

Critical Care Management of the Patient With Anaphylaxis: A Concise Definitive Review

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OBJECTIVES: Anaphylaxis is a rapidly progressive life-threatening syndrome manifesting as pruritus, urticaria, angioedema, bronchospasm and shock. The goal of this synthetic review is to provide a practical, updated approach to the evaluation and management of this disorder and associated complications.

DATA SOURCES: A MEDLINE search was conducted with the MeSH of anaphylaxis, anaphylactic reaction, anaphylactic shock, refractory anaphylaxis and subheadings of diagnosis, classification, epidemiology, complications and pharmacology. The level of evidence supporting an intervention was evaluated based on the availability of randomized studies, expert opinion, case studies, reviews, practice parameters and other databases (including Cochrane).

STUDY SELECTION: Selected publications describing anaphylaxis, clinical trials, diagnosis, mechanisms, risk factors and management were retrieved (reviews, guidelines, clinical trials, case series) and their bibliographies were also reviewed to identify relevant publications.

DATA EXTRACTION: Data from the relevant publications were reviewed, summarized and the information synthesized.

DATA SYNTHESIS: This is a synthetic review and the data obtained from a literature review was utilized to describe current trends in the diagnosis and management of the patient with anaphylaxis with a special emphasis on newer evolving concepts of anaphylaxis endotypes and phenotypes, management of refractory anaphylaxis in the ICU setting and review of therapeutic options for the elderly patient, or the complicated patient with severe cardiorespiratory complications. Most of the recommendations come from practice parameters, case studies or expert opinions, with a dearth of randomized trials to support specific interventions.

CONCLUSION: Anaphylaxis is a rapidly progressive life-threatening disorder. The critical care physician needs to be familiar with the diagnosis, differential diagnosis, evaluation, and management of anaphylaxis. Skilled intervention in ICUs may be required for the patient with complicated, severe, or refractory anaphylaxis.

KEY WORDS: allergic reaction; anaphylactic shock; anaphylaxis; angioedema; epinephrine; food allergy

Anaphylaxis refers to an acute onset illness characterized by involvement of the skin, mucosa, respiratory, gastrointestinal, and cardiovascular systems in various combinations (**Fig. 1**). This results from a systemic, immediate hypersensitivity reaction mediated by the release of a plethora of mediators by mast cells and basophils in response to immune and nonimmune

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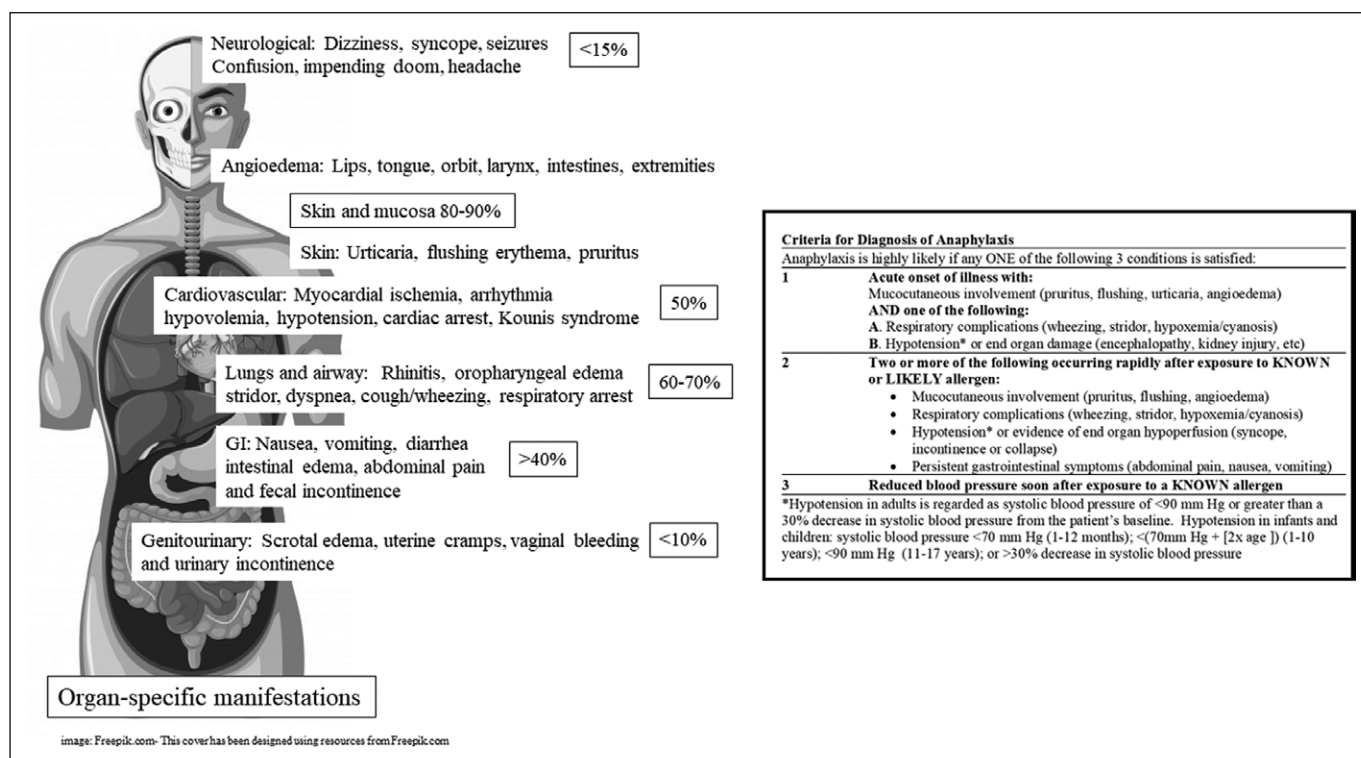


Figure 1. Clinical manifestations of anaphylaxis. Multisystem involvement in anaphylaxis showing various systems involved and the frequency of involvement. Box on the *right* shows accepted criteria for the diagnosis of anaphylaxis. GI = gastrointestinal.

triggers (1). The full-blown anaphylaxis syndrome culminates in angioedema/airway obstruction, hypotension, distributive or mixed shock, cardiorespiratory arrest, and death if not recognized and managed (1–5). Anaphylaxis is defined by a set of criteria, as shown in the box in Figure 1 and discussed later in this review. Several patterns of anaphylaxis have been described based on presentation, recurrence of symptoms, and severity of the illness. Uniphasic anaphylaxis is common and accounts for 70–90% of patient presentations, with symptoms peaking at 30–60 minutes and resolving completely over an hour. Biphasic anaphylaxis is defined by the recurrence of symptoms hours after resolution of the initial event in the absence of re-exposure to the trigger (6). Early administration of epinephrine may be beneficial in preventing biphasic reactions, although the role of early administration of glucocorticoids and antihistamines is unclear. The estimated lifetime prevalence of anaphylaxis is 0.05–2.0% with a mortality rate of 0.5–1% (7, 8). Wood et al (8) reported their findings on a telephone survey of unselected adults (public survey) and of patients who reported prior reactions. The commonest allergens triggering anaphylaxis were medications (34%), foods (31%), and insect stings (20%). Forty-two percent of patients sought treatment within

15 minutes of onset of symptoms, but only 11% self-administered epinephrine. Fifty-two percent of the patients had never been prescribed an epinephrine auto-injector, whereas 60% did not have an active prescription for an autoinjector (8).

The goal of this review is to present the physician in the ICU with an updated summary of the recent advances in the mechanistic and diagnostic classification of anaphylaxis, grades of severity, strategies for epinephrine administration, adjunctive therapies, and also provide options for refractory disease.

