World Allergy Organization Guidelines for the Assessment and Management of Anaphylaxis

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Abstract: The illustrated World Allergy Organization (WAO) Anaphylaxis Guidelines were created in response to absence of global guidelines for anaphylaxis. Uniquely, before they were developed, lack of worldwide availability of essentials for the diagnosis and treatment of anaphylaxis was documented. They incorporate contributions from more than 100 allergy/immunology specialists on 6 continents. Recommendations are based on the best evidence available, supported by references published to the end of December 2010.

The Guidelines review patient risk factors for severe or fatal anaphylaxis, co-factors that amplify anaphylaxis, and anaphylaxis in vulnerable patients, including pregnant women, infants, the elderly, and those with cardiovascular disease. They focus on the supreme importance of making a prompt clinical diagnosis and on the basic initial treatment that is urgently needed and should be possible even in a low resource environment. This involves having a written emergency protocol and rehearsing it regularly; then, as soon as anaphylaxis is diagnosed, promptly and simultaneously calling for help, injecting epinephrine (adrenaline) intramuscularly, and placing the patient on the back or in a position of comfort with the lower extremities elevated. When indicated, additional critically important steps include administering supplemental oxygen and maintaining the airway, establishing intravenous access and giving fluid resuscitation, and initiating cardiopulmonary resuscitation with continuous chest compressions. Vital signs and cardiorespiratory status should be monitored frequently and regularly (preferably, continuously).

The Guidelines briefly review management of anaphylaxis refractory to basic initial treatment. They also emphasize preparation of the patient for self-treatment of anaphylaxis recurrences in the community, confirmation of anaphylaxis triggers, and prevention of recurrences through trigger avoidance and immunomodulation. Novel strategies for dissemination and implementation are summarized. A global agenda for anaphylaxis research is proposed.

Key Words: anaphylaxis, risk factors, clinical diagnosis, epinephrine (adrenaline), antihistamines, glucocorticoids

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DISCLAIMER: The information contained in the text, figures, and tables of the WAO Anaphylaxis Guidelines is correct at the time of publication; however, recommendations, for example, those for medications and doses, might need to be individualized according to the needs of the patient, and the medications, supplies, equipment, and skilled support available; moreover, recommendations change over time.

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Worldwide, anaphylaxis definitions in common use are: "a serious, life-threatening generalized or systemic hypersensitivity reaction" and "a serious allergic reaction that is rapid in onset and might cause death."[1–3] The true global rate of occurrence of anaphylaxis from all triggers in the general population is unknown because of under-recognition by patients and caregivers and under-diagnosis by healthcare professionals. In addition, under-reporting, use of a variety of case definitions, use of different measures of occurrence such as incidence or prevalence, and under-coding are problematic in many epidemiologic studies. Despite this, anaphylaxis is not rare and the rate of occurrence appears to be increasing, although there are geographic variations.[4–7] Lifetime prevalence based on international studies is estimated at 0.05–2%.[4]

In public health terms, anaphylaxis is considered to be an uncommon cause of death.[7–13] The case fatality rate is difficult to ascertain with accuracy. Anaphylaxis fatalities are often not diagnosed as such because of absence of historical details from eyewitnesses, incomplete death scene investigations, paucity of specific pathologic findings at postmortem examination, and lack of disease-specific laboratory tests.[11]

The evidence base for the assessment and management of patients with anaphylaxis is weak[14–16] in comparison to, for example, the evidence base for the assessment and management of patients with asthma or allergic rhinitis.[17–19] It is likely to remain so in the absence of randomized, controlled studies of therapeutic interventions performed during an anaphylactic episode.[20]

WAO ANAPHYLAXIS GUIDELINES DEVELOPMENT

The WAO is an international federation of 84 regional and national allergy and clinical immunology societies dedicated to raising awareness and advancing excellence in clinical care, research, education, and training in allergy and clinical immunology. The WAO Anaphylaxis Guidelines were created in response to absence of global guidelines for anaphylaxis.

Unique Aspects

Before the Guidelines were developed, worldwide lack of essentials for the diagnosis and treatment of anaphylaxis was documented.[3] The Guidelines review patient risk factors for severe or fatal anaphylaxis, co-factors that amplify anaphylaxis, and anaphylaxis in vulnerable patients, including pregnant women, infants, and the elderly. The biologic role of cardiac mast cells is examined, and anaphylaxis presenting as an acute coronary syndrome is discussed. The Guidelines focus on the supreme importance of making a prompt clinical diagnosis and on the basic initial treatment that is urgently needed and should be possible even in a low resource environment such as a country, a region, or a specific location, for example, an aircraft cabin or a remote area. Recommendations for cardiopulmonary resuscitation are based on 2010 guidelines that advise initiating chest compressions before rescue breathing. The role of the allergy/immunology specialist is highlighted, particularly with regard to prevention of recurrences. Recommendations are supported by citation of references published to the end of 2010. A global research agenda for addressing uncertainties in the assessment and management of anaphylaxis is proposed. In order to transcend language barriers, 5 comprehensive illustrations summarize the principles of assessment and management set forth in the Guidelines.

Rationale, Objectives, and Scope

Global guidelines for the assessment and management of anaphylaxis have not previously been published. In many countries, there are no anaphylaxis guidelines in use.[3] Anaphylaxis guidelines developed by national and regional allergy/immunology organizations, or with substantial input from such organizations, vary in scope and comprehensiveness. Some of them are not evidence-based. Only a few of them have been published in indexed, peer-reviewed medical journals and can be found by using Pub Med or other search engines.[21–29] With the important exception of epinephrine (adrenaline) ampules, many of the essential medications, supplies and equipment for the management of anaphylaxis are not universally available worldwide.[3]

The objectives of the WAO Anaphylaxis Guidelines are to increase global awareness of current concepts in the assessment and management of anaphylaxis in healthcare settings, to prevent or reduce anaphylaxis recurrences in the community, to propose a research agenda for anaphylaxis, to contribute to anaphylaxis education, and to improve allocation of resources for anaphylaxis.

