

Idiopathic anaphylaxis

Canting Guo, M.D. and Paul A. Greenberger, M.D.

ABSTRACT

Idiopathic anaphylaxis (IA) is defined as anaphylaxis without any identifiable precipitating agent or event. The clinical manifestations of IA are the same as allergen-associated (immunologic) anaphylaxis and include urticaria, angioedema, hypotension, tachycardia, wheezing, stridor, pruritus, nausea, vomiting, flushing, diarrhea, dysphagia, light-headedness, and loss of consciousness. Patients usually tend to have the same manifestations on repeated episodes. IA is a prednisone-responsive disease that is ultimately a diagnosis of exclusion. Approximately 40% of patients are atopic. Serum tryptase (or urine histamine or its metabolite) will be elevated acutely, but, if elevated in the absence of anaphylaxis, should suggest alternative diagnoses, including indolent systemic mastocytosis. A focused history, examination, and follow-up will dictate whether a patient's symptoms may be attributable to disorders that mimic anaphylaxis, such as indolent systemic mastocytosis, carcinoid syndrome, pheochromocytoma, hereditary angioedema or acquired C1 esterase inhibitor deficiency, or panic attacks. The presence of urticaria may help limit the differential diagnosis because urticaria does not usually accompany any of the above-mentioned disorders, except for indolent systemic mastocytosis. IA is classified according to the symptoms as well as the frequency of attacks. Patients who experience six or more episodes in a year, or two or more episodes in 2 months are classified as having IA-frequent (IA-F). Patients who experience fewer episodes are classified as having IA-infrequent (IA-I). This distinction is important because patients with IA-F will initially require prednisone as disease-modifying therapy, whereas most patients with IA-I will not require prednisone. Patients with IA must carry and know when and how to self-administer epinephrine.

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Idiopathic anaphylaxis (IA) is defined as anaphylaxis without any identifiable precipitating agent or event after an appropriate diagnostic evaluation. IA is essentially a diagnosis of exclusion; it is only after food allergy, drug hypersensitivity, Hymenoptera hypersensitivity, indolent systemic mastocytosis, galactose- α -1,3-galactose (α -gal) allergy, and other etiologies have been considered and eliminated that the diagnosis of IA is made. IA was first described in 1978 by Bacal *et al.*,¹ who reported 11 patients whose episodes of anaphylaxis could not be explained, despite careful evaluation and follow-up. This series was expanded to include > 335 patients who had been followed up for > 1100 patient-years without an external allergen being implicated.² Even though much is still unknown with regard to the etiology of IA, treatment is associated with a good prognosis.

Multiple theories on the pathogenesis of IA have been proposed, but none has successfully explained why these patients experience episodic release of bioactive mediators from mast cells and basophils.³ To

date, studies have not shown that basophils or mast cells exhibit a lower response threshold when releasing histamine or other mediators. No hidden culprit allergens have been found, despite investigations into metabisulfite (a common food additive and/or preservative) or progesterone sensitivity. Although anti-immunoglobulin E (IgE) autoantibodies have been shown to play a role in idiopathic urticaria by activating mast cells *via* cross-linking surface IgE (or Fc epsilon receptor 1 (Fc ϵ RI)),⁴ preliminary studies at Northwestern University were unable to detect any significant differences in anti-IgE levels between patients with IA and controls. Grammer *et al.*,⁵ reported that B cells in the peripheral blood of patients with IA are more activated than B cells from the controls and that patients with symptomatic IA demonstrated a higher percentage of activated T lymphocytes than patients with IA and in remission. The role of these activated T and B cells in the pathogenesis of IA has yet to be determined. It is important to note that up to 80% of the patients are atopic (food allergy, asthma, atopic dermatitis, urticaria, allergic rhinitis, venom hypersensitivity) and that the prevalence is higher in women than in men.⁶

The clinical manifestations of IA are indistinguishable from that of allergen-associated anaphylaxis and include urticaria, generalized pruritus, and angioedema, including oropharyngeal or laryngeal swelling, hypotension tachycardia, wheezing, stridor, nausea, vomiting, flushing, diarrhea, dysphagia, light-headedness, and loss of consciousness.^{1,2,6} Patients may expe-

From the Division of Allergy and Immunology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois

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Address correspondence to Paul A. Greenberger, M.D., 211 E. Ontario Street, no. 1000, Chicago, IL 60611

