2012 Update: World Allergy Organization Guidelines for the assessment and management of anaphylaxis

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Purpose of review
The World Allergy Organization (WAO) Guidelines for the assessment and management of anaphylaxis published in early 2011 provide a global perspective on patient risk factors, triggers, clinical diagnosis, treatment, and prevention of anaphylaxis. In this 2012 Update, subsequently published, clinically relevant research in these areas is reviewed.

Recent findings
Patient risk factors and co-factors that amplify anaphylaxis have been documented in prospective studies. The global perspective on the triggers of anaphylaxis has expanded. The clinical criteria for the diagnosis of anaphylaxis that are promulgated in the Guidelines have been validated. Some aspects of anaphylaxis treatment have been prospectively studied. Novel investigations of self-injectable epinephrine for treatment of anaphylaxis recurrences in the community have been performed. Progress has been made with regard to measurement of specific IgE to allergen components (component-resolved testing) that might help to distinguish clinical risk of future anaphylactic episodes to an allergen from asymptomatic sensitization to the allergen. New strategies for immune modulation to prevent food-induced anaphylaxis and new insights into subcutaneous immunotherapy to prevent venom-induced anaphylaxis have been described.

Summary
Research highlighted in this Update strengthens the evidence-based recommendations for assessment, management, and prevention of anaphylaxis made in the WAO Anaphylaxis Guidelines.

Keywords
clinical diagnosis of anaphylaxis, epinephrine (adrenaline) in first-line treatment of anaphylaxis, patient risk factors for anaphylaxis, prevention of anaphylaxis

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KEY POINTS

- The World Allergy Organization (WAO) Guidelines for the assessment and management of anaphylaxis published in early 2011 remain a useful global resource on anaphylaxis with regard to patient risk factors, triggers, clinical diagnosis, treatment, and prevention.
- Since the Guidelines were published, progress in research that is relevant to human anaphylaxis has resulted in more than 500 publications in peer-reviewed, indexed medical journals.
- These subsequent publications, many of which are summarized in this Update, strengthen the evidence base for the recommendations made in the Guidelines.

INTRODUCTION

The World Allergy Organization (WAO) Guidelines for the assessment and management of anaphylaxis (subsequently referred to as the Guidelines) were published on 3 March 2011 [1▪▪] in response to the need for global guidelines on anaphylaxis diagnosis and treatment. Unique aspects of the Guidelines are summarized below.

The Guidelines were developed without corporate funding in response to absence of global guidelines for anaphylaxis, absence of national guidelines in most countries, and for use as an additional resource in countries with their own national guidelines. They were based on the best evidence available from publications in indexed, peer-reviewed journals to the end of 2010. They highlighted the role of the allergy/immunology specialist, particularly in prevention of anaphylactic episodes; however, they have been widely used by a broader group of healthcare professionals [1▪▪].

The Guidelines were preceded by documentation of global availability of essentials for assessment and management of anaphylaxis. They provide a global perspective on anaphylaxis with regard to vulnerable patients, risk factors for severe or fatal anaphylaxis, and co-factors that amplify anaphylaxis symptoms, as well as perspective on mechanisms and triggers. They emphasize prompt clinical diagnosis, basic initial treatment, and prevention of anaphylaxis recurrences. They are written in a concise format (22 pages) with recommendations supported by citation of 150 references, most of which were published from 2006 to 2010. They include color illustrations that highlight the key concepts in the text. They propose a global agenda for anaphylaxis research (Table 1).

Since co-publication (open access) in the *Journal of Allergy & Clinical Immunology* and the *World Allergy Organization Journal* in early 2011, the Guidelines have been disseminated worldwide in a variety of formats. They have been posted on the WAO website and on WAO member society websites. Summary posters and pocket cards have been translated into 10 languages, with additional translations pending. They have been presented in keynote and plenary sessions in congresses and meetings around the globe. They are used in undergraduate and postgraduate medical courses. They have become a resource for specialty areas beyond allergy/immunology, including sports medicine, for example, the 2012 Olympic Games Therapeutic Use Exemption Committee. They are also used in primary care and allied health.

In parallel, progress has been made on the global agenda proposed for anaphylaxis research (Table 1), and more than 500 papers on human anaphylaxis have been published in indexed peer-reviewed medical journals, hence the need for this Update. During 2011 and early 2012, members of the WAO Special Committee on Anaphylaxis independently searched for and selected relevant publications, which were then collated and independently ranked for inclusion in the Update.

