

Idiopathic Anaphylaxis



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KEYWORDS

• Anaphylaxis • Idiopathic anaphylaxis • Mast cell activation syndrome

KEY POINTS

- Idiopathic anaphylaxis (IA) is a diagnosis of exclusion after other causes, such as foods, medications, exercise, insect stings, C1 esterase inhibitor deficiency, and mastocytosis, have been excluded.
- A significant proportion (24%–59%) of anaphylaxis cases are classified as idiopathic in several reported patient series. There is a higher prevalence of idiopathic anaphylaxis in women compared with men and a high prevalence of atopy in patients with IA.
- Classification of IA is based on frequency of episodes and clinical manifestations; frequent episodes are defined as at least 2 episodes in the preceding 2 months or at least 6 episodes in the preceding year.
- Treatment of IA is individualized based on severity and frequency of symptoms.
- Acute treatment of IA is the same as treatment of anaphylaxis from other causes, except that prolonged tapering of prednisone is usually required to induce remission. All patients should possess an epinephrine autoinjector and an anaphylaxis emergency plan.
- The prognosis of IA is generally favorable with appropriate treatment and patient education.

BACKGROUND AND DEFINITION

The term idiopathic anaphylaxis (IA) refers to anaphylaxis without a discernible cause after completion of an appropriate diagnostic evaluation. It is a diagnosis of exclusion after other causes, such as foods, medications, exercise, insect stings, C1 esterase inhibitor deficiency, and mastocytosis, have been thoroughly considered and excluded. In 1978, Bacal and colleagues¹ reported the first cases of IA. In that report, of the 21 patients in the series, 11 had no causal explanation for anaphylaxis and the term IA was given. Initially, the medical community received the term IA with considerable doubt and skepticism because it was thought that an external cause or factors should

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be found for each case of anaphylaxis.² In addition, reports of IA were initially limited to the United States. However, in the 1990s, reports emerged from European countries, such as Spain, France, Ireland, Germany, and Brazil.³ Subsequently, IA has become widely accepted as a disease process worthy of closer attention.

The pathophysiology of IA has not been fully elucidated, although elevated concentrations of urinary histamine and its metabolite, methylimidazole acetic acid, plasma histamine, and serum tryptase found in patients with this disorder is consistent with mast cell activation.⁴ Manifestations of IA are identical to those episodes with a known cause. Despite early use of epinephrine autoinjector, some patients continue to experience life-threatening events, and there have been fatalities. There is a high prevalence of atopy in patients with IA with the rate found to be as high as 59% in one case series.⁵ There is also a significantly higher prevalence in women compared with men.⁶ However, after puberty and until menarche, the incidence has been reported to be similar in men and women.⁶

CLASSIFICATION

The classification of IA is based on frequency of episodes and clinical manifestations.⁷ Frequent episodes are defined as having at least 2 episodes in the preceding 2 months or at least 6 episodes in the preceding year. Patients who do not meet either of these 2 criteria are categorized as having infrequent IA (Table 1). Generalized IA (IA-G) is characterized by urticaria and/or angioedema in addition to systemic symptoms, including cardiovascular, respiratory, and/or gastrointestinal symptoms. Some patients are categorized as IA-angioedema (IA-A), which is characterized by significant upper airway obstruction due to severe angioedema of the tongue, pharynx, or larynx without other signs of systemic anaphylaxis; patients may also have urticaria.

Table 1 Classification of idiopathic anaphylaxis		
	Parameter	Comments
Classification	IA-G	Urticaria or angioedema with bronchospasm, hypotension, syncope
	IA-A	Angioedema with upper airway compromise (laryngeal, pharyngeal, tongue); may also have urticaria
Frequency	Frequent (F)	Definition: At least 2 episodes in the preceding 2 mo or at least 6 episodes in the preceding year
	Infrequent (I)	Definition: Fewer than 6 episodes a year
Severity	CSD-IA	Patient cannot be tapered off prednisone
	MCSD-IA	Patient requires at least 20 mg every day or 60 mg every other day prednisone to control IA
Variations of IA	IA-Q	Patient has possible IA but documentation of objective findings are unsuccessful and diagnosis is uncertain
	IA-V	Applied when symptoms of IA vary from classic IA
	Somatoform IA (IA-S)	Symptoms mimic IA but patients have no organic disease, documented objective findings, and are nonresponsive to the treatment regimen for IA

Adapted from Patterson R. Idiopathic anaphylaxis. East Providence (RI): OceanSide Publications, Inc; 1997. p. 20.

