal airway obstruction and culminate in cardiorespiratory arrest resulting in hypoxemia and/or shock, requiring management in an intensive care unit (ICU) setting¹⁻³. Recent reports suggest that underdiagnosis and undertreatment of anaphylaxis are common⁴. Anaphylaxis is presumably an ancient disease, though several developments in the last century have led to enormous insights and treatment advances⁵. In the early 20th century, the French physiologist, Charles Richet, along with Paul Portier, undertook a study of hypnotoxin, an urticaria-inducing toxin and other toxins derived from *Physalia* (Portuguese man o'war or "floating terror" found in the Atlantic, Indian and Pacific Oceans) extracts⁶. An important series of experiments were conducted on the dog, Neptune, wherein an initial injection of toxin was followed by a second injection 22 days later. Within minutes of the second injection, Neptune began to gasp, wheeze and collapsed with bloody emesis only to die within 25 minutes. Richet termed the condition "anaphylaxis" as opposed to prophylaxis and was awarded the Nobel prize in Medicine for this work in 1913⁵. Supplemental Table A provides a historical perspective of events leading to our current understanding of anaphylaxis.

Anaphylaxis has been defined as a systemic, immediate hypersensitivity reaction mediated by immunoglobulin E (IgE) and resulting in mast cell and basophil mediator release. This results in multiple clinical effects leading to the diagnosis (Table 1). Anaphylactic reactions result from release of mediators by mast cells and basophils activated either by IgE termed "immunologic" or by direct activation of these cells by certain agents, termed "non-immunologic anaphylaxis"^{1,7-10}. While the term "anaphylactoid" was previously used to describe non-IgE-mediated anaphylaxis, this terminology is no longer recommended¹¹.

Anaphylaxis patterns: Uniphasic, Biphasic and Protracted

Three patterns of anaphylactic syndromes have been described based on the disease expression: uniphasic, biphasic and protracted. Uniphasic type accounts for 70-90% of anaphylaxis cases, peaks at 30-60 minutes and resolves over the next hour with no recurrence of symptoms. Biphasic anaphylaxis is defined by recurrence of symptoms hours after resolution of the initial event in the absence of re-exposure to the trigger¹². Biphasic type has been variably reported to occur in <1¹³ to up to 23% of reactions with a recent report suggesting that 3% of adults and up to 15% of children experience biphasic anaphylaxis¹². Early administration of epinephrine may be beneficial in preventing biphasic reactions; the role of glucocorticoids in preventing this type is unclear but physiologically reasonable. Protracted or persistent anaphylaxis refers to the rare reaction lasting for days or even weeks¹⁴.

Fatal Anaphylaxis and Time to Death

Jerschow et al. examined rates of fatal anaphylaxis in the United States (U.S.) from 1999-2010. Using ICD-10 system diagnostic codes on death certificates, they identified 2458 anaphylaxis-related deaths over an 11-year period with a prevalence of 0.69 people per million¹⁵. In this study population (>96% adult), medication-induced anaphylaxis fatalities were the most frequent (58.8%), followed by “unspecified” (19.3%), venom (15.2%) and food (6.2%). Fatal anaphylaxis in the outpatient setting was most commonly food-induced while drug-induced anaphylaxis was most frequent in the inpatient setting. Two case series reported median time from clinical manifestation to death as 30-35 minutes for food, 10-15 minutes for insect venom, and 5 minutes for intravenous medications^{16;17}.

Epidemiology: Prevalence, hospitalization and anaphylactic shock

Determining the prevalence of anaphylaxis is challenging as it is underdiagnosed¹⁸ and estimates are based on studies with variable study designs that are not always comparable^{4;19}. In

2006, the American College of Allergy Asthma and Immunology Epidemiology of Anaphylaxis Working Group estimated a 0.05% to 2% lifetime prevalence of anaphylaxis²⁰. Children and adolescents made up the largest number of cases based on prescription information of epinephrine auto-injectors²⁰. Multiple studies support the notion that the prevalence of anaphylaxis is increasing, especially in industrialized nations²¹. Wood and colleagues conducted two nationwide, cross-sectional random-digit-dial surveys to estimate lifetime prevalence of anaphylaxis in the U.S. 7.7% of the 1000 adults included in the public survey reported prior anaphylactic reactions and were classified as “possible” anaphylaxis²¹. The study defined “probable” anaphylaxis as reports of allergic symptoms involving two or more organ systems with respiratory and/or cardiovascular involvement and “very likely anaphylaxis” as “probable anaphylaxis” coupled with hospital presentation and a feeling that one’s life was in danger. Using these more stringent criteria for anaphylaxis, this study estimates between 1.6% and 5.1% of adults surveyed have a history of “probable” or “very likely” anaphylaxis²¹. Increasing rates of anaphylaxis have been reported in the United States as well as in Asia^{22;23}. 186-225 deaths/year were reported in the United States by Ma and co-workers²⁴ using multiple cause of death databases. Rohacek et al. reported that of 532 anaphylactic episodes in emergency departments, 507 (45%) had uniphasic and 25 (<5%) had biphasic disease, with 12 of the latter being clinically significant and 1 patient being transferred to the hospital for refractory anaphylaxis²⁵. Jeppensen et al. reviewed anaphylactic shock in a cohort study using a national database from Denmark between 1995 and 2012²³. 6,707 patients had anaphylactic shock, with a 65% hospitalization rate that increased 2-fold during the observation period in adults and 10-fold in children. 15% were admitted to the ICU and 0.7% (50 patients) died of the disease. Between 2005 and 2009, there were 81 pediatric and 1269 adult admissions with anaphylaxis admitted to

UK critical care units with a 90% survival rate²⁶. The authors noted increased absolute numbers of patients admitted for anaphylaxis each year of the study period, with female predominance in adult patient admissions.