Here, we recapitulate the evidence-based recommendations in the Guidelines and support them with additional recent references. The Update is intended for use in conjunction with the Guidelines and the references cited therein [1▪▪].

ASSESSMENT OF PATIENTS WITH ANAPHYLAXIS

Information about patient risk factors, triggers and mechanisms, and clinical diagnosis [1▪▪,2–7,8▪,9–12,13▪,14–16,17▪,18–22,23▪,24▪▪,25] is updated in this section, which includes case series from five continents focusing on anaphylaxis in community settings, emergency departments (EDs), and hospitals.

Patient risk factors

Patient risk factors, including age or physiologic state-related vulnerability, concomitant diseases, concurrent medications, and co-factors, are similar worldwide [1▪▪,7,8▪,9–12,13▪,14,15].

Vulnerable patients include infants, teenagers, pregnant women, and the elderly. Although anaphylaxis can be difficult to diagnose in infants, case series of patients with anaphylaxis, published from different countries, include infants [2–7,8▪], one as young as 2 weeks of age [5]. Adolescents and young adults are vulnerable to anaphylaxis because of

risk-taking behaviors as they transition between parental control and autonomous decision-making [1▪▪]. Some are not even aware of their life-threatening allergies and have never been instructed in allergen avoidance or the need for carrying an epinephrine auto-injector for self-administration [9]; others are aware, but ignore the risks. Anaphylaxis during labor and delivery can lead to fatality or permanent disability from hypoxic-ischemic encephalopathy in mothers and especially in neonates. The most common triggers are intra-partum injection of penicillin, natural rubber latex, and other agents encountered in medical or perioperative settings [1▪▪,10]. In patients with anaphylaxis who are more than 50 years old, typical triggers are stinging insect venoms, medications, and 'unknown' [1▪▪,2,3,11].

In young patients studied prospectively, asthma, especially when severe or uncontrolled, is strongly associated with anaphylaxis; additionally, during a food-induced anaphylactic episode, a history of asthma is predictive of dyspnea, wheezing, and respiratory arrest [1▪▪,7]. A history of chronic/relapsing gastrointestinal symptoms is reported to be predictive of abdominal pain, vomiting, hypotension, bradycardia, and cardiac arrest [7]. In patients with anaphylaxis due to insect venom, risk factors for increased severity include older age, pre-existing cardiovascular disease or mast cell disorder, elevated serum baseline total tryptase concentrations, concomitant treatment with a beta-adrenergic blocker and/or angiotensin-converting enzyme (ACE) inhibitor, a previous severe reaction, and the type of stinging insect (honey bees present the highest risk) [12,13▪]. Mast cell disorders are associated with an increased risk of severe or fatal anaphylaxis; of 137 consecutive patients with systemic mastocytosis, despite taking prophylactic medications, 12% had one or more life-threatening events [14]. After *Hymenoptera* stings, two patients suffered from severe recurrent hypotensive episodes and required repeated resuscitation and hospitalization, and two other patients (one of whom later died) were disabled by cerebral hypoxia [14].

Co-factors that amplify anaphylaxis [1▪▪] have been described in nearly 20% of young patients in a prospective registry study. They include exercise, fever, acute infection such as an upper respiratory tract infection, premenstrual status, and emotional stress. Interestingly, these co-factors are also reported to amplify some of the acute allergic reactions to food that occur during prospective studies of oral food immunotherapy [1▪▪,8▪,15].

Triggers and mechanisms

In contrast to older patients [1▪▪,2,3], foods are consistently reported to be the most common trigger of anaphylaxis in children and teenagers [4–7,8▪]. In infants, sensitization to one or more foods is common and is not necessarily accompanied by any symptoms; however, in one population-based sample, more than 10% of 1-year-olds had oral challenge-proven clinical reactivity to uncooked egg, peanut, or sesame [16].

Patients can react clinically to a specific allergen in different ways, possibly reflecting the allergen components to which they are sensitized. As an example, in different countries, patients with elevated serum IgE levels to peanut have predominant IgE antibodies directed to different allergen components, associated with different symptom patterns. In the US, IgE antibodies directed to r Ara h 1, 2 and 3 are associated with severe early-onset symptoms. In Spain, IgE antibodies directed to r Ara h 9 are associated with later onset of milder clinical reactivity to peanut and other plant-derived proteins such as peach. In Sweden, IgE antibodies directed to r Ara h 8, the Bet v 1 homolog, are also associated with later onset and milder clinical reactivity to peanut and other plant-derived proteins such as hazelnut [17▪].