Some cases of IA are unclear and cannot be classified as either IA-G or IA-A. These cases are classified as IA-questionable (IA-Q), IA-variant (IA-V), or undifferentiated somatoform IA (US-IA). IA-Q describes patients who possibly have IA but do not have any documented objective finding and do not show a response to appropriate doses of prednisone. Thus, the diagnosis of IA remains unclear. IA-V describes patients whose symptoms and clinical findings differ from classic IA. US-IA is applied to patients who describe symptoms consistent with IA but have no organic disease or documented objective findings, are nonresponsive to the treatment regimen for IA, and meet DSM criteria for an undifferentiated somatoform disorder.⁸ The patients with nonorganic disease present significant diagnostic and management issues and often cause considerable health care expenditure.⁸

In a study assessing the differences between IA-G and IA-A, a logistic regression model was constructed. Mast cell releasability was analyzed in the 2 groups using the log 10-wheal area produced by 4 consecutive concentrations of codeine. Using the logistic regression equation, IA-G and IA-A patients showed a higher cutaneous reaction to codeine than atopic patients. However, IA-G patients had a significantly lower reaction to codeine than those patients with chronic idiopathic urticaria.⁹ No differences were observed in patients with IA-A compared with urticaria patients and there was no difference in cutaneous response to codeine between IA-A and IA-G patients.

EPIDEMIOLOGY

The precise prevalence of IA is unknown. Patterson and colleagues¹⁰ performed a survey to estimate the prevalence of IA in the United States in 1995. In this survey, a questionnaire was mailed to all previous graduates of the Northwestern University Allergy and Immunology Fellowship program from the last 31 years. Of the 75 allergists surveyed, a total of 633 cases of IA were documented. By extrapolation of the cases of IA reported by the allergists surveyed to the approximately 4000 allergists in the United States at that time, it was estimated that the number of cases in the United States was between 20,592 and 47,024. In a recent study performed by Wood and colleagues,¹¹ 2 nationwide, cross-sectional random digit dial surveys were conducted in 2011. One of the surveys was a public survey of unselected adults and the other was a patient survey. Of the 1000 adult respondents, the prevalence of anaphylaxis in the general population was estimated at 1.6% or greater. Of these respondents, about 39% reported a possible idiopathic reaction. Webb and Lieberman⁵ conducted a retrospective medical record review and follow-up questionnaires of anaphylaxis. The review spanned 25 years (1978–2003). Of the 601 cases, the highest percentage of patients (59%), was diagnosed with anaphylaxis because of unidentifiable causes. In a 3-year survey from the Mayo Clinic, 34 of 142 (24%) cases of anaphylaxis were reported to be idiopathic.¹²

The initial reports of IA were primarily in adults. Subsequently, this was recognized in pediatric populations. In children, the diagnosis of IA is delayed as compared with adults. There is often a history of multiple emergency room visits or hospitalizations before a diagnosis. Ditto and colleagues¹³ published a case series of 22 pediatric patients with IA. They noted an increasing incidence of pediatric IA that they thought could be due to greater awareness that this condition does occur in the pediatric population.

The symptoms of anaphylaxis are similar to the adult population. In addition, the classification and treatment algorithm previously applied in the adult population are used in the pediatric population.^{13,14} In a retrospective review of medical records of children presenting to a pediatric allergy clinic, 8 children diagnosed with IA were identified. The patients' ages ranged from 11 months to 19 years at disease onset. All these patients had cutaneous findings of urticaria, angioedema, or generalized flushing.

Many of the children had experienced life-threatening events, despite using epinephrine autoinjectors at onset of symptoms. In this study, there was a generally good response to appropriate therapy.¹⁴

Currently, there are ongoing efforts to improve the prevalence estimates of all forms of anaphylaxis. In a 2014 consensus document from the World Allergy Organization, the international research agenda for anaphylaxis included obtaining the global incidence and prevalence of anaphylaxis in general populations in different countries to obtain reliable population estimates.¹⁵ The plan is to include data on anaphylaxis from all triggers and from specific triggers, including foods, stinging insects, other venoms and drugs with the goal being to collect data on anaphylaxis in different populations, such as infants, children, teenagers, pregnant women, the elderly, and patients with comorbidities such as asthma and cardiovascular disease. It is clear that regardless of the overall incidence of IA, it can have a significant, negative effect on quality of life as patients may have persistent anxiety about recurrent episodes and have neither a potential trigger to avoid nor a method to predict an episode.