Mechanisms

Anaphylaxis results from activation of inflammatory pathways (**Figure 1**) which are the result of mast cell and/or basophil degranulation²⁷. The traditional pathway is mediated via T cells, T helper cell 2 (Th2) cytokines (such as IL-4 and 5), B cell production of IgE and subsequent crosslinking of the high affinity IgE receptor on mast cells and basophils by IgE-antigen complexes. Other triggers could also lead to mast cell and basophil degranulation in a non-IgE dependent fashion, including IgG immune complexes, complement products, neuropeptides, opiates and radiocontrast media. Direct activation is secondary to drugs such as ibrutinib, fluoroquinolones and several neuromuscular blocking drugs.

These triggers result in activation of a signaling cascade, culminating in mast cell and basophil degranulation^{27;28}. The mediators expressed result in capillary leak, inflammatory cell recruitment as well as in the plethora of cardiopulmonary sequelae of anaphylaxis²⁷. In select situations, activation of the kinin pathway can lead to a mast cell-independent activation of vascular leakage, as described in reactions to contaminated Chinese heparin. Anaphylaxis with resultant inflammation and endothelial activation can result in recruitment of other inflammatory pathways that can amplify the pathophysiological processes. These include complement, kallikrein-kinin and coagulation pathways²⁷⁻²⁹. The role of platelets and platelet activating factor (PAF) is receiving renewed interest since recent publications suggested that deficiency of PAF acetyl-hydrolase could lead to more severe anaphylaxis in a PAF-dependent manner^{30;31}.

Anaphylactic shock and myocardial depression

The onset of shock in anaphylaxis is often rapid and multifaceted, comprised of features from cardiogenic, hypovolemic and distributive shock states. Hypovolemia and distributive shock result in the historically termed “empty heart syndrome.” Massive cytokine release results in extensive capillary leak and third spaced fluid with intravascular volume depletion. Histamine, tumor necrosis factor alpha (TNF α), prostanoids and interleukins can also produce vasoplegia with venous fluid sequestration. Taken together these processes decrease venous return and produce low cardiac filling pressures. Normally in these types of shock, tachycardia and increased stroke volume drives an increased cardiac output (CO) to preserve systemic perfusion, but this offers only a partial compensation, and only if sufficient cardiac pre-load and function exists. Anaphylactic shock is particularly problematic in this setting, as myocardial suppression and relative bradycardia are common features³².

Cardiogenic components of anaphylaxis are complex and not completely elucidated in the literature. They include myocardial depression, bradycardia, ischemia, diastolic and systolic impairment³³. Myocardial depression occurs secondary to the release of vasodepressor substances in anaphylaxis, including prostanoids and leukotrienes or some inflammatory cytokines (proposed mechanism). The role of cardiac mast cells in anaphylaxis has not been rigorously studied, but some data suggest coronary vasospasm with micro ischemia produce reduced systolic and diastolic function from histamine and PAF release³⁴. The Kounis syndrome refers to acute coronary syndrome occurring as a complication of anaphylactic reactions and may occur as vasospastic disease or atherothrombotic coronary disease³³. Finally, classical (transient hypo- or akinesis of the apical left ventricle) or reverse takotsubo syndromes (transient hypo- or akinesis of basal and mid-ventricular segments) have been implicated in case

reports and series³³. Combined distributive, hypovolemic and cardiogenic features can produce a profound state of mixed shock.

Anaphylactic shock refractory to vasopressors like epinephrine is a rare but ominous occurrence. It is presumably mediated by histamine activation of signaling pathways resulting in the production of endothelium-derived nitric oxide (NO). NO increases synthesis of the endogenous vasodilator cyclic guanylate monophosphate (cGMP) by activating guanylate cyclase. Animal studies have shown this process can be blocked by administering IV methylene blue, which competitively inhibits guanylate cyclase and reduces cGMP production³⁵. Myocardial depression and hypotension can lead to cerebral and renal hypoperfusion, with the former leading to syncope and seizures and the latter to renal insufficiency.

Classification and Etiology of Anaphylaxis

Table 2 discusses the classification and categories of anaphylaxis.

Immunologic IgE-mediated reactions

These include allergic reactions to food, airborne allergens such as pollen, animal dander and aerosolized foods, latex, medications (oral or parenteral), food dependent exercise-induced anaphylaxis (FDEIA), allergy to mammalian sugars like galactose-1,3-alpha-galactose (alpha-gal), anaphylaxis to seminal fluid and hormones (i.e. catamenial or progesterone-related anaphylaxis), and rarely, radiocontrast media reactions (**Table 2**). Common foods that trigger anaphylaxis include milk, egg, wheat, soy, fin fish, shellfish and nuts^{36;37}. Venoms (such as hymenoptera or imported fire ant) are common causes of anaphylaxis. Medications associated with IgE-mediated anaphylaxis include beta-lactams, cephalosporins, vancomycin, quinolones, and sulfonamides. Anesthetic drugs such as suxamethonium, pancuronium and atracurium have

also been implicated in perioperative anaphylaxis³⁸. Rarely, NSAIDs can cause anaphylaxis by an IgE-mediated mechanism³⁹. Fatal and near-fatal allergic reactions occur with 0.1-0.4% of all administered injections of subcutaneous immunotherapy with higher rates witnessed in accelerated or rush protocols. Reactions to newer biological agents and monoclonal antibodies have also been described⁴⁰.