Table 1. Progress on the global agenda for anaphylaxis research

Agenda item	Progress
Development of instruments to quantify patient-specific risk factors	Some
Validation of the clinical criteria for diagnosis	Good
Development of rapid in-vitro test(s) to confirm the clinical diagnosis	Some
Development of in-vitro tests to distinguish clinical risk of anaphylaxis from asymptomatic sensitization	Excellent
Epinephrine research [pharmacology, epidemiology, RCTs (not placebo-controlled) of dose versus dose and route versus route]	Good
RCTs of second-line medications such as H_1-antihistamines or glucocorticoids	Some
RCTs of immune modulation to prevent anaphylactic episodes	Excellent

RCT, randomized controlled trial. Adapted from [1▪▪].

Stinging insect venom-induced anaphylaxis has been extensively studied in Europe, North America, and Australia, where flying *Hymenoptera* insects are well documented anaphylaxis triggers [1▪▪]. In North America, stings from nonflying imported fire ants (*Solenopsis* species) are also typical triggers, and in Australia, stings from jumper ants (*Myrmecia* species) are also typical triggers [12,13▪,18].

In a review of nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity that included non-cross-reactive NSAID (single NSAID) anaphylaxis, the authors focused on stepwise investigation, emphasizing the importance of the history and the pros and cons of skin tests, specific IgE levels, and challenge/provocation tests [19].

In a survey of anaphylaxis during anesthesia, of 2516 patients, 72% had an IgE-mediated reaction. In adults, this commonly involved neuromuscular blocking agents (58%), latex (20%), or antibiotics (13%); in children, it commonly involved latex (42%), neuromuscular blocking agents (32%), or antibiotics (9%) [20].

A comprehensive review of subcutaneous immunotherapy (SCIT) with allergens includes new information about risk factors that increase the possibility of anaphylaxis during SCIT, and how to reduce this risk [21]. In one US study [22], systemic reactions were reported in 4% of 28 000 SCIT injections; 22% of the 773 patients had previously reacted to SCIT.

Human IgG-mediated anaphylaxis remains an enigma [1▪▪]. To facilitate its identification, decreased blood neutrophil Fc gamma RIII expression without increased IL-4 R alpha expression has been proposed as a marker [23▪].

Clinical diagnosis

A poster and pocket card that capture the key messages in the Guidelines about prompt clinical diagnosis and initial treatment of anaphylaxis have been translated into ten different languages [1▪▪] (Fig. 1).

The clinical criteria for the diagnosis of anaphylaxis that emphasize sudden onset of multisystem symptoms have been validated in a retrospective cohort study [24▪▪] of ED patients, in whom they had excellent sensitivity [96.7%, 95% confidence interval (CI) 88.8–99.9] and good specificity (82.4%, 95% CI 75.5–87.6). Additionally, use of these criteria in epidemiologic studies has significantly improved identification of patients with anaphylaxis [25].

Post mortem diagnosis of anaphylaxis can be difficult when little or no history is available, macroscopic signs are absent, and blood or other biologic fluids are unavailable or unsuitable for study [1▪▪]. Identification of tissue mast cells, for example, in the laryngeal wall, by staining for immunohistochemical markers such as CD117, has been proposed for use in this setting [26].

Serum total tryptase measurements are not helpful for confirmation of the diagnosis of anaphylaxis at the time of the episode because the assay takes several hours to perform; however, they can be useful later, more so for confirmation of the clinical diagnosis of venom or medication-induced anaphylaxis than for confirmation of food-induced anaphylaxis [1▪▪]. Serial monitoring of tryptase levels at the time of presentation, 1–2 h later, and at resolution is reported to improve the sensitivity of the test [27].

MANAGEMENT OF ANAPHYLAXIS IN HEALTHCARE SETTINGS

Appropriate preparation is the key to good patient outcomes in anaphylaxis [1▪▪,28]. In a pediatric ED, development and implementation of an anaphylaxis protocol significantly improved the rate of epinephrine administration, the rate of admission to an observation unit, and the duration of observation in this unit, and there were no significant adverse effects from epinephrine [29▪▪]. In a retrospective study [30] of pediatric ED patients with food-related allergic reactions, factors that were independently associated with a higher likelihood of hospitalization included pre-ED epinephrine treatment, and epinephrine treatment within 1 h of triage.