METHODS

A search for Mesh word “anaphylaxis” yielded 30,616 results on PubMed, with 3,987 papers listed under “anaphylaxis and shock” and 100 papers listed under “anaphylaxis and ICU”. Of these, published guidelines (9–17), published expert opinions (1, 4, 5, 18–25), systematic reviews and best practices (26–35), reviews of pathophysiology (36–43), pharmacotherapeutics (42–51), and selected case series/reports of severe anaphylaxis were used in the preparation of this review and generation of figures and tables. There were no randomized controlled trials of relevance to this review. However, several clinical trials have been

registered and include studies of serum tryptase in cardiac surgery (NCT02644785), pathogenesis of neuromuscular blocker reactions (NCT02250729), use of imbrutinib in managing food allergic reactions (NCT03149315), clinical determinants of perioperative reactions (CADECAP study NCT03918772), defining endotypes in perioperative anaphylaxis (ENDOPHEN NCT 0304006106) and epidemiology, and outcomes of anaphylactic shock admitted to ICU (NCT04290507). Detailed reporting on results from these studies is pending.

Grading of available evidence was obtained from published reviews and as follows: grading of evidence: Levels I (systematic reviews/randomized trials), Level II (Cohort or case-control), Level III (one group nonrandomized), Level IV (descriptive studies, case series) and Level V (case reports, expert opinion, narrative reviews, consensus statements). (Grades of recommendation are based on levels of evidence: A = Level I study; B = Level II/III studies, C = Level IV studies; D = Level V studies or inconsistent or inconclusive studies): strong recommendation (grade A), moderate recommendation (grades B and C), and weak recommendation (grade D).

EPIDEMIOLOGY OF ANAPHYLAXIS IN THE ICU SETTING

Gibbison et al (29) reporting on ICU admissions for anaphylaxis between 2005 and 2009 in the United Kingdom demonstrated almost 1,300 admissions to the ICU during that period, with a progressively rising incidence and survival rates more than 90%. In another study reported by Motosue et al (52), 38,695 patients seen in the emergency department for anaphylaxis were evaluated of whom 11.5% were hospitalized, with 5.3% being admitted to the ICU. Of these, a small number (1.5%) required endotracheal intubation, and an even smaller number (0.45%) were suspected of having a near-fatal episode (52). Medication-related anaphylaxis (odds ratio [OR], 1.50; 95% CI, 1.38–1.63; $p < 0.001$), patients who were 65 years or older (OR, 3.15; 95% CI, 2.88–3.44; $p < 0.001$), or patients who had underlying heart (OR, 1.56; 95% CI, 1.50–1.63; $p < 0.001$) or lung disease (OR, 1.23; 95% CI, 1.16–1.30; $p < 0.001$) had increased odds of needing hospitalization, ICU admission, and/or intubation. Ring and Messmer (27) developed a classification of anaphylaxis based on symptoms and organ involvement. Four categories of anaphylaxis were recognized: grade I-urticaria $\pm$ angioedema, grade II-diarrhea, hypotension, wheezing/dyspnea, grade

III-severe cardiorespiratory manifestations (collapse/shock, arrhythmias, severe bronchospasm), and grade IV-cardiac or respiratory arrest. Severe anaphylaxis is defined by the presence of hypoxemia (oxygen saturation $< 92\%$), hypotension (systolic blood pressure of < 90 mm systolic in an adult), altered consciousness, collapse, or fecal/urinary incontinence (53).

RISK FACTORS FOR SEVERE ANAPHYLAXIS AND ICU ADMISSION

Several risk factors portend severe anaphylaxis and include parenteral allergens, interrupted medication schedule (especially after desensitization), history of atopy (such as latex allergy and prior anaphylaxis), concomitant beta-adrenergic blockers or angiotensin converting enzyme inhibitors (ACEIs), history of poorly controlled asthma, living in northern latitudes, gender, and impaired cognition (1). Other known risk factors for severe, near-fatal, and fatal anaphylaxis include delayed use of epinephrine, severity of the initial reaction, absence of urticaria, biphasic reactions, age greater than 65 years, underlying cardiopulmonary disease, and mast cell disorders (such as systemic mastocytosis or clonal mast cell disease) (54). Brown et al (53) described several categories of patients who developed severe reactions older patients and those with pre-existing lung disease and drug-related anaphylaxis. Severe reactions were associated with low platelet-activating factor (PAF) acetyl hydrolase and elevated levels of mediators such as histamine, tryptase, and cytokines. Levels of mast cell tryptase, histamine, interleukin (IL)-6, IL-10, and tumor necrosis factor (TNF) receptor 1 were also associated with delayed deteriorations (majority within 4 hr of initial epinephrine administration) (53).

ETIOLOGY AND APPLICATION OF PRECISION MEDICINE

Phenotypes (clinical presentation or manifestation) and endotypes (molecular mechanisms or pathways) have been described recently in asthma and anaphylaxis with an intent to define pathways that can be treated in a more precise manner (precision medicine) (18) (**Fig. 2** and **Table 1**). Such classifications of anaphylaxis have included immune-mediated (immunoglobulin [Ig] E or IgG-mediated), contact system-mediated, complement-mediated, mast cell activation (direct mast cell activation or clonal mast cell disorders), cytokine release reactions

