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Idiopathic anaphylaxis

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ABSTRACT

Idiopathic anaphylaxis (IA) or spontaneous anaphylaxis is a diagnosis of exclusion when no cause can be identified. The exact incidence and prevalence of IA is not known. The clinical manifestations of IA are similar to other known causes of anaphylaxis. A typical attack is usually acute in onset and can worsen over minutes to a few hours.

The pathophysiology of IA has not yet been fully elucidated, although an IgE-mediated pathway by hitherto unidentified trigger/s might be the main underlying mechanism. Elevated concentrations of urinary histamine and its metabolite, methylimidazole acetic acid, plasma histamine, and serum tryptase have been reported, consistent with mast cell activation. There is some evidence that corticosteroids reduce the frequency and severity of episodes of IA, consistent with a steroid-responsive condition.

Important differential diagnoses of IA include galactose alpha-1,3 galactose (a carbohydrate contained in red meat) allergy, pigeon tick bite (*Argax reflexus*), pine processionary caterpillar allergy, wheat-dependent exercise-induced anaphylaxis, Anisakis simplex allergy and mast cell disorders. Other differential diagnoses include 'allergy-mimics' such as asthma masquerading as anaphylaxis, undifferentiated somatoform disorder, panic attacks, globus hystericus, vocal cord dysfunction, scombroid poisoning, vasoactive amine intolerance, carcinoid syndrome and phaeochromocytoma.

Acute treatment of IA is the same as for other forms of anaphylaxis. Long term management is individualised and dictated by frequency and severity of symptoms and involves treatment with H1 and H2 receptor blockers, leukotriene receptor antagonist and

consideration for prolonged reducing courses of oral corticosteroids. Patients should possess an epinephrine autoinjector with an anaphylaxis self-management plan. There are anecdotal reports regarding the use of omalizumab.

For reasons that remain unclear, the prognosis of IA is generally favourable with appropriate treatment and patient education. If remission cannot be achieved, the diagnosis should be reconsidered.

MAIN TEXT

INTRODUCTION

Anaphylaxis has been defined as a serious, potentially life-threatening generalised or systemic hypersensitivity reaction that is typically rapid in onset and is usually characterised by involvement of at least 2 different organs including the skin, respiratory, cardiovascular or gastrointestinal systems[1–4], although isolated severe hypotension may be a presenting feature in some patients. Idiopathic anaphylaxis (IA) is a form of anaphylaxis diagnosed when no trigger can be identified despite detailed clinical evaluation including a careful clinical history of the episode, skin tests and measurement of serum specific IgE levels to obvious and potentially hidden allergen and, if indicated in selected patients, a medically supervised, graded allergen challenge test [4].

The first report of anaphylaxis without discernible cause was published in 1978. Out of 21 subjects, 11 were considered to have IA and prophylactic treatment with antihistamines and corticosteroids resulted in reduction in severity and/or frequency of subsequent anaphylactic reactions [5]. For many years, reports of IA were limited to the United States. However, since the 1990s, similar reports have emerged from other countries, including Spain, France, Ireland, Germany, and Brazil, fostering the spread of IA awareness worldwide [6,7].

EPIDEMIOLOGY

The actual incidence of IA is unknown. Studies and registries have reported different figures, probably due to selection bias related to the type of patients attending medical centres, diagnostic limitations of the old studies (e.g. overlooked α -gal sensitizations and mastocytosis), and over-diagnosis of IA by no-specialist centres (e.g. emergency departments) (Table 1) [8–12]. In the United States, between 20,592 and 47,024 total cases of IA have been reported [7,13]. The prevalence of anaphylaxis in the U.S. general population has been estimated at nearly 1.6%, and about 39% were classified as possible IA [6]. A higher incidence (60%) in women has been described, although the real overall incidence is hard to estimate due to limitations of data reported by old literature [8,14]. On the other hand, IA seems to be less common in children [8,15]. Patients with IA were found to have a high incidence of atopy, as high as 58% in one series [16].

Although the incidence rates of anaphylaxis has been increasing in recent years, the number of cases of IA seems to be decreasing according to a recently published report, from 59% of IA (from 1978 to 2003) to 35% (from 2006 to 2016) [12]. The authors stated that this decrease may be explained by the discovery of an IgE mediated antibody response to the α -gal as a cause of anaphylaxis to mammalian meat products [12]. The lowest frequency of IA (6.5%) is reported by the European Anaphylaxis Registry [10], probably because data were recorded by a network highly specialised in allergy diagnostics.

PATHOPHYSIOLOGY

In the past, many theories were postulated to explain IA, however only a few studies have attempted to provide insight into the pathogenesis of this condition [17–20]. Reed et al proposed that defective programming of naïve T cells results in polarisation towards Th2 response with production of IL-4, IL-5 and IL-13. This aberrant cytokine profile can lower the threshold for MC degranulation in IA patients irrespective of their atopic status [17].

In a prospective cohort study of 38 patients, Grammar and colleagues examined expression of lymphocyte activation markers in IA patients. They demonstrated that subjects with acute IA had a significantly higher proportion of activated T cells expressing CD3+HLA-DR+ compared to those in remission. In addition, patients with IA on corticosteroids and patients in remission had higher frequencies of CD23+ CD19+ lymphocytes than healthy controls, suggesting a possible role of B cells in the pathogenesis of IA [21].

Increased sensitivity to histamine at the target organ sites has also been proposed, as some patients with IA have been found to have increased levels of histamine releasing factors with higher sensitivity to histamine [22,23]. Autoantibodies to the IgE receptor have also been described in cases of IA, but their active role in the pathogenesis has not been demonstrated[24].

Despite the above hypotheses, an IgE-mediated response by trigger/s that remain unidentified at least in part due to limitations in immunodiagnostics, remains the main mechanism underpinning IA.

CLINICAL MANIFESTATIONS

The manifestations of IA are identical to those that occur during anaphylaxis with known triggers, and include angioedema, urticaria, tachycardia, pruritus, flushing, dyspnoea, wheezing, tachypnoea, stridor, dysphagia, hoarseness, nausea, vomiting, diarrhoea, syncope, hypotension, and abdominal discomfort [6].

The first episode of IA usually is the most severe, probably because the patient subsequently learns to recognise prodromal symptoms in subsequent attacks and initiate appropriate early emergency treatment [6]. A typical episode is acute in onset and reaches a peak over minutes to a few hours. However, few patients reported urticaria for 3 days before anaphylaxis occurred [25].