Epinephrine is the preferred vasopressor for treatment of anaphylactic shock [1▪▪,31]; however, it is not always given promptly, even in hospitalized patients. As an example, anaphylaxis can be difficult to diagnose during anesthesia; consequently, treatment with epinephrine can be delayed. In a retrospective study [32], 45% of patients with anaphylaxis during anesthesia developed shock, circulatory instability, or cardiac arrest, yet only 83% of these patients received epinephrine.

Even if epinephrine has not been given at all, cardiovascular symptoms, including myocardial infarction and arrhythmias, can occur during anaphylaxis [1▪▪,33]. These complications also occur after epinephrine overdose, regardless of route of administration, but especially after an intravenous bolus dose or overly rapid intravenous infusion [34–36].

In a prospective randomized blinded study [37] of young patients with acute cutaneous allergic reactions during food challenges, in comparison with diphenhydramine 1 mg/kg, cetirizine 0.25 mg/kg had a similar onset of action, similar

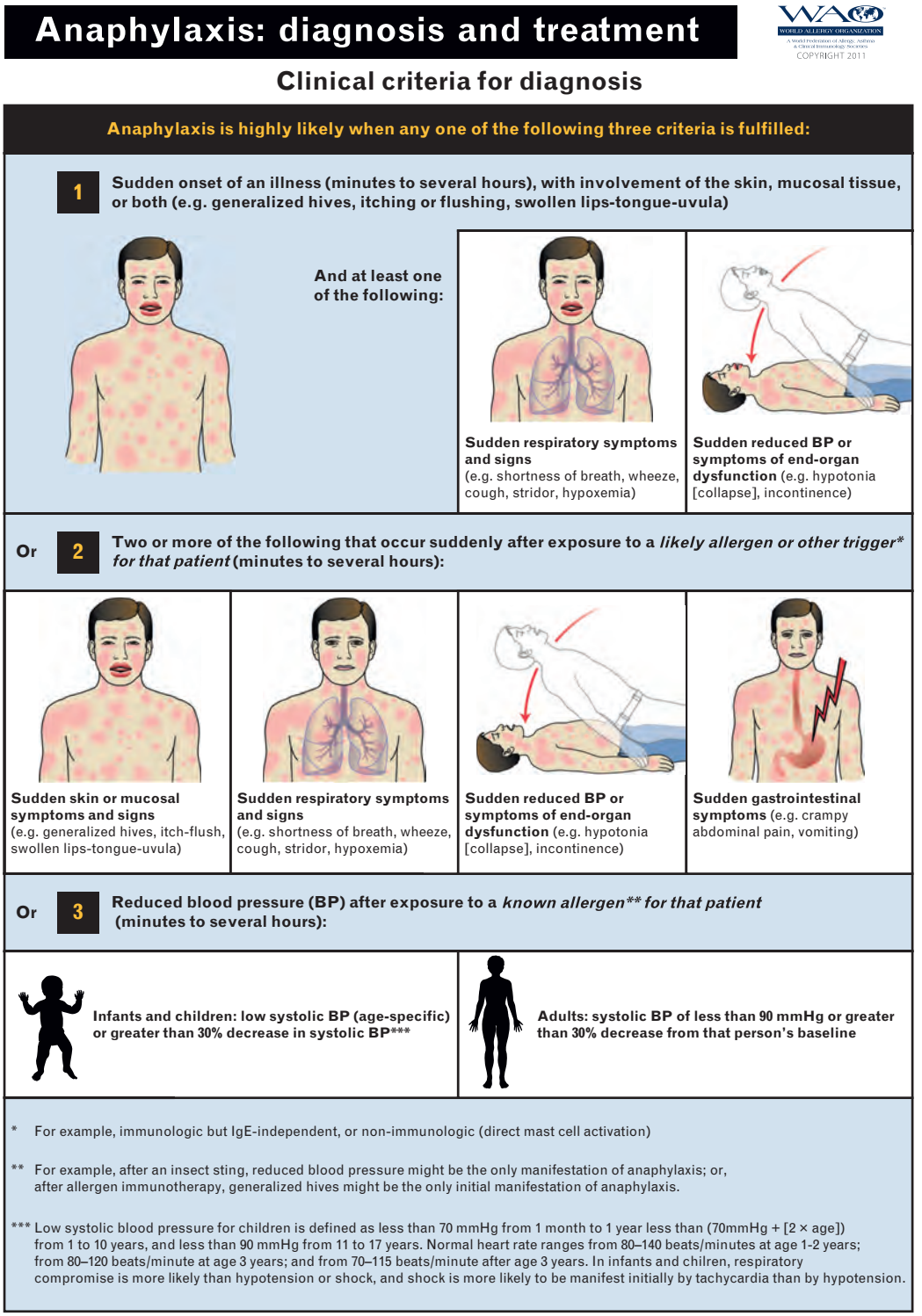


FIGURE 1. Anaphylaxis diagnosis and treatment. Clinical criteria for the diagnosis of anaphylaxis and initial treatment of anaphylaxis, as illustrated in the poster and the pocket card based on the 2011 WAO Anaphylaxis Guidelines. The first part of this figure summarizes a validated approach to the clinical diagnosis of anaphylaxis, which is highly likely when any one of the three criteria is fulfilled. The second part of the figure summarizes the basic initial treatment which is relatively inexpensive to implement and should be possible even in a low resource environment. Note that steps 4, 5, and 6 should be performed promptly and simultaneously as soon as anaphylaxis is diagnosed. If precious minutes are lost early in the diagnosis and treatment of an anaphylactic episode, subsequent management can become more difficult. Guidelines are not a substitute for appropriate preparation, good clinical judgment, and strong clinical skills (adapted from [1▪▪]). WAO, World Allergy Organization.

