Grand Rounds Review

Idiopathic Anaphylaxis

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1. Describe the prevalence and demographic characteristics of idiopathic anaphylaxis (IA).
2. Implement appropriate diagnostic tests in IA cases.
3. Use appropriate management strategies for patients with IA.

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ABSTRACT: Idiopathic anaphylaxis (IA) refers to recurrent, life-threatening hypersensitivity reactions without identifiable triggers, representing a diagnostic and therapeutic challenge. We describe a 17-year-old girl presenting with recurrent episodes of flushing, pruritus, and respiratory symptoms, without consistent allergen exposure or cofactor involvement. Evaluation revealed elevated acute tryptase levels with a normal baseline, negative skin testing results, and negative galactose-α-1,3-galactose (α-gal) and KIT mutation analysis. The patient improved on daily cetirizine with no further reactions. IA remains a diagnosis of exclusion, requiring careful consideration of IgE-mediated allergies, cofactor-dependent anaphylaxis,

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Abbreviations used
α-gal- galactose-α-1,3-galactose
CSU- chronic spontaneous urticaria
ED- emergency department
HaT- hereditary alpha tryptasemia
IA- idiopathic anaphylaxis
MCAS- mast cell activation syndrome
NSAID- nonsteroidal anti-inflammatory drug
PFAS- pollen food allergy syndrome
SM- systemic mastocytosis
SSD- somatic symptom disorder

clonal mast cell disorders, and systemic mimics such as neuroendocrine tumors or vasovagal syncope. We summarize current evidence on IA pathogenesis, epidemiology, differential diagnosis, and management. Although antihistamines and corticosteroids are commonly used prophylactically, emerging data suggest that anti-IgE therapy with omalizumab may offer benefit in refractory cases. Diagnostic workup should include serum tryptase measurement, trigger identification, and consideration of underlying mast cell disorders. Future research is needed to clarify the natural history, standardize diagnostic pathways, and evaluate long-term treatment strategies for this heterogeneous condition. **(J Allergy Clin Immunol Pract 2025;13:3165-78)**

Key words: *Anaphylaxis; Idiopathic anaphylaxis; Mast cell; Mast cell activation syndrome; Tryptase*

Case description

A 17-year-old girl presented to the emergency department (ED) with a 2-hour history of flushing, pruritus, and wheezing. The symptoms began after eating dinner, which included shepherd's pie and macadamia nuts, foods she had previously tolerated. There were no preceding exposures to medications, alcohol, or insect stings, and she did not engage in exercise before symptom onset. She reported 3 additional similar episodes. These were not consistently associated with eating, and there were no common foods or additives identified between episodes. There was no history of tick bite. There was no correlation between reactions and stage of her menstrual cycle. She did not have a personal or family history of atopy (atopic dermatitis, allergic rhinitis, asthma, and IgE-mediated food allergy) or anaphylaxis. There was no history of spontaneous or inducible urticaria. She did not have a history of spontaneous flushing, pruritus, abdominal pain, diarrhea, or presyncopal or syncopal episodes. She neither had a history of bony pain or fractures.

At the time of the medical assessment in the ED, the patient's examination was notable for facial erythema and diffuse hives. Respiratory symptoms had resolved by the time of assessment. There were no cutaneous lesions suggestive of cutaneous mastocytosis (Figure 1). The examination was otherwise unremarkable. She was given second-generation antihistamines, and symptoms gradually resolved over several hours. The serum tryptase drawn 2 hours following symptom initiation was 17.2 μg/L. A repeat level 5 days later was 3.2 μg/L.

During a follow-up visit 3 months after ED presentation, skin prick testing result was negative to various food and inhalant allergens, including macadamia nut, wheat, and beef. Serum IgE testing to α-gal had a negative result, and quantitative PCR analysis for the KIT D816V mutation in peripheral blood was also negative. The patient was prescribed prophylactic cetirizine (20 mg daily) for 3 months, during which she experienced no further reactions.

Given the clinical presentation, absence of identifiable triggers, and the tryptase levels obtained at the ED and 5 days later, the patient was diagnosed with idiopathic anaphylaxis (IA).

INTRODUCTION

Definition

The term "anaphylaxis" is used to describe potentially life-threatening combinations of symptoms that result from the release of chemical mediators from mast cells and, to a lesser extent, basophils.[1] The 2024 GA^{2}LEN consensus outlines that anaphylaxis is most likely when there is acute multisystem involvement, especially involving the skin/mucosa and either respiratory or cardiovascular compromise.[2] Isolated respiratory or cardiovascular symptoms can also indicate anaphylaxis if they occur after exposure to a known allergen. Although broadly recognizable by most clinicians, the diagnosis can be challenging to make because of the nonspecific nature of the symptoms involved and diagnostic criteria that are variable and depend on whether there was exposure to a known or likely allergen. Anaphylaxis is most commonly provoked by food, venom, or drugs[1] via an IgE-mediated mechanism. However, mast cells can be activated by a wide array of factors, and so anaphylaxis can also result from mast cell activation via other receptors (independent of IgE production), physical stimuli including heat and cold, autoantibody production, and clonal mast cell disorders. IA is a diagnosis of exclusion for anaphylaxis when no clear triggers can be defined.[3]

Pathogenesis

The term "idiopathic anaphylaxis" was first introduced by Bacal et al.[4] Different hypotheses accounting for the development of IA exist, but the underlying pathophysiology of the condition is uncertain. It is considered a mast cell activation disorder, although baseline elevation of mast cell mediators is not required for diagnosis. Multiple studies[5-7] have demonstrated the presence of clonal markers in mast cells in a subset of patients with IA, suggestive of hidden systemic mastocytosis (SM). Baseline increases in mast cell mediators have been observed in some patients, supporting overlap with mast cell activation syndrome (MCAS).[5] However, increased levels of activated lymphocytes, specifically CD3$^+$HLA-DR$^+$ cells, in patients with IA as well as clinical response to oral prednisone for episode prevention suggest that the mechanism may be distinct from monoclonal mast cell disorders and MCAS.[8] Other studies call into question the "idiopathic" label, supporting roles for hormonal fluctuations,[9] and COX blockers,[10] and it has been suggested that hidden food allergens may account for some IA cases.[11]

Epidemiology and classification

Data on the prevalence of IA are scarce and complicated by challenges in establishing the diagnosis. On the basis of extrapolation of the cases of IA reported by the allergists surveyed in the