Immunologic Non-IgE-mediated Reactions

Anaphylaxis has been reported to intravenous immunoglobulins⁴¹, NSAIDs³⁹, dialysis membranes⁴², dextrans, iron⁴³, biological agents and heparin. In the case of dialysis-associated anaphylaxis, most hypersensitivity reactions to components of the dialysis circuit are due to ethylene oxide or complement activating bio-incompatible membranes, while anaphylaxis to erythropoietin, latex, heparin and medications have also been recorded⁴².

Non-immunologic Anaphylactic Reactions

Non-immunologic triggers for anaphylaxis including physical factors (like exercise, cold, heat) and iatrogenic agents (including radiocontrast media and opiates) that can stimulate direct mast cell degranulation^{44;45}. In primary mast cell disorders, mast cells can degranulate both independently and in response to allergens such as foods and medications⁴⁶.

Specific Syndromes and Disorders Associated with Anaphylaxis

Varying degrees of anaphylaxis can accompany exercise in some individuals⁴⁵. The early prodrome during exercise include a sense of fatigue and warmth, flushing or generalized pruritus followed in sequence by urticaria, angioedema, bronchospasm, airway obstruction and vascular collapse⁴⁷. Some patients experience food-dependent exercise induced anaphylaxis, in

which anaphylaxis occurs only when preceded by food ingestion, especially foods to which the individual is allergic.

Individuals with severe adverse reactions to the oligosaccharide, alpha-gal, present in mammalian meats and in the chemotherapeutic medication cetuximab were recently described. These patients present with urticaria or delayed anaphylactic reactions to red meat (DARM) and often have a preceding history of tick bites^{36;48;49}. In the U.S., these patients often volunteer a history of pruritic tick bites by the Lone Star tick (*Amblyomma americanum*). The development of urticaria and anaphylaxis 3-5 hours after mammalian meat ingestion is consistent with the disorder^{50;51}. The pork-cat syndrome refers to sensitization to cat albumin that leads to cross-reactivity with pork albumin and resultant allergic reactions and anaphylaxis⁵². The bird-egg syndrome refers to cross-reactivity between proteins present in egg yolk and tissue albumin present in muscle tissue of birds⁵³. The protein alpha-livetin [also referred to as chicken serum albumin (Gal d 5)], is the allergen component in egg yolk that is involved in anaphylactic manifestations of the bird-egg syndrome.

In 2008, a world-wide recall of Chinese heparin was initiated based on severe anaphylactic reactions triggered by a contaminant, oversulfated chondroitin sulfate (OSCS), in several countries^{29;54}. Activation of the contact system culminating in kallikrein pathway activation and resultant bradykinin generation was deemed a likely mechanism⁵⁵.

It is estimated that 30-60% of patients presenting with anaphylaxis may have no obvious etiological trigger to explain the disease and hence are described as having idiopathic anaphylaxis (IA)-a diagnosis of exclusion⁵⁶⁻⁵⁸. Recent advances in pathophysiology have delineated novel etiologies, including mast cell activation disorders, hormone sensitivity syndromes (including catamenial anaphylaxis) and allergy to alpha-gal.

Mast cell activation disorders may be primary (including clonal disorders such as systemic mastocytosis/SM and monoclonal mast cell activation syndrome/MMAS), secondary (activation of mast cells by IgE-mediated allergic reactions) or idiopathic (such as the idiopathic mast cell activation syndrome/MCAS, idiopathic urticaria and idiopathic anaphylaxis/IA)^{46;59}. Patients with mastocytosis are more likely to develop anaphylactic reactions to hymenoptera stings⁶⁰. Confirmation of the diagnosis relies on evaluation of bone marrow and/or extra-cutaneous tissue biopsies. Indications for bone marrow evaluation include adult patients with urticaria pigmentosa (UP), patients with a baseline tryptase >20 ng/mL, recurrent hypotensive or syncopal episodes regardless of tryptase levels, hymenoptera anaphylaxis with tryptase >11.4 ng/mL and patients with REMA score ≥ 2 . REMA (Spanish Network on Mastocytosis) score is based on gender, clinical symptoms and tryptase levels. The management of mast cell activation disorders is similar to the management of anaphylaxis in general. Supplemental Table B discusses the evaluation of mast cell activation disorders.

Progesterone hypersensitivity can result in symptoms ranging from dermatitis to cyclical anaphylaxis during the luteal phase of the menstrual cycle⁶¹. The patients are usually young women with recurrent perimenstrual anaphylactic events⁶². Allergic reactions to human seminal fluid have been described in women manifesting as local urticaria and pruritus to florid anaphylaxis and death^{63;64}.

Clinical Presentation

Clinical manifestations are listed in **Table 3**. Almost every system can be involved. Severe presentations of anaphylaxis characterized by hypotension and/or hypoxemia and indicating cardiovascular and respiratory compromise have been associated with older age, pre-existing lung disease, and anti-hypertensive medications in one prospective study of anaphylaxis

³⁰. While mucocutaneous manifestations (**Figure 2**) occur in the majority of patients, they are absent in 10-20% of patients, including those who present with fatal or near fatal anaphylaxis⁶⁵. Risk factors for anaphylaxis are listed in **Table 4**⁶⁶.