In a series of 335 patients with IA, all had experienced angioedema and urticaria. In addition, 63%

experienced upper airway obstruction, 39% bronchospasm, 23% hypotension or syncope, and 22% gastrointestinal symptoms[26]. Isolated cardiovascular collapse was not reported in this case series.

Despite early use of adrenaline autoinjector, fatalities have been reported very rarely in some patients that continued to experience recurrent severe episodes [6].

For reasons that are unclear, the prognosis of IA is generally favourable with appropriate treatment and patient education. If remission cannot be achieved, it would be prudent to revisit the diagnosis and consider other possibilities.

CLASSIFICATION

Idiopathic anaphylaxis has been classified according to clinical parameters (IA-generalised, IA-angioedema), frequency of episodes (frequent, infrequent), and severity in terms of response to steroid-treatment (corticosteroid-dependent, malignant). This classification, in particular IA-angioedema, could be challenged in the context of the diagnostic criteria for anaphylaxis[1–4], as some cases with mucocutaneous involvement *only*, would clearly not meet the criteria for anaphylaxis. Thus, it is plausible that incidence rates of IA published prior to 2011 may be inaccurate and potentially be an over estimation. In addition, IA is defined as a “variant” when symptoms are not typical of classic IA and “undifferentiated” if symptoms are suggestive of IA, but no organic cause can be found (Table 2).

DIAGNOSTIC CONSIDERATIONS

Any patient with suspected anaphylaxis should undergo thorough evaluation with careful mapping of clinical presentation according to the current diagnostic criteria for anaphylaxis. Review of ambulance and emergency room records and acute serum tryptase measurements are invaluable in patients reporting recurrent episodes or those with atypical presentations [4]. A careful clinical history should be obtained for elicitors, cofactors and comorbidities to enable underpinning aetiology and appropriate risk stratification. It is important to evaluate underlying cardio-respiratory co-morbidities. Whilst data from North America suggests that underlying cardio-respiratory disease enhances the risk for severe anaphylaxis, this has not been confirmed from a large European registry [27,28]. A diagnosis of IA is based on exclusion of known triggers of anaphylaxis, as well as conditions that can masquerade as anaphylaxis. Differential diagnosis of IA and the related key points for diagnostic work-up are shown in Table 3.

Hidden allergens

Attention should be paid to **hidden allergens** as a possible cause of anaphylaxis; this is particularly relevant in food-induced hypersensitivity reactions, and apparent IA occurring within 1-2 hours after food ingestion should always raise the possibility of a food-related trigger. The commonest reasons for allergens being hidden are food mislabelling and cross-contamination during manufacturing process, cooking or handling. A retrospective study by Añibarro et al showed that 22.4% of food allergic reactions were due to hidden allergens; anaphylactic reactions were reported in one third of these patients [29]. Peanut proteins are one of the commonly reported hidden allergens that can lead to serious reactions [30]. Other implicated hidden allergenic food triggers include egg, milk, soy proteins, lupin and many others [31–34]. Although uncommon, spices, additives, and sulphites must also be considered as potential hidden allergens. In addition, in recent years, the number of novel foods addressing new market requests (e.g. vegan diets) has been increasing, and particular food allergens may be undeclared, mislabeled, or overlooked.

There are few interesting reports describing patients who developed anaphylaxis following ingestion of pollen-contaminated foods. These patients were known to have pollen-induced allergic rhinitis and it has been postulated that pollen contamination is a possible explanation for anaphylaxis. Various allergenic contaminants were identified as possible culprits including dust mites (pancake anaphylaxis syndrome), mealworms [35], weed pollens (bee pollen-induced anaphylaxis) and fungi [36–38].

In addition to foods and aeroallergens, other less commonly reported sources of unnoticed allergens include latex and “hidden medications” ingested unintentionally because they are present in over-the-counter products (e.g. enriched vitamin supplements) [39,40].

Heaps et al [41] examined the diagnostic utility of an allergen microarray (ImmunoCAP ISAC) in the detection of possible allergenic triggers in patients with unexplained anaphylaxis. In twenty percent of the IA cohort, ISAC array was able to show evidence of sensitisation to newly identified allergens that had not been detected during routine allergy work-up, the link between these new sensitisations and anaphylaxis was considered to be “highly likely”. A wide range of allergenic triggers were identified including wheat (32%), shrimp (27%), peanut (14%), peach (9%), milk (5%), latex (5%), hazelnut (5%), and kiwi (5%). The authors concluded that the ISAC array can offer additional information where a detailed allergy history and follow-on testing have not been conclusive. The main drawback of this study was that an allergen challenge procedure was not performed and hence some cases may have been *merely* sensitised.

Cofactor-dependent anaphylaxis

This is an increasingly recognised clinical entity characterised by cofactor-induced modulation of allergic response. Well described co-factors, such as physical exercise, nonsteroidal anti-inflammatory drugs (NSAID), alcohol, infection and menstruation may reduce allergen threshold

necessary for activation and degranulation of MCs. Because sole allergen exposure is not sufficient to elicit anaphylaxis, this condition can be easily overlooked and patients erroneously labelled as IA [42].

Delayed onset anaphylaxis

Differentiation between IA and delayed onset anaphylaxis can pose a diagnostic challenge to allergists. During the last decade, there has been an increasing awareness regarding the concept of delayed anaphylaxis; this is largely due to the discovery of galactose- α -1,3-galactose (α -gal) allergy. This interesting form of hypersensitivity reaction occurs due to development of specific IgE antibodies to the α -gal oligosaccharide moiety present in mammalian red meat. The primary sensitisation is linked to an IgE antibody response to tick bites [43] and upon ingestion of red meat containing α -gal; sensitised subjects develop anaphylaxis 3-5 hours later. Recently, it has been suggested that α -gal might be also present in other animal species known to feed parasitically on mammals, and in particular chiggers (mites of the *Trombiculidae* family at their larval stage) have been reported to be associated with sensitisation to α -gal and delayed allergy to red meat [44]. Carter et al [45] described, in a prospective study of 70 patients referred with a diagnosis of IA, six cases (9%) with sIgE to α -gal. Two of these six patients experienced more severe clinical symptoms with a higher baseline serum tryptase and were subsequently found to have indolent systemic mastocytosis. It was therefore concluded that α -gal sensitivity should be considered as a cause of unexplained anaphylaxis in subjects with or without clonal mast cell disorders.