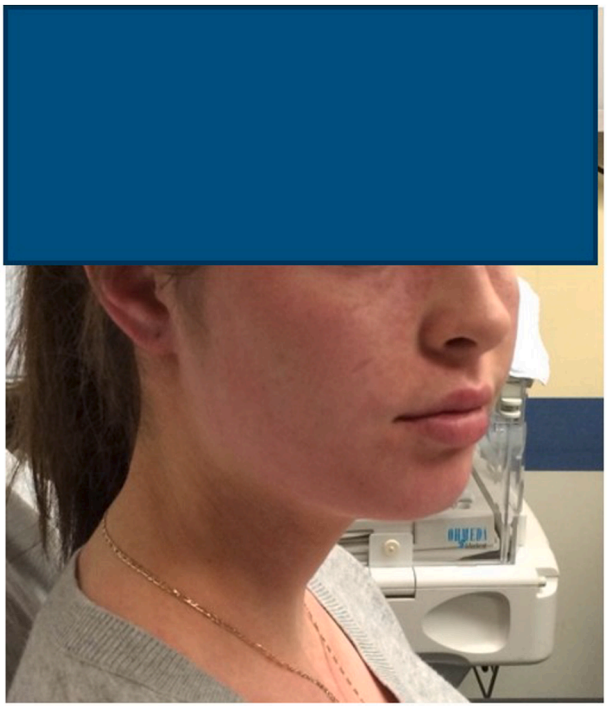

FIGURE 1. Cutaneous presentation of patient in ED.

TABLE I. Prevalence of IA depending on country

	Prevalence of IA	
Territory	**Children (<18 y)**	**Adults (>18 y)**
United States	Between 20,592 and 47,024 of total cases	
Canada	10% of anaphylaxis cases[15]	30%-60% of anaphylaxis cases[15]
Taiwan	NA	10%-22% of anaphylaxis cases[16]
Poland	3.5% of anaphylaxis cases[17]	

NA, Not available.

United States, the estimated number of cases in the United States was reported to vary between 20,592 and 47,024.[12] Studies in the United States suggest that more than a third of anaphylaxis cases in adults can be defined as IA.[13] In Canada, studies suggest that IA accounts for up to 10% of pediatric anaphylaxis cases and 30% to 60% of adult anaphylaxis cases.[14] In Asia, it was reported that 10% to 22% of adult anaphylaxis cases were idiopathic,[15] whereas European studies report that the percentage may be as low as 3.5%[16] (Table I). There is inconsistency regarding the impact of sex. Although some studies suggest that among adults IA is more likely to affect women than men,[17] others report the opposite.[18] Studies suggest that IA is more common in adults than in children.[19] These differences may relate to interstudy variability in IA diagnostic strategies or may be due to true differences in populations assessed.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Diagnosis

Symptoms of anaphylaxis are nonspecific. Numerous conditions, unrelated to the release of mediators from mast cells and basophils, can present similarly (Table II) and must be excluded. Identifiable causes of anaphylaxis (Table III) must also be ruled out before classifying an individual's symptoms as idiopathic. Identifiable causes can be roughly classified on the basis of the mechanism of mast cell activation: IgE-mediated (with or without cofactor involvement), activation through non-FcεRI receptors (unrelated to IgE), inducible urticaria with systemic symptoms, autoimmune or autoantigen-mediated mast cell activation, clonal mast cell disorders, and nonclonal MCAS (Table III). IA can be diagnosed when other causes of anaphylaxis have been excluded.

Evaluation

Figure 2 outlines the diagnostic approach for a patient presenting with suspected anaphylaxis. Clinical history is the single most important aspect of the evaluation. All patients undergoing assessment for anaphylaxis of uncertain cause should keep a detailed symptom diary. This should describe any food and beverage ingestion within 6 hours of symptom onset, any associated activities (such as exercise), medication use, alcohol use, general wellness at the time (ie, presence of concurrent illness or fatigue), relation to menstruation, and physical location during symptoms. Identifying patterns can help to elucidate potential hidden allergens or suggest alternative diagnoses. See this article's Online Repository at www.jaci-inpractice.org for a sample patient handout to facilitate symptom tracking.

Anaphylaxis is a clinical diagnosis, and there is no point of care laboratory testing to confirm the diagnosis at presentation. However, obtaining a baseline and event serum tryptase can be helpful to confirm an event as anaphylaxis retrospectively. An elevation in tryptase of 20% plus 2 ng/mL higher than a patient's baseline level is considered consistent with anaphylaxis.[25] Previous studies report specificities in the range of 80% to 99%, although sensitivities can be much lower (30%-69%).[26] Thus, although an elevated event tryptase can support a diagnosis of anaphylaxis, absence of this does not exclude the diagnosis.

Differential diagnosis

Excluding anaphylaxis mimics (symptoms unrelated to mast cell activation). These conditions include various disorders presenting with symptoms that may overlap with anaphylaxis, including vasovagal syncope, endocrine disorders, globus sensation, inducible laryngeal obstruction, somatic symptom disorder (SSD), and other causes of shock. Table II provides an overview of conditions that can mimic anaphylaxis with key investigations to consider.

Thyroid disease. Thyroid disease can present with systemic symptoms. Hyperthyroidism can have overlapping symptoms with IA, in particular flushing, presyncope, and shortness of breath.[27] Measurements of thyroid-stimulating hormone and free thyroxine are satisfactory screening tests.

Neuroendocrine tumors. Neuroendocrine tumors are a diverse group of rare malignancies arising from neuroendocrine cells.[28] These tumors include carcinoid tumors, VIPomas (vasoactive intestinal peptide), and pheochromocytomas among other neoplasms and can produce metabolites that cause diarrhea, flushing, diaphoresis, palpitations, and syncope.[28] Historical features to suggest a neuroendocrine tumor when evaluating someone for IA include signs and symptoms associated with malignancy generally (eg, weight loss, night

TABLE II. Systems-based differential diagnosis for conditions that can present similarly to anaphylaxis

System	Conditions	Key investigations
Cardiovascular	• Cardiogenic shock • Vasovagal syncope • Pulmonary embolism	• ECG, troponin, echocardiogram • Orthostatic vitals, tilt table test • D-dimer, CT pulmonary angiogram
Respiratory	• Asthma exacerbation • Inducible laryngeal obstruction • Airway foreign body	• Spirometry • Laryngoscopy • Bronchoscopy
Neuropsychological	• Seizures with autonomic features • Panic attacks • Somatization	• EEG • Psychiatric evaluation
Endocrine	• Neuroendocrine tumors o Carcinoid syndrome o Pheochromocytoma o VIPoma • Hypoglycemia • Thyroid storm	• Serum chromogranin A • 24-h urine 5-HIAA • Plasma/urine metanephrines • Serum VIP • Blood glucose, insulin levels • TSH, free T_3/T_4
Gastrointestinal	• FPIES	• Dietary history, food challenge
Dermatologic	• Urticarial vasculitis • Flushing syndromes	• Skin biopsy • Provocative testing
Hematologic	• Hereditary/acquired angioedema • Episodic angioedema with eosinophilia	• C4, C1 esterase inhibitor levels/function • Eosinophil count, IgM levels
Medication/toxin	• ACE inhibitor angioedema • MSG/sulfite sensitivity • Niacin toxicity • Scombroid poisoning	• Medication history review • Direct challenge • Dietary history • Dietary history, fish toxicology
Miscellaneous	• Capillary leak syndrome	• Serum protein electrophoresis

