

An Update on the Management of Anaphylaxis

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Abstract

Purpose of review To highlight the latest evidence supporting management recommendations in anaphylaxis and discuss the implications for further research in anaphylaxis management.

Recent findings The acute management of anaphylaxis is largely centered on resuscitation and administration of epinephrine. There is little evidence to support the use of antihistamines and corticosteroids in the acute management of anaphylaxis.

Summary Anaphylaxis is an acute, systemic, potentially life-threatening reaction caused by the release of mast cell and basophil mediators that could lead to distributive shock. Anaphylaxis is associated with increased healthcare utilization and costs. The definition of anaphylaxis is largely based on clinical criteria with no validated biomarker confirming the diagnosis. Long-term follow-up is recommended to identify triggers and co-factors of anaphylaxis. Further, this helps to establish a plan for trigger avoidance and emergency action plan to manage subsequent episodes. Given the significant morbidity and mortality associated with this diagnosis, high quality randomized controlled studies are lacking to support management decisions in anaphylaxis.

Introduction

Anaphylaxis is an acute, systemic, potentially life-threatening reaction that often results in emergency department visits and hospital admissions [1•,2••,3••]. It is caused by the release of mast cell and basophil

mediators that could lead to distributive shock [4]. The lifetime prevalence of anaphylaxis is estimated between 0.05 and 2% [5]. However, this is likely to be underestimated as anaphylaxis is largely underreported

[5, 6]. Anaphylaxis is largely recognized by the clinical manifestations following exposure to a plausible agent that is known to cause this systemic reaction [7]. Prescription data show that 1% of the population is prescribed epinephrine suggesting a similar outpatient population incidence of anaphylaxis [8]. The incidence of anaphylaxis has been increasing worldwide with a

marked increase reported in industrialized nations [9–11]. This has led to increased healthcare utilization and cost. This calls for increased vigilance and awareness among healthcare providers. This review aims to summarize the recent updates in diagnostic criteria for anaphylaxis and outlines the latest recommendations for anaphylaxis management.

Diagnosis of anaphylaxis

Anaphylaxis is a clinical term describing a severe hypersensitivity reaction that may be life-threatening. However, no consensus definition exists [12]. The lack of a consensus definition has implications on obtaining accurate epidemiologic data. The European Academy of Allergy and Clinical Immunology (EAACI) defines anaphylaxis as a severe generalized or systemic hypersensitivity reaction that is life-threatening by virtue of its rapid-onset cardiopulmonary compromise [13]. The World Allergy Organization (WAO) defines anaphylaxis as a rapid-onset and potentially deadly serious allergic reaction [1••,14]. The diagnosis of anaphylaxis is currently based on clinical criteria [7]. There is no currently accepted specific biomarker to diagnose this systemic reaction [15].

An elevated serum tryptase drawn within 6 h of symptom onset is helpful to ascertain the diagnosis of anaphylaxis [16]; however, serum tryptase may not be elevated in food-induced anaphylaxis, and a normal tryptase level does not rule out anaphylaxis [3••]. Most diagnostic data on anaphylaxis are obtained from retrospective registries [17]. Thus, a high clinical suspicion is warranted for prompt anaphylaxis-specific management.

Management of anaphylaxis

Acute management

The acute management of anaphylaxis is not supported by evidence from high-level clinical trials. This is due mainly to ethical reasons; epinephrine is life-saving medication, and a placebo controlled trial would place patients with anaphylaxis at risk of death. Another reason is logistic difficulties—difficulty obtaining informed consent prior to the need of epinephrine, since we are unable to predict when an anaphylactic event will occur. Most data at present is obtained from observational human studies inferring therapeutic treatment approaches as well as non-randomized assessments of therapeutic interventions [12, 18, 19]. In this manuscript, we present a review of the evidence supporting the use of the most frequently prescribed medications in acute anaphylaxis.

Epinephrine

Intramuscular epinephrine is regarded as the first-line therapy for the management of an acute anaphylactic reaction [20]. Guidelines emphasize the importance for early administration of the medication even in suspected “impending anaphylaxis” [12].

Early administration of intramuscular epinephrine is essential to reduce mortality [21, 22]. Delayed epinephrine administration is associated with increased morbidity and mortality [23]. A review of anaphylaxis mortality over a 6-year period found that only 14% of patients had received epinephrine prior to cardiac arrest [24]. A US study of food-induced anaphylaxis in children and adolescents found that only 33% of victims had received epinephrine in the first hour of allergen exposure. Epinephrine auto-injectors were prescribed to half of the patients with fatal anaphylaxis in this group [25]. However, none of the patients had the medication available at the time of the fatal reaction.

