Approach to Idiopathic Anaphylaxis in Adolescents

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KEYWORDS

• Anaphylaxis • Mast cell activation • Mastocytosis • Hereditary alpha tryptasemia • Adolescent

KEY POINTS

- Anaphylaxis is a potentially-life threatening syndrome of varied severity, presentation, and pathophysiology.
- Adolescents have increased risks for adverse outcomes from anaphylaxis and require unique support.
- Mast cell disorders, rare allergens, and cofactors may be etiologic factors in otherwise obscure cases of anaphylaxis.
- Mimic disorders may simulate anaphylaxis and require exclusion.
- A diagnosis of idiopathic anaphylaxis should only be considered only after an extensive review of rare causes and mimic disorders.

INTRODUCTION

Anaphylaxis is a potentially fatal acute syndrome resulting from the acute activation of cells including mast cells, basophils, and other effector cells. Symptoms often present with sudden onset, and often involve cutaneous (urticaria/angioedema, itching, and flushing), gastrointestinal (nausea, vomiting, diarrhea, and cramps), hypotensive (presyncope, syncope, confusion, and reflex tachycardia), or respiratory (laryngeal stridor, bronchospasm, coughing, dyspnea, and wheezing) features. Often, 2 or more of these systems are involved concurrently; however, anaphylaxis can present with sudden onset of just 1 of the noncutaneous systems as well (**Fig. 1**).[1]

Common triggers for anaphylaxis in adolescents include food, drugs, and venom. Food allergy to either tree nuts or shellfish is the most common cause of anaphylaxis in this age group.[2] Venom and drug-induced anaphylaxis is more common in adolescents than in younger children.[2]

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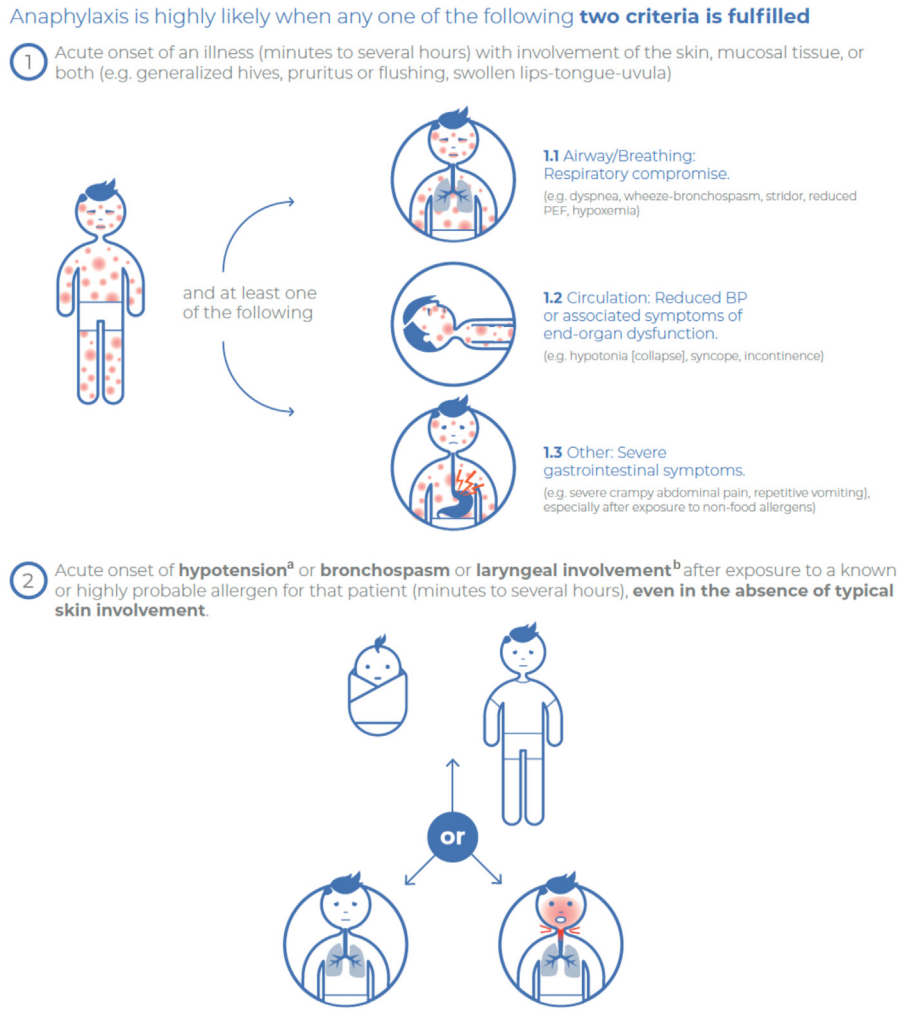

Fig. 1. WAO clinical criteria for diagnosis of anaphylaxis. BP, blood pressure; PEF, peak expiratory flow. [a]Hypotension defined as a decrease in systolic BP greater than 30% from that person's baseline, OR (i). Infants and children under 10 years: systolic BP less than (70 mm Hg + [2 × age in years]). (ii). Adults: systolic BP less than < 90 mm Hg. [b]Laryngeal symptoms include: stridor, vocal changes, odynophagia. Reproduced with permission from Cardona and colleagues 2020.[1]

The frequency of anaphylaxis is difficult to estimate; however, generally is thought to be increasing in developed and developing countries along with increases in the frequency of food allergy.[3] Adolescents have a disproportionate risk of fatal anaphylaxis.[3–5] Concerning adolescent behaviors such as rare utilization of epinephrine in emergencies,[6] insufficient perception of risk, and poor adoption of disease self-management strategies are commonplace.[7] Riskier exposures to food triggers are observed in adolescents; however, accidental food allergen exposures, misinformation, and inexperience seemed to be most prevalent.[8]

Generally, the cause for anaphylaxis is readily recognizable by a clinician because the cause often precedes symptom onset by only minutes. However, up to 17.5%

of pediatric cases can present with no clearly identifiable cause.[9] In these situations, a wide clinical differential and diagnostic evaluation is necessary before labeling the condition as idiopathic anaphylaxis.[10]

Pathophysiology

The most common cause of anaphylaxis is via immunoglobulin E (IgE)-mediated mast cell and basophil degranulation. Following immunologic sensitization to a foreign protein, IgE antibodies specific to the protein are produced by B-cells and plasma cells. These allergen-specific IgE antibodies bind to IgE receptors on the cell surface of mast cells and basophils.[11]

With subsequent exposure to the allergen, the protein cross-links adjacent allergen-specific IgE on the mast cell or basophil membrane. This leads to downstream intracellular cascades and ultimate degranulation of preformed signaling mediators such as histamine and proteases to the extracellular space. These mediators then result in cascades of rapid physiologic change, including sudden vascular permeability, smooth muscle contraction, and additional immunologic system activation. These events culminate with the clinical syndrome of anaphylaxis.[11]

Besides signaling through IgE, binding of other mast cell and basophil cell-surface receptors can induce degranulation. Complement, cytokine, prostaglandin, leukotriene, drug, toxin, and other IgG receptors have been demonstrated to independently result in degranulation and cause clinical anaphylaxis. Additionally, neutrophils and macrophages can be activated, in an IgE and mast cell/basophil independent manner, and result in anaphylaxis.[12]

Diagnostic Approach

When an adolescent presents with apparently unexplained anaphylaxis, a first necessary step is to obtain a detailed history[13] (**Box 1**). As anaphylaxis often begins outside of medical environments,[2] a clinician often depends on history from the patient or family members. Histories are subject to recall bias, second-hand information, and other omissions.