ACE, Angiotensin-converting enzyme; *CT*, computed tomography; *ECG*, electrocardiogram; *EEG*, electroencephalogram; *FPIES*, food protein–induced enterocolitis syndrome; *5-HIAA*, 5-hydroxyindoleacetic acid; *MSG*, monosodium glutamate; *TSH*, thyroid-stimulating hormone; *VIP*, vasointestinal peptide.

sweats, and recurrent fever) and a concerning family history. Evaluation can be performed for causative metabolites in the serum and urine,[28] including 24-hour urine 5-hydroxyindoleacetic acid, plasma and urine metanephrines, and serum vasointestinal peptide. More recently, chromogranin A was reported to be a promising biomarker for the diagnosis of neuroendocrine tumors with high sensitivity and specificity.[29]

Vasovagal syncope. Vasovagal syncope, or neurally mediated syncope, is commonly misdiagnosed as anaphylaxis.[30] In vasovagal syncope, an external stimulus triggers vagal nerve activation that causes vasodilation and bradycardia, leading to sudden but transient hypotension and cerebral hypoperfusion.[31] Thus, the hypotension of vasovagal syncope can sometimes be mistaken for the hypotension of anaphylaxis. Factors that distinguish vasovagal syncope from anaphylaxis include bradycardia, pallor and clammy skin, transient nature, absence of pruritus, and diaphoresis. Vasovagal syncope is usually in response to a noxious stimulus such as venipuncture or vaccine, and it is more commonly seen in adolescents and young adults.[32]

Somatic symptom disorder. SSD describes the presentation of physical symptoms without organic cause.[33] SSD can present with various symptoms that overlap with IA, including presyncope, palpitations, anxiety or sense of doom, and shortness of breath. Features of SSD that are distinct from IA include hypertension rather than hypotension, globus sensation without objective pharyngeal edema, and diaphoresis.[33] SSD is also a diagnosis of exclusion if objective causes for the patient's symptoms cannot be found. Management typically involves close follow-up with primary care and psychology or psychiatric services.[33]

Bradykinin-mediated angioedema syndromes. These conditions include hereditary angioedema and medication-induced angioedema from angiotensin-converting enzyme inhibitors and peptidase inhibitors. Historical features that suggest bradykinin-mediated angioedema include swelling without urticaria or pruritus, use of culprit medications, and a family history of angioedema. Evaluation includes serum complement levels and C1 esterase inhibitor function testing, although a diagnosis of drug-induced bradykinin-mediated angioedema is suggested by history and confirmed by symptom resolution following medication cessation.[34]

Approach to anaphylaxis

Modifying factors: the role of cofactors. Efforts to identify the underlying causes of anaphylaxis are complicated by modifying factors that can influence both the likelihood and the severity of an event. The term "cofactor" is used to describe exposures or conditions that reduce the threshold for mast cell activation and therefore increase the likelihood of anaphylaxis (Table IV). In the case of IgE-mediated allergy, some patients may tolerate an allergen in the absence of a cofactor but experience anaphylaxis with the same allergen when a cofactor is present (as occurs in food-dependent, cofactor-induced anaphylaxis). Figure 3 outlines the approach to recurrent anaphylaxis. Exposure to multiple concurrent cofactors can result in anaphylaxis unrelated to IgE production, as has been

TABLE III. Differential diagnosis for anaphylaxis on the basis of mechanism of mast cell activation

Mechanism	Subtype and examples	Key investigations	Management strategies
IgE-mediated allergy (type 1 hypersensitivity) *Mast cell activation secondary to cross-linking of allergen-specific IgE on mast cell surface*	• Drug or vaccine allergy • Food allergy o Hidden allergens o Additives (pectin) o Spices (fenugreek) o α-Gal syndrome o Lipid transfer protein allergy • Venom allergy • Systemic reaction to inhalant allergens o Pancake anaphylaxis o Cat-pork syndrome[20] o Animal danders (eg, horse dander)[21] o Animal bite[22,23] • Latex allergy • Hormone allergy o Progesterone o Estrogen	• Skin prick testing • Allergen-specific IgE testing ± component-resolved diagnostics • Intradermal testing (drug/venom) • Provocative challenges	• Epinephrine autoinjector • Anaphylaxis emergency plan • Allergen avoidance • Allergen desensitization or immunotherapy
Cofactor-dependent IgE-mediated allergy *Mast cell activation that requires BOTH allergen-specific IgE cross-linking on mast cell surfaces AND the presence of a cofactor**	• Food-dependent cofactor- induced anaphylaxis o Wheat-dependent exercise-induced anaphylaxis with ω-5-gliadin sensitization • PFAS with cofactor exposure o For example, celery ingestion followed NSAID ingestion • Systemic reaction to inhalant allergens o For example, dog exposure with illness as cofactor o For example, running on a hot day during grass pollen season	• Skin prick testing • Allergen-specific IgE testing • Component-resolved diagnostics (ω-5-gliadin IgE) • Intradermal testing (drug/venom) • Provocative challenges with cofactor exposure	• Epinephrine autoinjector • Anaphylaxis emergency plan • Cofactor ± allergen avoidance • Desensitization therapy
Non−IgE-mediated mast cell receptor activation *Mast cell activation due to binding of receptors other than FcεRI (unrelated to IgE production or cross-linking)*	• Medication-induced (including MRGPRX2 receptor−mediated activation) o NSAIDs o Vancomycin o Fluoroquinolones o Opioids o Some NMBAs • Toxin-induced o Ethanol • Hormonal changes o Progesterone hypersensitivity o Estrogen hypersensitivity o Catamenial anaphylaxis o Lactation-associated anaphylaxis	• Serum tryptase (acute/baseline) • Skin prick testing ± intradermal testing (drug) • Basophil activation test (where available) • Provocation testing with drug • Ice cube challenge for cold urticaria	• Avoidance of offending drug or toxin • Alternative medication selection (eg, COX-2 selective NSAID) • Reduced infusion rates for IV medications (vancomycin) • NSAID desensitization • Hormonal therapies • Epinephrine autoinjector • Anaphylaxis emergency plan • High-dose second-generation antihistamines

(continued)