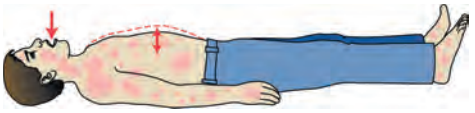
Anaphylaxis: diagnosis and treatment

Initial treatment

1 **Have a written emergency protocol** for recognition and treatment of anaphylaxis and rehearse it regularly.

2 **Remove exposure to the trigger** if possible, e.g. discontinue an intravenous diagnostic or therapeutic agent that seems to be triggering symptoms.

3



Assess the patient's circulation, airway, breathing, mental status, skin and body weight (mass).

Promptly and simultaneously, perform steps 4, 5 and 6.

4

Call for help: resuscitation team (hospital) or emergency medical services (community) if available.

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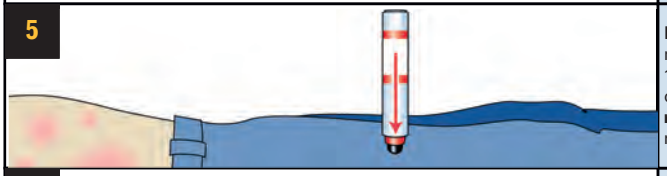
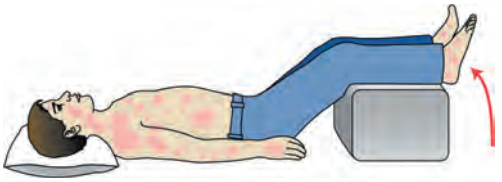


Inject epinephrine (adrenaline) intramuscularly in the mid-anterolateral aspect of the thigh, 0.01 mg/kg of a 1:1,000 (1 mg/mL) solution, maximum of 0.5 mg (adult) or 0.3 mg (child); **record the time of the dose and repeat it** in 5–15 minutes, if needed. Most patients respond to 1 or 2 doses.

6



Place patient on the back or in a position of comfort if there is respiratory distress and/or vomiting; **elevate the lower extremities;** fatality can occur within seconds if patient stands or sits suddenly.

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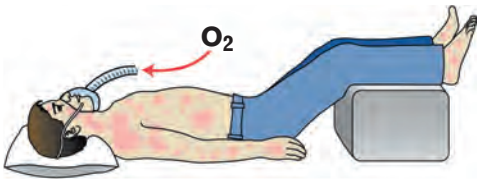

When indicated, give high-flow supplemental oxygen (6-8 L/minute), by face mask or oropharyngeal airway.

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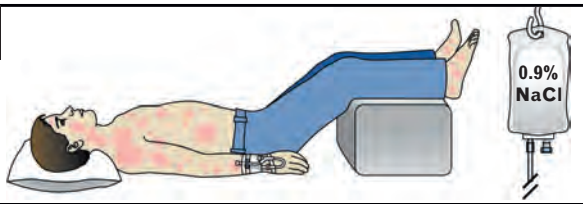

Establish intravenous access using needles or catheters with wide-bore cannulae (14 - 16 gauge): **When indicated, give 1–2 litres of 0.9% (isotonic) saline rapidly** (e.g. 5-10 ml/kg in the first 5-10 minutes to an adult; 10 ml/kg to a child).