Differential Diagnosis

Many conditions may mimic anaphylaxis or be accompanied by systemic manifestations that resemble allergy and need to be considered in the differential diagnosis. Important disorders that require consideration includes capillary leak, postural orthostatic tachycardia syndrome (POTS), carcinoid syndrome, neuroendocrine tumors, factitious anaphylaxis and undifferentiated somatoform anaphylaxis⁶⁷⁻⁷⁰. These disorders and their evaluation are summarized in **Table 5**.

Diagnostic Testing: Tryptase and Histamine

Total serum tryptase is the biomarker most widely used to confirm a diagnosis of anaphylaxis retrospectively⁷¹. Small amounts of the immature form of tryptase (beta-tryptase) are constitutively secreted into the systemic circulation. Following mast cell and basophil degranulation, total serum tryptase levels increase significantly due to release of mature beta-tryptase. Ideally, serum tryptase should be measured within 1 to 2 hours after symptom onset, since tryptase levels typically peak within 60-90 minutes after symptom onset but can persist for 6 hours⁷².

Plasma histamine levels rise 5 to 10 minutes after the onset of anaphylaxis and can also be assayed. However, plasma histamine levels are only transiently elevated, returning to normal within 60 minutes, making them of little utility if the patient is evaluated greater than 1 hour after symptom onset. 24-hour urinary histamine metabolites may be elevated for up to 24 hours after the index event.

Vadas and colleagues have shown that serum histamine and tryptase levels are not always elevated, even in patients with severe manifestations of anaphylaxis including cutaneous, gastrointestinal and respiratory or cardiovascular compromise³¹. In addition, serum tryptase levels are not always elevated during food-induced anaphylaxis⁶⁵. As a result, there is growing interest in identifying alternative serum biomarkers like platelet-activating factor or carboxypeptidase A3 that more accurately confirm the diagnosis of anaphylaxis and correlate with severity but these have not yet been developed for clinical use³¹.

Other diagnostic tests to consider are those that help evaluate for mimics of anaphylaxis and these are listed in Table 5⁸. If the clinical history is suspicious for IgE-mediated anaphylaxis, allergy testing (serum or epicutaneous) is indicated to identify the trigger and often requires referral to a board certified allergist-immunologist³⁷. This could be accomplished emergently in the ICU or as an outpatient after discharge.

Management

Anaphylaxis is considered a medical emergency with its immediate onset (seconds to minutes) and rapid progression to cardiovascular and/or respiratory collapse resulting in death within minutes of inception. Initial management principles are the same whether the patient is being managed in the outpatient, emergency room, operating room or hospital setting, since anaphylaxis can occur in any of these locations and are summarized in **Table 6**. Patients with more severe cardiorespiratory complications are best managed in an intensive care unit. **Tables 6 and 7** provide outlines in management and drug dosages respectively. **Figure 3** demonstrates medications commonly used in the management of anaphylaxis that all medical facilities and intensive care unit should have readily available.

Immediate measures (First-line treatment)

1. The immediate administration of 0.3 – 0.5mg of epinephrine (1:1000) in the antero-lateral aspect of the mid vastas lateralis muscle (VLM) is the most essential intervention (**Figure 3**). This may need to be repeated every 5-15 minutes^{1;7;8;73}. Studies show absorption is faster with higher tissue and plasma levels when injected in the VLM compared to other muscles or following subcutaneous administration^{1;7;8;73}. In emergencies, an epinephrine auto-injector may be used, realizing that the dose is fixed (0.3 mg in adult and 0.15 mg in children weighing below 15 Kg). In obese individuals, auto-injector needle length may not be sufficient for intramuscular epinephrine delivery⁷⁴.
2. Removal of the potential triggering antigen, placing the patient in a supine position and quickly addressing circulation-airway-breathing are critical. The position of the anaphylactic patient can have important implications. Vasodilation and hypovolemia prevail in anaphylaxis. As such, patients are extremely sensitive to fluid shifts and sudden postural changes can result in fatal cardiac arrest⁷⁵. Despite the lack of prospective data, there is uniform agreement that patients should be placed in the supine position unless contraindicated by active vomiting, respiratory distress or pregnancy; in which case the left lateral decubitus position is more appropriate^{3;8;75;76}. Elevation of the legs (or the Trendelenburg position using a tilting table) remains controversial. This position may play a role initially while the patient is undergoing fluid resuscitation if no vasopressors are available⁷⁷. It is important to note that this position is seldom used in the ICU (other than during procedures) as vasopressors and IV fluids are more effective and readily available⁸.
3. In the event of respiratory distress the patient should be placed in a position of comfort and restrictive clothing should be removed or loosened. A short acting β_2 agonist bronchodilator

(albuterol) should be administered as 2.5 or 5 mg in 3 mL nebulized or 2 puffs of a metered dose inhaler (MDI) every 2-4 hours until symptomatic relief or patient reaches a higher level of care¹⁰.

4. Intravenous (IV) access needs to be established using large bore catheters and fluids administered as rapidly as possible. Intraosseous (IO) access is an acceptable alternative.