E-mail address: p-greenberger@northwestern.edu

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Table 1 Classification of IA*

IA	Symptoms
Frequency of episodes	More than six times per year or more than once in 2 mo: frequent; fewer than six times per year or less than once every 2 mo: infrequent
Generalized Angioedema	Urticaria or angioedema with bronchospasm, hypotension, syncope Angioedema with upper-airway compromise (laryngeal, pharyngeal, tongue)
Summary of diagnoses	IA-G-F, IA-A-F, IA-G-I, IA-A-I
Corticosteroid-dependent IA	Used when a patient has recurrent IA symptoms below a threshold dose of prednisone
Malignant IA	Used when a patient requires high doses of prednisone for disease suppression, arbitrarily set at 30 mg a day or 60 mg every other day
IA-Q	Used when a patient has possible IA but when documentation of objective findings is lacking and/or lack of response to medications
IA-variant	Used when symptoms of IA vary from classic IA Diagnosis may eventually be changed to IA-A, IA-G, IA-Q, or undifferentiated somatoform IA
Undifferentiated somatoform IA	Used when stated symptoms mimic IA but no objective findings can be documented; should be suspected when the symptoms do not respond to treatment regimen and lack of objective findings should be documented, differentiating this from IA-Q

IA = Idiopathic anaphylaxis; G = generalized; F = frequent; A = angioedema; I = infrequent; Q = questionable.

*Adapted from Ref. 7, with permission.

rience different combinations of the mentioned symptoms but usually tend to have the same manifestations on repeated episodes. The first episode may be very severe because patients subsequently learn to recognize prodromal symptoms and self inject epinephrine. Progression from hives and pruritus to the life-threatening symptoms of syncope, wheezing, and laryngeal edema may vary from 10 minutes to hours, depending on the individual.

CLASSIFICATION

IA is classified according to the distribution of symptoms as well as the frequency of attacks. Patients who experience six or more episodes in the preceding year or two or more episodes in the preceding 2 months are classified as having IA-frequent (IA-F).⁷ Patients who experience fewer episodes are classified as having IA-infrequent (IA-I).⁷ This distinction is important because patients with IA-F initially will require prednisone as disease-modifying therapy, whereas most patients with IA-I will not require prednisone. Those patients who experience life-threatening upper-airway angioedema without other systemic signs and/or symptoms of anaphylaxis are described as having IA-angioedema (IA-A), whereas those who experience hypotension, bronchospasm, cardiovascular collapse, or gastrointestinal symptoms are classified as having IA-generalized

(IA-G). There are four ultimate combinations: IA-G-F, IA-G-I, IA-A-F, and IA-A-I. Several subclassifications of IA also exist (Table 1).⁷

DIAGNOSIS

IA remains a diagnosis of exclusion. IA should be considered as the working diagnosis in the absence of an identifiable trigger, after a thorough history, physical examination, and diagnostic evaluation. The four main goals to taking a thorough history are confirming the diagnosis of anaphylaxis, ruling out other causes of anaphylaxis (*e.g.*, foods, spices, medications, insect sting, exercise induced or food plus exercise induced, “ α -gal”), characterizing the disease subtype, and obtaining a response to previously tried therapies. Medical records from the emergency department and first responders are invaluable in the evaluation of IA because these often contain low blood pressure, heart rate, skin, and oropharyngeal examination information, which will help contextualize a patient’s subjective report of light-headedness or throat tightening as vocal cord dysfunction versus panic attacks or undifferentiated somatoform anaphylaxis⁸ may mimic IA. Other diagnoses on the differential include indolent systemic mastocytosis and hereditary angioedema or acquired C1 esterase inhibitor deficiency. The former condition is unlikely to have chronic urticaria, and the

latter is not associated with acute urticaria.⁹ Neither carcinoid syndrome nor pheochromocytoma have urticaria as manifestations.