TABLE III. *(Continued)*

Mechanism	Subtype and examples	Key investigations	Management strategies
Inducible urticaria with systemic symptoms *Mast cell activation induced by a physical stimulus (cold or exercise)*	• Physical triggers can be associated with systemic symptoms o Exercise-induced anaphylaxis • Cold urticaria • Cholinergic urticaria	• Provocation testing with exercise or passive heat • Ice cube challenge for cold urticaria	• Exercise modification (reduced intensity, duration) • Avoidance of systemic cold or heat exposure • Epinephrine autoinjector • Anaphylaxis emergency plan • High-dose second-generation antihistamines • Omalizumab • Limited evidence for cyclosporine in cholinergic urticariaClick or tap here to enter text.[24]
Autoimmune or autoantigen-mediated mast cell activation *Mast cell activation related to production of anti-FcεRI or anti-IgE autoantibody with cross-linking on mast cell surface*	• CSU with systemic symptoms (±NSAID exposure)	• Serum tryptase (acute/baseline) • Autologous serum skin test • IgG anti-FcεRI or anti-IgE antibodies	• Epinephrine autoinjector • Anaphylaxis emergency plan • High-dose second-generation antihistamines • Omalizumab • Cyclosporine • Systemic corticosteroids (short-term)
Clonal mast cell disorder *Physiologic or cofactor-induced mast cell activation in the context of increased mast cell burden, typically due to c-kit/CD117 gain-of-function mutation*	• Cutaneous mastocytosis • Monoclonal MCAS • SM	• Serum tryptase (acute/baseline) • c-kit/CD117 mutation analysis • 24-h urine *N*-methylhistamine and 2,3-dinor-11β-prostaglandin F2 α • Skin biopsy if lesions present • Bone marrow biopsy	• Epinephrine autoinjector • Anaphylaxis emergency plan • Cofactor avoidance • Second-generation H_1 antihistamines • H_2 antihistamines • Mast cell stabilizers (cromolyn) where available • Leukotriene receptor antagonist • Tyrosine kinase inhibitors • Omalizumab
Idiopathic *Mechanism unknown*	• MCAS (requires evidence of mast cell mediator release) • IA (evidence of mast cell mediator release not required for diagnosis)	• Serum tryptase (acute/baseline) • 24-h urine *N*-methylhistamine and 2,3-dinor-11β-prostaglandin F2 α • Trial of antimediator therapy • Extensive workup to rule out all other causes	• Epinephrine autoinjector • Anaphylaxis emergency plan • Cofactor avoidance • Second-generation H_1 antihistamines • H_2 antihistamines • Mast cell stabilizers (cromolyn) where available • Leukotriene receptor antagonist • Systemic corticosteroids • Omalizumab • Aspirin desensitization (select cases)

IV, Intravenous; *MRGPRX2*, mas-related G protein−coupled receptor X2; *NMBA*, neuromuscular blockade agent.
*For cofactors, see Table IV.

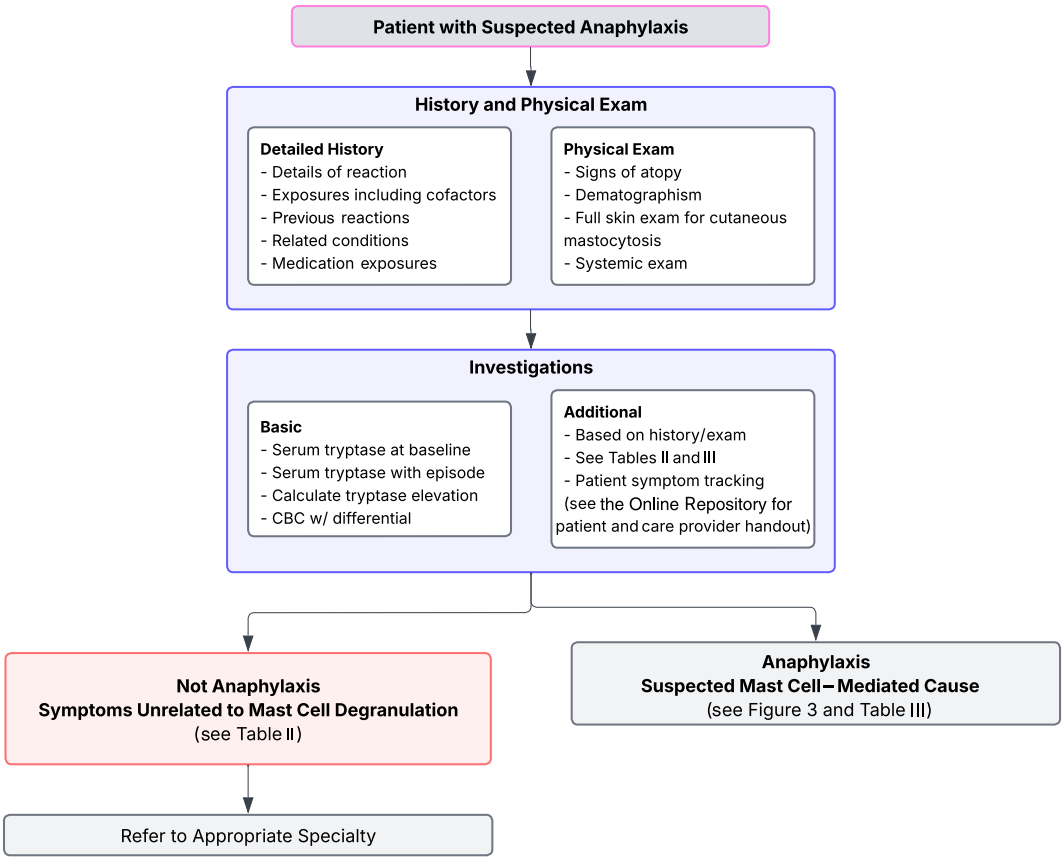

FIGURE 2. Diagnostic approach for suspected anaphylaxis.

described in patients with acute illness who take nonsteroidal anti-inflammatory drugs (NSAIDs) and develop anaphylaxis.[35,36]

IgE-mediated allergy. Anaphylaxis caused by IgE-mediated allergy results in mast cell activation secondary to cross-linking of allergen-specific IgE on mast cell surfaces. In cofactor-dependent IgE-mediated allergy, patients can be asymptomatic with allergen exposures unless a cofactor is present. Table III provides an overview of both common and less common culprits.

Hidden food allergens

It is important to consider hidden food allergens during assessment for IA. These include common food allergens in products not typically thought to contain those allergens, such as wheat and peanut proteins in beer[45] and pea protein,[46] as well as uncommon allergens in foods that are known causes of anaphylaxis but are sometimes neglected, such as the organic food dyes (carmine and annatto) and pectin. Anaphylaxis secondary to hidden allergens occurs acutely after food ingestion, and detailed examination of ingredient lists with targeted skin prick or serum IgE testing can help to identify the culprit.[10]

α-Gal syndrome

α-Gal syndrome is a delayed allergic reaction to the oligosaccharide α-gal.[47] In contrast to most IgE-mediated food allergies, α-gal syndrome is caused by sensitization to a carbohydrate rather than a protein. Reactions are typically delayed 2 to 6 hours after ingestion.[47] In North America, sensitization follows a bite from the lone star tick, *Amblyomma americanum.* Although endemic to the Eastern, Southeastern, and Southcentral United States,[48] reports have identified α-gal syndrome in individuals who have never visited these regions. Historical features to suggest α-gal syndrome include ingestion of mammalian meat 2 to 6 hours before anaphylaxis onset. Evaluation includes serum IgE testing for α-gal sensitization.