The WAO Guidelines were developed primarily for use by allergy/immunology specialists in countries without anaphylaxis guidelines and for use as an additional resource in those where such guidelines are available; however, they will also be of interest to a broader group of healthcare professionals. They provide recommendations for assessment and management of anaphylaxis in healthcare settings (hospitals, clinics, and medical offices) and recommendations for treatment and prevention of anaphylaxis in community settings. They focus on the basic initial management of anaphylaxis that should be possible even in a low resource environment. They also include a brief discussion of assessment and management of refractory anaphylaxis under optimal circumstances.

Methods

The Guidelines were developed by the Anaphylaxis Special Committee that was appointed by the WAO President in 2007. They are based on the best evidence available,[30] in the absence of randomized, controlled trials with which to answer most clinical questions relevant to anaphylaxis. In determining what is essential and what is not, the Committee drew extensively on the findings of the WAO Survey of Essentials for Assessment and Management of Anaphylaxis.[3] Other resources considered included allergy/immunology anaphylaxis guidelines or guidelines with substantial allergy/immunology input previously published in indexed peer-reviewed journals,[21–29] and anaphylaxis reviews, including Cochrane systematic reviews.[2,14–16,31,32] In 2009, drafts of the Guidelines were developed at face-to-face meetings and through e-mail correspondence among Committee members, distributed to members of the WAO Board of Directors for comment, and presented to and discussed with delegates at the World Allergy Congress in Buenos Aires. In 2010, the Guidelines were circulated to the WAO member societies and the WAO Board of Directors for review, additional comments, and approval. In all, more than 100 allergy/immunology specialists on 6 continents contributed to Guidelines development.

ASSESSMENT OF PATIENTS WITH ANAPHYLAXIS

The diagnosis of anaphylaxis is based on clinical findings[2,33,34] (Table 1). In this section of the Guidelines, we review patient risk factors for severe or fatal anaphylaxis, other co-factors that amplify anaphylaxis, triggers, the importance of the clinical diagnosis, the use of laboratory tests, and the differential diagnosis.

Patient Risk Factors for Severe or Fatal Anaphylaxis and Co-Factors that Amplify Anaphylaxis

Many of the patient factors that increase the risk of severe or fatal anaphylactic episodes are similar worldwide. They include age-related factors,[34–36] concomitant diseases such as asthma and other chronic respiratory diseases,[10,37,38] cardiovascular diseases,[39–41] mastocytosis[42] or clonal mast

TABLE 1. Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized urticaria, itching or flushing, swollen lips-tongue-uvula)

   AND AT LEAST ONE OF THE FOLLOWING:

   A) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

   B) Reduced blood pressure or associated symptoms of end-organ dysfunction (eg. hypotonia [collapse], syncope, incontinence) OR

2. Two or more of the following that occur rapidly after exposure to *a likely allergen*[a] *for that patient* (minutes to several hours)

   A) Involvement of the skin-mucosal tissue (eg, generalized urticaria, itch-flush, swollen lips-tongue-uvula)

   B) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

   C) Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)

   D) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting) OR

3. Reduced blood pressure after exposure to *known allergen*[b] for that patient (minutes to several hours)

   A) Infants and children: low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressure[c]

   B) Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF: peak expiratory flow.

[a]Or other trigger, for example, immunologic but IgE-independent, or nonimmunologic (direct) mast cell activation.

[b]For example, after an insect sting, reduced blood pressure might be the only manifestation of anaphylaxis; or, in a similar example, during allergen immunotherapy, after injection of a known allergen for that patient, generalized urticaria (only one body organ system affected) might be the only initial manifestation of anaphylaxis.

[c]Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years. Normal heart rate ranges from 80–140 beats/min at age 1–2 years; from 80–120 beats/min at age 3 years; and from 70–115 beats/min after age 3 years. Infants are more likely to have respiratory compromise than hypotension or shock, and in this age group, shock is more likely to be manifest initially by tachycardia than by hypotension.

Clinical criteria 1, 2, and 3 are taken from reference 2.

References 33 and 34 support footnotes b and c, respectively.

cell disorders,[43,44] and severe atopic disease, for example, allergic rhinitis.[45] Some concurrent medications such as beta-adrenergic blockers and angiotensin-converting enzyme (ACE) inhibitors might also increase the risk[40,41,46–48] (Fig. 1).

In addition, severe or fatal anaphylactic episodes might be associated with defects in mediator degradation pathways, resulting, for example, in elevated baseline levels of tryptase, histamine, bradykinin (because of low serum ACE activity), and platelet-activating factor (PAF) (because of low serum PAF acetylhydrolase activity).[45,49–52]

Co-factors that amplify or augment anaphylaxis are also universal. Of these, exercise-induced anaphylaxis is the best studied and often involves concomitant ingestion of a specific food (wheat/omega-5 gliadin, celery, or shellfish)–or any food at all. Less commonly, it involves concomitant ingestion of ethanol or a nonsteroidal anti-inflammatory drug (NSAID) that enhances intestinal permeability and allergen absorption.[53–56] Amplifying co-factors also include upper respiratory tract infections and other acute intercurrent infections, fever, emotional stress, travel or other disruption of routine, and premenstrual status in females.[2,45,57] Multiple factors and co-factors likely contribute to some anaphylactic episodes.[45,57]

Triggers of Anaphylaxis

The relative importance of specific anaphylaxis triggers in different age groups appears to be universal. Foods are the most common trigger in children, teens and young adults. Insect stings and medications are relatively common triggers in middle-aged and elderly adults; in these age groups, idiopathic anaphylaxis, a diagnosis of exclusion, is also relatively common.[31,32] Mechanisms and triggers of anaphylaxis are summarized in Figure 2.[2,22–25,31,32,53–87]

Many of the specific triggers for anaphylaxis are universal; however, some important geographic variations have also been reported. Food triggers differ according to local dietary habits, specific food exposures, and methods of food preparation.[58–67] In North America and in some countries in Europe and Asia, cow's milk, hen's egg, peanut, tree nuts, shellfish, and fish are common food triggers. In other European countries, fruits such as peach are common triggers; in the Middle East, sesame is a common trigger, and in Asia, foods such as buckwheat, chickpea, rice, and bird's nest soup need to be considered.