Insect bites and stings

Hymenoptera stings are not routinely considered to be a cause of unexplained anaphylaxis because they are perceived as markedly painful and patients usually give a clear account of the sting episode. However, at least one case of systemic anaphylaxis after gastroesophageal hymenoptera sting has been described [46] where a patient was presumably stung by an accidentally swallowed wasp. The

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patient had not been aware of the sting because nociceptors of distal oesophagus and stomach are relatively insensitive to such a stimulus that normally evokes superficial somatic pain. Without discovery of a wasp in the patient's vomit, the cause of anaphylaxis would have remained obscure, and a misdiagnosis of IA might have been made. Therefore, oesophageal insect stings should be considered when an unexplained anaphylactic episode occurs after open-air consumption of food or drinks during insect season. Wine-induced anaphylaxis in patients sensitised to hymenoptera venom has also been described [47].

There were few reported cases of nocturnal anaphylaxis which awakens patients from sleep [48]. After ruling out possible causes of delayed anaphylaxis (e.g. α -gal allergy), further investigations revealed the bite of *Argas reflexus* (an insect with nocturnal activity otherwise known as the pigeon tick) as the most likely trigger in those patients. Because allergen extracts for determination of sIgE are not yet commercially available, only the anamnesis and the clinical findings can point to the actual diagnosis, namely the history of severe anaphylactic reaction at night during a congruent season (i.e. spring or summer), the presence of pigeons in the patient's immediate environment, and signs of skin reactions suggestive of insect bites. Because of the growing number of pigeons in Middle and Southern Europe, some cases of IA could potentially be related to *A. reflexus*, in these countries.

Anaphylaxis mimics

Every effort should be made to distinguish anaphylaxis and from other causes of urticaria and angioedema; this is particularly challenging when evaluating a patient with suspected IA-angioedema phenotype. **Cholinergic urticaria** is a form of physical urticaria triggered by high ambient temperature, sudden changes in temperature, strenuous physical activity, and/or strong emotion, potentially leading to life-threatening multisystem reactions (e.g. cutaneous, upper and lower airway, and cardiovascular involvement) and occasionally culminating into anaphylaxis, mainly in young female adults. Anaphylaxis due to cholinergic triggers is rare as well as underreported [49].

A severe acute asthma exacerbation may also mimic an episode of anaphylaxis, with respiratory distress, wheezing, and facial erythema. A clinical and instrumental diagnostic examination, including laryngoscopy and respiratory function tests, is recommended to investigate both asthma and **vocal cord dysfunction**, a well recognised condition in which paradoxical adduction of the vocal cords during inspiration causes functional airway obstruction and 'stridor' - is triggered by stress, dust, cigarette smoke, odours, exercise, occupational or environmental irritant exposure, upper respiratory tract infection etc.

Psychiatric conditions such as somatoform disorders should be suspected when there are paucity or absence of clinical signs. Panic attacks causing acute dyspnoea, diaphoresis, and dizziness may occur in the absence of hypotension and resolve without epinephrine. Globus is a sensation of a "lump" in the throat without any clinical signs of anaphylaxis; it may mimic IA-angioedema and thorough evaluation is needed to avoid misdiagnosis. An association between IA and anorexia nervosa has also been postulated, with a possible mechanism related to the cellular metabolic changes induced by anorexia, enhancing MC degranulation [50].

Flushing and diarrhoea, in the absence of other clinical features of anaphylaxis, should raise the differential diagnosis of **carcinoid syndrome**. When dyspnoea and palpitations are present in addition to flushing and diarrhoea, **pheochromocytoma** should also be considered, but this is associated with hypertension rather than hypotension. Urinary tests should be performed to rule out these important differential diagnoses (i.e. 5-hydroxyindoleacetic acid and catecholamines).

BOX 1 – CASE REPORT (part 1/2)

We describe a case of suspected IA and all the diagnostic work-up performed, focusing on the different diagnoses that were excluded using a systematic clinical approach, before arriving at the final diagnosis. EG, a 32-year-old caucasian female, presented at the Allergy Unit of Ancona (Italy) in 2011, after her second episode of anaphylaxis with generalised urticaria, conjunctival hyperaemia, chest tightness, abdominal pain, tachycardia, and hypotension that needed emergency treatment with epinephrine. The first episode was documented by the Emergency Department four months before, with similar clinical manifestations and treatment, and discharged with an epinephrine auto-injector prescription. Since both episodes occurred 2-3 hours after eating, skin prick tests were performed with an appropriate short-listed food allergens, some allergens that were not reported or suspected as ingredients of the implicated meals: milk, egg, fish and sea food, anisakis, fruit and vegetables, soy, nuts, peanut, latex and airborne allergen (i.e. house dust mites, pet, fungal and major pollen allergens). These tests were uniformly negative. Serum specific IgE were investigated against an extensive panel of standard allergens by ISAC analysis (ImmunoCAP ISAC, Thermo Fisher Scientific), with no positive results. Even if the anaphylactic reactions seemed to be linked to the meals, there was a significant lapse of time before clinical manifestations (about three hours in the second episode), suggesting a non-immediate mechanism. Furthermore, red meat consumption was reported by the patient in at least one episode. Alpha-gal allergy could be consistent with the clinical history and timing of the reactions, therefore 'prick-to-prick' tests with bovine liver and kidney were performed and α -gal sIgE measured, but there was no demonstrable sensitisation. The patient underwent standard haematology, biochemistry, urine and serum tests for analysis of complement (i.e. C3, C4, C1-INH functional and quantitative), thyroid function and auto-immunity, endocrine profile (i.e. chromogranin A, ACTH, calcitonin, glucagon). Only a mild increase of thyroglobulin antibodies were found, not clinically significant (206 U/ml – n.v. 0-69). Serum and urinary catecholamine and serotonin levels were normal. Spirometry, thyroid ultrasonography, and chest X-ray did not show abnormalities. Baseline serum tryptase was 9.4 ng/ml.

Mast cell disorders misdiagnosed as idiopathic anaphylaxis

An international group has proposed a classification for mast cell activation syndromes (MCAS) into 3 types: Clonal mast cell disorders, Type 1 allergy or another underlying disease leading to mast cell activation and idiopathic. The idiopathic group has not yet been well characterised [51]. MCAS encompasses a wide range of systemic symptoms secondary to excessive release of MC mediators which can occasionally result in anaphylaxis [52]. Mastocytosis is an established condition and comprises of clonal MCs in various organs and tissues (mostly the bone marrow), and can be grouped into three main categories: cutaneous mastocytosis, systemic mastocytosis (SM), and mast cell sarcoma [53,54]. Systemic mastocytosis can be further subdivided into indolent systemic mastocytosis (ISM), systemic mastocytosis with an associated clonal haematologic non-MC lineage disease, aggressive systemic mastocytosis, MC leukaemia, and extracutaneous mastocytoma. The most frequent subtype of SM (accounting for about 80% of all SM cases) is ISM [55], which can present with or without skin lesions.