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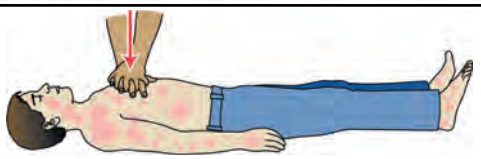

When indicated, at any time, perform cardiopulmonary resuscitation with continuous chest compressions and rescue breathing.

In addition,

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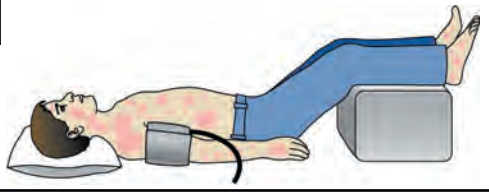

At frequent, regular interval, monitor patient's blood pressure, cardiac rate and function, respiratory status, and oxygenation (monitor continuously, if possible).

References: Simons FER et al, for the WAO. J Allergy Clin Immunol 2011;127:587-93.e22 and WAO Journal 2011;4:13-36. Illustrator: J Schaffer

efficacy, longer duration of action, and reduced sedation profile. A similar number of children in each treatment group were treated with epinephrine and glucocorticoids.

MANAGEMENT AT TIME OF DISCHARGE FROM HEALTHCARE SETTINGS

Information about preparation for self-treatment in the community [1▪▪,38–45], confirmation of the trigger of an anaphylactic episode [1▪▪,46–48,49▪,50–54], allergen avoidance [1▪▪,55–59], pharmacologic prophylaxis [60], and immune modulation [1▪▪,61▪,62–65,66▪] is updated in this section (given below).

Recommendations for prevention and treatment of anaphylaxis recurrences at the time of discharge from the healthcare setting are as follows [1▪▪]:

(1) Medication
   (a) self-injectable epinephrine/adrenaline from an auto-injector or
   (b) self-injectable epinephrine from an ampule/syringe or prefilled syringe (alternative but not preferred formulations).
(2) Other aspects of discharge management
   (a) anaphylaxis emergency action plan (personalized, written),
   (b) medical identification (e.g. bracelet, wallet card),
   (c) medical record electronic flag or chart sticker and
   (d) emphasis on importance of follow-up investigations, preferably by an allergy/immunology specialist.
(3) Assessment of sensitization to allergen
   (a) before discharge, consider measuring allergen-specific IgE levels in serum for assessment of sensitization to relevant allergens ascertained from the history of the anaphylactic episode,
   (b) at least 3–4 weeks after the episode, confirm allergen sensitization using skin tests; if these tests are negative in a patient with a convincing history of anaphylaxis, consider repeating them weeks or months later and
   (c) medically supervised challenge/provocation tests, for example with food or medication, might also be needed in order to assess risk of future anaphylactic episodes.
(4) Long-term risk reduction: avoidance and/or immune modulation
   (a) food-triggered anaphylaxis: strict avoidance of relevant food(s),
   (b) stinging insect-triggered anaphylaxis: avoidance of stinging insects; subcutaneous venom immunotherapy (protects up to 90% of adults and 98% of children against anaphylaxis from future stings),
   (c) medication-triggered anaphylaxis: avoidance of relevant medications and use of safe substitutes; if indicated, desensitization (using a published protocol) conducted in a healthcare setting and
   (d) unknown or idiopathic anaphylaxis: for frequent episodes, consider glucocorticoid and non-sedating H_1-antihistamine prophylaxis for 2–3 months; consider measurement of a baseline tryptase level to identify mastocytosis/clonal mast cell disorders.
(5) Optimal management of asthma and other concomitant diseases.

Allergy/immunology specialists play a uniquely important role in preparing the patient for self-treatment in the community, confirmation of the trigger of an anaphylactic episode, education regarding allergen avoidance, and immune modulation.

Preparation for self-treatment in the community

Under-prescription of self-injectable epinephrine auto-injectors for patients at risk of anaphylaxis recurrence in the community remains a concern [1▪▪] and has been described as 'alarming' [2,9]. One group of investigators has reported that patients older than 50 years of age discharged home from an ED after treatment of anaphylaxis were less likely to be prescribed self-injectable epinephrine than those younger than 50 years [11]. It is, however, possible to demonstrate improvement; in a prospective study [29▪▪], at the time of discharge from an ED after anaphylaxis treatment, epinephrine auto-injectors were prescribed for 6.7% of patients before implementation of an anaphylaxis protocol, and for 54.5% of patients afterwards.