Indigenous insect populations differ from continent to continent and from region to region on the same continent. Consequently, the likelihood of exposure to different orders and families of stinging or biting insects and the risk of anaphylaxis from these insects also differs.[68–71] Stinging insects (order Hymenoptera) have been extensively studied in relationship to anaphylaxis only in Europe, North America, and Australia. Anaphylaxis triggered by biting insects, for example, kissing bugs (order Hemiptera), mosquitoes (order Diptera), and ticks (order Acarina), is not optimally studied.

Medications, for example, antimicrobial, antiviral, and anti-fungal agents, are common triggers of anaphylaxis worldwide,[72,73] with variations among countries; for example, intramuscular penicillin is a common trigger where it remains in use for rheumatic fever, and antituberculosis medications are relatively common triggers in some countries. NSAIDs commonly trigger anaphylaxis that is medication-specific within this pharmacologic class and is not related to other NSAID-associated diseases such as asthma, rhinitis, nasal polyposis, and chronic urticaria.[74]

Anaphylaxis can also be triggered by chemotherapeutic agents such as carboplatin and doxorubicin, and biologic

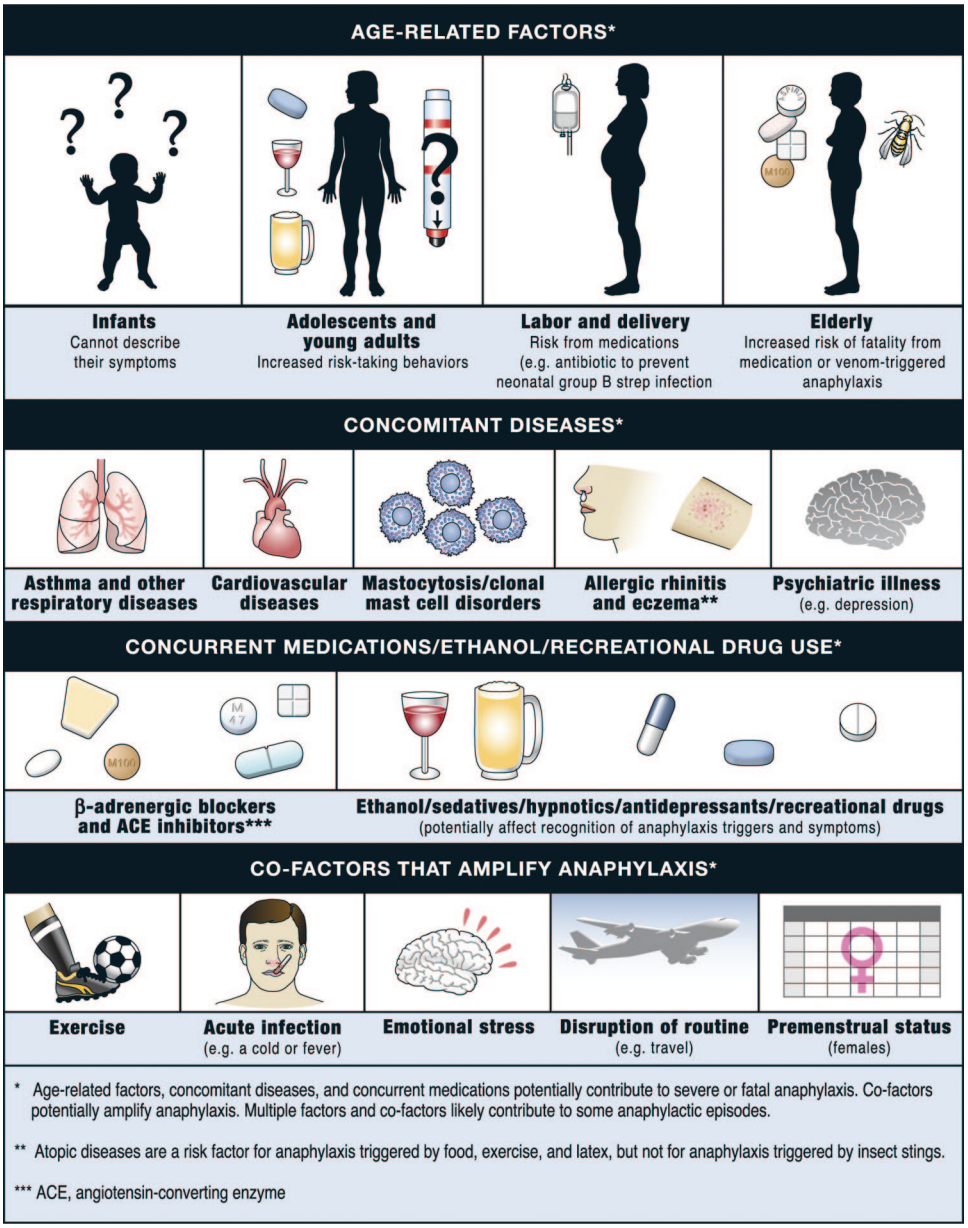

FIGURE 1. Patient factors that contribute to anaphylaxis. Age-related factors, concomitant diseases, and concurrent medications potentially contribute to severe or fatal anaphylaxis. Co-factors potentially amplify anaphylaxis. Multiple factors and co-factors likely contribute to some anaphylactic episodes ([2,8–13,31–47,57]). Atopic diseases are a risk factor for anaphylaxis triggered by food, exercise, and latex, but not for anaphylaxis triggered by insect stings and medications. Beta-blockers: beta-adrenergic blockers; ACE inhibitors: angiotensin-converting enzyme inhibitors.

