Management Strategies Of Idiopathic Anaphylaxis In The Emergency Room: Current Perspectives

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Background: Idiopathic anaphylaxis (IA) is a diagnosis of exclusion and represents a major diagnostic and management challenge. There are no current guidelines for diagnosis and management of IA. We aim to present a systematic review of the literature on adult and pediatric IA.

Methods: We conducted a systematic review of original articles published in the past 22 years regarding diagnosis and management strategies of adult and pediatric IA.

Results: The current proposed diagnostic approach and treatment regimens are based on a few small studies. Future large-scale studies are required. IA is a diagnosis of exclusion and should be made only after extensive evaluation excludes potential anaphylaxis triggers as well as non-allergic conditions with a similar presentation. There is currently no diagnostic consensus for IA. Furthermore, the current proposed treatment regimens are limited and rely on prophylactic treatment with antihistamines and prednisone for patients with frequent episodes. However, daily treatment with systemic steroids has well-recognized serious adverse effects. More recently, the use of biologics was suggested to benefit patients with IA, although the optimal management protocol is not yet established.

Conclusion: Future studies are needed to optimize diagnosis and treatment strategies in adult and pediatric cases of IA. Omalizumab may be a promising novel therapeutic option for adult and pediatric IA.

Keywords: anaphylaxis, diagnosis, management, treatment

Introduction
Idiopathic anaphylaxis (IA) is a diagnosis of exclusion after known causes for anaphylaxis and other diseases that mimic anaphylaxis have been ruled out. Known causes of anaphylaxis include mainly foods, medications and venom. IA was first described in 1978 by Bacal et al. Currently, there are four reported main phenotypes accounting for anaphylaxis: type I (IgE mediated related to food allergens mainly), cytokine released (associated with monoclonal antibodies/chemotherapy), mixed (associated with chemotherapy/monoclonal antibodies) and complement mediated (associated with contrast material, dialysis membranes, glycosaminoglycans and chondroitin sulfate). The pathogenesis in cases of IA, however, has not yet been well established. From previously published studies, it can be inferred that IA may cause a substantial decline in quality of life. Previous investigations on the quality of life in children with food allergies and their respective caregivers suggest that stress and anxiety associated with continuous allergen avoidance and the looming threat of anaphylaxis were associated with significantly impaired food allergy quality of life (FAQOL). Although no studies have been conducted to investigate the quality of...
life in patients with IA, given the lack of knowledge of the anaphylaxis trigger, it can be inferred that the anxiety experienced by these patients may be further elevated, and their quality of life may be further impaired than those with known allergies. The exact prevalence of IA is not currently known but has been estimated to be between 20,000 and 47,000 cases in the United States. IA is reported to affect 30% to 60% of cases of anaphylaxis in adults and 10% of pediatric cases. Given that there are no identifiable triggers of IA, there are substantial challenges in the diagnosis and management of these cases.

Presently, there are no guidelines on the diagnostic approach of IA, including assessment for underlying diseases and the use of confirmatory tests. Furthermore, guidelines for the appropriate management of IA cases have not yet been established. The current approach to treatment is based on disease frequency; short-term treatment, such as an epinephrine auto-injector, is used for infrequent attacks, while prophylactic treatment with daily H1-antihistamines, glucocorticoids, or omalizumab has been used in patients with more frequent episodes. Frequent episodes are defined as at least two episodes in the preceding two months or at least six episodes in the preceding year. Although several case series have been published regarding IA, few reviews have focused on the diagnosis and management strategies of IA. In this study, we aim to present a systematic review of the literature published in the past 22 years regarding IA in the adult and pediatric population with a focus on diagnosis and management strategies pertinent for the Emergency Room (ER) physician.

Methods

Original scientific studies pertinent to the clinical diagnosis and management of IA were searched in the PubMed literature database. Search terms “idiopathic anaphylaxis” were used, and the search was limited to articles published between June 1, 1998 and June 1, 2019, that were written in English. The abstracts of the resulting papers were reviewed and those that were relevant to the diagnosis and management of IA were included. In this manuscript, we define IA as an anaphylactic reaction where the diagnostic criteria include at least a negative tryptase test and normal bone marrow aspiration/biopsy.

Results

The initial PubMed search yielded 205 articles, which was reduced to 50 articles after applying the aforementioned filters. The resulting search was further narrowed to 28 articles after a more thorough assessment of article abstracts was done to ensure their relevancy to the systematic review (Figure 1).

Diagnosis Of IA

IA is a diagnosis of exclusion and should be made only after extensive evaluation to exclude other potential causes of anaphylaxis and other diseases with similar manifestations, such as mastocytosis. The classification of IA is based on frequency of episodes and clinical manifestations.