Further, delay in administering epinephrine increases the likelihood of biphasic anaphylaxis whereby symptoms recur within 1 to 72 h of initial symptom resolution [26, 27]. In a systematic review of 27 studies, 4.7% of the 4114 patients with anaphylaxis had biphasic episodes (range 0.4 to 23.3%). Patients with hypotension who had an unknown inciting trigger were at increased risk [28].

There are no absolute contraindications for epinephrine, and the medication can be administered repeatedly [29]. Maximal plasma concentration occurs quicker with intramuscular epinephrine than with the subcutaneous route [30]. Thus, subcutaneous epinephrine administration is not recommended for the acute management of anaphylaxis. A randomized controlled trial concluded that the vastus lateralis muscle was the optimal site for epinephrine injection [24].

Anaphylaxis fatality registries have highlighted under-prescribing, low carriage rates, under-use, delayed use, and incorrect use of epinephrine auto-injectors (EIA) as risk factors for anaphylaxis-related mortality [31, 32]. Despite this, some fatalities still occur after optimal and timely administration of the drug.

Corticosteroids

Previous studies have shown that patients treated for anaphylaxis in the emergency department of European and Latin American countries were more likely to receive corticosteroids than epinephrine on presentation [33, 34]. Hypothetically, in the initial phase of anaphylaxis, corticosteroids could reduce the severity of the reaction. However, the median time for maximum serum concentration of oral hydrocortisone is between 1 and 2 h after ingestion [35]. Pharmacodynamic data on corticosteroid bioavailability suggest that the medication would not be at peak concentration to improve clinical outcomes during initial anaphylaxis. Further, no randomized controlled trials exist to show that corticosteroids are effective in the treatment of anaphylaxis [36]. The rationale for corticosteroid use has mostly been extrapolated from its effectiveness in the acute exacerbations of asthma whereby corticosteroids have been shown to decrease hospitalization and relapse [37, 38].

Corticosteroids are commonly prescribed during an acute anaphylactic event to prevent biphasic anaphylaxis. This is defined as recurrence of anaphylaxis after an anaphylactic event without re-exposure to the trigger, following an asymptomatic interval of at least 1 h [29]. A prospective study of adult and pediatric patients presenting at an emergency department or hospitalized for anaphylaxis showed that patients who developed biphasic reactions were less likely to receive corticosteroids. Further, patients who developed biphasic anaphylaxis received

lower doses of corticosteroids. Both associations were not statistically significant. A recent systematic review identified 22 studies examining the association of corticosteroids with biphasic anaphylaxis [39]. The authors found that biphasic reactions are associated with more severe initial anaphylactic reactions (respiratory distress, hypotension) and delayed administration of epinephrine. Furthermore, 21 out of the 22 studies did not find any association between corticosteroids and prevention of biphasic anaphylaxis [39].

Antihistamines

Both H1 and H2-antihistamines are frequently co-prescribed during anaphylaxis. Data supporting the use of antihistamines in anaphylaxis is rather limited. Systematic reviews on prescribing antihistamines in anaphylaxis have failed to identify randomized controlled trials justifying their use [24, 30, 40]. A randomized controlled trial has shown that a combination of H1- and H2-antihistamines is superior to H1-antihistamines in treating urticaria but not angioedema [41]. Another trial has shown that H1-antihistamines are superior to H2-antihistamines in controlling pruritus [39].

Clinical guidelines stressed that standard life support procedures including airway management, oxygen administration, and cardiovascular support should be the primary intervention in the management of acute anaphylaxis. For this reason, epinephrine administration is recommended, including administration of intravenous epinephrine 1 mg every 2–3 min in the setting of cardiac arrest [12, 13]. Further, corticosteroids and antihistamines should be considered as second-line therapies if at all given, since that there is no strong evidence to advocate for their use in the management of acute anaphylaxis. There is no consensus for the definite observation period following symptomatic resolution of an acute episode of anaphylaxis. Concern for biphasic anaphylaxis has led most resuscitation guidelines to recommend prolonged observation between 8 and 24 h after symptomatic resolution [14, 42]. More recent data suggest that for patients with anaphylaxis were treated successfully in the emergency department, the duration of observation should be risk stratified according to the clinical characteristics and severity of the episode [28].