agents such as the monoclonal antibodies cetuximab, rituximab, infliximab, and rarely, omalizumab.[72,75–77] In addition, anaphylaxis can be triggered by contaminants in medications, for example, oversulfated chondroitin sulfate in heparin,[78] and by herbal formulations.[79]

Diagnostic agents that are relatively commonly triggers of anaphylaxis include radiocontrast media (RCM)[24,80] and medical dyes such as fluorescein. Peri-operative interventions that trigger anaphylaxis include suxamethonium, rocuronium, and other neuromuscular blocking agents; thiopental, propofol, and other hypnotics; opioids, antimicrobials, protamine, chlorhexidine, latex, and colloid plasma expanders such as dextran.[24,81,82] Anaphylaxis is also potentially triggered by allergen skin tests (especially intradermal tests), challenge/provocation tests with food or medication, allergen-specific immunotherapy, and medication desensitization.[33,59,72,73,83,84] Natural rubber latex (NRL) potentially triggers anaphylaxis in healthcare settings where it is found in equipment such as airway masks, endotracheal tubes, blood pressure cuffs, and stethoscope tubing, and supplies such as disposable gloves, catheters, adhesive tape, tourniquets, and vials with NRL closures. NRL can also trigger anaphylaxis in community settings, where it is found in disposable gloves, condoms, infant pacifiers, balloons, toys, sports equipment, and other articles; in some NRL-sensitive patients, cross-reacting foods also trigger anaphylaxis.[24] Importantly, vaccines to prevent infectious disease rarely trigger anaphylaxis.[85]

Occupational allergens such as bee venom in beekeepers and latex in healthcare workers can trigger anaphylaxis.[24,68,69] Uncommonly, in atopic women, seminal

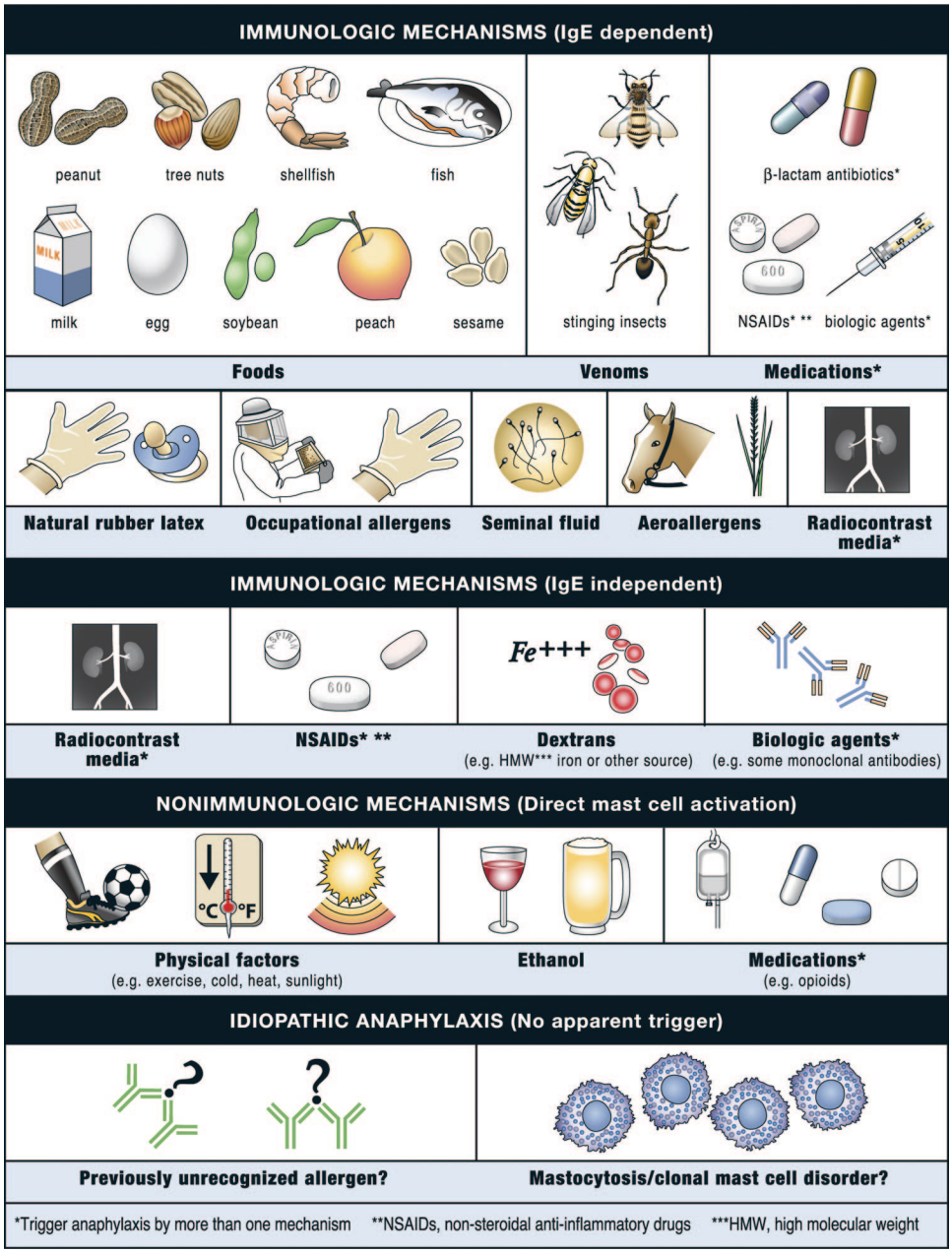

FIGURE 2. Anaphylaxis mechanisms and triggers. Anaphylaxis typically occurs through an IgE-dependent immunologic mechanism, most commonly triggered by foods, stinging insect venoms, or medications. Medications can also trigger anaphylaxis through an IgE-independent immunologic mechanism and through direct mast cell activation. Radiocontrast media can trigger anaphylaxis through both IgE-dependent and IgE-independent mechanisms. Anaphylaxis triggered by seminal fluid or inhalant allergens is rare, and likely involves some systemic absorption of the allergen. In patients with idiopathic anaphylaxis, the possibility of a novel allergen trigger or of underlying mastocytosis or a clonal mast cell disorder should be considered ([2,22–25,31,32,53–87]). NSAID, nonsteroidal anti-inflammatory drug; HMW, high molecular weight.