POSSIBLE PATHOGENIC MECHANISMS

Numerous theories have been proposed to explain this condition. One theory involves an increase in the number of mast cells in patients with IA. Studies evaluating the number of mast cells in IA patients have found only a modest increase or no difference compared with healthy individuals.^{16,17} In contrast with normal controls or IA patients, those with mastocytosis have a 10-fold increase in the density of cutaneous mast cells.

Another theory involves the release of mast cells or basophils. In a Spanish study, IA patients had more cutaneous reactivity to codeine than did atopic patients.⁹ However, in a study conducted by Keffer and colleagues,¹⁸ there was no difference in cutaneous response to intradermal morphine between IA patients and normal subjects. In addition, an *in vitro* study showed no difference in histamine release from peripheral blood basophils on stimulation with anti-immunoglobulin E (IgE) or with a calcium ionophore, A23187.¹⁹

In a case report published in 2007, a 30-year-old woman with multiple drug allergy syndrome who reported several episodes of anaphylaxis with angioedema and urticaria without any identifiable triggers for several episodes was found to have a positive *in vivo* autologous serum test and *in vitro* basophil histamine release assay.²⁰ This finding indicated the presence of circulating histamine-releasing factors. Thus, the authors proposed an autoreactive mechanism as the possible cause for IA.

Lymphocyte activation has been demonstrated in IA patients compared with normal patients. Grammer and colleagues²¹ used flow cytometric analysis of lymphocyte markers to evaluate potential immunologic differences between normal control patients and IA patients in remission and during acute episodes. Total lymphocyte numbers were decreased in IA patients taking prednisone, consistent with known steroid effects on lymphocytes. Patients during acute episodes of IA were found to have statistically significant increases in T-cell activation markers compared with those in remission who had higher numbers of activated T cells compared with controls. No specific T-cell subset was identified as the primary subset involved in activation. Surprisingly, there was increased B-cell activation in IA patients, both during acute episodes and in remission, compared with control patients. The findings in this study would suggest that IA is an immunologic activation phenomenon consistent with the established clinical pattern of steroid responsive disease.

Other theories to explain IA include increased levels of anti-IgE autoantibodies, dysregulation of chemokines, such as uncontrolled production of histamine-release factors, or loss of histamine release inhibitory factors. It has been proposed that autoantibodies against IgE could cross-link IgE on mast cells and lead to the activation of mast cells and mediator release. In a pilot project, however, there was failure to detect anti-IgE antibodies in any of the 10 samples tested.²²

In summary, many pathogenic mechanisms proposed to explain IA have not been supported by clinical and experimental studies.

CLINICAL MANIFESTATIONS

The signs and symptoms of patients diagnosed with IA are indistinguishable from the manifestations of other forms of anaphylaxis. The signs include angioedema, urticaria, wheezing, flushing, tachypnea, tachycardia, vomiting, diarrhea, syncope, hypotension, stridor, dysphagia, or hoarseness. The symptoms may include pruritus, dyspnea, lightheaded sensation, nausea, and abdominal pain/cramping, which can be severe, with urgent diarrhea. Urticaria is usually diffuse and severely pruritic and comprise erythematous well-circumscribed wheals with centers that blanch. Angioedema that frequently accompanies the urticaria usually presents in the form of swelling of the face, eyes, lips, genitals, or extremities. Angioedema may also affect the tongue, oropharynx, and larynx leading to severe life-threatening symptoms. The cardiac manifestations of anaphylaxis can be severe and are variable. Usually, tachycardia occurs as a compensatory mechanism for the decrease in effective vascular volume. Cardiovascular collapse may occur without any associated cutaneous or respiratory manifestations. Importantly, symptom onset may be sudden and progress at a rapid pace. Although some IA patients report that the time from onset of initial symptoms to life-threatening symptoms such as laryngeal edema, bronchospasm, and hypotension may be less than 10 minutes, others report several hours between symptom onset and anaphylaxis. In general, for a given patient, the timing and prodromal symptoms are similar with each episode. The first episode of IA usually is the worst, because the patient subsequently learns to recognize the prodromal symptoms and initiate emergency treatment in a timely fashion. Patients with rapid progression to life-threatening symptoms are at increased risk of more severe reactions in contrast with patients with slow progression of symptoms.