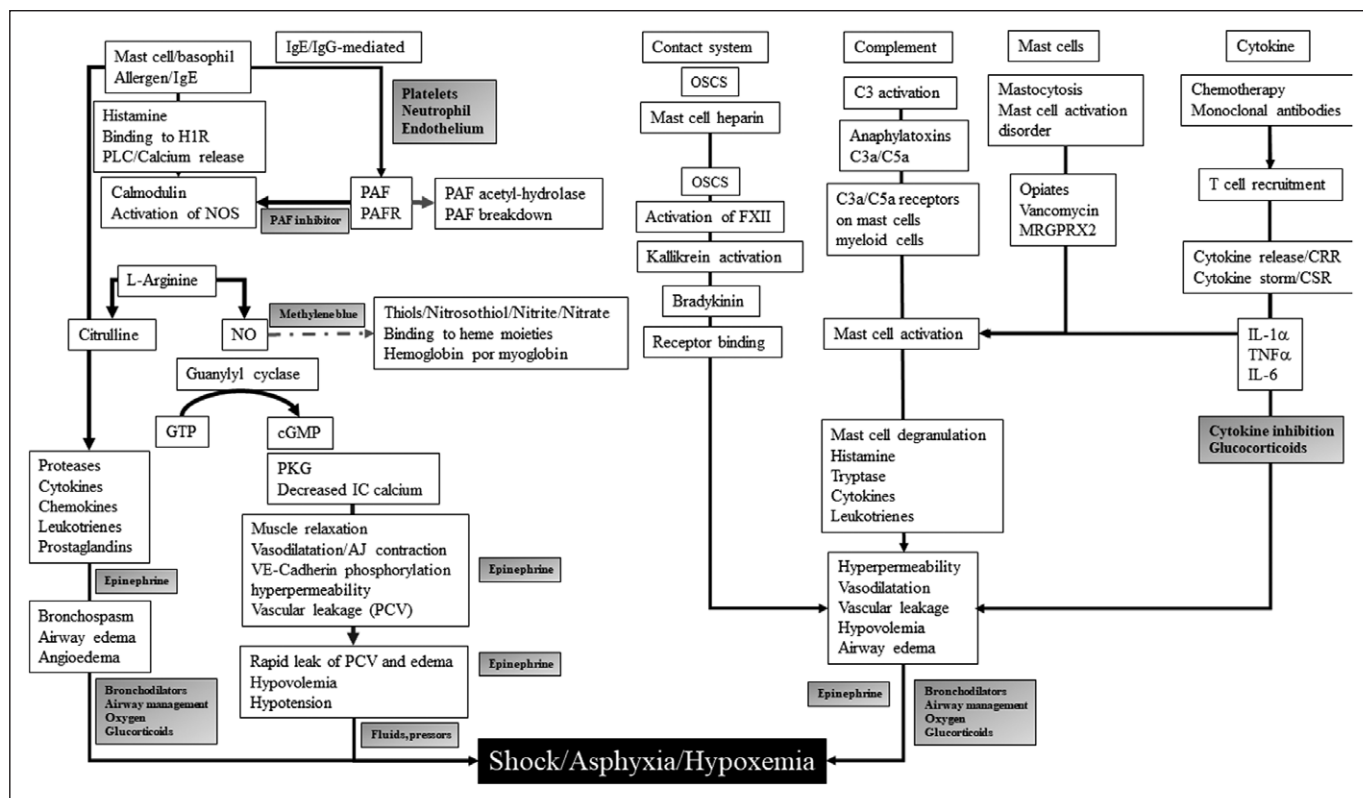


Figure 2. Endotypes and mechanisms involved in anaphylaxis. Mechanisms involving immunoglobulin (Ig) E/IgG-mediated anaphylaxis (with activation of a nitric oxide pathway), and other endotypes involving the contact system and kinins, complement and anaphylatoxins, mast cells and drug receptor activation, and cytokine cascades are shown. This figure is an overview to provide context, is not all inclusive, and has been modified from references (23–25), and all details provided may not be necessary for an adequate management of anaphylaxis in the ICU. AJ = adherens junctions, C3 = complement factor 3, cGMP = cyclic guanosine monophosphate, CRR = cytokine release reaction, CSR = cytokine storm reaction, FXII = factor 12, GTP = guanosine triphosphate, H1R = histamine type 1 receptor, IC = intracellular, IL = interleukin, MRGPRX2 = receptor related to Mas-related G-protein-coupled receptor: activation by certain medications can lead to mast cell degranulation, NO = nitric oxide, NOS = NO synthase, OCS = oversulfated chondroitin sulfate, PAF = platelet-activating factor, PAFR = PAF receptor, PCV = postcapillary venules, PKG = protein kinase G, PLC = phospholipase C, TNF α = tumor necrosis factor alpha, VE = vascular endothelial.

(which could be mixed due to co-occurrence of IgE-mediated reactions or involve severe reactions or cytokine storm reactions), and idiopathic categories (19, 20). Figure 2 attempts to summarize some of these endotypes, whereas Table 1 lists etiologies linked to these endotypes. Selected aspects of Figure 2 are discussed below.

“IgE-mediated anaphylaxis” results from the traditional pathway (Type 1) mediated via T cells, Th2 cytokines (such as IL-4 and 5), B cell production of IgE and subsequent cross-linking of the high affinity IgE receptor on mast cells and basophils by IgE-antigen complexes, culminating in mast cell, and basophil degranulation (55, 56). Histamine, tryptase, TNF alpha (TNF α), PAF, chemokines, cytokines, cysteinyl leukotrienes (LTC₄, LTD₄, LTE₄), prostaglandins, and proteases (tryptase, chymase) are released rapidly, resulting in decreased systemic vascular resistance (SVR), altered endothelial

function, and increased capillary permeability (1, 21, 40, 56). Anaphylactic shock can be ultimately mediated by a histamine-mediated PI3-kinase/e-nitric oxide (NO) synthase pathway with NO generation, endothelial barrier disruption through a RhoA and ROCK-mediated VE cadherin rearrangement, and subsequent modulation of vascular tone and hyperpermeability, as shown in Figure 2 (39, 57). Leukotrienes, TNF, and PAF can also induce the production of NO, which in turn inhibits the release and effects of catecholamines. NO causes vasodilation indirectly by increasing the activation of guanylyl cyclase, which then causes smooth muscle relaxation by increasing the concentration of smooth muscle cyclic guanosine monophosphate. These events culminate in distributive shock, whereas angioedema and resultant hypoxemia further exacerbate myocardial and vascular function in a vicious cycle (22, 23). Methylene blue inhibits guanylyl

TABLE 1.**Classification of Anaphylaxis According to Endotype (Mechanism)^b or Phenotype (Clinical)^a**

Endotype	Examples	Comments
Immune mediated		
IgE-mediated: mast cells, tryptase, cysteinyl leukotrienes, histamine, PAF, nitric oxide ^b		
Urticaria, angioedema, hypotension, vomiting, diarrhea ^a		
	Foods	Peanut, milk, egg, crustaceans, wheat, soy
	Latex	Cross-reactive foods (latex food syndrome)
	Hymenoptera	Yellow jacket, hornets, imported fire ant
	Drugs	Antibiotics, anesthetics, biologicals Taxanes and platins
	Alpha-Gal	Mammalian meat (beef, pork, lamb, deer) Gelatin, cetuximab
	Hormones	Progesterone
	Seminal fluid	Seminal plasma proteins
	Food dependent exercise-induced anaphylaxis	Food allergen and exercise
	Cryptic allergens	Celery-birch-mugwort-spice syndrome, carmines dye, annatto, guar gum, lupine flour
IgG-mediated: IgG immune complexes, low affinity IgG receptor, PAF synthesis, thromboxane A ₂ ^b		
Wheezing, diarrhea, hypotension, hypovolemia, angioedema ^a		
	Immune aggregates	Including immune complexes/complement
	IV IG	IgG or IgE anti-IgA antibodies (IgA deficiency, Common variable immune deficiency)
	Blood transfusion	IgA deficiency
	Biologicals	Chimeric/humanized/human (e.g., rituxan)
	Miscellaneous	Dextran, aprotinin, Von Willebrand factor
Nonallergic anaphylaxis: complement and contact system mediated		
Complement/contact system/factor XII/bradykinin ^b		
Angioedema, wheezing, hypotension ^a		
Contact system/ bradykinin	Heparin	Oversulfated chondroitin sulfate in contaminated heparin Direct effect of heparin in some patients
Complement factor 3a/ complement factor 5a)	Vespid toxin	In addition to IgE-mediated reactions
	Vehicles	Cremaphor EL, polyethylene glycol Polysorbate 80
	Selected drugs	Liposome infusion, protamine neutralization of heparin
	Membranes	Hemodialysis (cellulose membranes)

(Continued)

TABLE 1. (Continued).**Classification of Anaphylaxis According to Endotype (Mechanism)^b or Phenotype (Clinical)^a**

Endotype	Examples	Comments
Cytokine mediated		
Monocytes/T cells or mast cells elaboration of tumor necrosis factor alpha, IL-1 β /IL-6 that activate multiple target cell types ^b		
Fever, chills, flushing, nausea, headache, hypotension, hypoxemia ^a		
Cytokine release reaction	Chemotherapeutic drugs	Mixed sometimes with IgE-mediated reactions
Cytokine storm reaction	Monoclonal antibodies	
Predominantly mast cell mediated		
Mast cell activation, release of tryptase, histamine, cytokines ^a		
Urticaria, angioedema, flushing, hypotension, wheezing ^b		
Direct mast cell activation	Opioid receptors	
	Opiates	
	Phospholipase C/phospholipase A2 recruitment	Vancomycin
	Receptor related to Mas-related G-protein-coupled receptor ^{\$}	Fluoroquinolones, tubocurarine, atracurium Icatibant
	Physical	Cold, heat, exercise, sunlight
	Aspirin and nonsteroidal anti-inflammatory drugs	Leukotriene-driven and other mechanisms
	Miscellaneous	Radiocontrast media
Primary mast cell disorders (D816V mutation)	Systemic mastocytosis	Mast cell activation by exercise, venom, drugs
	Monoclonal mast cell activation syndrome/mast cell activation syndrome	Food allergy, alcohol, surgery/stress
Idiopathic	Idiopathic anaphylaxis	Unknown mechanism

IL = interleukin, IVIG = IV immunoglobulin, PAF = platelet-activating factor.