There are diagnostic criteria for SM [51]. The major diagnostic criterion is the multifocal clustering of MCs in one or more visceral organs, usually in the bone marrow. Minor diagnostic criteria include an abnormal morphology of MCs, expression of CD2 and/or CD25 in MCs, an activating mutation at codon 816 of KIT (most frequently KIT D816V) in extracutaneous tissues, and a persistent baseline serum tryptase concentration of >20 ng/mL. Diagnosis of SM can be established if at least one major and one minor criterion are detected, or with three minor criteria [53,54]. Indolent SM, especially without skin lesions, is frequently underdiagnosed, due to the 'silent' nature of the condition and lack of specificity of clinical symptoms[52]. Some patients may not meet the required criteria for SM, show no evidence of cutaneous manifestations but may have evidence for a clonal MCs on bone

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marrow examination [56,57]. These patients are also at a risk of severe anaphylaxis, in particular to hymenoptera stings. A mast cell disorder is considered in patients with severe anaphylaxis (cardiovascular collapse) in the context of hymenoptera venom allergy, a raised baseline serum tryptase and/or unexplained osteopenia/osteoporosis or vertebral collapse.

Due to the substantial overlap between the clinical manifestations of mastocytosis and IA, similarities in underlying pathogenic mechanisms have been proposed. Furthermore, clonal MC disorders can be potentially misdiagnosed as IA. Gulen et al [58] performed bone marrow examination in patients with IA to look for evidence of clonal MC population, and to try to identify predictive markers that can possibly distinguish between different IA phenotypes. Out of the 30 cases of IA with no signs of cutaneous mastocytosis, 47% were found to have an aberrant MC population and were subsequently diagnosed with clonal MC disorder. Similarly, Akin et al [57] reported presence of a clonal mast cell population with a diagnosis of IA in whom there were no features of urticaria pigmentosa or histological evidence for SM on bone marrow biopsy. These findings demonstrate a need for robust criteria for BM examination in cases of suspected clonal MC disorders in the context of IA. The only available validated tool is the Spanish Network on Mastocytosis (Red Española de Mastocitosis [REMA]) scoring system[59]. This model, is based on a combined clinical (i.e. gender and clinical symptoms) and laboratory (baseline tryptase value with 'cut-off' of 15-25 ng/ml) parameters, to predict underlying MC clonality in patients presenting with systemic MC activation symptoms, including anaphylaxis [52,59]. Gulen et al [58] recommended using a modified version of the REMA score with a baseline serum tryptase 'cut-off' values of 11.4-20.0 ng/ml, instead of 15-25 ng/ml, which resulted in a better sensitivity (93%) and specificity (94%) when retrospectively applied to their study cohort.

In another study, Carter and colleagues [60] investigated fifty-six subjects who had more than one episodes of unexplained anaphylaxis with BM examination and found evidence of MC clonal disease in 14% of cases. The authors proposed the "NIH Idiopathic Clonal Anaphylaxis Score" (NICAS) tool

which uses four parameters: gender, clinical symptoms, baseline serum tryptase level ('cut-off' at 11.4 ng/ml) and allele-specific PCR testing to detect the presence or absence of KIT D816V in peripheral blood. The NICAS has been shown to considerably increase sensitivity and specificity for prediction of an underlying clonal MC disorder in patients with IA, even without clinical signs of MC hyperresponsiveness or an abnormal baseline serum tryptase.

BOX 2 – CASE REPORT (part 2/2)

During the diagnostic work-up, E.G. reported one new episode of anaphylaxis with similar symptoms (April 2012). It was recorded in the emergency room. The reaction did not require epinephrine. Acute serum tryptase levels during the episode was high (143 mcg/L), with a baseline value of 9.5 mcg/L.

Since baseline serum tryptase was at the higher end of reference range, and the relative complexity of the case, dermatology and haematology consultations were requested to investigate possible manifestations of mastocytosis. There was no evidence of urticaria pigmentosa.

A bone marrow biopsy showed no histological evidence for mastocytosis. However, immunohistochemistry revealed the presence of CD117+ (c-KIT), CD25+ (4C9 interleukin-2 receptor), and tryptase+ MCs, supported by few atypical MCs detected in the bone marrow smear stained with toluidine blue. Additionally, flow cytometry characterisation showed CD117+ CD25+ CD2+/- cells in the bone marrow. Molecular analysis revealed D816V mutation of the cKIT gene. These findings fulfilled the diagnostic criteria for indolent SM.

The patient was therefore managed accordingly. She was trained for early identification of symptoms and self-administration of epinephrine. She reported three further episodes of anaphylaxis at the subsequent follow-up visits (between 2013 and 2014), with similar characteristics in terms of clinical manifestations and severity. She remained free of anaphylaxis from 2015 and had an uneventful pregnancy.

MANAGEMENT OF IDIOPATHIC ANAPHYLAXIS

Idiopathic anaphylaxis has a favourable prognosis if treated promptly. Regardless of the aetiology, all cases of suspected anaphylaxis should be treated promptly with intramuscular epinephrine and transferred to the emergency room for further management with antihistamines, corticosteroids and supportive care. All patients with IA should be issued with an emergency treatment kit consisting of epinephrine auto-injector device, corticosteroids, and antihistamines. Patient education and training are of paramount importance; this primarily includes early recognition of anaphylaxis, prompt use of emergency treatment, correct epinephrine administration technique, correct posture during hypotension and the importance of calling the ambulance service at the earliest opportunity.

Currently there is no standard long-term prophylaxis for IA and management plan should be tailored to individual cases. There is lack of high quality data and the available treatment regimens are based on case series, reports and expert opinion. The management of IA is shown in Table 4, taking into account that this should be tailored on a case-by-case approach under close specialist monitoring [13,24,61–63]. In the IA-frequent group, most patients managed to discontinue prednisone within one year and reported significant reduction of frequency and severity of IA episodes, but they may require to continue daily H1-antihistamines[13,24,61,64]. However, about 20% of patients with frequent IA may fail to wean from prednisone; these are thus considered as corticosteroid-dependent IA[64] and a prolonged regimen of prednisolone is often required for these patients.