In a series of 335 patients diagnosed with IA, including both pediatric and adult patients, all had experienced angioedema and urticaria.²³ In addition, 210 (63%) experienced upper airway obstruction, 132 (39%) experienced bronchospasm, 78 (23%) experienced hypotension or syncope, and 75 (22%) experienced gastrointestinal symptoms. Angioedema of the gut can produce severe abdominal cramping, which is the prodrome in some patients. These patients have urgent bowel movements, most often diarrhea, with urticaria appearing while in the bathroom, followed by lightheadedness, and oftentimes, hypotension. In the authors' experience, some of these patients have been found unconscious on the bathroom floor by family or spouses.

DIFFERENTIAL DIAGNOSIS

The diagnosis of IA should be made only after exclusion of other potential causes of anaphylaxis and other diseases with similar manifestations to anaphylaxis (**Box 1**). Some common causes of anaphylaxis include foods and exercise-induced anaphylaxis (EIA). EIA usually occurs after vigorous exercise and is a result of mast cell activation. Symptoms may include urticaria, angioedema, nausea, vomiting,

Box 1**Differential diagnosis of idiopathic anaphylaxis**

- i. Known causes of immediate generalized reactions
 - A. IgE-mediated
 - 1. Foods
 - 2. Medications (2 examples listed)
 - a. Penicillins
 - b. Platins
 - 3. Food supplements (2 examples listed)
 - a. Psyllium
 - b. Bee pollen
 - B. Exercise-induced anaphylaxis
 - C. Food plus EIA
 - D. Medication-induced reactions
 - 1. Aspirin
 - 2. NSAIDs
 - 3. Angiotensin-converting enzyme inhibitors
 - 4. Opiates
 - E. Radiographic contrast media reactions
- ii. Hereditary angioedema (HAE)
 - A. Classical form (also called type I)
 - 1. Absent C1 inhibitor
 - 2. Dysfunctional C1 inhibitor
 - B. Acquired form (also called type II)
 - 1. B-cell lymphoproliferative disorder
 - 2. Autoantibodies to C1 inhibitor
 - C. HAE with normal C1-INH (also called type III HAE)
- iii. Systemic mastocytosis
- iv. Asthma masquerading as anaphylaxis
- v. Munchausen stridor
- vi. Munchausen anaphylaxis
- vii. Undifferentiated somatoform IA
 - A. Prevarication-anaphylaxis
 - B. Simulated anaphylaxis
- viii. Miscellaneous diagnoses
 - A. Panic attacks
 - B. Globus hystericus
 - C. Vocal cord dysfunction
 - D. Histamine-rich food induced flushing
 - E. Carcinoid syndrome
 - F. Pheochromocytoma

Adapted from Patterson R. Idiopathic anaphylaxis. East Providence (RI): OceanSide Publications, Inc; 1997. p. 20.

bronchospasm, laryngeal edema, respiratory distress, shock, and loss of consciousness. Some patients may have both IA and EIA. EIA may be unrelated to food, may occur only with a specific food, or may occur with any food ingestion. Medications are another common cause of anaphylactic reactions. Nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin, may cause anaphylactic reactions through a non-IgE-mediated mechanism; there are also reports of IgE-mediated NSAID anaphylaxis. Although drugs such as β -lactams can cause IgE-mediated responses that occur within minutes to hours of ingestion, more severe reactions typically occur within 1 hour of ingestion or within minutes of parenteral administration.²⁴ Thus, a thorough medication history should be obtained from patients with anaphylaxis. Hereditary angioedema may also mimic anaphylaxis. It is characterized by recurrent episodes of angioedema usually involving the lips, tongue, or upper airway. The gastrointestinal tract may also be involved and may produce symptoms of cramping, abdominal pain, nausea, and diarrhea. Laboratory findings, including decreased levels of C4, CH50, and C1 esterase inhibitor level or function, may help differentiate this disorder from IA.