Follow-up management

Clinical follow-up of patients following an acute episode of anaphylaxis is imperative to prevent subsequent episodes. Clinical management is largely centered on the identification of triggers and co-factors for anaphylaxis [43]. Further, the allergist's role is to advise the patient and family members on how to minimize the risk of further reactions and provide education as well as skills on how to effectively manage further anaphylactic reactions [44]. Anaphylaxis action plans may reduce the risk of future, severe anaphylactic reactions; however, there is no universally accepted anaphylaxis management plan, and there is no randomized controlled trial data showing clinical effectiveness of such interventions to reduce recurrence or improve outcomes from subsequent anaphylactic episodes [44, 45]. Further, a retrospective review on anaphylaxis in a single center concluded that the most important aspect of anaphylaxis management continues to be prevention, highlighting the importance of performing a comprehensive allergic evaluation; without which, approximately one in six anaphylaxis cases would have been missed [11].

The WAO guidelines state that the history of the acute episode is important to investigate the etiology for triggers of anaphylaxis [14]. The AAAAI/ACAAI anaphylaxis practice parameter is the most thorough to describe specific investigations under different triggers [2••,3••]. The EAACI guidelines recommend interpretation of “validated tests” in the setting of a detailed allergy history to aid in the identification of triggers [13]. All three guidelines agree that allergen avoidance should be a standard component of preventing anaphylaxis recurrences. Venom immunotherapy, drug desensitization, and food oral immunotherapy are recommended to prevent anaphylaxis to specific triggers. Pharmacologic prophylaxis of anaphylaxis to radiographic contrast media is recommended in all three guidelines [1••, 2••, 13].

Prescription of intramuscular epinephrine via an auto-injector, having an anaphylaxis emergency plan as well as having a medical identification outlining triggers and comorbidities, is also recommended. Of note, The AAAAI/ACAAI practice parameter recommends prescribing more than one EAI. This is based upon concern that 20% of patients with anaphylaxis require more than one dose of epinephrine [2••]. EAI are available in several presentations (Fig. 1); the type of EAI will be determined by accessibility, type of insurance, cost, and patient preference. For example, EAI containing visual and audible cues may be preferred in younger and elderly patients. EAI are not readily accessible worldwide [46]; Fig. 2 demonstrates countries where EAI are obtainable. When EAI are not available, patients should carry an epinephrine vial with a needle and have knowledge of self-administration.

Due to the recent increase in cost of EAI in the USA (up to 400%), many patients ask health care providers whether they can use expired EAI. A study was performed where expired donated EAI were checked for drug stability by mass spectrometry (a quantitative test). The report concluded that even after 4-year post expiration date, the expired EAI would still be beneficial [47]. No prospective clinical trials have been performed to confirm this

Self Administration of Epinephrine

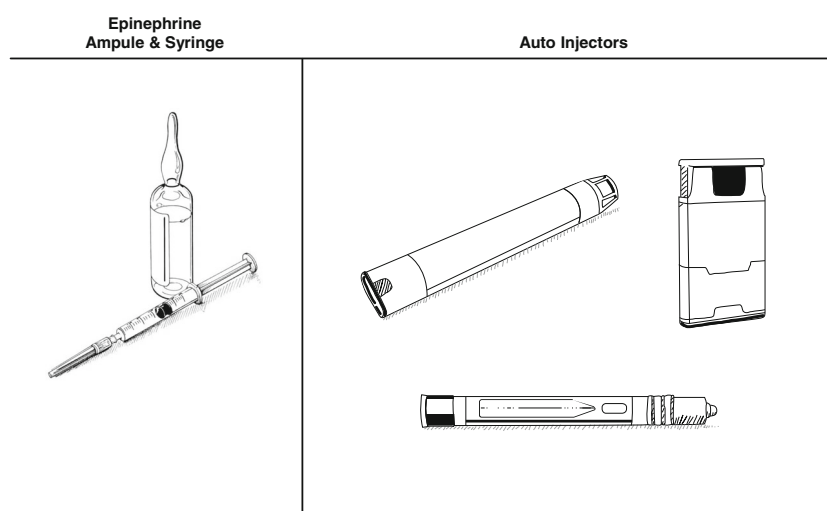


Fig. 1. Types of self-administered epinephrine.