New data lend additional support to the recommendation that patients leaving a healthcare facility after omalizumab injections should be taught how to recognize the signs and symptoms of anaphylaxis and equipped with, and trained to use, self-injectable epinephrine [1▪▪,38]. Prescribing self-injectable epinephrine for patients to use in the event of a delayed reaction to SCIT warrants further study [39]. Anaphylaxis after sublingual immunotherapy (SLIT) is rare; nevertheless, as maintenance SLIT is typically given at home rather than in healthcare settings, additional efforts are needed to identify risk factors for adverse effects from SLIT, standardize reporting

of these adverse effects, and provide patients with written instructions about prompt recognition and treatment of anaphylaxis [40].

Although epinephrine auto-injectors with needle protection features that deploy after use have been introduced, unintentional injections and injuries can still occur if the needle-containing end of the device is touched before use [41].

Many children and teenagers who experience anaphylaxis in the community, including some with throat tightness, difficulty in breathing, difficulty in swallowing, wheezing, or loss of consciousness, fail to use epinephrine, commonly because they think it is unnecessary [42]. The percentage of patients requiring more than one dose of epinephrine during anaphylactic episodes varies depending on the study [1▪▪]; the second dose is often administered by a healthcare professional [6,42].

In a qualitative study [43], most teenagers reported carrying epinephrine auto-injectors some of the time; however, only three had used an auto-injector, and one of these experienced difficulties; a comprehensive training approach was recommended. In another study [44], children and teenagers actually performed self-injection of epinephrine during auto-injector training sessions; apparently, this did not increase their anxiety about the procedure.

Anaphylaxis education is critically important for patients, and for those responsible for children and others at risk [1▪▪]. In this regard, mandatory education for school personnel about recognition of anaphylaxis and prompt epinephrine injection has been reported to improve the standard of care [45].

Confirmation of anaphylaxis triggers

Allergy/immunology specialists play an important role in identification of clinically relevant allergen triggers by performing and interpreting skin tests and measuring specific IgE levels [1▪▪]. These tests do not distinguish between sensitization associated with increased risk of anaphylaxis, which is relatively uncommon, and asymptomatic sensitization, which is widespread; therefore, the allergens selected for testing should be relevant to the history of the anaphylactic episode [1▪▪,46].

Medically supervised incremental challenge tests (also described as titrated or graded provocation tests) to food or medication conducted in an appropriately equipped and staffed healthcare setting are sometimes necessary to determine the risk of anaphylaxis recurrence in daily life [1▪▪,47,48]. An algorithm based on six clinical factors, including symptoms, sex, and age, as well as skin prick tests, allergen-specific IgE levels, and total IgE level, improved the prediction of positive food challenge outcomes, compared with skin prick tests and/or allergen-specific IgE levels alone [47].

Allergen component-resolved testing might help to identify patients sensitized to food, latex, or venom who are at increased risk of anaphylaxis after exposure to these allergens versus those who are sensitized but clinically tolerant (i.e. remain asymptomatic after exposure) to these allergens [1▪▪,48,49▪]. For example, patients with elevated specific IgE levels to food allergen components such as casein (Bos d 8), ovomucoid (Gal d 1), or r Ara h 2 are unlikely to tolerate milk, egg, or peanut, respectively [48,49▪,50]. The specific IgE ratio of omega-5 gliadin to wheat has been proposed as a marker for diagnosis of wheat-dependent, exercise-induced anaphylaxis and wheat-induced anaphylaxis [51], but requires confirmation.

Tests for drug allergy/hypersensitivity are not universally available; only 74.7% of WAO member societies report availability of skin testing and only 67.4% report availability of drug-specific IgE measurements [52]. The relative risk of acute systemic reactions from skin tests with beta-lactam antibiotics is proportional to the pretest probability of anaphylaxis or other acute systemic reactions as determined from the history; therefore, preferably, patients with high pretest probability of such reactions should be skin-tested and monitored in hospital settings [53]. Additional data are needed regarding the value of skin testing when selecting a well tolerated radiographic contrast media (RCM) in patients with a history of anaphylaxis to RCM [54].