Some patients with pheochromocytoma and carcinoid syndrome may present with symptoms similar to symptoms of anaphylaxis. These patients often present with flushing as a result of release of vasoactive substances, such as epinephrine, norepinephrine, and vanillylmandelic acid in pheochromocytoma, and 5-hydroxyindoleacetic acid in carcinoid syndrome. Detection of these mediators via laboratory tests helps differentiate these disorders from IA. Severe asthma attacks may also be mistaken for IA. These patients may present with severe bronchoconstriction leading to dyspnea and wheezing, which can occur in IA patients. Symptoms limited to the lungs and prior history of hospitalizations for asthma would make a diagnosis of IA less likely.

Patients with Munchausen stridor complain of dyspnea and imitate stridulous sounds over the neck region. This stridorous respiration has no organic cause. These patients usually overuse epinephrine autoinjectors and emergency phone numbers and visit the emergency room frequently.²⁵ Patients with Munchausen stridor usually fail to respond to antihistamines or steroids.

Rare disorders that may mimic IA include delayed anaphylaxis to red meat. In contrast with immediate food-induced anaphylaxis, symptoms of urticaria or anaphylaxis may occur more than 2 hours after exposure. The relevant IgE antibody is specific for the oligosaccharide galactose- α -1,3-galactose, a blood group substance of non-primate mammals.²⁶ There is evidence that the primary cause of this IgE antibody response is tick bites. Diagnosis can be made by the presence of specific IgE to beef, lamb, pork, and milk and lack of IgE to turkey, chicken, or fish. Skin prick tests are usually negative, yet intradermals are usually positive.²⁶ Another infrequent cause of anaphylaxis is hydatid cyst rupture. A case of relapsing generalized anaphylactic reactions associated with life-threatening laryngospasm in a previously healthy man was published in a report from Germany. Workup revealed cystic liver echinococcosis with spontaneous rupture of the hydatid cyst.²⁷

Other disorders included in the differential diagnosis of IA are systemic mastocytosis (SM), monoclonal mast cell activation syndrome, and mast cell activation syndrome. A certain subset of these patients has been shown to have evidence for clonal disorders of mast cells. In a study published by Akin and colleagues,²⁸ c-kit mutational analysis was positive in 3 of 12 patients with IA who did not exhibit either urticarial pigmentosa or characteristic bone marrow biopsy finding of multifocal mast cell aggregates observed in SM. Mast cell activation disorders are discussed in more detail elsewhere in this issue by Akin.

DIAGNOSTIC TESTS

The diagnosis of IA is one of exclusion. Thus, before arriving at this diagnosis, an extensive evaluation, including a thorough history, physical examination, and laboratory data, must be pursued. All hospitalization and emergency room records should be carefully examined for objective evidence of signs and symptoms, including hypotension, bronchospasm, and oropharyngeal angioedema. Particular attention must also be given to the treatment administered, response to treatment, and events surrounding the episode. Information on the severity and frequency of symptoms must also be obtained. The history should focus on the exclusion of potential allergens. Work and home environment history should include possible exposure to latex. The possibility of an association with insect stings, food or drug ingestion, and exercise (especially postprandial exercise) should be evaluated. Pigmented lesions that would suggest systemic mastocytosis must be excluded. If such lesions are present, then skin and bone marrow biopsies should be performed to confirm the diagnosis of mastocytosis. In rare cases, both upper and lower endoscopies may be performed to rule out a mastocytoma.

Laboratory data may include a complete blood cell count, chemistry panel, and liver function tests. Diagnostic tests to consider for a patient with unexplained anaphylaxis are listed in [Table 2](#). Antinuclear antibody, erythrocyte sedimentation rate, and rheumatoid factor should be checked if a collagen vascular disorder is a possibility. Urinary histamine levels and serum tryptase levels may be useful because they may be elevated in generalized anaphylactic reactions. Spot urinary histamine levels or 24-hour urinary histamine levels remain elevated during attacks of IA.²⁹ Because of the short half-life and rapid release of plasma histamine, it is not ordinarily useful for diagnosis. Serum tryptase is generally more useful because the levels peak 60 to 90 minutes after onset of anaphylaxis; generally, the tryptase returns to normal within 6 hours, but there is a report of tryptase remaining elevated for 24 hours.³⁰ A systematic retrospective survey from 2006 to 2010 evaluating 171 patients with systemic reactions showed that a significant portion of patients with elevated acute serum tryptase levels had mild reactions that did not meet the World Allergy Organization criteria for anaphylaxis. Of note, 50% of the cases were diagnosed with IA. The correlation between acute serum tryptase level and severity of anaphylaxis was weak. This finding may reduce the specificity of the serum tryptase test.³¹ Patients that have elevated tryptase both during acute attacks and at baseline should be evaluated for mastocytosis or other clonal mast cell disorders.