^aReaction phenotype (clinical manifestation).^bReaction endotype (mechanism).

cyclase, resulting in an increased SVR and reversal of shock in human and animal studies (38, 49, 58, 59). Epinephrine reverses many of these changes making it the most effective antidote for anaphylaxis (Fig. 2).

“IgG-immune complexes” can initiate anaphylaxis by binding to low affinity receptor, Fc γ RIII on macrophages, and activating PAF synthesis. PAF can in turn activate platelet aggregation, induce release of thromboxanes and serotonin, and lead to endothelial permeability and capillary leak, vasodilatation, decreased cardiac output, and bronchospasm or diarrhea (60). “Cytokine release”

induced by certain monoclonal antibodies (chimeric, humanized and fully human) or by chemotherapeutic agents can cause anaphylaxis-like reactions (19, 60). The reaction is mediated by TNF α , IL-1 β , and IL-6 produced by monocytes or macrophages, mast cells, and T cells. A more severe variant of this reaction is called “cytokine storm,” characterized by expression of larger quantities of cytokines (IL-8, interferon- γ , TNF α , IL-1 β and IL-6 among others), vascular leakage related to increased endothelial permeability, activation of thromboplastin and the coagulation system, and culmination

in a multisystem syndrome characterized by organ failure and disseminated intravascular coagulation (DIC). Fever, chills, hypotension, hypoxemia, and cardiovascular collapse ensue (19, 60).

“Other pathways” have been described (albeit less common but yet clinically relevant in select situations), including activation of the kinin pathway that can lead to a mast cell independent activation of vascular leakage (described in reactions to contaminated Chinese heparin), complement activation, anaphylatoxin generation, and direct mast cell activation (including drugs that bind the G-protein linked receptor, receptor related to Mas-related G-protein-coupled receptor, and in mast cell activation disorders) (20, 55, 56, 61).

It is estimated that 30–60% of patients presenting with anaphylaxis may have no obvious etiologic trigger to explain the disease and hence are described as having idiopathic anaphylaxis—often a diagnosis of exclusion (62–64).

The Unique Conundrum of Perioperative Anaphylaxis

Perioperative anaphylaxis is a common reason for patients to undergo transfer to an ICU. Perioperative anaphylaxis can occur during surgery or postoperatively with the patient in recovery (24). The National Audit Project 6 is a large prospective study of perioperative anaphylaxis (65, 66). The study evaluated 3 million anesthetics given in the United Kingdom over a year. The incidence of serious perioperative anaphylactic events was one in 10,000 anesthetics. The commonest triggers were antibiotics (47%), muscle relaxants (33%), chlorhexidine (9%), and patent blue dye (5%—used in breast surgery). Ninety-six percent of patients survived the event, after prompt intervention by anesthesiologists. The commonest presentation was intraoperative hypotension with 15% developing cardiac arrest, especially the elderly and obese individuals. Teicoplanin was 17-fold more likely to cause anaphylaxis than alternatives used for patients with a history of penicillin allergy. Seventy-five percent of patients required ICU admission, and most of these patients quickly recovered, but up to a third of patients developed anxiety about future procedures. Evaluation of the patient with perioperative anaphylaxis requires a detailed evaluation of the medical records, discussion regarding medications administered (with the surgeon and/or anesthesiologist), and recruitment of the help of an allergist skilled in testing for drug allergy. A tryptase

level needs to be drawn, and likelihood of the causative agent is determined clinically (opiates, nonsteroidal drugs, antibiotics, latex, chlorhexidine, and anesthetic agent) and by selected skin testing. Testing is usually carried out several weeks after the event and may involve incremental challenge testing (prick/puncture, intradermal, or provocative challenge testing).

ALGORITHMIC APPROACH TO MANAGEMENT OF ANAPHYLAXIS IN THE ICU: INITIAL WORKUP

The criteria for anaphylaxis diagnosis are reviewed in Figure 1, and the algorithmic approach to management is reviewed in **Figure 3**.

Establish a Diagnosis of Anaphylaxis

It is essential to determine if the patient dyspnea, wheezing, diarrhea, and/or hypotension has true anaphylaxis or one of the many conditions may mimic anaphylaxis. In many cases, anaphylaxis is unfortunately a retrospective diagnosis, leading to management delays. If anaphylaxis is strongly suspected, management including administration of epinephrine must proceed immediately while workup is also initiated. Accurate diagnosis is essential, and this is usually based on the constellation of symptoms and signs summarized in Figure 1.

The clinical criteria for diagnosis of anaphylaxis as proposed by second NIAID Food Allergy and Anaphylaxis Network symposium are reviewed below:

- With an unknown allergen, acute onset of skin/mucosal involvement with either lung (wheezing) or cardiovascular (hypotension) involvement.
- With a likely allergen, rapid onset of at least two or more of the following: skin/mucosal involvement, respiratory compromise, cardiovascular compromise (hypotension or end organ dysfunction), or persistent gastrointestinal symptoms (vomiting, diarrhea, etc.).
- With a known allergen, rapid occurrence of hypotension.

Hypotension in adults is regarded as systolic blood pressure of less than 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 less than 70 mm Hg (1–12 mo); less than $(70 \text{ mm Hg} + [2 \times \text{age}])$ (1–10 yr); less than 90 mm Hg (11–17 yr); or greater than 30% decrease in