When the current standard care is not able to induce remission and the dose of corticosteroids cannot be suspended (IA corticosteroid-dependent), or is considerably high (IA malignant), additional and/or alternative therapies should be considered aiming to improve the efficacy of treatment and to avoid long-term side effects of corticosteroids. Other treatment options such as leukotriene antagonists blocking mast cell derived leukotrienes, could result in beneficial effects, but

no evidence has been reported to date to prove its efficacy in IA. Ketotifen, oral cromolyn or oral albuterol have been trialled in some cases of IA corticosteroid-dependent. Their mast cell stabilising property, in addition to H1- and H2-blockers, may be beneficial as an 'add-on' treatment, for both preventing/lessening the severity of anaphylaxis episodes, and reducing corticosteroid use, but they also have side effects (e.g. sedation)[3,4,24,64,65].

Novel, steroid-sparing therapeutic options for long term management of IA are emerging and would be particularly beneficial for children with IA, in whom long-term corticosteroid treatment is undesirable. Omalizumab, an anti-IgE monoclonal antibody, blocking IgE binding to MCs and basophils, is currently used for the treatment of severe allergic asthma and chronic spontaneous urticaria. It has been used effectively in few young patients with resistant IA at 300 - 375 mg, every 2 - 4 weeks[14,66,67]. Rituximab, an anti-CD20 monoclonal antibody, is another novel agent warranting further exploration. Borzutzky et al [62] described complete remission with rituximab in a 17-year-old patient with resistant IA suggesting a role for B cells in the pathogenesis. Further research is warranted on corticosteroid-sparing therapies, mostly to establish an effective and safe treatment protocol for children, even though IA is less frequent in this population.

Based on data from experimental animal models of anaphylaxis, platelet-activating factor (PAF) is believed to play a role in pathogenesis of anaphylaxis. To evaluate this hypothesis, mice were treated with PAF antagonists and were shown to be resistant to anaphylaxis. To further support this hypothesis, epinephrine was shown to exert some of its therapeutic effect on anaphylaxis through inhibition of PAF signalling. [68]. These data obtained from mice models have demonstrated that therapeutic targeting of PAF pathway might prevent development of anaphylaxis, however, no clinical trials of PAF inhibitors in the treatment of anaphylaxis have been undertaken.

CONCLUSION

Idiopathic anaphylaxis is a life-threatening condition. It is a diagnosis of exclusion and mandates careful consideration of all recognisable and rare causes of anaphylaxis. The clinical manifestations and management of acute episodes are the same as for other forms of anaphylaxis. A good clinical history is paramount to direct further investigations. Particular attention should be paid to 'hidden allergens', co-factors, somatoform disorders and MC disorders. A systematic diagnostic work-up to a case of suspected IA is shown in Figure 1.

Although health-related quality of life of patients with IA may be severely compromised, prognosis is favourable with early diagnosis, counselling and appropriate management. Diagnosis must be revisited in cases with recurrent episodes, where there is paucity of clinical signs and/or in the context of refractoriness to corticosteroid therapy.

CONFLICT OF INTEREST

M.T. Krishna received funds from ALK Abello to attend a conference; his department has received funds from ALK, Thermo Fisher and MEDA for PracticAllergy course in recent years. Others authors have no conflict of interest to declare. The above companies were not involved in the review.

REFERENCES

- 1 Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF, Bock SA, Branum A, et al.: Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391–397.
- 2 Tanno LK, Bierrenbach AL, Simons FER, Cardona V, Thong BYH, Molinari N, et al.: Critical view of anaphylaxis epidemiology: Open questions and new perspectives. *Allergy, Asthma Clin Immunol* 2018;14:2.
- 3 Muraro A, Roberts G, Worm M, Bilò MB, Brockow K, Fernández Rivas M, et al.: Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy* 2014;69:1026–1045.
- 4 Simons FER, Arduoso LRF, Bilò MB, El-Gamal YM, Ledford DK, Ring J, et al.: World Allergy Organization anaphylaxis guidelines: summary. *J Allergy Clin Immunol* 2011;127:587-93–22.
- 5 Bacal E, Patterson R, Zeiss CR: Evaluation of severe (anaphylactic) reactions. *Clin Allergy* 1978;8:295–304.
- 6 Fenny N, Grammer LC: Idiopathic anaphylaxis. *Immunol Allergy Clin North Am* 2015;35:349–362.
- 7 Lieberman PL: Idiopathic anaphylaxis. *Allergy Asthma Proc* 2014;35:17–23.
- 8 Webb LM, Lieberman P: Anaphylaxis: a review of 601 cases. *Ann Allergy, Asthma Immunol* 2006;97:39–43.
- 9 Wood RA, Camargo CA, Lieberman P, Sampson HA, Schwartz LB, Zitt M, et al.: Anaphylaxis in America: The prevalence and characteristics of anaphylaxis in the United States. *J Allergy Clin*

Immunol 2014;133:461–467.

- 10 Worm M, Moneret-Vautrin A, Scherer K, Lang R, Fernandez-Rivas M, Cardona V, et al.: First European data from the network of severe allergic reactions (NORA). *Allergy* 2014;69:1397–1404.
- 11 Buka RJ, Crossman RJ, Melchior CL, Huissoon AP, Hackett S, Dorrian S, et al.: Anaphylaxis and ethnicity: higher incidence in British South Asians. *Allergy* 2015;70:1580–1587.
- 12 Pattanaik D, Lieberman P, Lieberman J, Pongdee T, Keene AT: The changing face of anaphylaxis in adults and adolescents. *Ann Allergy, Asthma Immunol* 2018;121:594–597.
- 13 Greenberger PA, Lieberman P: Idiopathic Anaphylaxis. *J Allergy Clin Immunol Pract* 2014;2:243–250.
- 14 Nwaru BI, Dhami S, Sheikh A: Idiopathic Anaphylaxis. *Curr Treat Options Allergy* 2017;4:312–319.
- 15 Ditto AM, Krasnick J, Greenberger PA, Kelly KJ, McGrath K, Patterson R: Pediatric idiopathic anaphylaxis: Experience with 22 patients. *J Allergy Clin Immunol* 1997;100:320–326.
- 16 Moneret-Vautrin DA: Idiopathic anaphylaxis. [French]. *Eur Ann Allergy Clin Immunol* 2004;36:13–19.
- 17 Reed J, Yedulapuram M, Lieberman P, Fitzpatrick E: Differences in Cytokine Production Between Idiopathic Anaphylaxis (IA) Subjects and Controls. *J Allergy Clin Immunol* 2006;117:S305.
- 18 Garriga MM, Friedman MM, Metcalfe DD: A survey of the number and distribution of mast cells in the skin of patients with mast cell disorders. *J Allergy Clin Immunol* 1988;82:425–432.
- 19 Irani AA, Garriga MM, Metcalfe DD, Schwartz LB: Mast cells in cutaneous mastocytosis:

- accumulation of the MCTC type. Clin Exp Allergy 1990;20:53–58.
- 20 Slater JE, Kaliner M: Effects of sex hormones on basophil histamine release in recurrent idiopathic anaphylaxis. J Allergy Clin Immunol 1987;80:285–290.
- 21 Grammer LC, Shaughnessy MA, Harris KE, Goolsby CL: Lymphocyte subsets and activation markers in patients with acute episodes of idiopathic anaphylaxis. Ann Allergy Asthma Immunol 2000;85:368–71.
- 22 Tejedor Alonso MA, Sastre Dominguez J, Sánchez-Hernández JJ, PérezFrances C, Hoz de la Caballer B: Clinical and functional differences among patients with idiopathic anaphylaxis. J Investig Allergol Clin Immunol 2004;14:177–86.
- 23 Tedeschi A, Lorini M, Suli C, Cugno M: Detection of serum histamine-releasing factors in a patient with idiopathic anaphylaxis and multiple drug allergy syndrome. J Investig Allergol Clin Immunol 2007;17:122–5.
- 24 Lenchner K, Grammer LC: A current review of idiopathic anaphylaxis. Curr Opin Allergy Clin Immunol 2003;3:305–11.
- 25 Wong S, Dykewicz M: Idiopathic anaphylaxis. Allergy Proc 1990;11:162.
- 26 Ditto AM, Harris KE, Krasnick J, Miller MA, Patterson R: Idiopathic Anaphylaxis: a Series of 335 Cases. Ann Allergy, Asthma Immunol 1996;77:285–291.
- 27 Motosue MS, Bellolio MF, Van Houten HK, Shah ND, Campbell RL: Risk factors for severe anaphylaxis in the United States. Ann Allergy, Asthma Immunol 2017;119:356–361.e2.
- 28 Worm M, Francuzik W, Renaudin J-M, Bilo MB, Cardona V, Scherer Hofmeier K, et al.: Factors increasing the risk for a severe reaction in anaphylaxis: An analysis of data from The European Anaphylaxis Registry. Allergy 2018;73:1322–1330.

- 29 Añibarro B, Seoane FJ, Múgica M V: Involvement of hidden allergens in food allergic reactions. *J Investig Allergol Clin Immunol* 2007;17:168–72.
- 30 Sicherer SH, Furlong TJ, Muñoz-Furlong A, Burks AW, Sampson HA: A voluntary registry for peanut and tree nut allergy: characteristics of the first 5149 registrants. *J Allergy Clin Immunol* 2001;108:128–32.
- 31 Radcliffe M, Scadding G, Brown HM: Lupin flour anaphylaxis. *Lancet* 2005;365:1360.
- 32 Enrique E, Cistero-Bahíma A, Alonso R, San Miguel MM: Egg protein: a hidden allergen in candies. *Ann Allergy Asthma Immunol* 2000;84:636.
- 33 Cantani A: Hidden presence of cow's milk proteins in foods. *J Investig Allergol Clin Immunol* 1999;9:141–5.
- 34 Vidal C, Pérez-Carral C, Chomón B: Unsuspected sources of soybean exposure. *Ann Allergy Asthma Immunol* 1997;79:350–2.
- 35 Freye HB, Esch RE, Litwin CM, Sorkin L: Anaphylaxis to the ingestion and inhalation of *Tenebrio molitor* (mealworm) and *Zophobas morio* (superworm). *Allergy asthma Proc* 1996;17:215–9.
- 36 Sánchez-Borges M, Suárez-Chacon R, Capriles-Hulett A, Caballero-Fonseca F, Iraola V, Fernández-Caldas E: Pancake Syndrome (Oral Mite Anaphylaxis). *World Allergy Organ J* 2009;2:91–96.
- 37 Popescu F-D: Cross-reactivity between aeroallergens and food allergens. *World J Methodol* 2015;5:31.
- 38 Choi J-H, Jang Y-S, Oh J-W, Kim C-H, Hyun I-G: Bee Pollen-Induced Anaphylaxis: A Case Report and Literature Review. *Allergy Asthma Immunol Res* 2015;7:513.

- 39 Beezhold DH, Reschke JE, Allen JH, Kostyal DA, Sussman GL: Latex protein: a hidden “food” allergen? *Allergy asthma Proc* 2000;21:301–6.
- 40 Cooper RJ: Over-the-counter medicine abuse – a review of the literature. *J Subst Use* 2013;18:82–107.
- 41 Heaps A, Carter S, Selwood C, Moody M, Unsworth J, Deacock S, et al.: The utility of the ISAC allergen array in the investigation of idiopathic anaphylaxis. *Clin Exp Immunol* 2014;177:483–490.
- 42 Wölbing F, Fischer J, Köberle M, Kaesler S, Biedermann T: About the role and underlying mechanisms of cofactors in anaphylaxis. *Allergy* 2013;68. DOI: 10.1111/all.12193
- 43 Tripathi A, Commins SP, Heymann PW, Platts-Mills TAE: Delayed Anaphylaxis to Red Meat Masquerading as Idiopathic Anaphylaxis. *J Allergy Clin Immunol Pract* 2014;2:259–265.
- 44 Stoltz LP, Cristiano LM, Dowling APG, Wilson JM, Platts-Mills TAE, Traister RS: Could chiggers be contributing to the prevalence of galactose-alpha-1,3-galactose sensitization and mammalian meat allergy? *J Allergy Clin Immunol Pract* 2019;7:664–666.
- 45 Carter MC, Ruiz-Esteves KN, Workman L, Lieberman P, Platts-Mills TAE, Metcalfe DD: Identification of alpha-gal sensitivity in patients with a diagnosis of idiopathic anaphylaxis. *Allergy Eur J Allergy Clin Immunol* 2018;73:1131–1134.
- 46 Stoevesandt J, Grundmeier N, Trautmann A: Gastroesophageal hymenoptera stings add to causes of idiopathic anaphylaxis. *Ann Allergy, Asthma Immunol* 2012;108:125–126.
- 47 Armentia A, Pineda F, Fernández S: Wine-Induced Anaphylaxis and Sensitization to Hymenoptera Venom. *N Engl J Med* 2007;357:719–720.
- 48 Rolla G, Heffler E, Boita M, Doyen V, Mairesse M, Cvackova M, et al.: Pigeon tick bite: A neglected cause of idiopathic nocturnal anaphylaxis. *Allergy Eur J Allergy Clin Immunol*

2018;73:958–961.