Box 1
Essential features of the history in the evaluation of a patient who has experienced an episode of anaphylaxis. Reprinted with permission from Lieberman P. 2013[13]

A. Detailed history of ingestants (foods/drugs) taken within 6 hours before the event.
B. Activity in which the patient was engaged at the time of the event.
C. Location of the event (home, school, work, indoors, or outdoors)
D. Exposure to heat or cold
E. Any related sting or bite
F. Time of day or night
G. Duration of the event
H. Recurrence of symptoms after initial resolution
I. The exact nature of the symptoms (eg, if cutaneous, determine whether flush, pruritus, urticaria, angioedema)
J. Assessing for physical factors or triggers
K. In a female, the relationship between the event and menstrual cycle
L. Was medical care given, and if so, what treatments were administered

Review of prehospital and emergency medical records for objective findings, in particular vital signs and evaluation of the airway and skin, is desirable for validation. Establishing a clear timeline of symptom onset and offset, especially in relationship to suspected triggers and treatments, is beneficial. Many suspected triggers can be deductively excluded from consideration if the exposure preceded symptoms by more than 2 hours; however, there are pertinent exceptions (galactose-alpha-1,3-galactose oligosaccharide motif [alpha-gal][14] and non-steroidal anti-inflammatory drugs [NSAIDs]).

Determining if the history and objective features meet anaphylaxis criteria should be the following step. To standardize diagnostic and treatment, the World Allergy Organization (WAO) established international criteria, most recently updated in 2020 (**Fig. 1**).[1] Multiple other guidelines and standards exist, however, many promulgated by national allergy organizations[15–18]; thus, there are some minor variances. Validation of the original 2005 National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria within emergency departments had shown a high diagnostic negative predictive value (96.4%) and high sensitivity (95%), although the specificity was less ideal (82%).[16]

Despite these efforts at standardization, it is widely apparent that clinical utilization of diagnostic guidelines remains poor in prehospital and emergency settings, and anaphylaxis remains heavily underdiagnosed, underreported, and undertreated.[19]

Immunoglobulin E-Mediated Allergy

Obscure food allergens

More than 90% of food allergies are triggered by egg, peanut, tree nut, fish, shellfish, sesame, wheat, milk, and soy; however, prevalence can vary extensively regionally (**Table 1**). As a result, other food triggers may be more obscure. Unusual allergens have been described, largely in case reports and case series, and the overall incidence is generally rare.

Ollen food syndrome

Pollen food syndrome is a very common disorder in atopic adolescents,[20] found in 5% to 48% of allergic children internationally. Symptoms often include rapid onset itchy mouth, throat discomfort, and occasional nausea following ingestion of fresh fruits, vegetables, legumes, or tree nuts. Cross-reactivity of food proteins with specific pollen proteins mediates this phenomenon. Cross-reactivities with profilin and pathogenesis-related class 10 (PR-10) proteins are generally mild and rarely induce anaphylaxis. However, other protein cross-reactivities to other proteins, such as to non-specific lipid transfer protein (nsLTP), are more commonly associated with anaphylaxis. The incidence of pollen food syndrome triggering anaphylaxis may range from 1.7% to 19% in varied studies.[21] Specific allergen component IgE serum testing, which can identify IgE binding specific cross-reactive protein components, are commercially available and may help identify higher risk pollen-food cross-reactivities.[22]

Food-exercise-induced anaphylaxis

Anaphylaxis symptoms occurring during or within an hour of exercise should prompt consideration of exercise itself being a trigger or a cofactor. The most common type of summation anaphylaxis, or anaphylaxis, which requires a trigger and a cofactor, is food-exercise-induced anaphylaxis (FEIA).[23,24] Trigger foods commonly associated with FEIA seem highly regionally variable, yet wheat proteins account for more than half of the cases in many studies.[23] Other common foods include tomato, celery, and shrimp. For some, no food cofactor is suggested, and the diagnosis is termed exercise-induced anaphylaxis (EIA).[25]

Table 1
Atypical or obscure triggers of anaphylaxis

	Prevalence in Teens	Unique/Distinct Features	Diagnostic Tools
IgE mediated			
FEIA	Common	• Onset during exertion, up to 6 h following ingestion of specific food(s) (such as profilin, PR-10, nsLTP, others) • Often aggravated by other cofactors (summation anaphylaxis)	Specific spices or herbs to common triggers: • Wheat Tri a 19 (ω5-Gliadin), also Tri a 20/21/26/36 • Celery • Shellfish • Peanut
Delayed mammalian meat allergy (alpha-gal polysaccharide)	Common	• Onset 4–6 h postprandially • Prevalence related to endemicity specific ticks • Reactions to mammalian but not avian meats • Cross-reactivity with biologic drugs derived from mammalian cell lines 14	• sIgE to alpha-gal, meats • Skin testing
Spice allergens	Rare	• May be associated with pollen-food syndrome patterns	• sIgE to specific spices or herbs
Rare drug/vaccine allergens • Gelatin[172] • Neomycin[173]	Rare		• Skin testing • sIgE testing
Pollen-food syndrome (oral allergy syndrome)	Common	• Patterned sudden onset of multiple fruit/vegetable/nut/legume intolerances • Often resolves if foods are cooked or heat treated • Usually coexists with seasonal allergic rhinitis	• sIgE • Component-resolved sIgE
Latex	Rare	• History of multiple surgical operations (including spina bifida) • Cross-reactivity with banana, avocado, chestnut, and kiwifruit	• sIgE (note: low sensitivity)

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Table 1
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	Prevalence in Teens	Unique/Distinct Features	Diagnostic Tools
Aeroallergen	Rare	• Marijuana • Bee pollen	• sIgE testing • Skin testing
Non-IgE mediated			
MRGPRX ligand	Common	• Can induce anaphylaxis on first exposure, without prior exposure to the drug	• Often associated with narcotics, vancomycin, quinolones, venoms, neuromuscular paralytics
NSAID/aspirin (aspirin exacerbated respiratory disease)	Common	• Triad of severe asthma, nasal polyposis and COX1 inhibitor reactions may not develop simultaneously • Celecoxib (strict COX2 inhibitor) and acetaminophen generally tolerated	• Urine LTE4 • Aspirin challenge
Exercise induced (EIA)	Common	• Preceding history of exercise	• Develops with or without preceding food
Summation[24]	Rare	• two or more triggers (co-factors) required together or sequentially • overlap with FEIA (above)	• history of 2 or more co-factors such as exercise, NSAID, menses, illness, alcohol, poor sleep
Venom mediated			
Mosquito	Rare	• Limited to endemic areas/seasons • Follows bites	• Serum IgE
Fire ants	Common	• Limited to endemic areas • Follows bites • Benefits from venom immunotherapy	• Skin testing • Serum IgE
Tick bites	Rare	• Limited to endemic areas in Europe and Australia • Follows bites	• Serum IgE

Alpha-gal oligosaccharide motif anaphylaxis (delayed mammalian meat syndrome)

Food proteins induce most food allergies; however, delayed mammalian meat syndrome is a clinically relevant oligosaccharide-mediated food allergy. Alpha-gal is foreign to humans and other higher order primates due to the loss of the alpha-gal glycosylase during evolution.[14] Most other mammals have retained the glycosylase, thus mammalian-sourced meats have the alpha-gal motif on many glycosylated proteins.