fluid can be a trigger.[24,32,86] Rarely, airborne allergens such as aerosolized food particles, pollen, or animal dander can trigger anaphylaxis; this likely involves some systemic absorption of the allergen through the airways and/or skin.

Idiopathic anaphylaxis is diagnosed when no trigger can be identified despite a detailed history of the episode, allergen skin tests, measurement of serum IgE levels to obvious and potentially hidden allergen triggers and, if indicated in selected patients, medically supervised, graded challenge/provocation tests.[24,32,87] The diagnosis of idiopathic anaphylaxis provides an opportunity to identify previously unrecognized triggers (for example, anaphylaxis to galactose alpha-1,3 galactose, a carbohydrate contained in red meat),[67] and to elucidate pathophysiologic mechanisms (eg, anaphylaxis triggered through the complement and coagulation pathways by oversulfated chondroitin sulfate contaminants in heparin).[78] The diagnosis of idiopathic anaphylaxis also provides an opportunity to identify patients with mastocytosis and clonal mast cell disorders through clinical history, physical examination, elevated baseline serum tryptase levels, and additional tests as indicated.[42–44]

The Importance of the Clinical Diagnosis

The diagnosis of anaphylaxis is based primarily on a detailed history of the episode, including information about all exposures and events in the hours preceding the onset of symptoms, for example, exercise, ingestion of prescription, nonprescription and recreational drugs, ethanol, acute infection such as a cold, emotional stress, travel or other disruption of

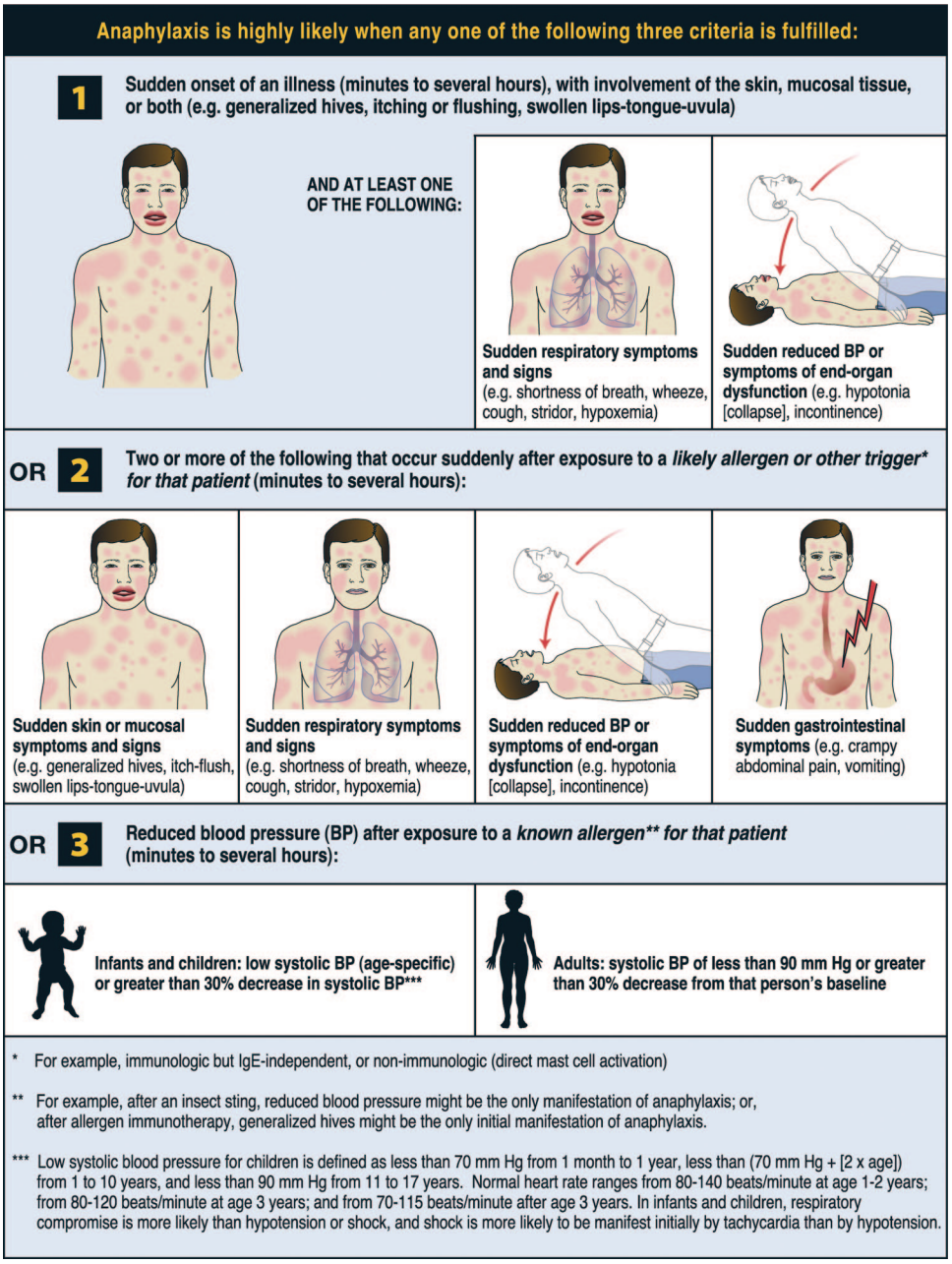

FIGURE 3. Clinical criteria for the diagnosis of anaphylaxis. The clinical criteria pictured are taken from reference 2. Anaphylaxis with involvement of only one body organ system is described in references 2 and 33. Anaphylaxis in infants and young children is described in reference 34.