Adjunctive therapies

Antihistamines (Antagonists- H_1 & H_2) as well as corticosteroids are considered adjunctive treatments and some guideline statements regard them as “optional” therapy. The administration of these treatments should never delay the administration of epinephrine^{8, 7, 10, 3}. Unfortunately, one of the most common reasons for delay of epinephrine administration is that caretakers “wait to see if the antihistamine will work.” This can be a fatal management error⁸. During anaphylaxis, antihistamines are effective only in treating cutaneous symptoms such as pruritus and urticaria⁷. It is worth noting that a recent retrospective Canadian study demonstrated that the use of H_1 antagonists in the emergency department on patients that had an allergic reaction without evidence of anaphylaxis reduced the likelihood that those patients progressed to anaphylaxis. The limits of this study should be acknowledged and epinephrine is still the first and only effective pharmacologic treatment for anaphylaxis^{10;78}.

Additional measures (In hospital/ICU)

Management of respiratory complications: Asphyxia/Respiratory compromise

Any patient with impending respiratory failure, evidence of obstructing oropharyngeal or laryngeal edema should undergo prompt endotracheal intubation with the most advanced airway tools available, by the most experienced provider trained to do so (ideally without paralytic so

the patient is still spontaneously breathing)². No published reports formally support this practice, but we strongly recommend an awake, fiberoptic intubation if laryngeal edema is suspected. Fiberoptic intubation requires special equipment and an operator skilled in this technique. The placement of a surgical airway such as a cricothyrotomy or tracheostomy should be a last resort, but should not be delayed if it is necessary, as in circumstances of significant upper airway obstruction.

We recommend against the use of non-invasive positive pressure ventilation, or a supraglottic airway such as a laryngeal mask airway (LMA) unless angioedema of the larynx and vocal folds has been ruled out by laryngoscopy (or there are no other airway options). These devices will not bypass the upper airway obstruction and local trauma could exacerbate angioedema of the larynx (if present), worsening the blockage and precipitating respiratory arrest².

Racemic epinephrine can be administered by nebulizer to decrease laryngeal edema and to facilitate intubation³. In some reports, epinephrine has been introduced by endotracheal administration or sublingually when there has been a delay in procuring IV access³. During intubation and mechanical ventilation, care should be taken to avoid use of sedatives or medications that lower blood pressure. Minimizing breath stacking and avoiding barotrauma are also essential to prevent further deterioration. Ketamine use in anaphylaxis has been associated with bronchodilation.

Refractory hypotension

Volume resuscitation (30cc/kg) should be initiated immediately with isotonic crystalloid fluid through multiple, large bore (≥ 20 gauge) angio-catheters, after which time supplementation

with colloid solutions has been suggested^{1;3;7;8;10}. During refractory shock in patients using beta blockers, glucagon can be administered. Glucagon bypasses the β_2 adrenergic receptor directly activating adenylyl cyclase, producing positive inotropy, bronchodilation and vasoconstriction⁸. Glucagon can be administered by slow IV push in doses of 1-5 mg in the adult followed by 5-15 mcg/min by IV infusion⁷⁹. Glucagon is associated with nausea, vomiting and hypoglycemia.

Patients who remain hypotensive or who have a recurrence of symptoms despite ≥ 2 doses of bolus epinephrine and adequate fluid resuscitation should be started on an epinephrine infusion, administered cautiously with adequate monitoring. Epinephrine is a α_1 -, β_1 - and β_2 -adrenergic receptor agonist that increases systemic vascular resistance, enhances cardiac chronotropy as well as inotropy (increasing cardiac output) and produces pulmonary bronchodilation^{3;73}. Epinephrine should be infused via a central venous catheter or intraosseous needle if possible^{1;7;8;76;80}. A 1:1,000,000 infusion solution needs to be compounded by the pharmacy-by diluting 1 mL of a 1:1000 concentration of epinephrine in 1000 mL of either 5% dextrose (avoid if using glucagon) or normal saline, resulting in a 1 mcg/mL concentration. This can be infused at 1-10 mcg/minute, titrating to mean arterial pressure >65 mmHg.

In rare cases where rapid deterioration is occurring, epinephrine can be administered by bolus injection (50 mcg or 0.5 mL of a 1:10,000 dilution by slow IV/IO push) or 1 mL of 1:1000 IV/IO bolus in the event of impending or current cardiac arrest. Adverse effects of epinephrine include anxiety, flushing, tachycardia, atrial or ventricular dysrhythmias, cerebrovascular accident (CVA) and hypertension. Special preparations may be available in the rare sulfite-allergic individual. Occasionally, patients may benefit from an infusion of adjuvant vasopressor to epinephrine in refractory anaphylactic shock. Vasopressin and/or phenylephrine can be used to increase systemic vascular resistance (SVR) without contributing to excessive tachycardia. If the

patient is relatively bradycardic, then norepinephrine or dopamine can be added. There has been anecdotal success in treating refractory anaphylaxis with methylene blue where synergy with epinephrine has been described, realizing that on rare occasions, methylene blue itself has been incriminated in inducing anaphylaxis^{35,81}.

Extra-corporeal life support (ECLS)

Anaphylactic shock refractory to multiple modalities; or in situations of catastrophic reductions in cardiac function may be treated effectively with veno-arterial ECLS which produces the best cardiac flow, aortic pressures and myocardial perfusion³. There are no prospective or trial data supporting the use of ECLS in patients with anaphylaxis⁸². The major limitation of this modality is that it requires advanced equipment and personnel trained in its proper use, which may only be available in tertiary care centers. ECLS also requires use of heparin and possibly protamine, which have both been linked to severe anaphylaxis⁷.