- 49 Vadas P, Sinilaite A, Chaim M: Cholinergic Urticaria with Anaphylaxis: An Underrecognized Clinical Entity. *J Allergy Clin Immunol Pract* 2016;4:284–291.
- 50 Shaker M, Yuan I, Kennedy KL, Capucilli P, Spergel JM: Idiopathic anaphylaxis and undiagnosed anorexia nervosa. *Ann Allergy, Asthma Immunol* 2019;122:215–217.
- 51 Valent P, Akin C, Arock M, Brockow K, Butterfield JH, Carter MC, et al.: Definitions, Criteria and Global Classification of Mast Cell Disorders with Special Reference to Mast Cell Activation Syndromes: A Consensus Proposal. *Int Arch Allergy Immunol* 2012;157:215–225.
- 52 González-de-Olano D, Álvarez-Twose I: Insights in Anaphylaxis and Clonal Mast Cell Disorders. *Front Immunol* 2017;8:792.
- 53 Valent P, Horny HP, Escribano L, Longley BJ, Li CY, Schwartz LB, et al.: Diagnostic criteria and classification of mastocytosis: a consensus proposal. *Leuk Res* 2001;25:603–25.
- 54 Valent P, Akin C, Metcalfe DD: Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. *Blood* 2017;129:1420–1427.
- 55 Escribano L, Garcia-Montero A, Sanchez-Muñoz L, Teodosio C, Alvarez-Twose I, Jara-Acevedo M, et al.: Diagnosis of Adult Mastocytosis: Role for Bone Marrow Analysis; in : *Laboratory Hematology Practice*. 2012 Oxford, UK, Wiley-Blackwell, 2012, pp 388–398.
- 56 Bonadonna P, Perbellini O, Passalacqua G, Caruso B, Colarossi S, Dal Fior D, et al.: Clonal mast cell disorders in patients with systemic reactions to Hymenoptera stings and increased serum tryptase levels. *J Allergy Clin Immunol* 2009;123:680–686.
- 57 Akin C, Scott LM, Kocabas CN, Kushnir-Sukhov N, Brittain E, Noel P, et al.: Demonstration of an aberrant mast-cell population with clonal markers in a subset of patients with “idiopathic” anaphylaxis. *Blood* 2007;110:2331–2333.

- 58 Gülen T, Hägglund H, Sander B, Dahlén B, Nilsson G: The presence of mast cell clonality in patients with unexplained anaphylaxis. *Clin Exp Allergy* 2014;44:1179–1187.
- 59 Alvarez-Twose I, González-de-Olano D, Sánchez-Muñoz L, Matito A, Jara-Acevedo M, Teodosio C, et al.: Validation of the REMA Score for Predicting Mast Cell Clonality and Systemic Mastocytosis in Patients with Systemic Mast Cell Activation Symptoms. *Int Arch Allergy Immunol* 2012;157:275–280.
- 60 Carter MC, Desai A, Komarow HD, Bai Y, Clayton ST, Clark AS, et al.: A distinct biomolecular profile identifies monoclonal mast cell disorders in patients with idiopathic anaphylaxis. *J Allergy Clin Immunol* 2018;141:180–188.e3.
- 61 Blatman KH, Grammer LC: Idiopathic Anaphylaxis; in : *Anaphylaxis and Hypersensitivity Reactions*. Totowa, NJ, 2011 Humana Press, 2011, pp 223–234.
- 62 Borzutzky A, Morales PS, Mezzano V, Nussbaum S, Burks AW: Induction of remission of idiopathic anaphylaxis with rituximab. *J Allergy Clin Immunol* 2014;134:981–983.
- 63 Fenny N, Grammer LC: Idiopathic anaphylaxis. *Immunol Allergy Clin North Am* 2015;35:349–362.
- 64 Fernandez J, Akin C: Management of Idiopathic Anaphylaxis: When Is Bone Marrow Examination Essential? *Curr Treat Options Allergy* 2014;1:221–231.
- 65 Lieberman P, Nicklas RA, Oppenheimer J, Kemp SF, Lang DM, Bernstein DI, et al.: The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol* 2010;126:477-80–42.
- 66 Ozdemir O, Bozkurt HB, Elmas B: Omalizumab's role in the treatment of steroid dependent malignant idiopathic anaphylaxis. *Türk Pediatr Arşivi* 2017;52:105–107.

- 67 Warrier P, Casale TB: Omalizumab in idiopathic anaphylaxis. *Ann Allergy, Asthma Immunol* 2009;102:257–258.
- 68 Upton J, Vadas P: Potential Therapeutic Strategies for Severe Anaphylaxis Targeting Platelet-Activating Factor and PAF Acetylhydrolase. *Curr Treat Options Allergy* 2014;1:232–246.

TABLES

Table 1 - Frequency of Idiopathic Anaphylaxis among anaphylaxis cases

Author	Year	IA among anaphylaxis in general (%)
Webb & Lieberman [8]	2006	59%*
Wood et al [9]	2014	39%
Worm et al [10] (European Registry)	2014	6.5%
Buka et al [11]	2015	55%
Pattanaik et al [12]	2018	35%

IA, idiopathic anaphylaxis

* Percentage calculated on the total cases of anaphylaxis of uncertain origin

Table 2 - Classification of idiopathic anaphylaxis.

Classification	Description
Clinical features	
Generalized (IA-G)	Urticaria or angioedema with systemic manifestations (bronchospasm, hypotension, syncope, or gastrointestinal symptoms).
Angioedema (IA-A)	Urticaria or angioedema with upper airway involvement (laryngeal, pharyngeal, tongue), without systemic manifestations.
Variant (IA-V)	symptoms of IA vary from classic IA
Undifferentiated somatoform IA (IA-US)	Symptoms mimic IA but no objective findings or response to treatments occurs. Patients meet criteria for somatoform disorder as described in the DSM-IV.
Questionable (IA-Q)	Presumptive/uncertain diagnosis of IA (no objective findings, no response to corticosteroids)
Frequency	
Frequent (IA-F)	more than 6 times per year or more frequently than once every 2 months
Infrequent (IA-I)	fewer than 6 times per year or fewer than once every 2 months
Severity (response to steroids)	
Corticosteroid-dependent (CSD-IA)	Steroids cannot be discontinued
Malignant (MCSD-IA)	High doses of steroids (prednisone >20mg daily or 60mg on alternate days) are required to control IA.