Patients sensitized to alpha-gal present with anaphylaxis following ingestion of mammalian meats such as beef and pork. Unlike protein-based food allergens that induce symptoms often within minutes after ingestion, alpha-gal-induced anaphylaxis is typically induced 4 to 6 hours after ingestion of mammalian meat. This can cause diagnostic delay because the association with meat may be difficult to deduce.[14]

Fascinatingly, the primary elicitor of sensitization to alpha-gal oligosaccharides is a tick bite. Patients at most risk tend to be hunters or hikers who live in endemic regions for specific ticks such as the Lone Star tick in North America, the Castor bean tick in Europe, and the Longhorn tick in Asia and Australia.[26] Patients with this syndrome may also develop anaphylaxis to certain biological drugs derived from mammalian cell lines.[14]

Food dyes and additives

In contrast to prevailing beliefs, synthetic food and drug dyes are rarely allergenic.[27] In contrast, naturally sourced dyes rarely trigger anaphylaxis. Dyes used from used in cosmetics and foods such as cochineal (carmine) extract derived from female *Dactylopius coccus* scale insects has been implicated.[28] Naturally sourced annatto seed coloring has also been associated with anaphylaxis.[29]

Generally, food additives and preservatives are very uncommon triggers of unexplained anaphylaxis.[30] Sulfite antioxidants, such as those in dried fruits generally trigger asthma rather than anaphylaxis.[31] Specific food additives implicated in anaphylaxis include mycoprotein used in vegan meat substitutes,[32] psyllium in fiber supplements,[33] erythritol in sugar-free products,[34–36] guar gum,[37] and inulin.[38,39]

Spice and rare food allergies

Herbal and spice allergies are generally rare.[40] Mustard is perhaps the most common, most extensively described in France with prevalence in children up to 6%.[41] Multiple case reports of anaphylaxis, most due to pollen cross-reactivities, have been described to chamomile,[42] fennel,[43] fenugreek,[44] oregano,[45] thyme,[45] coriander,[46,47] and others.

Dust mite-contaminated flour has been often implicated causing anaphylaxis. This syndrome, curiously often triggered following pancake ingestion, is most common in warm tropical environments where the mites can thrive.[48,49] Lupine flour, a legume powder added as a flour supplement popular in Europe, can trigger flour-associated anaphylaxis as well.[50]

There have been multiple case reports of bee pollen dietary supplements inducing anaphylaxis. Although sensitization is rare to insect-pollinated flower pollens, wind-pollinated flower pollens have been identified within bee pollen supplements.[51]

Nonfood Immunoglobulin E-Mediated Allergies

Anaphylaxis to marijuana has been rarely reported.[52] Nearly 3 of 4 patients with marijuana allergy are sensitized to Can s 3, a protein cross-reactive with other foods and pollens.[53] Because adolescents often initiate marijuana use surreptitiously, a careful history elicitation may be helpful.

Natural rubber latex exposures in adolescents are likely primarily via surgical exposures, yet children can become sensitized to natural rubber latex at home and other environments.[54] Particular efforts to avoid natural rubber latex exposure in surgical suites, and most specifically to eliminate exposure for children with spina bifida,

have resulted in markedly reduced incidence of latex anaphylaxis.[55] Although largely minimized, medical exposure to latex continues within developing nations and still exists in developed countries.[56] Anaphylaxis presenting during the maintenance phase of anesthesia should raise concerns for latex allergy.

Obscure Venom Allergens

Envenomation from hymenoptera insects is a very common source of IgE-mediated anaphylaxis and given the pain from a sting often easily identifiable as a trigger. In contrast, other insect bites have been rarely associated with anaphylaxis.

Despite expanding global distribution of mosquitos, systemic immediate type hypersensitivities and anaphylaxis to mosquito venom seem very rare.[57,58] In one case, systemic mosquito allergy without evidence of specific immunoglobulin E (sIgE) sensitization was revealed to be due to systemic mastocytosis (SM).[59] Treatment with immunotherapy to whole mosquito body extracts may be beneficial.[60]

Imported fire ant (*Solenopsis invicta*) stings are nearly universal in endemic areas, with sting rates of ~51% within first weeks of arrival in endemic areas.[61] Children aged younger than 10 years in endemic areas have an attack rate of 55%, and 40% are stung monthly in peak seasonal exposure.[62] As such, the potential for allergic sensitization is significant, up to 17% within in endemic areas. The clinical phenotype of patients with fire ant-induced anaphylaxis seems clinically similar to those with hymenoptera stings.[63] Fire ant immunotherapy is highly efficacious.

Anaphylaxis to proteins (independent of alpha-gal hypersensitivity) in certain ticks has been described but poorly understood.[26] This is best described in Europe from pigeon tick (*Argas reflexus*) bites, and in Australia from the common bush tick (*Ixodes holocyclus*) bites.[64–66]

Non–Immunoglobulin E-Mediated Allergy

Mastocyte-related G-protein coupled receptor X2

Mast cell degranulation via ligands binding the mastocyte-related G-protein coupled receptor X2 receptor has been identified as the etiologic factor for multiple non–IgE-mediated drug allergies and some venom reactions.[67] The receptor seems to be a polyvenom receptor, and interestingly many endogenous ligands (substance P, vasoactive intestinal peptide [VIP], cortistatin, and somatostatin) and exogenous medications (narcotics, neuromuscular paralytics, vancomycin, fluoroquinolones, and leuprolide) may induce anaphylaxis through this receptor. At the present time, loss-of-function polymorphisms have been described but gain of function or activating autoantibodies to this receptor has not yet been described.[67]

NSAID induced

AERD/NERD (aspirin-NSAID exacerbated respiratory disease), a COX1-inhibitor drug hypersensitivity, typically presents in young adults. The incidence in adolescence is uncertain; however, it was found to be 6% in a recent study with retrospective recall of age of onset.[68] Severe asthma and nasal polyposis may precede anaphylactic reactions to NSAIDs with this diagnosis, thus the diagnosis can be elusive in adolescence. Normal urine leukotriene E4 (LTE_4) levels may help exclude an AERD diagnosis.[69]

Clonal Mast Cell Disorders

Mastocytosis

Mastocytosis is a neoplastic disorder leading to proliferation of mast cells and a common cause of obscure anaphylaxis (**Table 2**). Criteria and subtypes are promulgated by the WHO[70] and have been recently refined within a 2022 consensus.[71]

Table 2
Mast cell disorders

	Prevalence in Adolescents	Unique Features	Diagnostic Tools
Clonal mast cell disorders			
MCAS (monoclonal subtype, MMAS)	Rare	• Episodic anaphylaxis-like symptoms *and* response to antimediators *and* biomarker evidence of mast cell activation • Evidence of clonal surface markers or KIT mutation • Not meeting WHO SM criteria	N-methylhistamine urine Prostaglandin F2a Prostaglandin D2 Leukotriene E4 Tryptase Evidence of clonal surface markers or KIT mutation
CM	Common	• Pigmented macules/papules that urticate with pressure (Darier sign) or heat • Often involutes during puberty • Anaphylaxis risk associated with skin involvement, serum tryptase	Whole skin examination Darier sign Skin biopsy SCORMA score[171]
SM (indolent)	Rare	• Risk of osteoporosis • Venom-induced hypotension without venom allergy • Frequent intolerance to alcohol and NSAIDs	Bone marrow biopsy WHO diagnostic criteria D816 V high-sensitivity PCR (ddPCR or allele specific)
SM (smoldering, aggressive) Mast cell leukemia	Extraordinarily rare	• Organ infiltration (B-symptoms): • Hepatomegaly/splenomegaly, marrow infiltration • Organ dysfunction (C-symptoms): • Liver, splenic dysfunction • Cytopenias • Weight loss • Malabsorption • Osteoporosis	Evaluation for end-organ injury, hepatosplenomegaly Blood count with differential, flow cytometry, hematopathology/genetics DEXA (dual x-ray absorptiometry) bone density assessment scan Oncology consultation

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Table 2
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	Prevalence in Adolescents	Unique Features	Diagnostic Tools
Nonclonal mast cell activation			
HAT [85]	Common (Up to 1 in 20)	• Common in Caucasians • Autosomal dominant inheritance • Highly variable penetrance • Severity associated with copy number • Retained primary dentition common	• Baseline serum tryptase >6.5 • Tryptase gene copy number variation ddPCR test
Chronic urticaria/angioedema	Very common	• Autoimmune in ~40%, idiopathic in remainder • Not due to drug allergy, but often aggravated by NSAIDs • Only cold-induced urticaria associated with anaphylaxis risk	• Basophil activation test • Anti-IgE autoantibodies • Anti-CD24 autoantibodies • Ice cube skin test
MCAS (nonclonal)	Rare	• Episodic anaphylaxis-like symptoms AND response to antimediators AND biomarker evidence of mast cell activation • No evidence of clonal surface markers or KIT mutation • Not meeting SM criteria	• N-methylhistamine urine • Prostaglandin F2a • Prostaglandin D2 • Leukotriene E4 • Tryptase • No evidence of clonal surface markers or KIT mutation
Complement activation (CARPA)	Unknown	• Preceding exposure to nanomedicines or biological drugs	• C4, sC5a, sC3a • Serum sC5-9 • Rheumatologic serologic and clinical evaluation

Cutaneous mastocytosis. Cutaneous mastocytosis (CM) is a relatively common disease of childhood and adolescence. Maculopapular CM (MCPM)/urticaria pigmentosa (UP) is the most common subtype of CM of childhood, usually presenting within the first year of life.[72] Multiple polymorphic pigmented skin lesions are the primary symptom, which urticate with applied pressure (Darier's sign).