Allergen avoidance

For prevention of food-induced anaphylactic episodes, strict avoidance of the implicated food and cross-reacting substances is recommended. This often leads to stress in affected individuals and their families and, despite vigilance, unintentional exposures occur [1▪▪]. Depending on dietary habits and methods of food preparation, people sensitized to the same food allergen might require specific, detailed information with regard to avoidance of that allergen [55]. Recall of dietary advice is variable, and food avoidance may be more stringent or less stringent than recommended by a healthcare professional [56]. Unintentional exposures and clinical reactions are common. Eating away from home can be dangerous; as an example, although restaurant staff might appear confident and knowledgeable about food allergy and anaphylaxis, many of them hold serious misconceptions about these

subjects [57]. Persons who are highly sensitized to a food can experience anaphylaxis after exposure by any route, for example, ingestion of trace amounts in presumably 'safe' food or medication, or topical application of soaps or cosmetics [58,59].

Patients who have reacted to a medication such as an antibiotic or an NSAID should ideally be given written information about strict avoidance of the incriminated medications and a list of the alternative medications (if possible, from a different pharmacologic class) they are likely to tolerate without adverse effects [1▪▪,19].

Additional prospective studies of pharmacologic premedication to prevent allergic reactions to diagnostic and therapeutic agents are necessary. For those at risk for anaphylaxis to RCM, pharmacologic premedication might not always be effective [54]. For those receiving snake antivenom, pretreatment with epinephrine, an H_1-antihistamine and a glucocorticoid, has been reported to reduce the risk of acute reactions, and to be safe [60].

Immune modulation

Natural desensitization is possible in some carefully selected and monitored pediatric patients with a history of clinical reactivity to baked milk or baked egg [50,61▪,62]. As an example, if a child with a history of clinical reactivity to milk can subsequently tolerate small amounts of unintentionally ingested, extensively heated milk in foods such as pizza or muffins, this clinical tolerance should be recognized as a marker of transient IgE-mediated allergy; moreover, addition of extensively heated milk to his/her diet might accelerate development of tolerance to unheated milk. Conversely, ongoing reactivity to small amounts of extensively heated milk portends a more persistent phenotype and the need for continued strict dietary avoidance of milk in all forms, even in trace amounts [61▪,62].

Medically supervised clinical trials using incremental dosing of specific food through oral, sublingual, or epicutaneous routes are ongoing [1▪▪,15,61▪,63]. In the first ever randomized controlled study [63] of peanut oral immunotherapy, clinical desensitization and concurrent immune modulation of the allergic response were conclusively demonstrated. Patients with a history of severe life-threatening anaphylaxis and patients with moderate-to-severe persistent asthma were excluded from this study; however, adverse events were common, particularly on the initial dose escalation day and on dose build-up days. Long-term immune tolerance remains to be confirmed [15,63]. Despite steady progress, food oral immunotherapy is not yet recommended for use in clinical practice [1▪▪,61▪].

An elevated baseline serum total tryptase level is a predictor of severe insect sting reactions, frequent systemic reactions during venom immunotherapy, the possibility of venom immunotherapy failure, and the risk of relapse if venom immunotherapy is stopped [12,13▪,64]. Current strategies for reducing adverse reactions include pretreatment with an H_1-antihistamine or anti-IgE monoclonal antibody [12]. Patients with honey bee venom allergy and intense occupational exposure should be treated with an increased maintenance dose of 200 mcg honey bee venom [12,65].

In patients sensitized to a medication, when substitution of an agent from a different pharmacologic class is not possible, rapid desensitization is an effective means of administering the medication of interest while minimizing or circumventing adverse reactions to it [1▪▪,66▪]. The molecular mechanisms leading to the temporary tolerance induced by this approach are incompletely understood. In a 10-year review of patients sensitized to antibiotics, chemotherapeutics such as taxanes and platins, and monoclonal antibodies, a full dose of the desired agent was reached in 99.9% of 796 rapid desensitization regimens. Reactions that occurred during desensitization were generally less severe than the initial reaction. There were no fatalities [66▪].

CONCLUSIONS

The evidence base for the recommendations to improve the assessment, management, and prevention of anaphylactic episodes made in the 2011 WAO Anaphylaxis Guidelines is even stronger now than at the time they were published. As highlighted in this Update, important advances have subsequently been made in the areas of: validation of the clinical criteria for diagnosis, use of epinephrine, development of in-vitro tests to distinguish clinical risk from asymptomatic sensitization, and immune modulation to prevent anaphylaxis. Additional studies relevant to human anaphylaxis, particularly prospective studies, are needed.

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Conflicts of interest

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 442–443).

1. ■■ Simons FER, Ardusso LRF, Bilo MB, *et al.* World Allergy Organization guidelines for the assessment and management of anaphylaxis. J Allergy Clin Immunol 2011; 127:593.e22.

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