The majority of studies included in this review (Table 1) describe an extensive evaluation in adults and children with suspected IA including diagnostic testing for possible triggers of IgE-mediated anaphylaxis such as food, drugs and exercise four hours prior to the reaction. Only 2 of 22 articles describing IA did not specify the diagnostic tests used to determine the diagnosis. The most common diagnostic tests done were tryptase levels and skin prick test. Six IA studies conducted a bone marrow aspiration of which, four studies reported a concomitant tryptase level to rule out mastocytosis. Five studies conducted diagnostic tests to rule out neuroendocrine tumors, such as pheochromocytoma and carcinoid.

Records identified through PubMed search N=205

Records excluded (review articles which were not relevant) N=177

Studies relevant to the systematic review included N=28

Figure 1 Results of the systematic review using PubMed database. Excluded papers were either review articles rather than original papers or not relevant to the diagnosis or management of idiopathic anaphylaxis in adults and children.
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<th>Type Of Study</th>
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<td>1. Cross-sectional descriptive study of patients with IA. 2. Prospective longitudinal evaluation</td>
<td>Tejedor et al, 2002</td>
<td>N = 81</td>
<td>A &gt; P</td>
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<td>Geller et al, 2002</td>
<td>N = 1</td>
<td>A</td>
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<td>Dreyfus et al, 2003</td>
<td>N = 2</td>
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<td>Case report</td>
<td>Shanmugam et al, 2006</td>
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<td>Number Of Patients</td>
<td>Age Range</td>
<td>Diagnostic Tests To Establish IA</td>
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<td>Gelincik et al. 2007^{-12}</td>
<td>N = 1</td>
<td>A</td>
<td>48 yo</td>
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<td>Case report</td>
<td>Tedeschi et al. 2007^{-5}</td>
<td>N = 1</td>
<td>A</td>
<td>30 yo</td>
<td>X</td>
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<td>Jones et al. 2008^{-12}</td>
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<td>A</td>
<td>48 yo</td>
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<td>Case report</td>
<td>Warrier &amp; Casale, 2009^{-5}</td>
<td>N=1</td>
<td>P</td>
<td>12 yo</td>
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<td>Case report</td>
<td>Pitt et al. 2010^{-13}</td>
<td>N=1</td>
<td>P</td>
<td>15 yo</td>
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<td>N = 1</td>
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<td>Case report</td>
<td>Boboles et al, 2012&lt;sup&gt;26&lt;/sup&gt;</td>
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<td>Case report</td>
<td>Kim et al, 2013&lt;sup&gt;18&lt;/sup&gt;</td>
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<td>36 yo</td>
<td>X</td>
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<td>Prospective study</td>
<td>Heaps et al, 2014&lt;sup&gt;29&lt;/sup&gt;</td>
<td>N = 110 A</td>
<td>20-76 yo</td>
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<td>Clinical Outcome – Resolved?</td>
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Case report Tripathi et al, 2014[^2^]  
N = 1  
A  
79 yo  
X X  
Avoid ingestion of beef, pork, and lamb meat.  
Delayed anaphylaxis to red meat (positive IgE for α-gal)

Case report Kibsgaard et al, 2014[^3^]  
N = 1  
A  
31 yo  
X X  
Patient diagnosed with indolent systemic mastocytosis

N = 1  
A  
41 yo  
X X  
Histamine-free diet

N = 3  
P  
11–15 yo  
X X  
Histamine-free diet

Case report Jung et al, 2015[^6^]  
N = 1  
A  
21 yo  
X X  
Patient 1: Cromolyn  
Patient 2: Ranitidine, montelukast

Case report Stone and Choi, 2016[^7^]  
N = 2  
A  
36 yo, 19 yo  
X X X  
Patient 1: Cromolyn  
Patient 2: Ranitidine, montelukast

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<td>Keber et al., 2017&lt;sup&gt;1&lt;/sup&gt;</td>
<td>N = 1</td>
<td>A</td>
<td>N/A</td>
<td>X</td>
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<td>Case report</td>
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<td>N = 1</td>
<td>P</td>
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<td>Case report</td>
<td>Peppers et al., 2018&lt;sup&gt;4&lt;/sup&gt;</td>
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<td>Prospective study</td>
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<td>N = 70</td>
<td>A, P</td>
<td>15-70 yo</td>
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<td>Rolla et al, 2018</td>
<td>N = 1</td>
<td>A</td>
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<td>Case report</td>
<td>Shaker et al, 2019</td>
<td>N = 1</td>
<td>P</td>
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Note: Each X represents each patient receiving the respective treatment.