Anaphylaxis from CM in children and adolescents is unusual (up to 9%) but the risk is largely associated with extensive body surface area involvement or elevated basal serum tryptase.[73,74] Roughly 70% of children with CM carry a mutation within the *cKIT* gene, a mast cell growth-promoting tyrosine kinase. Only 30% are due to D816V associated mutations, whereas this is more than 90% in adult populations.[75]

More than 80% of children with MCPM/UP experience involution or resolution of CM lesions during adolescence.[76] Certain features of CM may suggest systemic disease, particularly a positive D816V peripheral blood mutation,[77] persistent tryptase elevation, and lack of involution after puberty.[78]

Systemic mastocytosis. SM is a rare hematologic neoplastic disorder of mast cells, which is definitively associated with a higher risk of spontaneous or minimally triggered anaphylaxis. The most prevalent type is indolent systemic mastocytosis (ISM). Not all adolescents who present with CM also have SM, unlike in adult populations. Advanced SM is extraordinarily rare in adolescent populations.[76] Nearly all pediatric SM presents with concomitant CM, unlike in adult populations.[79]

Mast cell activation syndrome. Consensus criteria for mast cell activation syndrome (MCAS) were developed in 2011 and reinforced by expert consensus in 2019.[80,81] There are 3 necessary conditions to be met for diagnosis (simplified).

1. spontaneous anaphylaxis, without other known cause,
2. acute elevation of a relevant biomarker with symptoms, and
3. clinical response to antimediator medications.

For patients meeting MCAS criteria, abnormalities on bone marrow and intestinal pathologic condition often but do not always demonstrate abnormal clustering, spindled cell morphology, and/or clonal markers.[82,83] Acute elevation with symptoms of biomarkers serum tryptase is found in roughly one-third, and elevations of urinary n-methylhistamine in over half, and of prostaglandin D2 in less than half with prostaglandin D2.[84] Prognosis seems excellent as two-thirds of MCAS patients experience complete or major response to antimediators such as antihistamines or mast cell inhibitors.[84]

Nonclonal Mast Cell Disorders

Hereditary alpha tryptasemia

Described first in 2016 as a genetically defined clinical disorder,[85] hereditary alpha tryptasemia (HAT) is a gene copy number variation with a clinical syndrome including in some series an increased risk of anaphylaxis.[85] Tryptase is a protease released exclusively by mast cells, encoded by sets of alpha and beta tryptase genes. The total gene copies of both alpha and beta tryptase (between alpha and beta) should equal 4; however, additional alpha gene copies can be observed in approximately 6% of Caucasian Americans. These additional copies of alpha-tryptase correlate with baseline serum tryptase levels as well as with HAT symptom severity.[85] Overexpression of α-tryptase protein due to coinheritance of a linked overactive promoter seems to explain the observed serum tryptase concentrations.[86]

Genetic copy number variation testing via a droplet digital polymerase chain reaction (PCR) assays available to screen for HAT and has very high sensitivity and

specificity for the disorder.[87] The wide variation of symptoms and penetrance with a set genotype is still poorly understood and debated.[85,88,89] Surprisingly, coexisting clonal mast cell disease may be present in 10% to 17% of HAT patients, so screening for both disorders may be necessary.[86,90,91]

Cold-induced urticaria

Unlike other forms of chronic urticaria, patients with cold triggers have a high prevalence of anaphylaxis (up to 21%).[92] Most anaphylaxis cases follow exposure to cold water, which has a high heat of vaporization and enthalpy and can cool the core body temperature readily. Ice cube skin testing can help diagnose; however, it has low sensitivity for the diagnosis and risk for anaphylaxis in children and adolescents.[93]

Mimic Disorders

Validation studies of clinical anaphylaxis criteria pose the hazard of false positives, leading to diagnostic misclassification.[16] Common mimic disorders (**Table 3**), which can present in adolescence include hereditary angioedema (HAE), panic and somatoform disorders, and inducible laryngeal obstruction. Additionally, extremely rare disorders such as neuroendocrine tumors could also present similarly to anaphylaxis.

Neuroendocrine tumors

Neuroendocrine neoplasms such as carcinoid or VIPomas may episodically release hormones, causing mediator symptoms that can overlap with anaphylaxis.[94] Most carcinoids do not cause carcinoid syndrome due to first-pass hepatic metabolism; however, carcinoid tumors presenting in the lung or liver can produce anaphylaxis-mimicking episodic diarrhea, flushing (80%), and/or bronchospasm (25%).[95] Carcinoid symptoms can be triggered by cofactors such as anaphylaxis, including alcohol, exercise, or stress. Diagnostic screening via 5-hydroxyindoleacetic acid (5-HIAA), a serotonin metabolite, via a 24-hour urine collection is recommended. VIPomas similarly can produce profound secretory diarrhea and flushing and are often associated with elevated VIP serum levels and osmolality defects. Higher specificity studies including gallium-tracer based positron emission tomography/computed tomography (PET/CT) or PET/MRI have high diagnostic sensitivity for disease.[96]

Bradykinin-mediated angioedema

Bradykinin-induced angioedema can seem indistinguishable from angioedema from histaminergic causes. However, angioedema from bradykinin induces neither hypotension nor urticaria, and it is not responsive to corticosteroids, epinephrine, or antihistamines. Generally, angioedema from bradykinin pathophysiology has a slower onset and much slower offset than with anaphylaxis.

Hereditary angioedema. HAE often initially presents in adolescence, with episodic recurrent vomiting and abdominal pain attacks and/or orofacial angioedema.[97] Attacks can be spontaneous or associated with menses but in contrast to anaphylaxis can be triggered by trauma such as dental procedures. Screening for HAE types I and II can be performed with convalescent complement 1 esterase inhibitor (C1INH; functional and quantitative) and C4 serum levels. HAE with normal C1INH remains diagnostically challenging; however, genetic sequencing for known mutations is commercially available.[98]

ACE-I-induced angioedema. Angioedema due to angiotensin-converting enzyme inhibitors (ACE-I) drugs is thought to be bradykinin mediated, and clinically the swelling