On physical examination, one should inspect for urticaria pigmentosa and signs of atopy, *e.g.*, atopic dermatitis. Cellphone pictures that document findings during the IA attack are helpful. If present, note the distribution of urticaria and/or angioedema, and, in particular, the size of the purportedly enlarged tongue. Both the history and results of the physical examination will guide testing and laboratory work for causes of anaphylaxis, such as food allergy, drug allergy (nonselective nonsteroidal anti-inflammatory drugs), venom hypersensitivity, latex allergy, exercise-induced anaphylaxis, and indolent systemic mastocytosis. If appropriate, obtain skin-prick testing to foods, venom, latex, penicillin, and certain medications. Testing with an indiscriminate food panel is not recommended. Baseline (and acute phase) serum tryptase is recommended to evaluate for mast cell disorders. If the suspicion for a mast cell disorder is high, then a 24-hour urine collection for the metabolites of mast cell mediators should be obtained (N-methyl histamine and 2,3 dinor 11 β -prostaglandin F2 α). If suspected, a 24-hour urine collection for 5-hydroxyindoleacetic acid (5-HIAA) for carcinoid syndrome or serum fractionated catecholamines and fractionated metanephrines for pheochromocytoma may be ordered.

A rare mimic of IA is mammalian meat allergy (also known as α -gal allergy). In 2009, Commins *et al.*¹⁰ reported a novel food allergy related to IgE antibodies to the carbohydrate α -gal from patients who experienced delayed symptoms of anaphylaxis, angioedema, or urticaria 3 to 6 hours after ingestion of beef, pork, or lamb. The α -gal is a carbohydrate that is expressed in all mammals except primates (humans, chimpanzees, and monkeys) and is present in the gastrointestinal tract of ticks. Humans may become sensitized to α -gal through a tick bite when the tick's stomach contents are regurgitated onto the victim's skin. *Amblyomma americanum* (also known as the lone star tick) is the most commonly implicated tick.

If the baseline serum tryptase value is ≥ 15 ng/mL, then the possibility of indolent systemic mastocytosis should be considered.^{9,11} Approximately 80% of patients with this condition have urticaria pigmentosa.

TREATMENT

Although treatment for patients with IA should be individualized, there are some guidelines that can be applied (Fig. 1). All patients with IA should be educated about their disease and taught how to manage an acute attack. At the first signs of anaphylaxis, adult patients should inject 0.3 mL (1:1000) of aqueous epi-

nephrine intramuscularly in the vastus lateralis, followed by oral intake of prednisone 50–60 mg, and either cetirizine 10 mg or levocetirizine 5 mg. In cases in which a patient has a characteristic prodrome, *e.g.*, in which lip tingling precedes lip and pharyngeal angioedema, the patient may take the antihistamine immediately and be prepared to self administer epinephrine. The emergency kit should be carried on the person at all times and occasionally monitored for expiration. All patients who use epinephrine should be prepared to call for help and go to the nearest emergency department for further evaluation. A second self injection of epinephrine can be administered in 5 minutes if needed. The epinephrine dosage for children is weight based: 0.15 mg if between 10 and 22 kg, and 0.10 mg if ≤ 10 kg.

Patients with IA-F benefit from IA-modifying suppressive therapy, which should include 40–60 mg of prednisone daily as well as an H₁ antihistamine, either cetirizine 10 mg or levocetirizine 5 mg. Patients should be given at least 1 week of daily prednisone, although some may require 2 weeks. It is rare that IA does not respond to daily systemic steroids, that the diagnosis should be called into question if a patient's IA is not controlled after 2–3 weeks of daily prednisone or is having symptoms (hypotension, upper-airway angioedema, generalized urticaria) on higher doses of prednisone, *e.g.*, 40–60 mg daily after 2 weeks. Once symptoms resolve for 7 days, patients may be tapered to every-other-morning dosing. If no relapses occur, then the patient may be further weaned by 5 mg every other day every 2 weeks. The H₁ antihistamine is usually maintained on a daily therapy for at least a year, or longer.

Steroid-dependent IA that requires at least 30 mg prednisone daily or 60 mg every other day is uncommon, but alternative medications, such as ketotifen, oral cromolyn, oral albuterol, or montelukast, can be tried in those patients for whom prednisone cannot be discontinued. To avoid complex and costly medication regimens, these second-line agents should be discontinued if they do not clearly decrease the patient's prednisone requirement. In those patients with frequent attacks who are refractory to corticosteroids, omalizumab should be considered.¹² Recent case reports and case series⁶ have successfully demonstrated reduction, if not cessation, of anaphylaxis in this population.