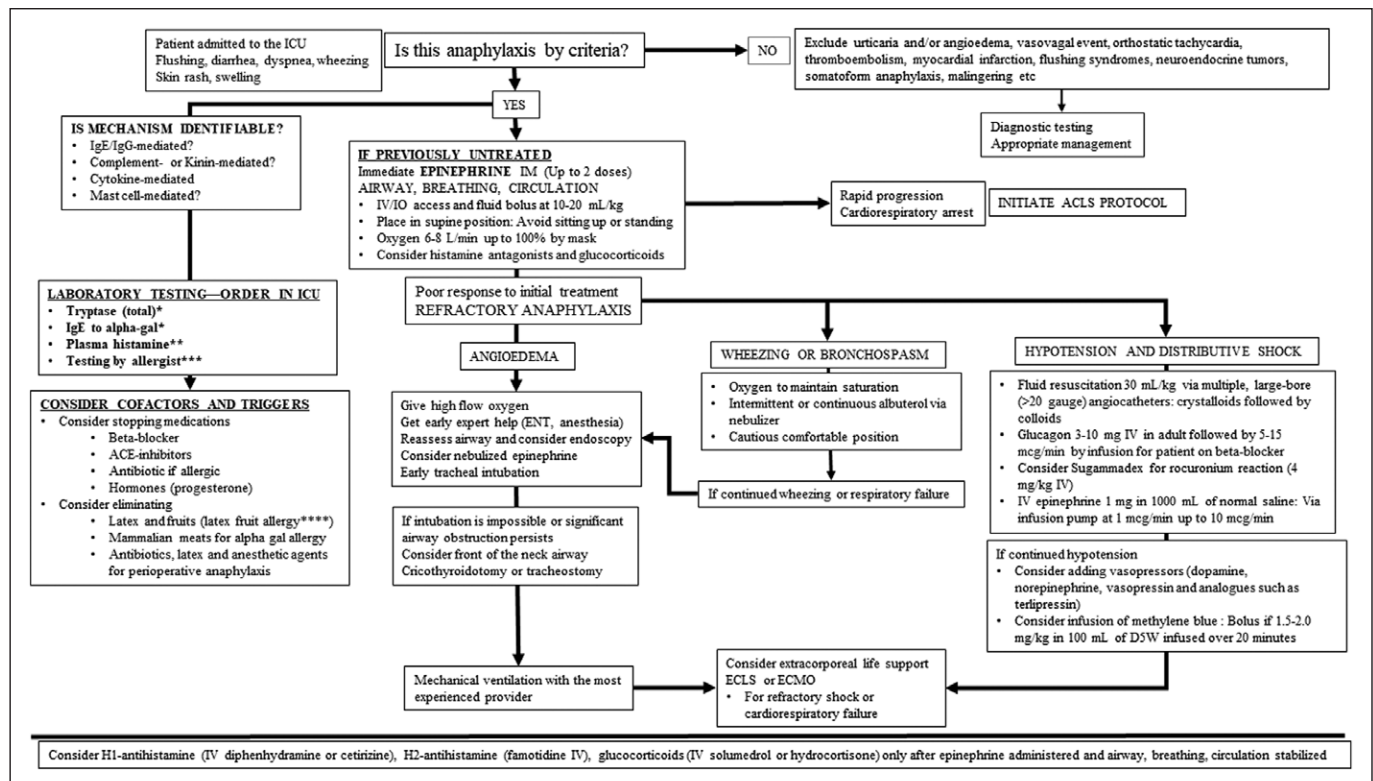


Figure 3. Algorithm for the management of severe or refractory anaphylaxis and related airway and vascular complications in the ICU.

*Some specialized laboratory results may not be immediately available but may help confirm diagnosis or assist in outpatient management and follow-up. **Histamine levels may be relevant in the first few hours after a perioperative or in-hospital event but decay rapidly thereafter and may not be detectable by the time a patient reaches the ICU. ***Consulting an allergist will assist in evaluation of severity, specific management issues as well as in diagnostic testing and post-ICU follow-up. ****Latex cross-reactive foods include avocado, banana, chestnut, kiwi, peach, tomato, potato, and bell pepper. ACE = angiotensin converting enzyme, ACLS = advanced cardiac life support, D5W = 5% dextrose, ENT = ear, nose and throat specialist, H1/H2 = histamine receptor, Ig = immunoglobulin, IO = intraosseous.

systolic blood pressure from baseline for the patient (1, 10–12, 67).

Establish a Mechanism/Endotype and Etiology

If the diagnosis of anaphylaxis is confirmed, then it is essential to understand the etiology and endotype as described in Table 1, so that management (elimination of trigger, start specific therapies) can be tailored.

Exclude Other Disorders If Anaphylaxis Criteria Are Not Met

Disorders that may be confused for anaphylaxis need to be excluded (evidence level D) and include the flushing syndromes (neuroendocrine tumors and medications), vancomycin-induced red man syndrome, vasovagal reactions (bradycardia, history of noxious stimulus, or medication injection), pulmonary embolism, panic attacks, malingering or Munchausen stridor, somatoform anaphylaxis, vocal cord dysfunction, and anaphylaxis mimics

such as scombroid syndrome (mediated by histamine-rich scombroid fish) (68–71). Somatoform anaphylaxis is characterized by the following aspects: 1) presenting symptoms mimicking anaphylaxis, 2) the absence of objective findings of anaphylaxis (such as wheezing, laryngeal edema, urticarial eruption, or hypotension), 3) resistant to therapy, and 4) meeting the Diagnostic and Statistical Manual of Mental Disorders criteria for undifferentiated somatoform disorder.

Initiate Laboratory Testing

Total serum tryptase is the biomarker most widely used to confirm a diagnosis of anaphylaxis retrospectively (1, 72). Small amounts of the immature form of tryptase (beta-protryptase) 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 1–2

hours after symptom onset, since tryptase levels typically peak within 60–90 minutes after symptom onset but can persist for 6 hours (73). Tryptase level is drawn immediately after the event and again in follow-up a few weeks after resolution of anaphylaxis. The presence of a persistently elevated tryptase level several weeks after the event would suggest mast cell disorders such as mastocytosis.

Tests that may assist in diagnosis include IgE to alpha-gal (mammalian meat allergy), serum chromogranin, urine hormone levels for neuroendocrine tumors, urine levels of histamine, 11β PGF 2α , prostaglandin D 2 , and blood testing for D816V mutation for clonal mast cell disorders. Consider evaluation by an otolaryngologist in cases of suspected factitious stridor. Plasma histamine levels rise 5–10 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. Allergy testing (skin testing and serum/immune-CAP assays) can help establish the specific diagnosis and requires consultation with an allergist.

Consider Cofactors and Triggers

Addressing cofactors is important (evidence level B) as these may affect management and prognosis. Cofactors of importance include hormones (estrogens and progesterone), lipid-lowering drugs, nonsteroidal anti-inflammatory drugs, ACEIs, and beta-blockers, some of which may need to be discontinued after careful consultation. Other cofactors such as age-related morbidities, mast cell disorders, and asthma or heart disease will need to be factored in as they may also influence outcomes (36).

AN ALGORITHMIC APPROACH TO THE MANAGEMENT OF ANAPHYLAXIS IN THE ICU: THERAPEUTIC PRINCIPLES

The Patient in Cardiorespiratory Arrest

If the patient develops rapid progression to cardiorespiratory arrest, management follows recommended protocols for advanced cardiopulmonary life support.

The Untreated Patient

When the patient is moved to the ICU emergently with no specific intervention or if the diagnosis of

anaphylaxis is made in the ICU, immediate epinephrine administration (initially intramuscular immediately followed by IV route depending on the patient's response to therapy), starting fluids, paying attention to posture, and the initiation of oxygen are all essential (4, 5, 9–17). **Table 2** lists interventions and medication dosages in the management of anaphylaxis in the ICU.

Administer Epinephrine Without Delay (Evidence Level B). 0.3–0.5 mg of 1 mg/mL solution intramuscularly into the lateral thigh and repeat every 5–15 minutes as needed; or 0.01 mg/kg body weight given intramuscularly (for children weighing 30 kg or less). This is first-line therapy. Immediate administration of epinephrine is essential as delays have resulted in poorer outcomes, including hypoxic encephalopathy and death (5, 34, 44, 75). The recommended concentration of epinephrine is 1 mg/mL (referred to earlier as 1:1,000), and the recommended dose of epinephrine is 0.01 mg/kg body weight given intramuscularly (for children weighing 30 kg or less) and a dose of 0.3–0.5 mg (in adults), given in the anterolateral aspect of the mid vastus lateralis muscle (VLM) (1, 51, 76, 79, 80). There is no absolute contraindication to epinephrine administration in anaphylaxis (1, 76). This dose may need to be repeated every 5–15 minutes or even earlier as the clinical situation demands (4, 5, 9, 10, 12, 15). Pharmacologically, epinephrine binds to α_1 (vasoconstriction, raised blood pressure, reduction of capillary leak and edema), α_2 (lowers intraocular pressure and has central and peripheral neurologic effects), β_1 (chronotropic and inotropic effects), β_2 (bronchodilatation), and β_3 (promotes lipolysis) adrenergic receptors with global beneficial effects in anaphylaxis, reversing most abnormalities (22, 76).