routine, and premenstrual status in females. The key to diagnosis involves pattern recognition: sudden onset of characteristic symptoms and signs within minutes to hours after exposure to a known or potential trigger, often followed by rapid progression of symptoms and signs over hours.[2,32] Clinical criteria for the diagnosis of anaphylaxis are detailed in Figure 3 and Table 1.[2,31–34]

Target organ involvement is variable. Typically, symptoms occur in 2 or more body systems: skin and mucous membranes, upper and lower respiratory tract, gastrointestinal tract, cardiovascular system, and central nervous system.[2] In certain circumstances, anaphylaxis can be diagnosed when only one body system is involved; for example, after an insect sting, sudden onset of cardiovascular symptoms might be the only manifestations, and after allergen immunotherapy, sudden onset of generalized urticaria might be the only initial manifestation.[2,33]

Characteristic symptoms and signs of anaphylaxis are listed in Table 2.[2,22–25,31,32] Skin signs are present in 80–90% of all patients, and when they are absent, anaphylaxis is harder to recognize. The pattern (onset, number, and course) of symptoms and signs differs from one patient to another, and even in the same patient from one anaphylactic episode to another. At the beginning of an episode, it can be difficult to predict the rate of progression or the ultimate severity. Fatality can occur within minutes.[2,13,22–25,31,32]

TABLE 2. Symptoms and Signs of Anaphylaxis

Skin, subcutaneous tissue, and mucosa[a,b,c]
Flushing, itching, urticaria (hives), angioedema, morbilliform rash, pilor erection
Periorbital itching, erythema and edema, conjunctival erythema, tearing
Itching of lips, tongue, palate, and external auditory canals; and swelling of lips, tongue, and uvula
Itching of genitalia, palms, and soles
Respiratory[a]
Nasal itching, congestion, rhinorrhea, sneezing
Throat itching and tightness, dysphonia, hoarseness, stridor, dry staccato cough
Lower airways: increased respiratory rate, shortness of breath, chest tightness, deep cough, wheezing/bronchospasm, decreased peak expiratory flow
Cyanosis
Respiratory arrest
Gastrointestinal[a]
Abdominal pain, nausea, vomiting (stringy mucus), diarrhea, dysphagia
Cardiovascular system[a]
Chest pain
Tachycardia, bradycardia (less common), other arrhythmias, palpitations
Hypotension, feeling faint, urinary or fecal incontinence, shock
Cardiac arrest
Central nervous system[a]
Aura of impending doom, uneasiness (in infants and children, sudden behavioral change, eg. irritability, cessation of play, clinging to parent); throbbing headache (pre-epinephrine), altered mental status, dizziness, confusion, tunnel vision
Other[a]
Metallic taste in the mouth
Cramps and bleeding due to uterine contractions in females

[a]**Sudden onset** of symptoms and signs is characteristic of anaphylaxis.
[b]The purpose of listing signs and symptoms in this Table is to aid in prompt recognition of the onset of anaphylaxis and to indicate the possibility of rapid progression to multi-organ system involvement, **not to grade severity**.
[c]Skin and mucosal symptoms are reported to occur in 80–90% of patients with anaphylaxis, respiratory tract involvement in up to 70%, gastrointestinal tract involvement in up to 45%, cardiovascular system involvement in up to 45%, and central nervous system involvement in up to 15%.
Symptom patterns vary from one patient to another, and even in the same patient, from one anaphylactic episode to another. Only a few symptoms might be present.
Adapted from references 2, 22–25, 31, 32.

Anaphylaxis can sometimes be difficult to diagnose. Patients with concomitant impaired vision or hearing, neurologic disease, psychiatric illness, such as depression, substance abuse, autism spectrum disorder, attention deficit hyperactivity disorder, or cognitive disorders, might have diminished awareness of anaphylaxis triggers and symptoms.[32] At any age, concurrent use of CNS-active medications such as sedatives, hypnotics, antidepressants, and first-generation sedating H_1-antihistamines can interfere with recognition of anaphylaxis triggers and symptoms and with the ability to describe symptoms. In patients with concomitant medical conditions, for example, asthma, chronic obstructive pulmonary disease, or congestive heart failure, symptoms and signs of these diseases can also cause confusion in the differential diagnosis of anaphylaxis.[32]

Vulnerable Patients

Anaphylaxis in pregnancy places both mother and baby at increased risk of fatality or hypoxic/ischemic encephalopathy. During the first, second, and third trimesters, potential triggers are similar to those in nonpregnant women. During labor and delivery, anaphylaxis is usually triggered by iatrogenic interventions such as oxytocin, or more commonly, an antimicrobial such as a penicillin or a cephalosporin administered to the mother for prophylaxis of group B hemolytic streptococcal infection in the neonate.[36]

In infancy, anaphylaxis can be difficult to recognize. Infants cannot describe their symptoms. Some of the signs of anaphylaxis are also normal daily occurrences in babies; for example, flushing and dysphonia after crying, spitting up after feeding, and incontinence. Healthy infants have a lower blood pressure and a higher resting heart rate than older children and adults do; therefore, age-appropriate criteria should be used for documenting hypotension and tachycardia[34] (Table 1).