In a study of 102 patients with an initial diagnosis of IA evaluated with a battery of 79 selected food antigen skin prick tests, 32 (31%) had a positive test to one or more food antigens. In 5 of the patients, subsequently eating a food that was skin test positive provoked an anaphylactic reaction. Two patients completely eliminated the foods and ceased to experience reactions.³² Thus, this may be a useful method for identifying an offending antigen in some cases. In another study, 110 patients with IA were tested with the Immuno Solid phase Allergen Chip (ISAC) allergen array containing 103 allergens. A wide range of major allergens was identified with ω -5-gliadin and shrimp, accounting for 45% of the previously unrecognized sensitizations. Twenty percent of the arrays were classified with a high likelihood of identifying the cause of anaphylaxis. The authors noted that the ISAC array contributed to the diagnosis in 20% of patients with IA.³³ Patients with IA may also have anaphylaxis because of known causes, including food, medications, or exercise.^{19,23} It should also be noted that there are false positive food tests using either in vivo or in vitro tests for food-specific IgE, so testing should correlate with a history that is consistent with food allergy.

Table 2
Diagnostic tests to consider for a patient with unexplained anaphylaxis

Procedure	Comment
Urine histamine	To help confirm mast cell activation to secure the diagnosis
Serum tryptase	Supportive if elevated
Immediate skin testing for foods	May help to confirm or exclude food allergies as etiologic
Immediate skin testing for spices	To confirm or exclude an implicated spice
Immediate skin testing for penicillin	To confirm that penicillin was responsible for the anaphylaxis
Immediate skin testing for latex	May masquerade as idiopathic or food-induced anaphylaxis
Test dosing with NSAIDs	To demonstrate or exclude these as possible agents
Test dosing with a medication or food additive	To demonstrate or exclude these as causes for anaphylaxis
Complement determinations	To confirm or exclude C1 esterase inhibitor: deficiency/dysfunction C4, CH50
Bone marrow biopsy, skin biopsy, bone scan, liver scan	To exclude or confirm systemic mastocytosis or urticaria pigmentosa
Diagnostic therapeutic trial with prednisone for 2–3 mo	IA is prednisone responsive

Note: In vitro testing by RAST (radioallergosorbent test) or ELISA is less sensitive and can be less specific. Positive skin tests demonstrate IgE antibodies that may be related to episodes of anaphylaxis. However, they may occur in patients with IA and not make a diagnosis of an external cause for anaphylaxis.

Adapted from Patterson R. Idiopathic anaphylaxis. East Providence (RI): OceanSide Publications, Inc; 1997. p. 20.

TREATMENT

The treatment of IA is individualized based on the severity and frequency of a patient's symptoms. A general IA management algorithm appears in [Fig. 1](#). Patients should receive instruction on the management of an acute episode. At the first sign of anaphylaxis, patients should administer 0.3 mL (1:1000) of aqueous epinephrine intramuscularly or subcutaneously, 60 mg of prednisone orally, and an oral H1 antihistamine. Hydroxyzine HC1 25 mg, diphenhydramine 50 mg, and chlorpheniramine 4 mg are the most studied, but second-generation antihistamines have also been used. Depending on the response to the initial injection, epinephrine administration may need to be repeated; this may be particularly true if the patient is taking β -blockers. However, these patients may also have a prominent α -adrenergic, hypertensive response. The patient should then proceed to the nearest emergency room in the safest and fastest way, which often means calling 911 for emergency medical services. Qualified personnel should follow Advanced Cardiac Life Support protocol. The patency of the airway must be assessed. If airway obstruction is severe and compromises ventilation, then intubation or tracheostomy may be necessary. Patients with severe hypotension may require rapid administration of intravenous crystalloid fluids preferably through 2 large-gauge venous catheters. Vasopressors such as dopamine or norepinephrine may be used for additional hemodynamic support, and epinephrine may need to be repeated or added as an infusion.