Table 3
Anaphylaxis mimic disorders

	Prevalence	Distinct Features from Anaphylaxis	Shared Features with Anaphylaxis	Diagnostic Tools
Neuroendocrine Disorders				
Carcinoid	Rare[94]	• Bowel obstruction • Mesenteric ischemia • Right heart failure • Tricuspid regurgitation • Pulmonary valve stenosis • Prolonged hypotension (crisis)97	Flushing Hypotension	• Elevated 5-HIAA, urinary (24 h collection) • Elevated chromogranin A • ^{68}Ga-DOTATATE or DOTATOC PET/CT response to somatostatin analogs
VIPoma	Rare	• Copious secretory diarrhea • Hypokalemia • Hypochlorhydria • Weight loss • Hypercalcemia • Hyperglycemia	Diarrhea Flushing	• Stool osmolarity gap • Serum electrolytes • Elevated serum VIP • ^{68}Ga-DOTATATE or DOTATOC PET/CT response to somatostatin analogs
Familial medullary thyroid carcinoma	Rare	• Telangiectasias • Thyroid nodules	Flushing	• Elevated calcitonin • Elevated carcinoembryonic antigen • Family history (spontaneous disease rarely presents before the age of 20 years)
Pheochromocytoma	Rare	• Hypertension • Diaphoresis • Headaches • Insulin resistance	Flushing Tachycardia	• Elevated metanephrines/catecholamines • Family history of MEN2, NF1, VHL or PHEO (spontaneous disease rare in adolescents) • CT for adrenal mass

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	Prevalence	Distinct Features from Anaphylaxis	Shared Features with Anaphylaxis	Diagnostic Tools
Bradykinin Disorders				
HAE[97,168]	Rare	• Erythema marginatum • Absent hypotension • Absent urticaria • Abdominal pain • No response to corticosteroids, antihistamines, epinephrine	Angioedema Vomiting	• Low basal/acute serum C1INH (functional or quantitative) • Low C4 • Positive genetic screen for mutations: SERPIN1, Factor 12, PLG, ANGPT1, KNG1, MYOF
ACE-I induced angioedema	rare	• Absence of hypotension, urticaria, bronchospasm	Angioedema	• Preceding ACE-I exposure • No biomarker
Unexplained Disorders				
Systemic capillary leak syndrome (Clarkson's)[169,170]	Rare	• Hemoconcentration and hypoalbuminemia • Prolonged episodic hypotension • Common associations with monoclonal gammopathy, infection (COVID-19, dengue), drug triggers including IL2, autoimmunity (psoriasis)	Hypotension Angioedema Gastrointestinal symptoms	• Response to immunoglobulin
Inducible laryngeal obstruction (paradoxic vocal cord dysfunction)	Common	• Absent wheezing, hypotension, urticaria/flushing • Inspiratory stridor • On-off symptoms	Acute dyspnea presyncope	• Pittsburgh VCD Index 115 • Laryngoscopy demonstrating abnormal inspiratory adduction of the vocal cords • Spirometry demonstrating flattening of inspiratory flow volume loop

Exogenous Source				
COX1 inhibitors Aspirin/NSAIDs	Common	• Delayed onset symptoms after exposure (common) • Nasal polyps/severe asthma often precedes NSAID intolerance	Flushing Wheezing Bronchospasm Hypotension Diarrhea	• Urine LTE4 (high negative predictive value)[69]
Niacin (nicotinic acid)	Unknown	• Improvement with NSAIDs	Flushing Nausea Vomiting Pruritis	• Vitamin supplements/energy drinks transaminitis
Histidine (scombroid poisoning)	Rare	• Spoiled scromboid fish ingestion, without fish allergy • More than one person with simultaneous symptoms	No clinical distinguishing symptoms	Tryptase (acute level should be normal because there is no degranulation)
Psychiatric				
Somatoform	Common	• Absence of hypotension, wheezing, urticaria, and vomiting	Throat tightness common	Formal anaphylaxis criteria utilization
Panic attacks	Common	• Paresthesias • Absent urticaria/angioedema • Diaphoresis • Hyperventilation	Intense fear Shortness of breath	Formal anaphylaxis criteria utilization
Factitious (Munchausen's)	Unknown	• Secondary gain	Intentional access and exposure to known anaphylaxis trigger	Formal anaphylaxis criteria utilization

can be poorly distinguished from HAE.[99] Although ACE-I are rarely used in adolescents; similar to adults, adolescents seem at risk for angioedema.[100] Continued angioedema despite cessation of an ACE-I drug has been described; however, whether this occurs in adolescents is unknown.[101] ACE-I-induced angioedema regrettably is a diagnosis of exclusion without a diagnostic biomarker to date.

Exogenous

Niacin (vitamin B3). Adolescents are known to take multivitamins and nutritional supplements for purported benefits. Energy drinks are marketed to adolescents, and many contain milligram quantities of niacin per serving.[102] Niacin can induce anaphylaxis-mimicking flushing and hypotension via release of prostaglandin D2 (PGD_2) from mast cells and serotonin from platelets.[103] Diagnosis can be made rapidly via resolution after discontinuation of niacin. Although nondiagnostic, NSAIDs may help resolve symptoms by blocking prostaglandin.

Histidine (scombroid) poisoning. Consumption of spoiled pelagic fish, often in the scombroid family including tuna and grouper, can lead to postprandial anaphylaxis-like symptoms. These symptoms are caused by direct ingestion of histidine produced by spoilage bacteria, and the tyramine can be converted to histamine. Clues suggesting the poisoning include others with similar acute symptoms eating the same meal, and subsequent tolerance to fish.[104]

Food additives. Although commonly perceived by the public as allergens, food additives such as synthetic food dyes, glutamates, and benzoates are rarely triggers of pseudo-allergic symptoms in double-blinded challenges.[105] Similarly, naturally occurring food salicylates, vasoactive amines have minimal-quality or poor-quality data supporting risk of anaphylactic symptoms.[105] Low-histamine, dye or preservative-free diets are not presently endorsed by any organizational practice parameter for the management of idiopathic anaphylaxis or food allergies.

Infectious

Evaluating patients for a history of potential exposure to helminths, in endemic areas, is recommended. Anaphylaxis from rupture of echinococcus cysts has been well described, often during surgery but it may be spontaneous.[106] Ingestion of raw or undercooked fish and cephalopods can lead to *Anisakis simplex* nematode infections, which have been associated with anaphylaxis. Disease is most common in Japan and Spain.[107] *Taenia solium* tapeworm-induced anaphylaxis and other allergic manifestations have been reported in rare cases.[108] Roundworm *Ascaris lumbricoides* infections have been associated with intense allergic reactions.[109]

Upper airway

Inducible laryngeal obstruction. Stridulous, often inspiratory, dyspnea caused by paradoxic closure of the vocal cords may mimic airway angioedema and bronchospasm present with anaphylaxis. This syndrome has had a multitude of other names including vocal cord dysfunction and paradoxic vocal cord movement.[110] The overall prevalence in adolescents may be around 5% to 7%.[111]

A clinical index of suspicion can be bolstered via screening tools and intermittent flattening of inspiratory flow volume loops on spirometry.[110] The Pittsburgh Index, which uses variables of throat tightness, dysphonia, absence of wheezing, and triggering odors, has favorable screening sensitivity and specificity.[112] Direct laryngeal evaluation of abnormal movement via flexible rhinolaryngoscopy, using provocative maneuvers, is the gold standard diagnostic evaluation. Unfortunately, the sensitivity of these tests and provocative maneuvers is likely poor.[110]

Although multiple treatments have been studied, laryngeal/speech therapy or botulinum toxin therapy for refractory cases are commonly considered for long-term management. Pathophysiology, diagnosis, and treatment remain with significant knowledge gaps at the present time.[110]

Psychiatric

Somatoform disorder. Proposed criteria for nonorganic symptoms mimicking anaphylaxis were developed in 1995, termed undifferentiated somatoform-idiopathic anaphylaxis.[113] In the original description, cutaneous and laryngeal symptoms were found in most patients, and these patients reported no response to medication. All the patients were ultimately diagnosed with undifferentiated somatoform disorder (DSM3). Over half of the patients had defensive responses to the consideration of a somatoform disorder.