Abbreviations: P, Pediatric; A, Adult; sIgE, specific Immunoglobulin E; sIgE for α-gal, specific Immunoglobulin E for α-galactose; T, Tryptase; BM, Bone Marrow aspiration; SPT, Skin Prick Test; OC, Oral Challenge; EC, Exercise Challenge; M of NET, Metabolites of Neuroendocrine Tumors; E, Epi for acute reaction; AH, Antihistamines; CS, Corticosteroids; O, Omalizumab.
tumors. Oral and exercise challenge tests were conducted less frequently, with only one article reporting an exercise challenge test. Specific Immunoglobulin E for α-galactose to exclude the diagnosis of delayed anaphylaxis to red meat were conducted in three of the presented studies. Overall, none of the studies had diagnostic consensus to establish the diagnosis of IA in patients.

In several of the studies presented, additional considerations were made for the method of diagnosis of IA. In a Spanish series by Tejedor and Alonso, insect bites, latex and other rare causes of anaphylaxis such as anaphylaxis attributed to Anisakis simplex or rupture of hydatid cyst were also excluded. Psychiatric disorders were also ruled out in addition to having performed the aforementioned extensive diagnostic evaluation. Of note, in certain case reports, Type I Kounis syndrome has been reported as a concomitant diagnosis of IA. Kounis syndrome is defined when anaphylaxis causes cardiovascular signs and symptoms. Specifically, Type I Kounis syndrome is described in patients with no evidence of coronary artery disease. In addition, certain studies have reported syndrome of idiopathic urticaria and angioedema (ICUA) with thyroid autoimmunity involved with the diagnosis of IA.

In the recent case reports by Wolver et al, 2013 and Tripathi et al, 2014, the authors suggest that rare disorders may mimic IA, which includes delayed anaphylaxis to red meat. In contrast with immediate food-mediated anaphylaxis, symptoms may occur more than two hours after exposure. Initial clues for the reaction to mammalian oligosaccharide α-gal in the published cases were based on medical history, which indicated ingestion of mammalian products.

An interesting case series by Ivkovic-Jurekovich in 2015 describes three patients with a clinical picture suggestive of histamine intolerance associated with IA. Interestingly, all three patients were found to have a positive autologous serum tests (ASST), but a histamine release test was negative and the presence of circulating auto-antibodies against IgE and FcεRIα could not be confirmed. In addition, they determined a very low activity of histamine-inactivating enzyme (DAO) for all three patients, which indicated high histamine intolerance. Histamine intolerance describes a state where an individual has a decreased ability to catabolize endogenous or exogenously administered histamine, leading to histamine-mediated adverse reactions. Diagnosis is based on careful clinical history and identification of intestinal or serum activities of DAO and histamine N-methyltransferase. However, there are no large-scale studies published establishing the sensitivity and specificity of these tests.

Several case reports have identified rare causes of anaphylaxis in patients who were initially diagnosed with IA. Such causes of anaphylaxis include pigeon tick, A. Reflexus, lymphocytic hypophysitis in the context of complicated adrenal crises in an asthmatic patient, and wheat-dependent exercise-induced anaphylaxis. In fact, in a study done by Heaps et al, 2014, wheat protein, omega-5-gliadin, and shrimp were the main causes of anaphylaxis in the study’s cohort of patients who were initially diagnosed with IA.

Management Of IA

Classification of the disease as frequent or infrequent IA is necessary to determine the appropriate treatment course. Frequent episodes are defined as at least two episodes in the preceding two months or at least six episodes in the preceding year. For patients with frequent IA, all studies in this review report a treatment of continuous prednisone at a dosage of 20 to 80 mg, antihistamines (e.g. cetirizine 10 mg), and sympathomimetics (e.g. albuterol). In asymptomatic patients, prednisone may be gradually tapered every two to four weeks. Patienst with infrequent episodes of IA are treated with epinephrine, antihistamines and oral steroids during the episode. The same treatment regimens have been recommended for children with pediatric dose adjustments. The authors in the presented studies report that the current treatment regimens are successful in controlling the disease and induce remission in the majority of patients, although no large-scale studies have been conducted to assess the adequacy of control.

Patients requiring long-term prophylactic treatment with prednisone are at risk for significant side effects. Alternative prophylactic management strategies are limited. A few reports suggest that ketotifen, a mast cell stabilizer, is effective in patients with corticosteroid dependent-IA. Recently, the use of the biologic omalizumab has been suggested to benefit patients with recurrent and frequent episodes of IA. Over one-third of the studies included in this review included omalizumab in the prophylactic treatment of IA among patients in which continuous treatment with prednisone and antihistamines did not prevent further episodes of IA. Doses of omalizumab ranged from 225 to 375 mg administered at a...
Two case reports included in a histamine and in 20% of adults initially. The authors suggest that the rate of IA is lower than previously described if an appropriate anaphylaxis work up is conducted by allergists/immunologists. In these studies, a trigger for the anaphylactic reaction was identified in 75% of children and 20% of adults initially presenting with AUT after appropriate investigations were conducted. These results further support the importance of a consultation to an allergist/immunologist for patients who are diagnosed with AUT in the ER.