There are many reasons why epinephrine may not completely reverse anaphylaxis and include suboptimal dosing or route, hypovolemic or distributive shock, medications such as beta-blockers that interfere with epinephrine action, and incorrect diagnosis (5). Studies show absorption is faster with higher tissue and plasma levels when injected in the VLM compared with other muscles or following subcutaneous administration, whereas failure to administer this drug immediately is associated with fatal outcomes in food reactions (9, 10, 12, 15, 51, 81). In emergencies, an epinephrine autoinjector 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 (weight >

TABLE 2.
Management of Anaphylaxis: Medications, Dosing and Adverse Events

Intervention	Recommendation	Comments	Evidence Level	Selected References
Epinephrine 1 mg/mL concentration	Intramuscular 0.3–0.5 mg	Intramuscular injection preferred	B	(9–17) guidelines/practice parameters
	Mid-outer thigh	Pediatric: 0.01 mg/kg		(1, 2, 5, 7, 8, 18, 22, 27, 32–34, 74) expert reviews
	Give immediately	Repeat every 3–5 min May repeat every 5–15 min Pallor, headache, dizziness And tremor may occur		(35, 54) systematic review/ Cochrane (44, 51, 75–78) epinephrine reviews (52, 53, 79–81) fatal anaphylaxis studies
Posture	Recumbent posture	Sitting or standing can cause cardiac arrest	C	(82) case studies of posture and sudden death
O ₂	8–10 L/min up to 100% O ₂ And in heart or lung disease	Low flow O ₂ in severe chronic obstructive pulmonary disease or hypercapnia	D	(9–17) guidelines/practice parameters (1, 2, 5, 7, 8, 18, 22, 27, 32–34, 74) expert reviews
Fluids	Crystalloid (normal saline) Administer boluses 1–2 L IV or intraosseous; (20 mL/kg) boluses	Fluid overload Pulmonary edema	B	(9–17) guidelines/practice parameters (1, 2, 5, 7, 8, 18, 22, 27, 32–34, 74) expert reviews (27, 50, 83) fluids in shock/ intraosseous access
Albuterol via nebulizer	2.5–5 mg in 3 mL saline every 20 min for three doses or as 10–15 mg continuous nebulizer	Can cause irritability, tremor, pharyngitis, tachycardia	B	(9–17) guidelines and reviews (1, 2, 5, 7, 8, 18, 22, 27, 32–34, 74) expert reviews
H1-antihistamine	Cetirizine 10 mg IV slow push	IV given undiluted in 2 min	B	(9–17) guidelines/practice parameters
Use after adrenaline	Diphenhydramine 25–50 mg IV	Can cause drowsiness and headaches		(1, 2, 5, 7, 8, 18, 22, 27, 32–34, 74) expert reviews (48, 84–86) systematic reviews/Cochrane
H2-antihistamine	Famotidine 20 mg IV—slow 0.25 mg/kg/ dose for children	Can cause agitation, headache, dizziness, and diarrhea	B	(9–17) guidelines/practice parameters
Use after adrenaline				(87) systematic review/ Cochrane
Glucocorticoids	Methylprednisolone 125 mg IV 1–2 mg/kg dose	Plethora of side effects Hypertension, hyperglycemia	B	(9–17) guidelines/practice parameters (88–99) systematic reviews/expert opinion

(Continued)

TABLE 2. (Continued).**Management of Anaphylaxis: Medications, Dosing and Adverse Events**

Intervention	Recommendation	Comments	Evidence Level	Selected References
Epinephrine infusion	0.1–0.5 µg/kg/min IV with pump, titrating to blood pressure cardiac function and O ₂ level	Refractory anaphylaxis	C	(9–17) guidelines/practice parameters (1, 2, 5, 7, 8, 18, 22, 27, 32–34, 74) expert reviews
Nebulized epinephrine	Epinephrine 1 mg/mL 5 mL dose	Via nebulizer	D	(1, 2, 16)
	Racinepinephrine 0.5 mL (1 vial) with 3 mL saline by nebulizer	For use in an atomizer		
IV bolus epinephrine	50 µg bolus (0.5 mL of 1:10,000)	Used only for impending collapse	D	(1, 11) (use cautiously or acceptable advanced cardiac life support protocol)
Additional vasopressor	Vasopressin 0.03–0.07 units/min	Refractory hypotension	D	(9–17) guidelines/practice parameters (1, 2, 5, 7, 8, 18, 22, 27, 32–34, 74) expert reviews (100–108) reviews/vasopressors in shock
	Norepinephrine 2–100 µg/min			
	Dopamine 2–5 µg/kg/min			
Glucagon	1–5 mg slow IV push Infusion 5–15 µg/min	Can cause nausea Used for patient treated with beta-blocker	B	(9–17) guidelines/practice parameters (45, 109) focused reviews
Sugammadex	4 mg/kg IV slow push	Reverses rocuronium reaction Rarely causes anaphylaxis	D	(110, 111) case reports
Methylene blue	1–2 mg/kg IV over 20–60 min	Refractory anaphylaxis Refractory hypotension	C	(9–17) guidelines/practice parameters (110–122) case reports and expert opinion
Tranexamic acid	200–1,000 mg IV	For disseminated intravascular coagulation	D	(123, 124) case reports
Extracorporeal life support/ extracorporeal membrane oxygenation		Refractory disease	D	(125–136) case reports/ expert opinion/review

Grading of evidence: Level I (systematic reviews/randomized trials); Level II (cohort or case-control); Level III (one group nonrandomized); Level IV (descriptive studies, case series); and Level V (case reports, expert opinion, narrative reviews, consensus statements). (Grades of recommendation are based on levels of evidence: A = Level I study, B = Level II/III studies, C = Level IV studies, D = Level V studies or inconsistent or inconclusive studies): strong recommendation (grade A), moderate recommendation (grades B and C), and weak recommendation (grade D).

100 kg), an intramuscular dose of 0.5 mg administered by needle and syringe may be better as studies have shown that autoinjector needle length may not be sufficient for proper delivery (77). The FDA recommends using a 1.5-inch needle for adults, especially males weighing more than 118 kg and women weighing more than 91 kg for deltoid injection, whereas requirements for lateral thigh injection are not reviewed (51). Injection in the buttock has been associated with severe clostridial infections and gas gangrene (51).

Many studies have demonstrated a low rate of epinephrine administration in anaphylaxis (14–19% receive epinephrine at admission to an emergency facility or following hospitalization) (18, 74). Despite observed clinical efficacy, there are no prospective studies of epinephrine efficacy in management of anaphylaxis (35, 76, 78, 137). A systematic review published recently found 15 studies of epinephrine, of which four systematic reviews found no randomized trials of the efficacy of drug in epinephrine, probably due to the ethical difficulties of such a study (35, 78). The authors discovered two case series and five fatality reports that reported underuse, delayed use, or incorrect use of epinephrine autoinjectors (35). Although rare serious adverse events are mentioned in the literature, decades of experience with epinephrine provide a strong safety record (4, 22, 35, 51).

Posture (Evidence Level C). The patients are extremely sensitive to fluid shifts, and sudden postural changes such as sitting a patient up to insert a foley catheter can induce fatal cardiac arrest (82). Recumbent posture is recommended, and pregnant women are asked to be recumbent but turned to one side.

Administer Oxygen and Maintain the Airway (Evidence Level D). Administer oxygen by nasal cannula or by face mask. Treatment may be initiated with a reservoir mask at 15 L/min, aiming to reach a saturation range of 94–98%. This approach may also be relevant for patients at risk for hypercapnia and modified appropriately when results of blood gas measurements and expert assessment opinion are available. Lower concentrations of oxygen may be used in stable patients (grade D) (138, 139).

Administer nebulized short-acting beta-2 agonists for wheezing. For the initial assessment, checking the airway and assessing the level of consciousness, blood pressure, and oxygenation can assist in triaging the patient. An one-way valve facemask with oxygen inlet port

or artificial ventilation via the mouth-to-mask technique with oxygen attached to the inlet port can provide adequate oxygen saturation in some patients, whereas others may be able to breathe through the mask.

Administer Fluids (Evidence Level B). IV access needs to be established using large bore catheters and fluids (crystalloid such as normal saline or lactated Ringers) administered (30 mL/kg, usually 1–2 L immediately and up to 7 L may be required to replenish extravasated fluid) as rapidly as possible (4, 5, 9–17). This can also be accomplished using a central venous catheter or a by insertion of an ultrasound-guided peripheral venous catheter if access of a peripheral route has failed. In select situations, the intraosseous access may be required, which has a shorter procedure time and a higher success rate compared with the other two routes (140). Intraosseous route is considered a safe and rapid technique to infuse fluids in patients with poor venous access due to severe hypovolemia or shock (140).