Conclusion

Anaphylaxis is a rapidly progressive life threatening disorder. It is often under-recognized and undertreated. Early recognition, high index of suspicion, early removal of potential triggers and administration of epinephrine can be life-saving. Skilled intervention in intensive care units may be required for the patient with complicated, prolonged or severe anaphylaxis.

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Table 1. Criteria for Diagnosis of Anaphylaxis

Anaphylaxis is highly likely if any ONE of the following 3 conditions is satisfied:

1	Acute onset of illness with: Mucocutaneous involvement (pruritus, flushing, urticaria, angioedema) AND one of the following: A. Respiratory complications (wheezing, stridor, hypoxemia/cyanosis) B. Hypotension* or end organ damage (encephalopathy, kidney injury, etc.)
2	Two or more of the following occurring rapidly after exposure to KNOWN or LIKELY allergen: • Mucocutaneous involvement (pruritus, flushing, urticaria, angioedema) • Respiratory complications (wheezing, stridor, hypoxemia/cyanosis) • Hypotension* or evidence of end organ hypoperfusion (encephalopathy, kidney injury, etc.) • Persistent gastrointestinal symptoms (pain, nausea, vomiting)
3	Reduced blood pressure soon after exposure to a KNOWN allergen.

*Hypotension in adults is regarded as systolic blood pressure of <90 mm Hg or greater than a 30% decrease in systolic blood pressure from the patient's baseline. Hypotension in infants and children: systolic blood pressure <70 mm Hg (1-12 months); <(70mm Hg + [2x age]) (1-10 years); <90 mm Hg (11-17 years); or >30% decrease in systolic blood pressure

Table 2. Classification of Anaphylaxis according to causative mechanism

Mechanism	Examples	Comments
Immunologic-IgE (Secondary MCD)	Food allergens ¹ Airborne allergens Latex Hymenoptera venom Medication allergy Alpha-Gal FDEIA Hormones Seminal fluid Radiocontrast media*	8 common food allergens listed below Animal dander, aerosolized foods, pollen Gloves, catheters, masks, medication vials Honey bee, wasp, yellow jacket, hornet, IFA Antibiotics, biologicals*, vaccines, NSAID* Mammalian meat (beef, pork, venison, lamb) Exercise + food (wheat, nuts, legumes etc) Progesterone or estrogens (catamenial) Post-coital anaphylaxis IgE-mediated reactions have been reported.
Immunologic-Non-IgE	Immune aggregates IVIG Aspirin and NSAID* Dialysis membranes Radiocontrast media* Dextran/HMW iron Biologics* Heparin	Includes immune complexes/complement Due to IgG or IgE anti-IgA antibodies Leukotriene-driven and other mechanisms Complement activation, kinin generation Cytokine inhibitors, Omalizumab etc Generation of kinins by contaminated Chinese heparin
Non-immunologic		
Direct effects Primary MCD ²	Opiates, Physical MMAS and systemic mastocytosis	Cold, heat, exercise, sunlight Genetic defects affect proliferation or activation pathways
MCAS ²		Can be associated with germline replications of TBSAB gene encoding α -tryptase ³
Idiopathic		Increased mast cell sensitivity/degranulation Th2-cytokine polarization Unrecognized allergens
Masqueraders	Munchausen stridor Undifferentiated somatoform anaphylaxis Vocal cord dysfunction	

FDEIA=food dependent exercise-induced anaphylaxis; IFA=imported fire ant; MCD=mast cell activating disorder; MMAS=monoclonal mast cell activation syndrome; MCAS=mast cell activation syndrome; IVIG=immunoglobulin, intravenous; NSAID=nonsteroidal anti-inflammatory drugs; HMW=High Molecular Weight

*=Both IgE-mediated and non-IgE mediated reactions have been reported

1=Milk, egg, wheat, soy, tree nuts, peanut, shellfish and fin fish are commonly incriminated

2=Mast cell disorders are associated with both IgE-mediated allergic reactions as well as spontaneous mast cell degranulation

3= Lyons JJ et al., Nat Genet. 2016 Dec;48(12):1564-1569.

Table 3. Clinical features of anaphylaxis.

Organ system	Presentation	Sequelae
Skin/Mucosa (80-90%)	Urticarial eruption Angioedema -Oropharyngeal -Laryngeal -Intestinal Flushing Pruritus (palms/soles/oral/genitalia)	Hypovolemia Airway obstruction Stridor Airway obstruction Abdominal pain Hypotension
Bronchopulmonary (60-70%)	Laryngeal edema Wheeze/Cough Rhinitis	Hoarseness/Stridor Dysphonia Respiratory failure Hypoxemia/Cyanosis Nasal obstruction
Cardiac (40-50%)	Vasodilation/Reduced SVR Myocardial vasoconstriction Myocardial Depression	Hypotension/Shock Reduced CO Myocardial ischemia Arrhythmia Cardiac arrest
Gastrointestinal (40-50%)	Nausea, Vomiting Diarrhea Intestinal edema	Dehydration Hypovolemia Abdominal pain
Neurological (<15%)	Dizziness Confusion Headache Feeling of impending doom Tunnel vision	Syncope Seizures
Genitourinary	Uterine cramps (♀) Uterine bleeding (♀) Scrotal Edema (♂)	Pain Pain
Miscellaneous	Urinary/Fecal incontinence	