A follow-up modern study found patients with somatoform anaphylaxis were more likely to complain of subjective throat tightness or swelling. Past psychiatric histories were not unique compared with confirmed anaphylaxis patients in this study.[114]

Somatic symptom disorder per the present international reference DSM 5[115] is defined as one or more somatic symptoms that cause distress or psychosocial impairment, and excessive thoughts about the seriousness, feelings including persistent or severe anxiety, or behaviors such as excessive time and energy devoted to the concern. There is no present subset defined in DSM 5 for somatic anaphylaxis.

Fictitious (Munchausen's) anaphylaxis. Fictitious (feigned or intentionally induced) anaphylaxis has been reported in multiple case reports.[116–119] In contrast to somatoform disorders, there is an intentional intent to deceive for secondary gain. Suspected cases should be referred to specialists in behavioral medicine.

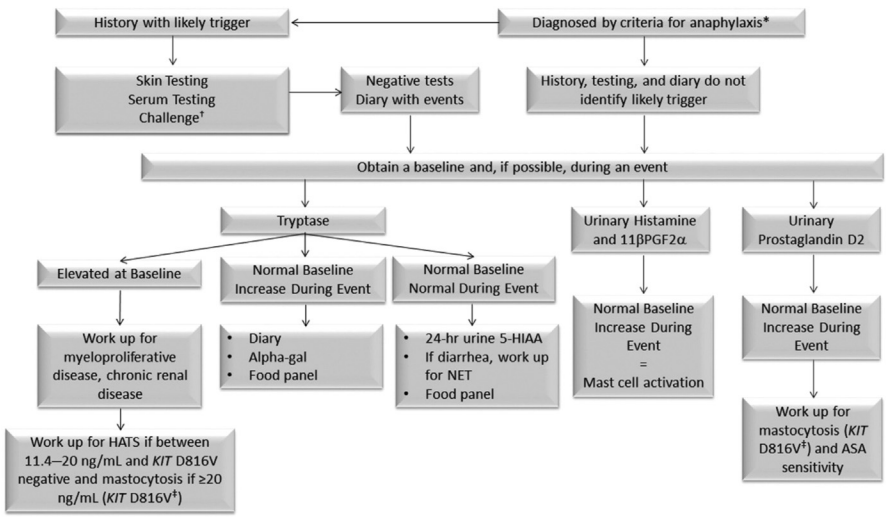

Fig. 2. Proposed diagnostic evaluation for occult anaphylaxis (excluding evaluation for non-neuroendocrine tumor mimic disorders). *Diagnosis according to accepted criteria. †Because challenges can have safety risks, a challenge should not be conducted if history is conclusive or serum-specific IgE is >15 kU/L and should be conducted with caution in patients with serum-specific IgE from 0.35 to 15 kU/L, in consideration with concurrent atopic diagnoses. ‡Peripheral blood. Reprinted with permission from the Idiopathic Anaphylaxis Yardstick, Carter M. et al. 2020.[10]

Diagnostic Evaluation Workflow

A staged diagnostic approach is recommended to address both mimic disorder concerns, as well as anaphylaxis causes (**Fig. 2**). Routine screening with allergen skin prick testing, sIgE testing, and/or observed challenge to the allergen is recommended if there is a likely trigger.[10]

Routine allergy evaluations

Established screening tools for allergen sensitization may assist if rare allergens are suspected. Commercial ELISA-like sIgE tests are widely available, and skin prick/intradermal testing is a standard diagnostic offered by allergists.

Whereas testing for aeroallergen and foods have reasonable test characteristics, drug allergy skin and sIgE testing generally has very poor sensitivity/specificity characteristics and is often unhelpful.[120] Graded supervised allergen challenges remain the gold standard for clinical exclusion of an allergy to a substance and should be considered if there is a low prechallenge concern for reactivity.[120] Basophil activation tests are an emerging diagnostic with some commercial availability but suffer from uncertain test characteristics and uncertain role in diagnostic evaluation.[121]

If no cause is evident but a trigger is still suspected, a patient diary may help recall of preceding triggers. Laboratory evaluation for mast cell biomarkers is often the next step (**Fig. 2**).

Tryptase

Tryptase is a protease selectively produced by mast cells and is the most useful initial laboratory marker. Mature tryptase is produced following mast cell degranulation. It has a short half-life, peaking between 30-minute and 90-minute postanaphylaxis, and declining 2 hours after degranulation. Obtaining tryptase draws rapidly during suspected reactions can be helpful diagnostically. Significant tryptase elevation suggesting degranulation have been defined as levels greater than 120% of the baseline serum tryptase plus 2ng/dL.[122] A fractionated serum tryptase laboratory test can quantify mature from immature tryptase. Mature tryptase levels greater than 1 ng/dL may suggest recent degranulation, whereas low levels with high total tryptase suggest a high mast cell burden.[123]

Other biomarkers

Mild anaphylaxis symptoms, and food-induced anaphylaxis, often do not present with elevated acute tryptase levels. Other biomarkers may be diagnostic for evidence of mast cell/basophil activation. Urinary N-methyl histamine, prostaglandin F2a or D2, and leukotriene E4 levels above normal may be noted following anaphylaxis. Serum histamine is a difficult biomarker is generally not recommended for the assessment of anaphylaxis.[124,125]

Complement-mediated anaphylaxis might be suggested if consumable components such as C4 are low acutely, and/or if soluble sC5-9 levels are elevated.[126] Complement activation-induced anaphylaxis (CARPA) has been proposed as the underpinning of anaphylaxis induced from nanoparticle and some biologic medicines, including coronavirus disease 2019 (COVID-19) mRNA vaccines.

Convalescence

Tryptase. A baseline serum tryptase is a recommended initial screen for SM and HAT.[10] Basal serum tryptase less than 6.5 ng/mL are not observed with HAT but generally one supernumerary copy leads to tryptase levels 13.6 ng/mL (95% CI 12.6–14.4).[127] Baseline serum tryptase levels less than 11.4 ng/mL are uncommon with SM, whereas levels above 20 ng/mL suggest disease and are a minor criterion.

KIT proto-oncogene receptor tyrosine kinase mutation. High sensitivity allele-specific or digital droplet KIT proto-oncogene receptor tyrosine kinase (KIT) D816 V mutation serologic tests are available.[128] False negatives can occur due to low precursor frequency because mastocytosis and monoclonal mast cell disorders have somatic rather than germ-line mutations, and thus restricted to a mast cell hematopoetic lineage.[129] Sequencing for other KIT mutations in select exons is commercially available; however, the sensitivity may be poor.[75] In children/adolescents, the specific KIT mutation does not predict the evolution of disease.[130]

Bone marrow evaluation. Bone marrow biopsy remains the gold standard site for biopsy to consider clonal mast cell disorders and consider abnormal nonclonal disorders.[71] Special immunohistochemistry stains to identify mast cells with clonal markers,[131] and special genetic evaluations are required for diagnostic purposes.[75] Flow cytometry inclusive of CD117/CD25/CD2/CD35 can help identify rare clonal mast cell populations. Very rarely, mastocytosis can be missed on a bone marrow biopsy, and repeat biopsies, screening for extramedullary disease,[132] or expert pathologic review using special approaches might be necessary.[133]

Acute treatment

Anaphylaxis self-recognition and self-management. Often, anaphylaxis occurs outside of medical environments, which requires patient or parent self-recognition and initial management of anaphylaxis. The recognition (**Fig. 1**) and initial emergency management (**Fig. 3**) of anaphylaxis have been standardized.[1,17] These standards are generally uniform, without regard to the pathophysiology or etiologic cause.

Self-recognition and self-management are critical and can be taught to adolescents. Obstacles to anaphylaxis self-management in adolescents include recognition, self-efficacy to request assistance with peer pressures, needle phobia, and epinephrine not readily available.[134]

Rapid administration of intramuscular epinephrine, lying down with legs elevated, and emergency medical systems activation are initial management steps.