Adapted from Ditto et al[15].

Table 3 - Differential diagnosis of idiopathic anaphylaxis.

Differential diagnosis	Key points for diagnosis
Food allergy (including hidden allergens)	Onset timing, product labelling, <i>in vivo/vitro</i> allergy tests
Delayed allergy (α -gal, food allergy with cofactors)	Cofactor investigation, <i>in vivo/vitro</i> allergy tests (red meat skin tests and α -gal sIgE included)
Drug allergy	<i>In vivo/vitro</i> drug diagnostic work-up
Insects and parasites (Hymenoptera, Anisakis simplex, pigeon tick, pine processionary caterpillar)	Nocturnal anaphylaxis, environment, season, <i>in vivo/vitro</i> allergy tests
Latex allergy	Occupational risk, <i>in vivo/vitro</i> allergy tests
Exercise-induced anaphylaxis	Clinical history, <i>in vivo/vitro</i> allergy tests
Mast cell disorders	Dermatological examination, bone marrow exam, molecular tests
Hereditary/acquired angioedema	Complement C4, clinical/family history
Cholinergic urticaria and anaphylaxis	Clinical history
Psychiatric conditions (Somatoform disorders, panic attacks)	Clinical history, serial tryptase measurements, review of emergency room/ambulance records to confirm there are no physical signs of anaphylaxis
Severe asthma exacerbations (masquerading as anaphylaxis)	Pulmonary function testing
Vocal cord dysfunction	ENT, intentional provocation followed by laryngoscopy
Hydatid cyst rupture	Immunodiagnosis
Globus	Endoscopy
Phaeochromocytoma	Urinary tests, hypertension
Carcinoid syndrome	Urinary tests
Scombroid syndrome	Clinical history, negative <i>in vivo/vitro</i> allergy tests

Table 4 - Management of idiopathic anaphylaxis.

IA type	Treatment
IA acute episode	"Triple" Therapy Epinephrine Prednisone 50 mg H1 antihistamine 10 mg (eg: cetirizine, loratadine) Management E.D. access
IA Frequent long term management	Therapy Prednisone 60 ± 20 mg daily 1-2 w. Gradual reduction if symptom free (5-10 mg every 2w), until discontinuation (9-12 month) H1 antihistamine 10-30 mg daily (eg: cetirizine, loratadine) Management Follow-up for clinical and treatment re-assessment
IA Infrequent long term management	Therapy n/a Management Follow-up for clinical and treatment re-assessment
IA Frequent steroid-dependent long term management	Therapy Prednisone at the lowest effective dose*. H1 antihistamine 10-30 mg daily (eg: cetirizine, loratadine). Management Consider steroid sparing agents and other alternatives (leukotriene antagonists, ketotifen) Follow-up for clinical and treatment re-assessment
IA Frequent malignant long term management	Therapy Prednisone ≥ 20 mg daily or 60 mg every other day. H1 antihistamine 10-30 mg daily (eg: cetirizine, loratadine). Management Consider steroid sparing agents and other alternatives (leukotriene antagonists, ketotifen) Follow-up for clinical and treatment re-assessment

All patients with IA are provided with an emergency kit (corticosteroid and antihistamine tablets, epinephrine auto-injector) and self-management training and a written plan.

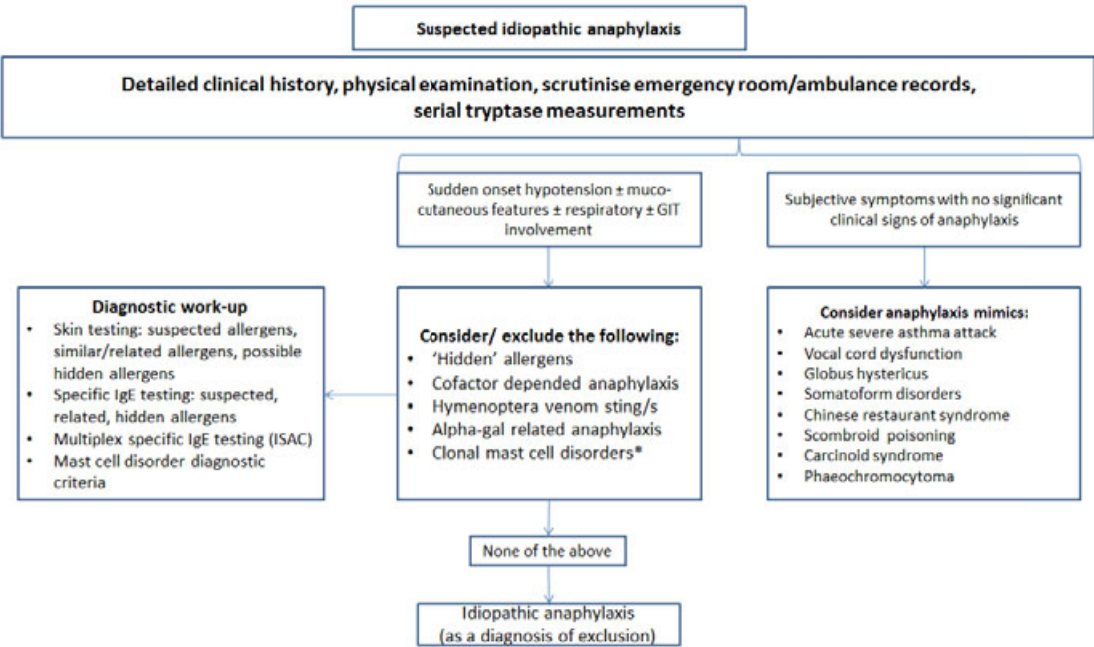
IA, idiopathic anaphylaxis; w, week.

*Following tailored steroid tapering schemes

Adapted from Fenny and Grammer[63]

FIGURE LEGENDS

Figure 1 - A systematic diagnostic work-up to a case of suspected idiopathic anaphylaxis.



* Consider clonal mast cell disorders in cases presenting as isolated severe hypotension and/or cardiovascular collapse