Anaphylaxis due to inhalant allergens including pollen food allergy syndrome

Pollen food allergy syndrome (PFAS) occurs when patients ingest foods that contain proteins that cross-react with aeroallergens to which they are sensitized.[49] Historical features to suggest PFAS include a history of allergic rhinitis and/or inhalant sensitization and complementary food associations, such as birch and pitted fruits and ragweed and melons. Cross-reactive proteins are heat-labile, and so foods are generally tolerated in heated or processed forms. Although symptoms are often limited to the oropharynx, a minority of patients (1%-3%) may experience systemic symptoms.[49] In our clinic, anaphylaxis secondary to PFAS is generally limited to ingestion of large quantities, such as in the form of smoothies or shakes, or ingestion with concurrent cofactor exposure. Skin prick testing and/or serum IgE testing to confirm pollen sensitization can be helpful in the evaluation. In contrast with PFAS, IgE-mediated allergy to heat-stable lipid transfer proteins in some plants can occur regardless of method of preparation (heated or raw) and is more likely to result in

TABLE IV. Summary of common cofactors and mechanisms by which they reduce the threshold for mast cell activation

Cofactor	Possible mechanisms of reduced threshold for mast cell activation	References
NSAIDs	• COX inhibition leads to reduced PGE_2 production. • PGE_2 maintains mast cell stability, and reduction in PGE_2 levels reduces stability and therefore threshold for activation on exposure to further stimuli.	37,38
Alcohol	• The mechanism is poorly understood. • It inhibits diamine oxidase (reduces breakdown of histamine). • It increases gut permeability, resulting in increased absorption of allergenic proteins in context of IgE-mediated food allergy.	39
Stress, fatigue	• These result in release of compounds from peripheral and central nervous system including corticotropin-releasing hormone, substance P, and neurotoxin. • These bind receptors on mast cells, triggering activation or lowering activation threshold. • Disruption of circadian rhythm can reduce threshold for mast cell degranulation.	40,41
Exercise	• Increased body temperature reduces activation threshold. • Oxidative stress results in production of compounds that also directly affect the mast cell to reduce threshold for activation.	42,43
Heat	• Increased body temperature reduces activation threshold.	42
Illness	• Activation of the complement system results in production of anaphylotoxins (C3a, C5a). • It binds mast cells and reduces the threshold for mast cell activation.	44

PGE_2, Prostaglandin E_2.

anaphylaxis, particularly if a cofactor is present.[50] Inhalant allergens may also result in anaphylaxis through animal bites,[22] cross-reactivity with ingested foods (cat-pork syndrome[20]), and rare but reported hidden contamination in food, including "pancake syndrome" (alternatively called oral mite anaphylaxis)[51] and pollen in honey.[31]

Food-dependent, cofactor-induced anaphylaxis

Exercise-induced anaphylaxis is described as anaphylaxis induced by physical exertion.[51] It has historically been categorized as food-dependent or food-independent, although more recent literature is increasingly using the term "cofactor" to describe other contributors beyond food, such as alcohol or medications (in particular, NSAIDs). IgE-mediated triggers should be considered for any patients presenting with anaphylaxis in the presence of a cofactor (exercise or NSAIDs). Wheat is among the most common causes of cofactor-dependent anaphylaxis, and if this condition is suspected, testing for ω-5-gliadin sensitivity should be performed.[51]

Non−IgE-mediated mast cell activation

Chronic spontaneous urticaria and inducible urticaria. Chronic spontaneous urticaria (CSU) is characterized by transient hives with or without angioedema lasting more than 6 weeks.[34] Patients with CSU can present with a predominant urticarial phenotype, angioedema phenotype, or a mixture of both. As such, symptoms can resemble anaphylaxis, especially if angioedema involves the oropharynx causing respiratory distress. CSU has been variably associated with autoimmunity,[34,52] and so CSU should be considered in patients being evaluated for IA who have a history of autoimmune disease.

In addition, studies report that anaphylaxis may occur in the context of inducible urticaria, particularly with exercise, heat, and cold triggers. Anaphylaxis was reported in the context of cholinergic urticaria and is often underreported. Reactions are multisystem with cutaneous, upper and lower airway, and cardiovascular involvement in most patients.[53] Almost 20% of patients with cold urticaria report anaphylaxis mainly following swimming but also following exposure to cold air, contact with cold water (eg, being splashed with cold water), and consumption of cold food or beverages.[54]

Systemic mastocytosis. SM describes a group of disorders characterized by clonal mast cell proliferation with infiltration into tissue, most commonly the bone marrow.[55] SM is a clonal disorder of the mast cell or its progenitor driven by the D816V somatic gain-of-function mutation in KIT in most cases. Clinical manifestations include characteristic skin lesions, flushing, gastrointestinal distress, and syncope. Although the diagnosis is fairly straightforward in a patient presenting with typical skin lesions, approximately 20% of patients with SM do not have skin lesions and can also present with severe anaphylaxis, either in association with an allergic trigger such as hymenoptera stings or without apparent cause.[55] Some of these patients may have been diagnosed as having IA. Anaphylaxis is especially a common presentation in the variant of SM called "bone marrow mastocytosis." These patients lack skin lesions and usually have low mast cell burden and low tryptase levels, making the diagnosis challenging. Anaphylaxis in the setting of SM usually presents with hypotensive syncope or presyncope, as opposed to hives and angioedema. On the basis of this clinical distinction, predictive scoring systems have been established to decide which patients to refer for further workup. One commonly used scoring system is the REMA score, established by the Spanish Network of Mastocytosis. In REMA scoring, points are assigned on the basis of sex (male, +1; female, −1), symptoms (absence of urticaria and angioedema, +1; presence of urticaria and angioedema, −2; presence of syncope or presyncope, +3), and tryptase levels (<15 ng/mL, −1; >25 ng/mL, +2).[56] Another study incorporated detection of KIT D816V in peripheral blood, showing that its presence is highly predictive of SM in bone marrow.[57] Patients scoring 2 points or higher in these systems should be referred for bone marrow biopsy and aspiration to check for diagnostic criteria for SM.