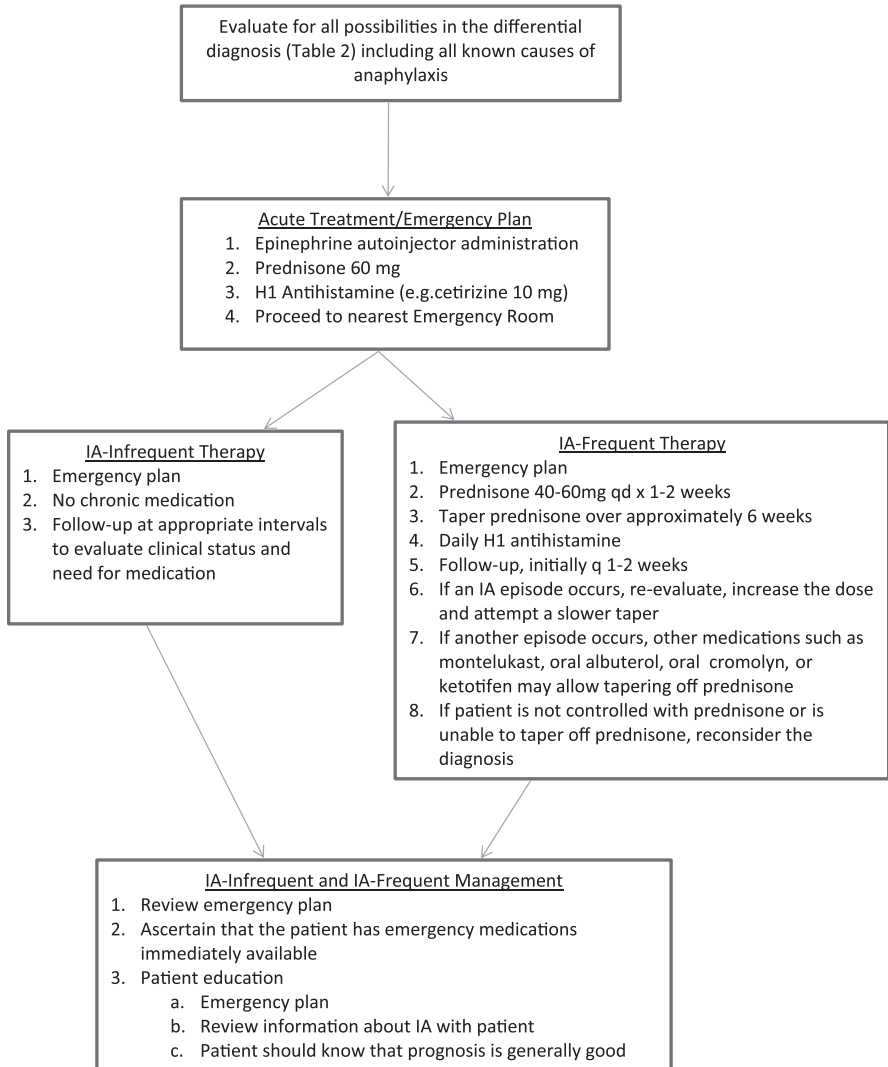


Fig. 1. IA management algorithm for the patient presenting with compatible history and objective signs of anaphylaxis.

Patients who experience frequent episodes are placed on prednisone to induce remission, at a dose 40 to 60 mg once daily for 1 week until symptoms are controlled, as well as an antihistamine (eg, hydroxyzine 25–50 mg 3 times daily or cetirizine 10 mg twice daily). However, higher doses of prednisone may be necessary in some patients. Daily dosing of prednisone for 1 to 2 weeks is usually required to achieve symptom control. If a longer daily prednisone course is required, the diagnosis of IA should be questioned. Once symptoms are stable, the dosing of prednisone may be converted to alternate day dosing. Prednisone should be tapered carefully (by 5 mg every other day every 1–2 weeks). Once prednisone is successfully tapered, the antihistamine may be gradually discontinued.³⁴

Certain patients may be unable to discontinue prednisone because of recurrent symptoms. These patients have corticosteroid-dependent-IA (CSD-IA). If the prednisone dose required to control the IA is at least 20 mg every day or 60 mg every other day, the disease is termed malignant corticosteroid-dependent IA (MCSD-IA). In patients unable to taper off prednisone, drugs such as montelukast or an oral sympathomimetic such as albuterol could be used. Such patients may be given a trial of a mast cell stabilizer such as oral cromolyn (especially if gastrointestinal symptoms are prominent) or ketotifen. If the prednisone requirement does not change once the mast cell stabilizer is added, the drug should be discontinued because there has been no benefit. Of note, oral ketotifen is not commercially available in the United States. This treatment may allow tapering and eventual discontinuation of steroids, thus achieving a remission.³⁵ In a series of 5 patients with either severe IA or CSD-IA, all 5 patients had a reduction or resolution of their episodes of IA while on ketotifen. If a patient does not respond to the outlined IA treatment, the diagnosis must be seriously re-evaluated and the diagnoses in **Box 1** should be reconsidered.