Following the diagnosis of AUT and after conducting a thorough clinical history and physical exam, we suggest considering additional diagnostic tests done by the specialist (Table 2). Immediate skin testing, in vitro tests for specific IgE and oral challenges under the supervision of an allergist should be conducted for relevant drugs or foods which may help to confirm or exclude food or drug allergy as a possible trigger including sIgE to o-5 gliadin and alpha-gal in the case of a clinical history suggestive of delayed anaphylaxis to red meat. This rare disorder should be suspected as a culprit in any case of AUT, especially in events occurring three to six hours after eating, particularly when reactions start in the early morning hours. Other potential causes that should be considered are exercise and food-dependent exercise-induced anaphylaxis. Exercise and/or food-dependent exercise challenges should thus be considered in the case of a suggestive history.

Systemic mastocytosis, monoclonal mast cell activation syndrome and mast cell activation syndrome are disorders that may also mimic IA. Elevated serum tryptase levels during attacks are suggestive for IA and patients with elevated tryptase levels both at baseline and during attacks should be evaluated with a bone marrow biopsy to rule out mastocytosis or other clonal mast cell disorders. All patients with suspected IA should have tryptase levels done at baseline and during attacks in order to confirm the presence of anaphylaxis as the difference in these levels rather than the absolute level of tryptase is crucial for the diagnosis of anaphylaxis. Bone marrow biopsy should be considered in all cases of frequent AUT with tryptase levels consistent with anaphylaxis even if baseline levels are within the norm given that some studies have suggested that systemic mastocytosis may present with values that are within the norm.
Pheochromocytoma and carcinoid syndrome are rare disorders in which patients may also present with symptoms similar to anaphylaxis, such as flushing induced by release of vasoactive substances: vanillylmandelic acid in pheochromocytoma, 5-hydroxyindoleacetic acid (5-HIAA) in a 24 hr urine collection, and chromogranin A in blood, which is a recently proposed biomarker for the diagnosis of neuroendocrine tumors. Detection of these mediators may help exclude or confirm the diagnosis in patients with a suggestive history.

Hereditary angioedema may mimic IA as it presents as recurrent episodes of angioedema as a principal symptom. Laboratory investigations should include serum levels of C4 and C1 inhibitor in selected patients.
who present with corresponding symptoms of hereditary angioedema (Table 2).

The current proposed treatment regimens are based on small and outdated studies. Daily treatment with systemic steroids, such as prednisone, are associated with an increased risk of long-term side effects, including osteoporosis, adrenal suppression and immunosuppression, in both adults and children. We, therefore, recommend a change in the current practice relying on the use of systemic steroids for the treatment of IA. Based on recently published case reports and case series, we suggest the following algorithm for the management of adult and pediatric IA (Figures 2 and 3). All patients should be instructed on the management of acute episodes and should be prescribed an epinephrine auto-injector. In patients with frequent episodes, daily H1-antihistamines at regular doses should be prescribed and the patient should have close clinical follow-up. If there is no improvement after one month, the physician should consider increasing the daily antihistamine dose up to four times the regular dose. If no improvement is demonstrated with the increased dose of daily antihistamines after one to two months, treatment with omalizumab should be considered. Omalizumab is a humanized monoclonal antibody that binds to the FcεRI receptor on IgE. Allergen-specific IgE plays a central role in IgE-mediated anaphylaxis. Cross-linking of the receptor bound IgE on mast cells and basophils by allergens leads to activation of those cells and subsequent release of inflammatory mediators causing anaphylaxis. The exact mechanism of IA remains unknown, but it has been postulated that the high affinity IgE receptors may be cross-linked by autoimmune mechanisms. Omalizumab may prevent IgE expression on effector cells and subsequent cross-linking of IgE.

Omalizumab is considered a promising prophylactic therapy for IA in treatment-resistant patients. This therapy has been shown to have both rapid and long-term benefits in multiple case reports. The dosage and treatment regimen should be determined on an individual basis. Further large-scale studies are needed to assess the efficacy of

**Figure 2** Anaphylaxis management algorithm.
omalizumab therapy for IA in both adults and children. Hence, we believe that prophylactic glucocorticoid treatment should be reserved only for cases that are not well controlled with omalizumab.

**Conclusion**

In conclusion, few studies have evaluated the diagnosis and management strategies of true IA. Future studies are needed to optimize treatment regimens for IA in both children and adults. Health care providers should be aware of the potential differential diagnosis and underlying causes in order to develop an appropriate management strategy.

Omalizumab is a promising therapeutic option for IA as a novel approach to prophylactic treatment. We recommend conducting large-scale studies on the use of omalizumab in IA and a shift in treatment paradigm that will prioritize omalizumab over glucocorticoids as an efficacious and safe second-line prophylactic treatment.

**Disclosure**

The authors report no conflicts of interest in this work.

**References**