The World Health Organization's diagnostic criteria for SM include 1 major and 4 minor criteria.[58] The major criterion is demonstration of multifocal aggregates of mast cell collections (15 or more in an aggregate) in tissue other than skin (usually bone marrow). Minor criteria include aberrant phenotype of

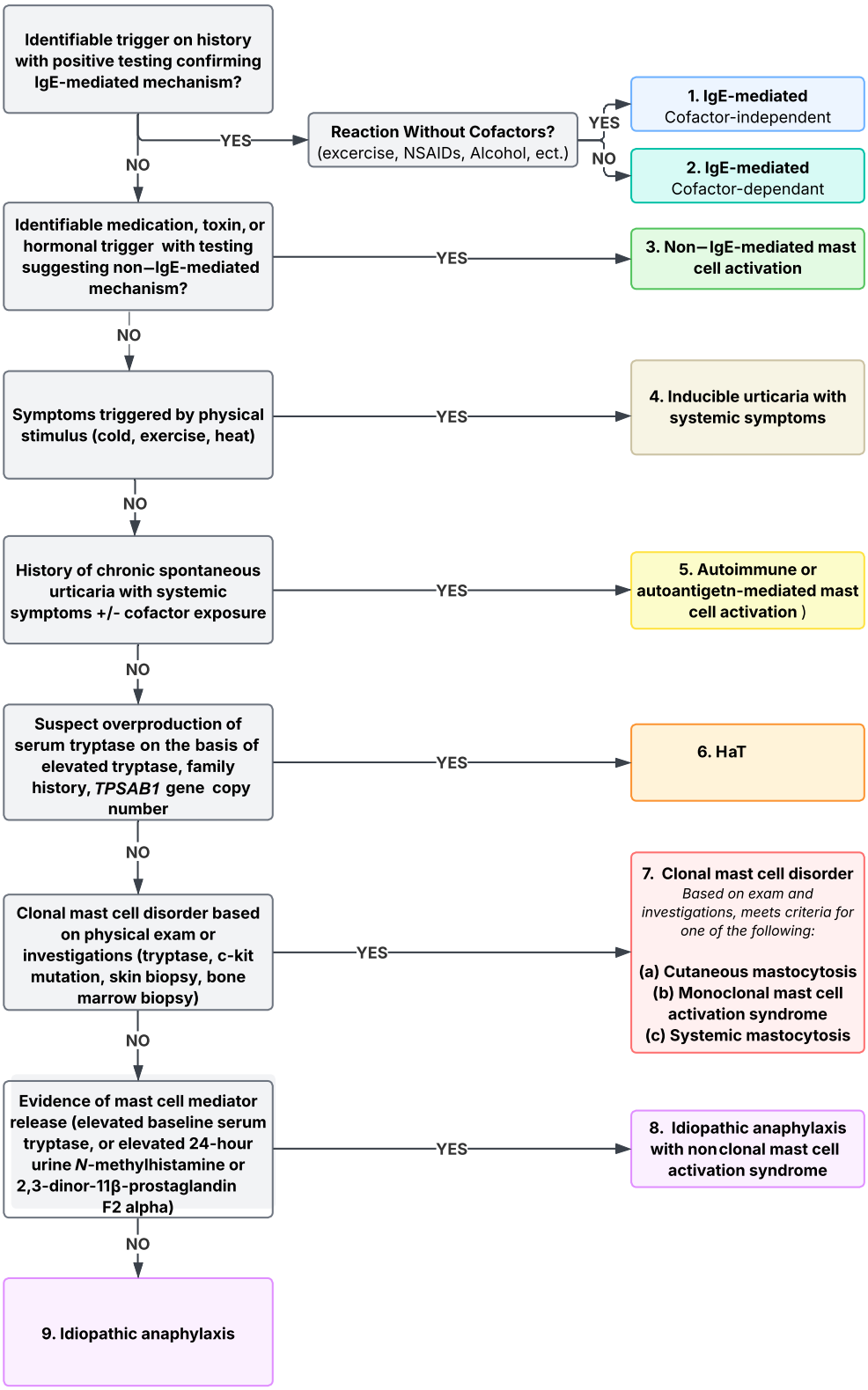

FIGURE 3. Diagnostic approach for recurrent anaphylaxis.

mast cells such as spindle shapes, elevated baseline tryptase level of more than 20 ng/mL, demonstration of KIT D816V or another activating KIT mutation, and aberrant surface marker expression of CD25, CD2, or CD30 (by flow cytometry of the bone marrow aspirate or immunohistochemical examination of the biopsy). One major and 1 minor criteria (or in the absence