Medical management. Prehospital and hospital emergency medical management also includes IV fluid resuscitation, provision of bronchodilator and oxygen, and assessment and management of the airway as indicated by symptoms.[1] Adjunctive systemic corticosteroids and antihistamines are not required given the lack of evidence for benefit and a high number to treat. Provider discretion is still permitted for consideration of these medications for management.[18]

Prolonged observation periods are recommended if there is a high risk for second phase reaction. Major factors for prolonged observation include requiring 2 or more doses of epinephrine, severe initial symptoms, and an unknown trigger.[18] Escalation to intensive care unit level care is indicated if airway protection or need for central pressor support, and/or if there was cardiopulmonary arrest or end-organ injury. At discharge, provision and education about indications for epinephrine autoinjectors, written action plans, and follow-up care is required.[18]

Prevention

Avoidance of known triggers. For known triggers, avoidance represents first-line prevention.

- *Cold urticaria*: Avoidance of cold exposures with appropriate protective clothing, and avoidance of situations of risky exposure.[135]
- (*Food*)*/Exercise-induced anaphylaxis*: Patients with FEIA/EIA should exercise before breakfast on empty stomach, and exercising with epinephrine autoinjectors

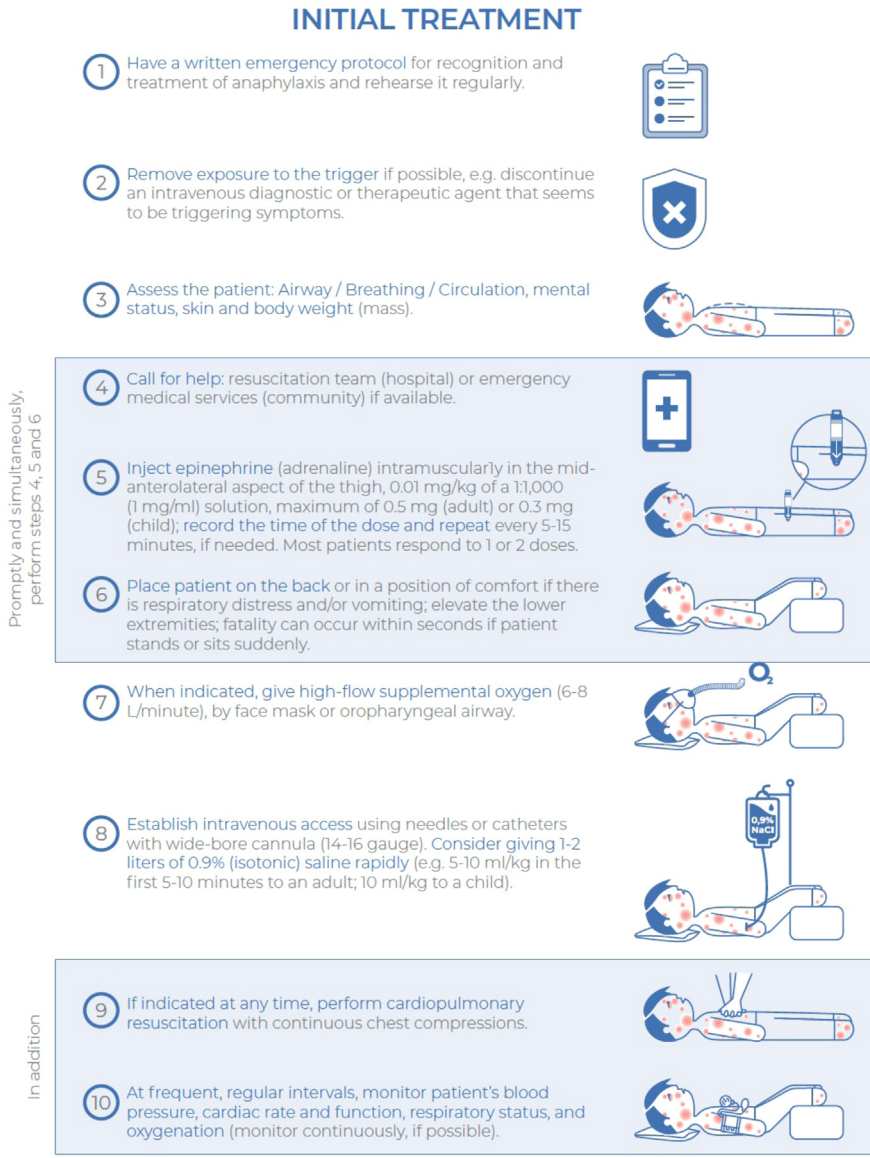

Fig. 3. WAO criteria for the initial treatment of anaphylaxis. Disclaimer: In no event shall WAO be liable for any damages arising out of any use of or reliance on this material (see www.worldallergy.org for full disclaimer). Not for commercial use. (*Source*: Cardona V, Ansotegui IJ, Fbisawa M et al. World Allergy Organization Anaphylaxis Guidance 2020. World Allergy Organization Journal 2020; 13(10):100472. Doi:https://doi.org/10.1016/j.waojou.2020.100472. Reproduced with permission from Cardona and colleagues 2020.[1])

and with a partner able to recognize, treat reactions, and call for emergency assistance.[25]

- *Drug allergy*: Strict avoidance of triggering or cross-reactive medications is the mainstay of present management.[120] Inpatient desensitization can permit safer exposure to the drug if a drug is medically necessary.
- *Food allergy*: Strict avoidance of triggering foods and cross-reactive foods is the mainstay of present management of anaphylaxis. Desensitization via oral immunotherapy has been intensely studied especially for peanut. There is strong evidence that oral immunotherapy (OIT) increases food tolerance; however, the benefit is often transient or marginal and with an increased risk of anaphylaxis compared with avoidance.[136]
- *Pollen-food syndrome*: Theoretically, subcutaneous and sublingual allergen immunotherapy could have benefit for pollen-food syndrome (PFS); however, there have been few studies to date with varied responses.[137,138] Strictly avoiding PFS foods that trigger anaphylaxis is recommended.

Medications. Treatment to suppress both the severity and frequency of spontaneous anaphylaxis has been poorly studied, and often medication trials are necessary to find a suitable controller. A threshold for when to initiate suppressive therapy has been defined as frequent idiopathic anaphylaxis, defined least 2 episodes during 2 months or at least 6 episodes during 12 months; however, this commonly used threshold was arbitrarily defined.[139]

Prolonged courses of systemic corticosteroids with oral antihistamines were initially recommended for unexplained anaphylaxis, often achieving disease stabilization and resolution.[139,140] The health risks for adolescents of prolonged systemic steroids are significant however, and a risk/benefit ratio consideration may be needed. Other approaches may need to be considered in adolescents.

- *H1:* Prophylactic use of newer (3rd generation) antihistamines following chronic urticaria guidelines is recommended for frequent idiopathic anaphylaxis[10]; however, there is minimal data supporting benefit to date. Urticaria guidelines recommend up to 4 times standard dosing over a day of newer H1 antagonists such as cetirizine/levocetirizine, fexofenadine, or loratadine/desloratadine.[141] These antihistamines, in contrast to earlier generations, have longer half-lives and less anticholinergic side effects.
- *H2*: The prophylactic benefit of H2 specific antagonists, such as famotidine, is uncertain. Famotidine can be considered in trial, however, especially if gastritis symptoms while taking systemic steroids concurrently.[10] In chronic urticaria, only 1 in 3 have clinical response to H2-specific antagonists.[141]
- *Leukotriene targeting drugs*: Leukotriene receptor antagonists, such as montelukast or zafirlukast, and 5-lipoxygenase inhibitors, such as ziluteon, have not been well studied in idiopathic anaphylaxis (IA).[10]
- *Mast cell inhibitors (MCI)*: Cromolyn has not been well studied in IA. Given poor absorption from the gastrointestinal (GI) tract, benefit is largely expected for GI symptoms only.
- *Combination medicines*:
  - Doxepin (H1/H2): Doxepin is an oral tricyclic drug with superpotent H1/h2 antagonism. Unfortunately, sedation, prolonged QTc intervals, and interaction with selective serotonin reuptake inhibitor (SSRI) antidepressants make use for anaphylaxis prophylaxis challenging in adolescents.[10]
  - Ketotifen (H1/MCI): Ketotifen, a first-generation oral antihistamine, has both mast cell stabilization and antihistamine properties. Benefit of ketotifen for