Administer Antihistamines (Evidence Level B). Antihistamines, like corticosteroids, are considered adjunctive treatments, and administration of these drugs should never delay the administration of epinephrine (9–11, 13). Even though histamine is a major mediator produced by mast cells in anaphylaxis, blocking histamine receptors has not been effective in reversing anaphylaxis (11). Although H1-receptor blockers may help decrease flushing, pruritus, and urticaria, they are ineffective in reversing oropharyngeal or laryngeal edema and do not improve hypotension (4, 13). Recently cetirizine, a second-generation antihistamine, has been approved for parenteral use for urticaria, but a role for this parenteral drug in anaphylaxis is unclear (84). Prospective studies are required to evaluate efficacy of H1-antihistamines in anaphylaxis (85, 86). Likewise, although H2-antihistamines (example famotidine 20 mg IV) are often used in anaphylaxis, the correct dosing and efficacy are unclear, and evidence is lacking in randomized studies (87). In the individual patient with histamine-sensitive urticaria and angioedema, these medications may prove beneficial. In general antihistamines are ineffective in managing wheezing, diarrhea, hypotension, or shock. Antihistamines need to be infused slowly to avoid a hypotensive adverse effect.

Glucocorticoids (Evidence Level: B). Glucocorticoids such as parenteral methylprednisolone or hydrocortisone have been used frequently in the management of

severe anaphylaxis (35, 88, 89). Earlier recommendations suggested that glucocorticoid administration prevented biphasic or late reactions, but recent studies have refuted this finding (89). Data supporting the use of glucocorticoids acutely in the management of anaphylaxis is weak, and randomized studies are not available (89–99). It is common practice to administer parenteral glucocorticoids in anaphylaxis and especially in a patient with pre-existing asthma (methylprednisolone 1–2 mg/Kg can be given IV), but the physician has to balance the possible benefits with adverse effects including hyperglycemia, hypertension, and infection. Severe reactions including generalized urticaria and/or angioedema may be indications for steroid therapy as these reactions are often histaminergic and respond to steroids.

MANAGEMENT OF REFRACTORY ANAPHYLAXIS IN THE ICU

Refractory anaphylaxis can be defined as anaphylaxis that is unresponsive to treatment with at least two doses of at least 300 µg epinephrine given intramuscular (7, 30, 141). This occurs in 3–5% of all anaphylaxis cases, with most patients managed in the ICU (30). Refractory or severe anaphylaxis may be related to patient dependent factors (age, male gender, underlying coronary artery disease of obstructive lung disease, psychologic stress, and mastocytosis or elevated basal tryptase levels); procedure-dependent factors (especially perioperative anaphylaxis); and therapy-dependent factors (medication allergy, delayed epinephrine dosing, delayed diagnosis of anaphylaxis, or concomitant beta-blocker or ACEI use) (22, 30, 141, 142). One study from the European Anaphylaxis Registry identified 42 cases of refractory anaphylaxis out of a total of 11,596 cases and compared their risk factors and outcomes to 4,820 patients with severe anaphylaxis (141). The refractory cases occurred mostly in a perioperative setting (45.2 vs 9.05; $p < 0.0001$) and were often (50%) due to medication allergy compared with cases with severe anaphylaxis. Intramuscular epinephrine was administered in 16.7% and IV in 83.3% of cases. The investigators reported that the mortality rate was significantly higher (26.2%) in refractory than in severe cases (0.353%; $p < 0.0001$) (141).

The following sections review the management of specific aspects of severe or refractory anaphylaxis in an inpatient and preferably an ICU setting.

Angioedema of the oropharynx, larynx, or airway leads to hypoxemia and respiratory failure, making

airway management a cornerstone of successful intervention in anaphylaxis (9–13, 17). Patients with obvious swelling of the face, lips, larynx, and oropharynx (uvula and tongue) are most susceptible to this complication. Patients may present initially with a sensation of dyspnea, hoarseness, or difficulty speaking. Direct visualization via awake video laryngoscopy or fiberoptic nasopharyngoscopy is an effective way of evaluating these patients. In stable patients with suspected airway edema, CT of the neck can be helpful. Similarly, some patients with concurrent abdominal pain may have angioedema of the bowel, and contrast-enhanced abdominal CT may be required. If angioedema does not respond to epinephrine, prompt endotracheal intubation (early awake flexible scope intubation or awake intubation with a rigid video laryngoscope and mild sedation) is indicated urgently in such patients and is supported by expert opinion and published guidelines (1, 2, 4). It is essential to have the most experienced provider managing the patient. Racemic epinephrine administered by nebulizer (0.01 mL/kg bodyweight, maximum dose of 0.5–0.75 mL) can decrease laryngeal edema temporarily and has been shown to assist with intubation (11, 13). If intubation is difficult due to the severity of upper airway swelling, cricothyrotomy, tracheostomy, or catheter jet ventilation can be considered (143). Mechanical ventilation should be carefully managed minimizing breath stacking, barotraumas, and medications that exacerbate hypotension.

“Bronchospasm” in a patient with anaphylaxis can worsen hypoxemia and lead to fatigue and respiratory failure. Per AAAI anaphylaxis guidelines, a short-acting β_2 agonist bronchodilator (albuterol) can be administered as 2.5 or 5 mg in 3 mL every 2–4 hours (or as continuous therapy) via a nebulizer until symptomatic relief is obtained, in any patient with anaphylaxis and wheezing, especially if refractory to epinephrine (13). There are no randomized studies supporting the use of nebulized β_2 -agonists in anaphylaxis (1, 4, 11). This treatment does not prevent or treat upper airway obstruction or laryngeal edema.

“Hypotension and shock” are hallmarks of severe anaphylaxis. Anaphylaxis falls into the category of distributive or vasodilatory shock, and appropriate management (careful but aggressive fluid administration and cardiac/hemodynamic monitoring) is essential (50). Aggressive management of hypovolemia is essential, and large volumes of fluid may be required (83).

Persistent hypotension may indicate the need for non-invasive and/or invasive hemodynamic monitoring of myocardial function and peripheral vascular resistance which could help with management fluids and pressors. "Glucagon" is an option in patients who have been treated with beta-blockers and thus fail to respond to epinephrine. Rukma (109) reported on a case of refractory anaphylaxis who was also on metoprolol and failed to respond to epinephrine (45). Glucagon bypasses the β_2 adrenergic receptor directly activating adenylyl cyclase, producing positive inotropy, bronchodilation, and vasoconstriction. There are no randomized studies, and most recommendations come in the form of case studies or expert opinion. Glucagon can be administered by slow IV push in doses of 1–5 mg in the adult followed by 5–15 $\mu\text{g}/\text{min}$ by IV infusion (1, 45). "Vasopressors such as epinephrine" that are properly diluted can be infused peripherally (in order to avoid delays) or via a central venous catheter or intraosseous needle for refractory hypotension and anaphylaxis in an individual patient where peripheral access is difficult (1, 5, 11). A 1:1,000,000 infusion solution needs to be compounded by the pharmacy, by diluting 1 mL of a 1 mg/mL concentration of epinephrine in 1,000 mL of 5% dextrose or normal saline, resulting in a 1 $\mu\text{g}/\text{mL}$ concentration. This can be infused at 1–10 $\mu\text{g}/\text{min}$, titrating to mean arterial pressure greater than 65 mm Hg.