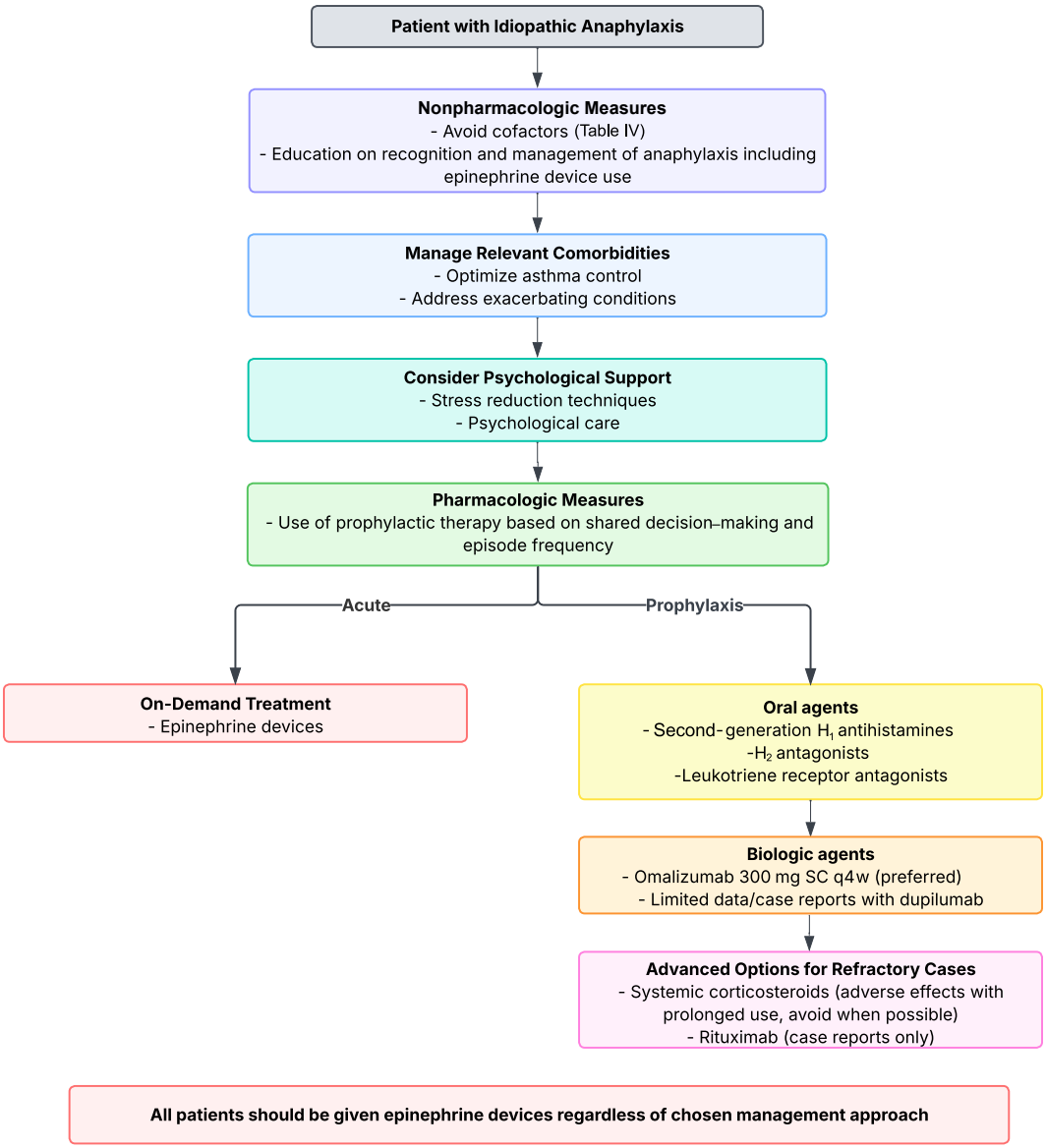

FIGURE 4. Management algorithm for IA. *q4w,* Every 4 weeks.

of the major criterion, 3 minor criteria) are needed for a diagnosis of SM. In 2022, an alternative diagnostic scheme called the International Consensus Classification was published.[59] This largely overlaps with the World Health Organization classification, with the major difference including the major criterion alone is sufficient for the diagnosis without needing to demonstrate an additional minor criterion. The first study to demonstrate underlying mastocytosis in patients diagnosed as having IA was published in 2007.[7] In the study, 5 of 12 patients with a previous diagnosis of IA met full diagnostic criteria for mastocytosis or had 1 or 2 minor criteria designated as MCAS.

Evaluation for SM includes a complete blood cell count and tryptase level. If elevated and clinical symptoms are concerning, further evaluation for SM can be completed.[55] We suggest obtaining a tryptase level in any patient being evaluated for IA. The most common cause of an elevated baseline tryptase level is hereditary alpha tryptasemia (HaT). This is an autosomal dominantly transmitted genetic variant characterized by increased copy number of TPSAB1 encoding alpha tryptase. It is detected in up to 7% of the general population. Individuals with HaT generally have baseline tryptase levels of more than 8 ng/mL. We suggest consideration of bone marrow examination in any patient with a REMA score of 2 or higher or with a presence of KIT D816V mutation in peripheral blood. If the REMA score is less than 2 but tryptase level is higher than 8 ng/mL, we suggest proceeding with testing to look for HaT. If such patients do not have HaT, we suggest a bone marrow biopsy and aspiration to rule out SM. Most individuals with HaT are asymptomatic; however, presence of HaT has been shown to augment the severity of anaphylaxis including in those with IA and hymenoptera anaphylaxis.[36]

Mast cell activation syndrome. MCAS is characterized by recurrent systemic symptoms associated with the release of mast cell mediators with specific diagnostic criteria.[55,59,60]

TABLE V. Summary of findings regarding management of IA reported in the literature (H_1 and H_2 antihistamines, T2DM, and SC)

Management group	Study	N (male/female)	Comorbidities	Management strategy	Details	Response
Omalizumab	Kaminsky et al[63]	14 (1/13)	Allergic rhinitis (9), asthma (6), atopic dermatitis (2), food allergy (4)	Omalizumab	300 mg SC q4w (2 patients started)	↓ frequency in 13
	Borzutzky et al[64]	1 (0/1)	Asthma, allergic rhinitis	Omalizumab → rituximab	300 mg q2w × 8 mo → no response	Resolved with rituximab
	Warrier and Casale[65]	1 (1/0)	Asthma, allergic rhinitis, food allergies	Omalizumab	375 mg SC q2w	Complete resolution
	Ozdemir et al[66]	1 (0/1)	Food and dust allergy	Omalizumab	225 mg SC q2w	Resolution
	Pepper and Pittman[67]	1 (0/1)	None	Omalizumab → dupilumab	300 mg q4w → q3w	Resolved with dupilumab
	Kibsgaard et al[68]	1 (1/0)	Indolent SM	Omalizumab	300 mg q4w	Resolved
	Jones et al[69]	1 (1/0)	NR	Omalizumab	375 mg bimonthly	Resolved
	Sanchez-Valenzuela et al[70]	1 (1/0)	NR	Omalizumab	150 mg SC q4w	Lower rate of attacks, with 3 episodes in first 9 mo, then none
Corticosteroids	Geller et al[71]	1 (1/0)	Anaphylaxis history, T2DM, hypertension	Corticosteroids	Prednisone 40 mg qod → flared <25 mg	Prednisone 20 mg daily resolved
	Wiggins et al[72]	5 (1/4)	Asthma (2), allergic rhinitis (2)	Corticosteroids	Prednisone 50-60 mg qod	Recurred <35 mg in 4/5
	Hogan et al[73]	8 (5/3)	Asthma (3), allergic rhinitis (2)	Corticosteroids + H_1/H_2	Prednisone + H_1/H_2	6 needed steroids, 1 resistant
	Ivkovic-Jurekovic et al[74]	3 (1/2)	Asthma (1)	Corticosteroids + antihistamines	Methylprednisone 40 mg + H_1	1 resolved, 1 needed high-dose steroids
Other immunosuppressants	Borzutzky et al[65]	1 (0/1)	Asthma, allergic rhinitis	Rituximab (after omalizumab failure)	Rituximab 1000 mg × 2, 14 d apart	Resolved 10 d after second dose
Dupilumab	Pepper and Pittman[67]	1 (0/1)	None	Dupilumab	300 mg q2w after omalizumab failure	Resolution

NR, *Not reported*; *qod*, every other day; *q2w/q3w/q4w*, every 2/3/4 wk; *SC*, subcutaneous; *T2DM*, type 2 diabetes mellitus.

Idiopathic MCAS can present as IA if the symptoms meet the criteria of anaphylaxis.[5] Evaluation for MCAS includes obtaining a baseline and event tryptase and urinary mast cell mediators.[61]

Management of IA

Acute management of IA is in line with published guidelines for anaphylaxis treatment,[2] and hence this review focuses on prophylactic treatment. IA prophylactic management is challenging given endotype and phenotype heterogeneity among IA cases, lack of controlled trials, and generally small sample sizes in published studies. An optional management strategy for IA is outlined in Figure 4, which includes both nonpharmacologic and pharmacologic approaches. Although evidence for nonpharmacologic interventions in IA is limited, avoidance of cofactors (Table IV) and optimizing asthma control are measures commonly used for patients with known causes of anaphylaxis and other conditions caused by mast cell activation. Physicians may consider adjusting angiotensin-converting enzyme inhibitors or β-blockers when alternatives are available, although there is limited evidence to support this practice. Anaphylaxis has a significant negative impact on quality of life; psychological interventions should also be considered.[62]

To evaluate pharmacologic management strategies for IA, a search of the MEDLINE database from conception to March 30, 2025, without language restrictions was designed. The search queried management used in IA by physicians, including a general focus on antihistamines, epinephrine, glucocorticoids, and biologic therapy including anti-IgE treatments (omalizumab). Findings are provided in Table V. Studies that explicitly mentioned a diagnosis of IA were included, whereas studies that did not were excluded. Reviews, abstracts, and animal studies were excluded.