Access to Epinephrine Auto-Injectors by Country

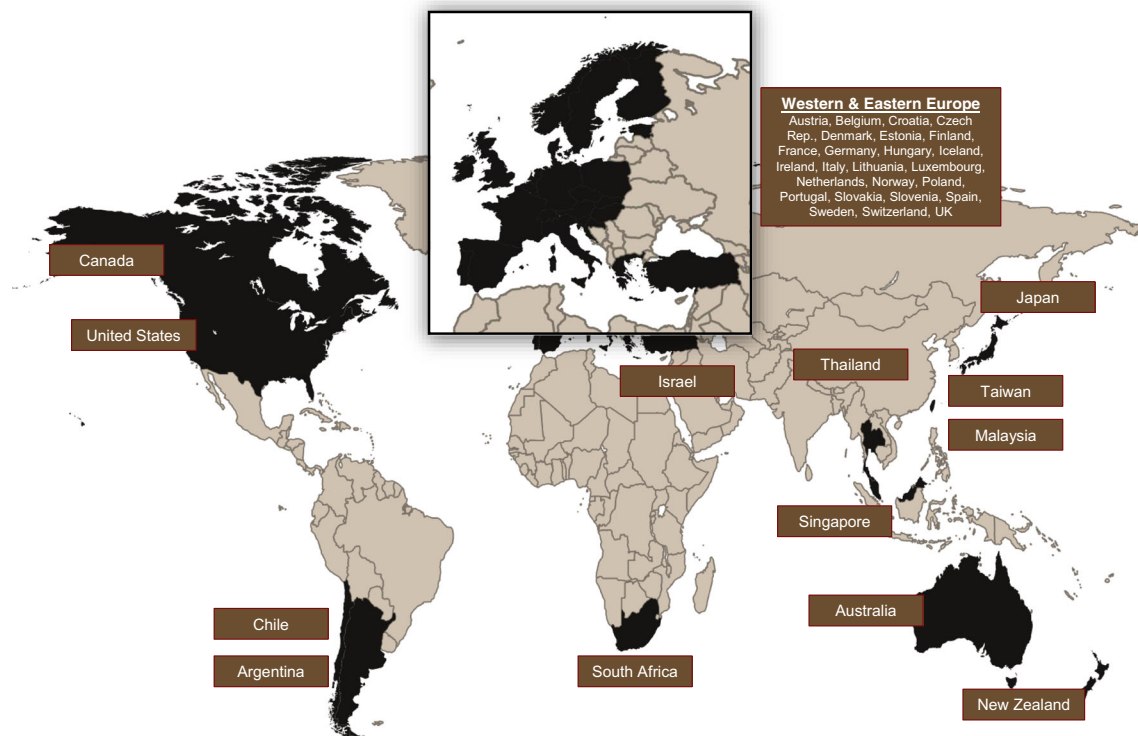


Fig. 2. Access to epinephrine auto-injectors by country [46].

finding; however, one of the authors from the previously mentioned report concluded that in setting of a potential life-threatening allergic reaction, the benefits of using an expired EAI product probably outweigh the risk of no treatment at all [48].

Education

A number of studies focused on improving anaphylaxis education, pertaining to guideline adherence and availability of epinephrine [49, 50]. A number of gaps in the management of anaphylaxis have been described. A systematic review identified more than 202 gaps in knowledge and anaphylaxis management at both patient and physician level [51]. Further, deficiencies in physician follow-up care and quality of life of patients and caregivers are present [51, 52].

Two reports of emergency department management of anaphylaxis suggest decreased epinephrine use when indicated as well as lack of allergy referral [53, 54]. Patients would benefit from referral to allergist as previously unknown triggers are more likely to be identified [55, 56]. A prospective observational study of emergency department patients presenting with possible allergic reactions showed that more than 60% of patients with anaphylaxis did not receive epinephrine in the emergency department; however, a review of the allergist's deemed management was appropriate in 98% of total cases [57]. This suggests

that it is difficult to assess management practices in anaphylaxis, particularly given the difficulties with establishing a definite diagnosis on presentation.

Errors in using intramuscular epinephrine have been identified at both health-care provider and patient level [58, 59]. A number of initiatives have targeted increasing the availability of epinephrine through education of both providers and patients alike [27, 49]. Most of the education is centered on the available data suggesting that epinephrine is the sole drug that has shown to improve clinical outcomes during acute anaphylaxis [23, 27, 50].

Conclusion

Anaphylaxis is a serious, life-threatening disease with increasing prevalence in the developed world. This review highlights that at present, there is little robust evidence to guide decisions on the acute and long-term management of anaphylaxis. Diagnosis is largely based on clinical criteria which hinders appropriate patient selection. Further, the high mortality associated with this condition impairs undertaking studies to investigate drug effectiveness versus placebo [43]. At present, there is a great need for evidence to address pharmacodynamics of adrenaline and epinephrine dosage in children as well as the benefits of educational plans in anaphylaxis [60].

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Compliance with Ethical Standards

Conflict of Interest

Keith Sacco and Alexei Gonzalez-Estrada each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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