Patients with IA should be informed of a medical alert bracelet, and the medical record should have the diagnosis identified for other physicians and health care professionals. They should also be educated and frequently reminded about how to administer their epinephrine, prednisone, and H₁ antihistamine. Although the potential life-threatening nature of their disease should be reinforced, physicians should re-

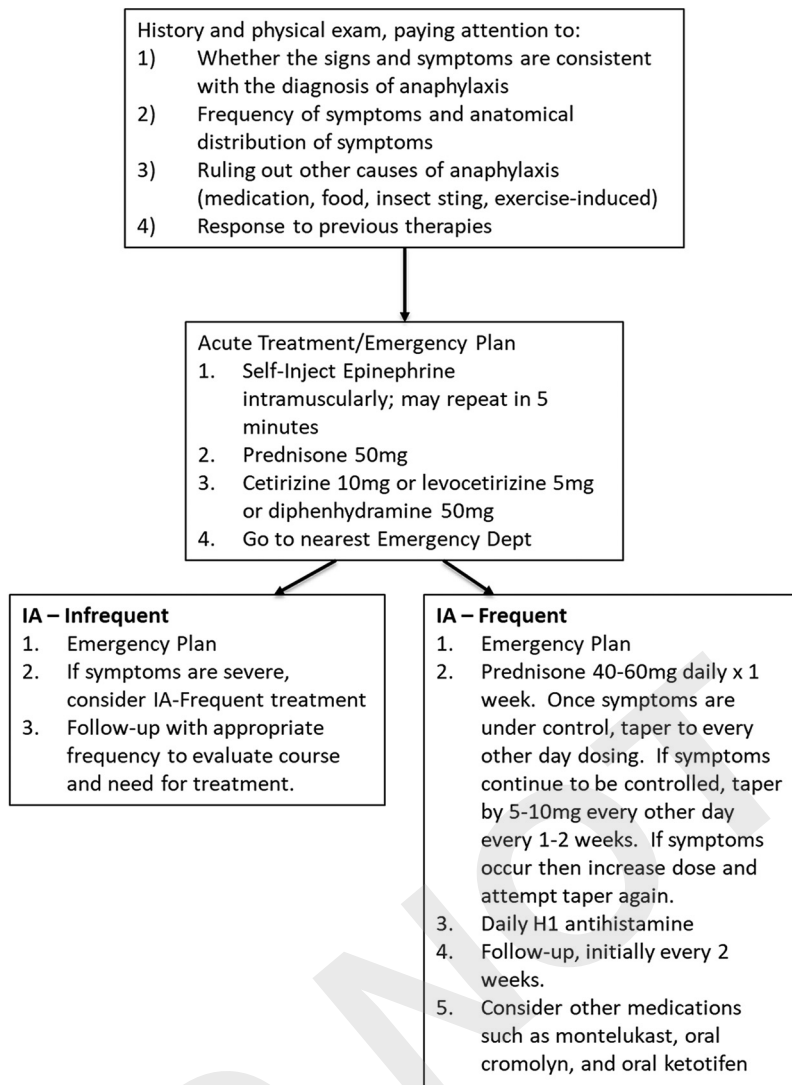


Figure 1. Algorithm for the management of idiopathic anaphylaxis.

assure their patients that compliance with the prescribed regimen offers a remission rate in excess of 80%.² Alternatively, physicians and health-care professionals should reassess their patients and monitor for response to treatment or possible overlooked diagnoses.¹³

IMMUNOLOGY

- Symptoms of IA occur as a result of episodic activation of mast cells and basophils *via* an unknown mechanism.
- Patients with IA display more activated B cells in their peripheral blood.
- Patients with IA who experience an acute episode display a higher percentage of activated T lymphocytes than those patients in remission.
- It is uncertain whether anti-IgE autoantibodies play a role in the pathogenesis of IA.

CLINICAL PEARLS

- IA is a diagnosis of exclusion. It is only after food allergy, drug hypersensitivity, Hymenoptera hypersensitivity, indolent systemic mastocytosis, α -gal allergy, and other etiologies have been considered and eliminated that the diagnosis of IA is made.
- Its underlying pathogenesis is unknown but may be autoimmune in nature.
- All patients with IA should carry an emergency kit that includes epinephrine, oral corticosteroid, and oral H₁ antihistamine.
- If symptoms are not responsive to systemic steroids administered over several weeks, then the diagnosis of IA should be reconsidered.
- For patients with frequent episodes, recommend treatment with a prolonged empiric course or prednisone and daily oral H₁ antihistamine as initial disease-modifying therapy.

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