Key: CO=Cardiac Output; SVR=Systemic Vascular Resistance

Prevalence of symptom cluster is showed as percentages (%)

Table 4. Risk factors for anaphylaxis and disease severity.**Risk factors for anaphylaxis**

1. Age:	Males <15 years and females >15 years of age.
2. Route of allergen introduction:	Parenteral > ingested.
3. Interruption of medication:	Example insulin interruption after desensitization.
4. Atopic history:	Example latex anaphylaxis, RCM, EIA and IA
5. Prior exposure:	Example protamine/zinc insulin (NPH) use and reaction to protamine used for heparin reversal
6. Asthma:	More severe asthma increases risk for anaphylaxis.
7. Geography:	Higher incidence in Northern latitudes.
8. Gender:	Latex, aspirin and certain medication reactions more common in women. Venom reactions more common in men.

Risk factors for severe anaphylaxis

1. Infants and elderly	
2. Comorbidity:	Asthma, Ischemic dilated cardiomyopathy, CAD.
3. Medication use:	Anti-hypertensive medications* Monoamine oxidase inhibitors and tricyclic anti-depressants
4. Impaired cognition:	Alcohol, sedative medications, recreational drugs

*Beta-adrenergic blockers, Calcium channel blockers, Angiotensin converting enzyme inhibitors, Angiotensin receptor blockers, Direct renin inhibitors.

Key: RCM=Radiocontrast Media; EIA=Exercise Induced Anaphylaxis; IA = Idiopathic Anaphylaxis; NPH=Neutral Protamine Hagedorn; CAD=Coronary Artery Disease;

Table 5. Differential Diagnosis of Anaphylaxis

Neurologic / Autonomic Dysregulation		Suggested tests
1. Vasovagal and vasodepressor reactions		Clinical/EKG/BP
2. Postural Orthostatic Tachycardia Syndrome (POTS)		Tilt table testing
3. Seizure		EEG
4. Cerebrovascular Accident (CVA)		CT or MRI of the brain
Cardiovascular		
1. Cardiogenic Shock		TTE or RHC
2. Hemorrhagic Shock		Clinical bleeding/CBC*
3. Vasodilatory/Distributive/Endotoxic Shock		Bacterial cultures
4. Capillary Leak Syndrome (Hypovolemic Shock)		Paraproteinemia
Endocrine/Flushing		
1. Carcinoid		Urine 5-HIAA
2. Pheochromocytoma		Urine/serum catecholamines
3. Vasoactive intestinal polypeptide secreting tumors		VIP level
4. Thyroid medullary carcinoma		Serum calcitonin
5. Menopause (flushing, hot flashes)		LH, FSH, estrogen level
6. Hypoglycemia		Blood sugar
Iatrogenic / Drugs		
1. Vancomycin (Red Man syndrome)		History/Clinical
2. Niacin (flushing)		History/Clinical
3. General anesthetics (hypotension)		History/Clinical
Toxic		
1. "Restaurant Syndromes"		
a. Scombroidosis		History/Tryptase/Histamine
b. Monosodium Glutamate (MSG)		Toxicology
2. Alcohol		EtOH level/Osmolar Gap ^{&}
3. Sulfites		Clinical/Toxicology
Hematologic / Malignant^{\$}		
1. Systemic mastocytosis		Tryptase, bone marrow
2. Urticaria pigmentosa		Skin biopsy, tryptase
3. Basophil leukemia		Bone marrow
4. Acute promyelocytic leukemia with tretinoin treatment		Bone marrow
Immunologic		
1. Bradykinin-mediated angioedema		C4, C1 inhibitor levels
Infection		
1. Hydatid cyst (Echinococcus granulosus)		Clinical, serology, radiology
2. Sepsis/Septic Shock		Blood cultures
Psychosomatic / Functional disorders		
1. Panic attack		Psychiatric consultation
2. Factitious Anaphylaxis		
a. Munchausen's stridor		Psychiatric consultation
3. Undifferentiated somatoform anaphylaxis		Psychiatric consultation
4. Vocal cord dysfunction		Spirometry/Flow volume loop

*CBC=Complete Blood Count and may be normal in acute loss of whole blood

&Osmolar gap = allows for the assessment of other toxic alcohols

^{\$}Clonal and malignant mast cell disorders often demonstrate mutations of stem cell factor receptor, c-kit
 Key: ACE=Angiotensin Converting Enzyme; 5-HIAA=urine 5-hydroxy indole acetic acid; LH=lutenizing hormone; FSH=follicle stimulating hormone; EKG=electrocardiogram; BP = Blood Pressure; CT=computerized tomography; MRI=magnetic resonance imaging; EEG=electroencephalography; TTE=transthoracic echocardiogram; RHC=Right Heart Catheterization; VIP=Vasoactive Intestinal Peptide; EtOH=Ethanol; C1=Complement 1; C4=Complement 4.