Teens are vulnerable to anaphylaxis recurrences in the community because of risk-taking behaviors such as failure to avoid their trigger(s) and failure to carry self-injectable epinephrine.[31]

Middle-aged and elderly patients are at increased risk of severe or fatal anaphylaxis because of known or subclinical cardiovascular diseases and the medications used to treat them.[39–41,46,47] In the healthy human heart, mast cells are present around the coronary arteries and the intramural vessels, between the myocardial fibers, and in the arterial intima.[39] In patients with ischemic heart disease, the number and density of cardiac mast cells is increased in these areas, and in addition, mast cells are present in the atherosclerotic plaques. During anaphylaxis, histamine, leukotrienes, PAF, and other mediators released from cardiac mast cells contribute to vasoconstriction and coronary artery spasm.[39] Anaphylaxis can present as an acute coronary syndrome (ACS) (angina,

myocardial infarction, arrhythmias) before, or in the absence of, epinephrine injection. This potentially occurs in patients with known coronary artery disease, those in whom subclinical coronary artery disease is unmasked, and, due to transient vasospasm, those in whom no cardiovascular abnormalities can be detected after recovery from anaphylaxis.[39,88,89]

Role of Laboratory Tests

Blood samples for measurement of tryptase levels are optimally obtained 15 minutes to 3 hours after symptom onset. Blood samples for measurement of histamine levels are optimally obtained 15–60 minutes after symptom onset (Table 3). These tests are not universally available, not performed on an emergency basis,[3,24,50,51,90] and not specific for anaphylaxis.

Increased serum tryptase levels often support the clinical diagnosis of anaphylaxis from insect stings or injected medications and in patients who are hypotensive; however, levels are often within normal limits in patients with anaphylaxis triggered by food and in those who are normotensive.[90] Serial measurement of tryptase levels during an anaphylactic episode, and measurement of a baseline level after recovery are reported to be more useful than measurement at only one point in time. Normal levels of either tryptase or histamine do not rule out the clinical diagnosis of anaphylaxis[50,51,90] (Table 3). Blood tests for other biomarkers, such as PAF and carboxypeptidase A3 remain experimental.[52,90]

Differential Diagnosis

In anaphylaxis, some of the most common diagnostic dilemmas involve acute asthma, syncope, and anxiety/panic attacks[2,22–25,31,32] (Table 4). A severe asthma episode can cause diagnostic confusion because wheezing, coughing, and shortness of breath can occur in both asthma and anaphylaxis; however, itching, urticaria, angioedema, abdominal pain, and hypotension are unlikely in acute asthma. An anxiety/panic attack can cause diagnostic confusion because a sense of impending doom, breathlessness, flushing, tachycardia, and gastrointestinal symptoms can occur in both anxiety/panic attacks and in anaphylaxis; however, urticaria, angioedema, wheezing, and hypotension are unlikely during an anxiety/panic attack. Syncope (faint) can cause diagnostic confusion because hypotension can occur in both syncope and anaphylaxis; however, syncope is relieved by recumbency and is usually associated with pallor and sweating, and absence of urticaria, flushing, respiratory symptoms and gastrointestinal symptoms.[2,24,32]

Postprandial syndromes, excess endogenous histamine syndromes, flush syndromes, nonorganic diseases, and other diseases should also be considered in the differential diagnosis[2,24,31,32] (Table 4). Important advances in the understanding of some of these diseases have been described.[91,92]

Awareness of age- and sex-related diagnostic dilemmas is helpful in the differential diagnosis of anaphylaxis; for example, amniotic fluid embolism during labor and delivery, choking and aspiration of a nut or other foreign body in infants and young children, and cerebrovascular events, pulmonary embolus, and myocardial infarction that is unrelated to anaphylaxis in middle-aged or older adults.[34–36,39–41]

MANAGEMENT OF ANAPHYLAXIS IN A HEALTHCARE SETTING

Anaphylaxis is a medical emergency. Prompt assessment and management are critically important. In this section of the Guidelines, we discuss a systematic approach to the basic initial management of anaphylaxis, emphasizing the primary role of epinephrine in treatment. We discuss the importance of having an emergency protocol, removing exposure to the trigger if possible, assessing the patient rapidly, simultaneously calling for assistance, injecting epinephrine intramuscularly, and positioning the patient appropriately. We review the initial management of respiratory distress and of hypotension and shock. We describe use of second-line medications such as antihistamines, beta-2 adrenergic ago-

TABLE 3. Role of Laboratory Tests in the Diagnosis of Anaphylaxis

Total tryptase (pro, pro', and mature forms of alpha/beta tryptases)
Obtain blood sample within 15 minutes to 3 hours of symptom onset[a,b]
Consider measuring levels in accurately timed serial blood samples during the anaphylactic episode
Consider comparing levels measured during the episode with a baseline level[c,d]
Histamine
Obtain blood sample within 15 minutes to 1 hour of symptom onset[a]
Special handling of the blood sample is required (use wide-bore needle, keep sample at 4°C and centrifuge it promptly, freeze plasma promptly)
Measure histamine and its metabolite *N*-methylhistamine in a 24-hour urine sample
Other[e]

[a]Tryptase levels can also be elevated acutely in myocardial infarction, trauma, amniotic fluid embolus, sudden infant death syndrome and other diseases; histamine levels can also be elevated in scombroid poisoning (usually affects more than 1 person eating the same fish).

[b]Tryptase levels can be measured in postmortem serum, preferably in blood samples obtained from femoral vessels rather than the heart. The levels need to be correlated with the clinical history because increased levels are also found in patients who die from other conditions such as myocardial infarction unrelated to anaphylaxis, trauma, amniotic fluid embolism, and sudden infant death syndrome. Conversely, levels can be within normal limits in patients with clinically documented anaphylaxis.

[c]Obtained either 24 hours after resolution of the acute episode or on frozen serum, if available; tryptase levels are stable for at least 1 year in sera stored at −20°C.