In rare cases where rapid deterioration is occurring and a patient is evolving to cardiac arrest, a recommended ACLS protocol should be resorted to (see earlier section on cardiopulmonary arrest) (1, 15). Norepinephrine, dopamine, dobutamine are alternative agents for distributive shock and can be administered along with epinephrine (25, 30). Although newer agents such as vasopressin, angiotensin II, selexpressin, and terlipressin have been introduced recently (100–102), no randomized human trials have compared these medications to epinephrine in refractory anaphylactic shock.

Vasopressin is an endogenous hormone released from the posterior pituitary gland, binds to AVPR2 receptors in the distal convoluted tubule of the kidney, and promotes water retention (25, 27, 103). Vasopressin also acts as a powerful vasoconstrictor, by binding to AVPR1a receptors, and may also have beneficial renal effects. Vasopressin has been shown to be anecdotally effective in refractory anaphylactic shock and shock related to reactions to insect stings and aprotinin and in perioperative anaphylaxis where doses of 0.01–0.04 U/

min have been used (104–107). Schummer et al (105), reported on six cases where administration of epinephrine and infusion of IV fluids did not stabilize cardiocirculatory function, whereas adding vasopressin resulted in prompt hemodynamic stabilization. Tsuda et al (108) hypothesized, based on in vitro experiments, that epinephrine only partially reversed histamine-induced vasodilatation, whereas vasopressin and drugs inhibiting NO and prostaglandin generation could lead to a complete reversal of the vascular relaxation. Studies with vasopressin suggest a lower propensity for arrhythmias (including atrial fibrillation) and decreased overall mortality rate, making it a safer alternative in some patients with underlying cardiopulmonary disorders (103). There is a small risk for digital ischemia, and hence careful patient selection may be necessary (103).

"Methylene blue" is a phenothiazine-related heterocyclic aromatic molecule that has been traditionally used to treat patients with methemoglobinemia (58). Most recently, methylene blue has been used as a treatment for refractory distributive shock resulting from sepsis and anaphylaxis. Synergy between epinephrine and methylene blue has been shown in an animal model (112). Evora et al (38), reported on the successful treatment of 11 patients with severe anaphylactic hypotension. Bauer et al (113), reported on the rapid reversal of distributive shock in a patient with anaphylaxis who failed epinephrine and found the treatment to be very safe. Methylene blue has been reported to be effective in patients who develop anaphylactic shock secondary to antivenom, protamine, radiocontrast media, and plasma (114–117). In a retrospective study of 20 patients with refractory shock, nine (45%) responded to methylene blue administration (49), but a Cochrane review concluded that a definite recommendation was not possible regarding methylene blue administration in drug-induced shock (118). Methylene blue is administered in doses of 1–2 mg/kg body weight given over 20–60 minutes by slow infusion. Although generally safe, rare cases of anaphylaxis, hemolysis, and serotoninergic syndrome have been reported following infusion of methylene blue (115, 119–121). In one systematic review in sepsis, only increased pulmonary vascular resistance was noted following bolus administration (122). The drug is best avoided in patients with glucose-6-phosphate dehydrogenase deficiency, in patients with pulmonary hypertension and those with severe lung injury.

“Sugammadex” is a cyclodextrin, the first in a new class of selective relaxant binding agents, which reverses neuromuscular blockade induced by aminosteroid nondepolarizing muscle relaxants such as rocuronium and vecuronium. Case reports and anaphylaxis management reviews suggest this drug, administered by slow IV push, might be beneficial in reversing anaphylaxis related to rocuronium (110, 111).

“Extracorporeal life support (ECLS)” may become essential when anaphylactic shock is refractory to multiple modalities and/or associated with catastrophic reductions in cardiac function. These patients may be treated effectively with venoarterial ECLS (125). There are no prospective or trial data supporting the use of ECLS in patients with anaphylaxis, but recommendations come from either expert opinion (11, 27) or small case studies (126–136). Carelli et al (126) reported on two patients with perioperative arrest secondary to an anaphylactic reaction to rocuronium (neuromuscular blocker). These patients failed all traditional therapies but responded after institution of urgent venoarterial extracorporeal membrane oxygenation with good neurologic recovery. ECLS should be considered early in such cases, before irreversible hypoxemic encephalopathy or multiple organ dysfunction set in (11, 125). ECLS also requires use of heparin and possibly protamine, which rarely can cause severe anaphylaxis (9).

Special Circumstances in the ICU

“Anaphylaxis in elderly patients” presents a special challenge, as these patients tend to have pre-existing cardiovascular disease and are more likely to be hospitalized after venom or drug allergic reactions (80, 144, 145). The use of beta-blockers and ACEI in this subgroup of patients makes management more problematic (146).

“Patients admitted for stroke” and who have hypersensitivity reactions to recombinant tissue plasminogen activator (rtPA) also pose difficult management issues (147). The frequency of reactions to rtPA is 0.54%, 1.9% in some studies (148) with a tendency toward a higher risk for anaphylaxis in patients with acute stroke undergoing thrombolysis. The reactions include anaphylactic angioedema (mast cell mediated) and bradykinin-related reactions (activation of kinins by factor XIIa with generation of bradykinin) worsened by ACEIs. In managing these patients, the rtPA infusion needs to be discontinued, and some patients

may require antihistamines, steroids, epinephrine, and other interventions for anaphylaxis. Patients who have received rtPA and have been intubated pose a dilemma due to the possibility of airway bleeding and swelling.

“Cardiovascular disease” occurring in patients with anaphylaxis can be daunting, especially as underlying cardiac disease increases the likelihood of severe or fatal anaphylaxis (22). Medications used to treat cardiac diseases such as beta-blockers and ACEIs make anaphylaxis worse or difficult to manage (22, 23, 146). The Kounis syndrome results from the cardiac injury resulting from anaphylaxis, and three variants have been described, vasospastic angina, myocardial infarction, and stent thrombosis, with the occlusive thrombus demonstrating mast cells and eosinophils (149, 150). This syndrome appears to be mediated by proteases, PAF, and inflammatory cytokines. Routine cardiac care, administering corticosteroids and antihistamines, and avoiding beta-blockers (due to exaggerated vasospasm related to overactive α -adrenergic receptors) are recommended (149–153). Takotsubo cardiomyopathy is a disease manifesting with the clinical, electrocardiographic, and biochemical evidence of myocardial infarction, but the ventricular dysfunction is transient (23, 154–156). Patients with long QT syndrome (LQTS) who develop anaphylaxis can receive glucagon, steroids, and epinephrine (157). Most of the currently available H1-antihistamines pose minimal risk for arrhythmia. There is little to no risk for arrhythmias in any antihistamine currently on the U.S. market at approved dosages, and fexofenadine, levocetirizine, desloratadine, or cetirizine and corticosteroids can be safely used. Epinephrine may be less effective in reversing anaphylaxis in patients with LQTS treated with beta-blockers, and this may necessitate the use of glucagon. For wheezing, ipratropium bromide is preferred, but no contraindication exists for inhaled beta-2-adrenergic medications (157).

“DIC” can complicate anaphylaxis, due to activation of the contact system and resulting in accelerated thrombosis, a potentially lethal complication. Anecdotal reports suggesting tranexamic acid may have benefits in DIC have appeared in the literature (123, 124).

POST-ICU MANAGEMENT

Following discharge, the patient needs to be provided with an epinephrine autoinjector and an anaphylaxis action plan. Education on avoidance of triggers (latex, mammalian meat, antibiotics, hormones, foods, or

Hymenoptera venom) and any identified cofactors (alcohol, medications, exercise) is essential. A follow-up tryptase level will assist in diagnosis of the occasional patient with a mast cell disorder. A referral to an allergist is also recommended.

CONCLUSIONS

Anaphylaxis is a rapidly progressive life-threatening disorder. Skilled intervention in ICUs may be required for the patient with complicated, severe, or refractory anaphylaxis.

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