Table 6. Overall Approaches to Managing Systemic Anaphylaxis

Initial Management (Office/Emergency Room/Hospital)	Level of Evidence
Base diagnosis on clinical assessment	C
Early intervention is recommended	
Assess risk for serious/fatal reactions (See Table 7)	C
Immediate general measures (First-line treatment)	
Place patient in supine position	C
Remove inciting trigger/allergen	C
Address circulation-airway-breathing	C
Epinephrine administration (ALVLM, intramuscular) (1 ml/kg of 1:1000 epinephrine or 0.3-0.5 mg)	B
1. Repeat up to 3 injections every 5-15 minutes	
2. If patient is not responding to IM epinephrine move patient to monitored setting and attempt intravenous (IV) epinephrine	C
3. If IV access is difficult to obtain, then obtain Intraosseous (IO) access and administer epinephrine	D
Airway management	C
Oxygen (up to 100% by face mask)	D
Administer nebulized albuterol for bronchospasm	B
Prepare for intubation if stridor or airway compromise	
Administer IV fluids/crystalloids rapidly	B
30cc/kg with large bore catheters in first hour for hypotension – if volume responsive, continue fluids.	
Adjunctive therapies (After epinephrine is administered)	
Administer H1 antihistamine ^s	B
Administer H2 antihistamine [%]	B
Administer corticosteroids	
Methylprednisolone (1-2 mg/Kg) IV	B
Additional measures (Hospital/Intensive Care Unit)	
Refractory hypotension	
After beta-blockade	
Glucagon (1-5 mg slow IV in adults) followed by IV infusion of 5-15 mcg/min (caution due to emesis)	B
After several doses of IM epinephrine	
Continuous IV infusion of epinephrine	C
(Mix 1 mL of 1:1000 epinephrine in 1000 mL of 5% dextrose or 0.9 normal saline; infuse at 1 mcg/min to maximum of 10 mcg/min)	
Bolus epinephrine: For impending cardiovascular collapse (50 mcg/0.5 mL of 1:10,000 slow IV push)	
Consider other pressors- including dopamine or vasopressin	
Asphyxia/Respiratory compromise/Respiratory arrest	

Oxygenation

Evaluation of airway for extent of edema

Nebulized/racemic epinephrine (0.5 mL of 2.25% every 20 minutes for stridor)

Intubation/post-intubation ventilator management

C

Avoid medications that lower BP

Avoid paralytics if possible for intubation

Recommend awake fiberoptic intubation if possible.

(If laryngeal involvement is suspected)

Sedate and allow adequate expiration time

Minimize breath stacking and barotrauma

Ketamine use is associated with bronchodilatation

(Caution advised with ketamine in cardiac patients)

For difficult airway, consider cricothyroidotomy**Extracorporeal membrane oxygenation**

D

Consider when response is poor

Consider early and often if patient limited responsive to vasopressors

Post-Discharge management**Education**

Trigger detection and avoidance

Anaphylaxis action plan

Prescription of an epinephrine autoinjector

Key: ALVLM – Anterolateral Vastus Lateralis Muscle.

\$ ie: Diphenhydramine 1-2 mg/kg

% ie: Ranitidine 1-2 mg/kg

(Grades of recommendation are based on levels of evidence: A= randomized studies; B=controlled study without randomization; C=case control, comparative or correlation studies; D=expert opinion/reports or based on experience of authorities): strong recommendation (grade A), moderate recommendation (grades B and C) and weak recommendation (grade D).

Adapted from: Campbell RL, Li JT, Nicklas RA et al. Emergency department diagnosis and treatment of anaphylaxis: a practice parameter. Ann Allergy Asthma Immunol 2014; 113(6):599-608.

Table 7. Medications used in anaphylaxis management.

Medication effects	Concentration	Dose	Route	Frequency	Adverse effects
Epinephrine	1:1000 (1mg/mL)	0.01 mg/kg 0.5 mg (0.5mL)	IM	Every 5-15min	Tachycardia, Palpitations, Tachyarrhythmia, Anxiety, Palpitations, Flushing
	1:10,000 (0.1mg/mL)	0.01 mg/kg 0.5mg (5mL)	IV	Every 5-15min Continuous	As above
Vasopressin	N/A	0.04U	IV	Per minute	Ischemia
Dopamine	N/A	1-50 mcg/kg	IV	Per minute	Tachycardia, Tachyarrhythmia
Norepinephrine	N/A	0.02-1 mcg/kg	IV	Per minute	Tachycardia, Tachyarrhythmia
Albuterol MDA	2.5mg per puff	1-2 puffs (2.5-5 mg)	INH	Every 2-4hrs	Tachycardia, Palpitations, Anxiety
Nebulized	2.5mg/3mL	3 mL	INH	Every 2-4hrs	As above
	5mg/3mL	3 mL	INH	Continuous	As above
Glucagon		1-5 mg*	IV	Once	Nausea, vomiting,
		5-15 mcg/min	IV	Continuous	Tachycardia
Diphenhydramine Treatment	N/A	25-50 mg	IV, PO**	Once	Drowsiness, Sedation
Prophylaxis	N/A	25-50 mg		Once ^{\$}	
Corticosteroids Hydrocortisone	N/A	100 mg	IV	Every 8hrs	Hyperglycemia
Prednisone ^{&} Treatment	N/A	1-2 mg/kg	PO**	Once	Agitation, Anxiety, Psychosis
Prophylaxis	N/A	50 mg	PO**	13hrs then, 7hrs then, 1hr before	As above

*= Infuse slowly over 2-5min to minimize nausea and vomiting.

**= Avoid PO medications in patients who are nauseated, vomiting or unable to protect their airway (unless intubated and gastric tube in place).

\$= 1hr before procedure

&= Intravenous alternatives should be dosed in prednisone equivalents.