steroid-dependent IA has been reported[142,143]; however, evidence for superiority over other H1 antihistamines for pediatric mastocytosis is lacking.[144]
  - Rupatadine (H1/PAF): Rupatadine, a loratadine analog, has unique antiplatelet activating factor function.[145] PAF has been associated with hypotension and fatal anaphylaxis.[146] Benefit for prophylaxis or treatment of anaphylaxis is presently unknown.
- Immunosuppression/Immunomodulators:
  - Calcineurin inhibitors: Data supporting immunosuppression in unexplained anaphylaxis is minimal; however, off-label use for chronic urticaria is more robust. Supportive data for the use of cyclosporine in chronic urticaria exist, and it is a second-line recommendation for management per international chronic urticaria guidelines.[141]
  - Bruton's tyrosine kinase inhibitors (BTKi): Recent studies have found BTKi drugs abrogate mast cell degranulation via signaling via sIgE. Low doses of BTKi drugs are well tolerated and immunosuppression seems to be minimal.[147] Although not yet studied in idiopathic anaphylaxis, phase 2B chronic urticaria studies of remibrutinib were highly suppressive of symptoms at even the lowest dose studied.[148]
- Biologics
  - *Anti-IgE*
    - Off-label benefit of omalizumab has been extensively reported in case series for IA and mast cell disorders; however, there have been few controlled studies. A major review of 55 CM, ISM, and MCAS patients demonstrated a complete response in more than 1%, a major response in 54% and a 21% a partial response. Response was sustained in three-fourths and seemed most beneficial for vasomotor and gastrointestinal symptoms.[149]
    - In contrast, a prospective RCT in frequent idiopathic anaphylaxis cohort however failed to find a significant benefit at 6 months with idiopathic anaphylaxis yet trended toward benefit and drug tolerance was good.[150]
    - Although not yet studied for unexplained or idiopathic anaphylaxis, there are several anti-IgE biologics under active evaluation for chronic urticaria. Ligelizumab has demonstrated benefit in chronic urticaria over omalizumab.[151,152] Candidate drugs TEV-45779 and UB-221 are also under study.[153,154]
  - *Dupilumab (anti-Th2)*: Dupilumab, a marketed anti-interleukin 4 and 13 receptor (anti-IL4R/IL13R) biologic, has been under study for chronic urticaria with mixed positive and negative phase 3 trials.[155,156] Benefit for IA is limited to case reports to date.[157]
  - *Anti-KIT*: KIT both a surface marker on mature mast cells and progenitor stem cells, thus is a challenging drug target. Phase I human studies of CDX-0159 seem to result in both a profound and durable mast cell compartment suppression.[158] There are no studies to date of use for idiopathic anaphylaxis.
  - *Anti-SIGLEC8*: SIGLEC-8 is a surface receptor on mast cells, basophils, and eosinophils, and ligation induces apoptosis and suppression of mediator production.[159,160] AK002 (lirentelimab) is under study for chronic urticaria[161]; however, there are no studies to date of use for idiopathic anaphylaxis.

Patient/family support and resources

The psychosocial impact of unexplained or IA in adolescents has been minimally studied. Adolescent and parent anxiety regarding food allergy have been extensively studied; a balanced level of anxiety promoting appropriate anaphylaxis preparedness without debilitating fears is often difficult to achieve.[162] A challenging consequence

of severe or frequent anaphylaxis in adolescents is the development of post-traumatic stress disorder (PTSD).[163] Adolescents with medically unexplained syndromes are known to very commonly suffer from emotional distress, often not well addressed in the search for a suitable diagnosis and treatment plan.[164] Interventions focused on parental responses to illness and family communication seemed to be most beneficial in a systematic review.[164]

Provision of a written anaphylaxis emergency plan is recommended for all with food allergies.[165] Emergency anaphylaxis action plan form templates are widely available and free from many organizations, in many languages. Formal written and posted emergency action plans, as well as chronic illness accommodation plans, can provide the link between family, medical provider, and schools to ensure safety, preparedness and minimized impairment to the adolescent. Formally assessing and supporting the needs of adolescents in their transition to independent self-management of anaphylaxis is recommended by the age of 11 to 13 years.[166]

Adolescents and parents with medically unexplained or idiopathic disorders symptoms may be susceptible to pseudoscientific or alternative medicine treatments, presently a particularly common problem with mast cell disorders.[81] Multiple national nonprofit patient support organizations may offer community of support and guidance for patients with idiopathic or yet unexplained anaphylaxis. Often IA resources are housed within mastocytosis organizations such as the Canadian Mastocytosis society (Canada), the Mast Cell Society (US), UK Masto (UK), Assomast (FR), or the Selbsthilfeverein Mastozytose (GER).

Provider support

Development of guidelines for the evaluation and management of idiopathic and occult anaphylaxis and screening for mimic disorders are in their infancy. The development of an idiopathic anaphylaxis yardstick: a set of practical recommendations published in 2020[10] is one of the first efforts to guide diagnostic efforts. Superspecialist referral networks are in development, particularly via the European Competence Network on Mastocytosis (ECNM) group, for obscure cases needing support.

There are emerging research networks to support unexplained anaphylaxis and to support researchers studying rare disorders. The ECNM provides expert referrals and scientific registry (ECNM Registry). Additionally, there is a long-standing etiologic study (NCT00719719) at the National Institutes of Health (US).[167]

SUMMARY

1. Diagnosis
   a. In summary, clinical features suggestive of anaphylaxis, without a readily evident trigger, should prompt expanded diagnostic considerations.
   b. A comprehensive history and timeline of exposures and subsequent symptoms is the most useful diagnostic tool. Objective findings as available, such as vital signs and observations of the airway and skin, can help validate anaphylaxis or suggest an alternative disorder.
   c. Using anaphylactic diagnostic criteria is recommended given strong positive and negative predictive values.
   d. For obscure causes of anaphylaxis, a broad differential of rare food, drug, venom triggers should be considered, with additional consideration of summative anaphylaxis, which may involve 2 or more cofactors.
   e. Patients with unexplained anaphylaxis require evaluation for an underlying mast cell disorder. Multiple laboratory diagnostics can help confirm or refute certain etiologies and aid to narrow the differential diagnoses.

f. Referral to an allergy specialist is strongly recommended to guide evaluation when confronted with anaphylaxis of uncertain cause. Hematologist support is necessary to assist with the diagnosis of clonal mast cell disorders.

2. Management
   a. Medical management of anaphylaxis should follow guideline-based practices. This includes preparedness with epinephrine autoinjectors and extensive training with the adolescent and their family. Provision of written action plans is recommended.
   b. As adolescents mature, they should have guided support for symptom self-recognition and management responsibilities.
   c. Preparation with written emergency action plans and emergency simulations can reduce feared poor outcomes and provide confidence.
   d. As unexplained recurrent and unpredictable anaphylaxis can cause significant anxiety, addressing mental health concerns early and often with this invisible disability is important.
   e. Although medical options to prevent anaphylaxis without cause are presently few, there is significant hope that what is presently idiopathic will be later diagnosable.
   f. Existing pharmacologic drugs, many used off-label, may minimize the frequency and/or severity of reactions in the interim. Future medications in research and development offer significant hope for future control of anaphylaxis.

DISCLOSURE

Neither author declares relevant financial conflicts of interest.

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