A total of 56 patients with IA were described across 13 studies, including 1 randomized controlled trial, 2 case series, 1 prospective study, and 9 case reports (Table V). Commonly used medications included oral corticosteroids (eg, prednisone) and H_1 and H_2 antihistamines, with epinephrine used acutely across all cases. The use of steroids prophylactically although frequently reported for IA may be associated with severe side effects even with short-term use.[75] Omalizumab, an anti-IgE mAb, was frequently trialed in patients with persistent or recurrent IA despite maximum conventional therapy and contributed to symptom improvement or remission in at least 9 patients, with multiple reports of complete resolution.[63-70] In rare cases in which omalizumab failed (eg, in 1 patient treated for 8 months), dupilumab[67] (anti−IL-4/IL-13) or rituximab[64] (anti-CD20) was used successfully. Comorbidities were common and included asthma (at least 27%), allergic rhinitis (27%), food allergy (19%), and psychological or autoimmune conditions in a smaller subset. Overall, omalizumab was the most frequently reported biologic leading to remission, with dupilumab and rituximab reserved for refractory cases.

At this point it is unclear when prophylactic treatment should be offered to patients, and hence use of prophylaxis should be a shared decision with patients. It is reasonable to consider such treatment in cases that will be considered frequent, for example, monthly episodes or 6-yearly episodes.[76] Selection of treatment agents for prophylaxis will be influenced by availability, access, and potential adverse effects.

RESEARCH NEEDS AND FUTURE DIRECTIONS

The primary challenge facing IA research is diagnostic accuracy and the need for evidence based on long-term prophylaxis for recurrent/refractory cases. Standardization of the diagnostic workup to ensure that alternative causes of anaphylaxis are appropriately identified is essential. Wider access to diagnostic biomarkers beyond serum tryptase as well as genetic testing could improve diagnostic accuracy and provide greater insight into the underlying pathophysiology of this disease and may allow identification of distinct subgroups that would benefit from different management approaches. The natural history and long-term prognosis of IA are poorly characterized; although anecdotal evidence supports spontaneous resolution in some patients, longitudinal studies and registry data are urgently needed to identify patient characteristics that will predict disease persistence versus remission and to establish evidence-based guidelines for discontinuing treatments, particularly biologic agents such as omalizumab.

As summarized herein, evidence supporting specific pharmacologic therapies in IA is limited. Clinical registry data could facilitate larger studies evaluating treatment responses and long-term outcomes. Efforts should be made to increase the number of pediatric patients included. Studies have identified reduced quality of life and frequent comorbid psychological conditions in patients with IA.[62,77,78] Further work should be done to evaluate the use of psychological and other nonpharmacologic interventions in this population.

Although significant support exists for acute management of anaphylaxis (anaphylaxis recognition and epinephrine administration) for patients with IgE-mediated allergy (particularly to food), there are currently no resources designed specifically for patients with IA. Future IA-specific resources should touch on nonpharmacologic aspects of management including cofactor avoidance and tracking of episode characteristics. Future studies should also consider whether patients with a confirmed diagnosis of IA would be candidates for home management of anaphylaxis (administration of epinephrine at home without reflex presentation to a health care provider), as is the current recommendation for anaphylaxis in the context of food allergy.[79]

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ONLINE REPOSITORY

Section 1: For Patients

Emergency Information. If you have signs or symptoms of anaphylaxis, administer epinephrine and seek immediate medical attention.

Signs and symptoms of anaphylaxis may include:

- Skin reactions (hives, flushing, itching)
- Swelling of lips, tongue, or throat
- Difficulty breathing or wheezing
- Drop in blood pressure, dizziness, or fainting
- Abdominal pain, nausea, vomiting, or diarrhea

Follow-Up Instructions. After your symptoms have resolved:

1. Pick up a new epinephrine administration device if yours was used.
2. Contact your allergist/immunologist to review this event.
3. Bring this completed form to your follow-up appointment.

Anaphylaxis Event Documentation. Complete this section to help your allergist identify the cause of your reaction.

Date of reaction: _____ **Time of reaction:** _____

Did you see a health care provider? ☐ Yes ☐ No

If yes, please include provider name and service location if known:

Detailed exposure history (activity, foods, medications within 6 hours before reaction):

Current prescription and nonprescription medications:

New foods or products consumed? ☐ Yes ☐ No

- If yes, please attach photo or copy of ingredient list.

Activity at time of reaction:

_____

Location: ☐ Home ☐ School ☐ Work ☐ Other:

Environment: ☐ Indoors ☐ Outdoors

Temperature exposure: ☐ Heat ☐ Cold ☐ Neither

Insect sting or bite? ☐ Yes ☐ No

If female, relationship to menstrual cycle:

_____

COFACTORS PRESENT (check all that apply). ☐ Exercise ☐ Alcohol consumption ☐ NSAIDs (aspirin, ibuprofen, naproxen)

☐ Heat exposure ☐ Cold exposure ☐ Emotional stress ☐ Extreme fatigue

☐ Concurrent illness ☐ Pollen season/significant allergen exposure

☐ Other: _____

SYMPTOM CHECKLIST (check all that apply). **Skin/mucosal:**

☐ Flushing ☐ Itching (without rash) ☐ Hives/urticaria ☐ Angioedema (swelling)

☐ Other: _____

Respiratory:

☐ Shortness of breath ☐ Wheezing ☐ Cough

☐ Throat tightness

☐ Other: _____

Cardiovascular:

☐ Dizziness/light-headedness ☐ Fainting/loss of consciousness ☐ Chest pain ☐ Palpitations

☐ Other: _____

Gastrointestinal:

☐ Nausea ☐ Vomiting ☐ Abdominal pain

☐ Diarrhea

☐ Other: _____

Other symptoms:

Section 2: For Health Care Providers

Patient name: _____

Date of birth: _____

Medical Notification. This patient is undergoing workup for possible anaphylaxis.

Treating allergist/immunologist

Dr _____

Contact information

_____

_____

Please send copies of all documentation to this physician.

Important Clinical Requests.

1. Please draw serum tryptase within 2 hours of symptom onset if possible.
   - Optimal: 15 minutes to 2 hours after reaction begins
   - Still valuable: Up to 4 hours after symptom onset
   - Baseline tryptase (for comparison): At least 24 hours after symptom resolution
2. Please check if the patient requires a new epinephrine administration device prescription.

Thank you for your care of this patient.

For questions or concerns, please contact the treating allergist.