Omalizumab has also been found to induce remission in an IA patient who was recalcitrant to other therapies.³⁶ There are other case reports in the literature documenting similar results with omalizumab.³⁷

Patients with IA-infrequent generally do not require maintenance therapy unless the most recent episode was considered very severe or if the patient has significant comorbidities putting them at risk of hypotension, arrhythmias, and so on. Patient education and an emergency action plan are very important elements of their treatment.

Patients who have experienced anaphylactic episodes should be offered the option of wearing jewelry or carrying identification cards stating their diagnosis of IA. Patients who are taking β -blockers and ACE inhibitors are at increased risk of treatment-resistant anaphylaxis. If possible, those drugs should be avoided in IA patients. Education remains the major goal in the prevention and management of serious episodes of IA. Patients should be well versed regarding the emergency treatment plan for acute episodes, including injectable epinephrine syringes, prednisone, antihistamine, as well as in seeking further care at the nearest emergency department.

PROGNOSIS

The prognosis of IA is generally favorable. In a retrospective study of 37 patients with IA ranging from 26 to 71 years, frequent episodes of IA defined as greater than 5 episodes per year occurred in 31% at presentation.¹² At follow-up, 21 patients (60%) had resolution of IA and the frequency of anaphylaxis decreased in 9 patients, increased in 2 patients, and remained the same in 3 patients. Only 3 patients were still experiencing frequent episodes and only 2 required chronic glucocorticoids. Patients with frequent IA treated with only antihistamines achieved remission or improvement at the same rate as those treated with chronic steroids.¹² In studies from Northwestern University, the overwhelming majority of patients achieve remission.^{13,19,23} If a remission cannot be achieved, other diagnoses should be reconsidered. Recurrence of anaphylaxis in idiopathic anaphylactic patients does occur. In a study by Alonso and colleagues³⁸ assessing the risk of recurrence of different subtypes of anaphylaxis, recurrence of anaphylaxis was higher for idiopathic, foods, and exercise compared with other subtypes of anaphylaxis, such as medications and hymenoptera stings. The total incidence of recurrence was 3.2 episodes per 100 person-years, whereas the incidence of recurrence for IA subtype was 4.9 episodes per 100 person-years. Thus, if a cause has been identified, particular care should be given to prevention in this population with recurrent anaphylaxis.

Despite appropriate treatment, fatalities from IA can occur. Krasnick and colleagues³⁹ reported one fatality. However, the authors note that compliance with prednisone was not certain because the patient had reported dislike of prednisone to his friends. In addition, the patient had asthma, which has been associated with an increased risk of fatal anaphylactic reactions.

SUMMARY

- IA is a diagnosis of exclusion after other causes, such as foods, medications, exercise, insect stings, C1 esterase inhibitor deficiency, and mastocytosis, have been excluded. The signs and symptoms of patients diagnosed with IA are indistinguishable from the manifestations of other forms of anaphylaxis.
- A significant proportion (24%–59%) of anaphylaxis cases are classified as idiopathic in several reported patient series. There is a higher prevalence of IA in women compared with men. There is also a high prevalence of atopy in patients with IA. IA is less common in children but does occur.
- The classification of IA is based on frequency of episodes and clinical manifestations. Frequent episodes are defined as at least 2 episodes in the preceding 2 months or at least 6 episodes in the preceding year. Patients who do not meet either of these 2 criteria are categorized as infrequent.
- The treatment of IA is individualized based on the severity and frequency of a patient's symptoms. The acute treatment of IA is the same as treatment of anaphylaxis from other causes, except that prolonged tapering of prednisone is usually required to induce remission. All patients should possess an epinephrine autoinjector and an anaphylaxis emergency plan.
- The prognosis of IA is generally favorable with appropriate treatment and patient education.

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