[d]If tryptase level is >11.4 ng/mL in baseline serum, the diagnosis of mastocytosis or clonal mast cell disorder should be considered; if tryptase level is higher during the acute anaphylactic episode than in baseline serum, the diagnosis of anaphylaxis is confirmed; if tryptase level is within normal limits during a clinically diagnosed acute anaphylactic episode, the normal tryptase level cannot be used to rule out the diagnosis.

[e]Although not universally available, other specific laboratory tests might be needed to rule out carcinoid syndrome, paradoxical response to a pheochromocytoma, and other uncommon entities in the differential diagnosis of anaphylaxis.

Adapted from references 3, 24, 42–44, 50, 51, 90.

TABLE 4. Differential Diagnosis of Anaphylaxis

Common diagnostic dilemmas	Flush syndromes
Acute asthma[a]	Peri-menopause
Syncope (faint)	Carcinoid syndrome
Anxiety/panic attack	Autonomic epilepsy
Acute generalized urticaria[a]	Medullary carcinoma of the thyroid
Aspiration of a foreign body	
Cardiovascular (myocardial infarction[a], pulmonary embolus)	Nonorganic Disease
	Vocal cord dysfunction
Neurologic events (seizure, cerebrovascular event)	Hyperventilation
	Psychosomatic episode
Postprandial syndromes	
Scombroidosis[b]	Shock
Pollen-food allergy syndrome[c]	Hypovolemic
	Cardiogenic
Monosodium glutamate	Distributive[d]
Sulfites	Septic
Food poisoning	
Excess endogenous histamine	Other
Mastocytosis/clonal mast cell disorders[e]	Nonallergic angioedema
	Hereditary angioedema types I, II, & III
Basophilic leukemia	ACE inhibitor-associated angioedema
	Systemic capillary leak syndrome
	Red man syndrome (vancomycin)
	Pheochromocytoma (paradoxical response)

[a]Acute asthma symptoms, acute generalized urticaria, or myocardial infarction symptoms can also occur *during* an anaphylactic episode.

[b]Histamine poisoning from fish, eg. tuna that has been stored at an elevated temperature; usually, more than one person eating the fish is affected.

[c]Pollen-food allergy syndrome (oral allergy syndrome) is elicited by fruits and vegetables containing various plant proteins that cross-react with airborne allergens. Typical symptoms include itching, tingling and angioedema of the lips, tongue, palate, throat, and ears after eating raw, but not cooked, fruits and vegetables.

[d]Distributive shock may be due to anaphylaxis or to spinal cord injury.

[e]In mastocytosis and clonal mast cell disorders, there is an increased risk of anaphylaxis; also, anaphylaxis may be the first manifestation of the disease.

Adapted from references 2, 22–25, 31, 32, 91, 92.

nists and glucocorticoids. We also discuss management of anaphylaxis refractory to basic initial treatment, management of anaphylaxis in vulnerable patients, and duration of monitoring in a healthcare setting.[2,22–25,31,32,93–99]

Epinephrine and many antihistamines and glucocorticoids used in the treatment of anaphylaxis were introduced before the era of randomized controlled trials and before the era of evidence-based medicine, defined as "the explicit and judicious use of current best evidence in making decisions about the care of individual patients."[100] In anaphylaxis, no randomized controlled trials that are free from methodologic problems and meet current standards have been performed with any of these medications.[14–16,20] In the absence of such trials, the best available external evidence with which to answer clinical questions[100] has been used to support the recommendations made.

Systematic Approach to Anaphylaxis Treatment

A systematic approach is critically important. The principles of treatment apply to all patients with anaphylaxis, from all triggers, who present at any time during an acute episode.[2,22–25,31,32,93–99] Basic initial treatment (what all healthcare professionals should be able to provide, even in a low resource environment, is outlined in Fig. 4 and Table 5).[2,3,22–25,32,93–99] Preparation involves having a written emergency protocol, posting it, and rehearsing it regularly. Medications, supplies, and equipment are listed in Table 6.[2,3,21–25] Throughout these Guidelines, a child is defined as a prepubertal patient weighing less than 35–40 kg, rather than by age.

After rapid assessment of the patient, treatment begins with implementation of the protocol. Remove exposure to the trigger, if possible (eg, discontinue an intravenously administered diagnostic or therapeutic agent) and rapidly assess the patient's circulation, airway, breathing, mental status, and skin, and estimate the body weight (mass). Promptly and simultaneously, call for help, inject epinephrine intramuscularly in the mid-anterolateral thigh, and place the patient on the back (or in a position of comfort if there is respiratory distress and/or vomiting), with the lower extremities elevated. When indicated at any point in time, as soon as the need is recognized, administer supplemental oxygen, insert an intravenous catheter and give intravenous fluid resuscitation, and initiate cardiopulmonary resuscitation with continuous chest compressions. At frequent and regular intervals, monitor the patient's blood pressure, cardiac rate and function, respiratory status and oxygenation and obtain electrocardiograms; start continuous noninvasive monitoring if possible[2,22–25,31,32,93–99] (Fig. 4, Tables 5 and 6).

Epinephrine (Adrenaline): Evidence-Base for Use as First-Line Treatment

The World Health Organization (www.who.int) classifies epinephrine (adrenaline) as an essential medication for the treatment of anaphylaxis. Previous WAO publications[3,99,101,102] and anaphylaxis guidelines published in indexed, peer-reviewed journals[21–29] consistently emphasize prompt injection of epinephrine as the first-line medication of choice in anaphylaxis.

Epinephrine is life-saving because of its alpha-1 adrenergic vasoconstrictor effects in most body organ systems (skeletal muscle is an important exception) and its ability to prevent and relieve airway obstruction caused by mucosal edema, and to prevent and relieve hypotension and shock.[97–99] Other relevant properties in anaphylaxis include its beta-1 adrenergic agonist inotropic and chronotropic properties leading to an increase in the force and rate of cardiac contractions, and its beta-2 adrenergic agonist properties such as decreased mediator release, bronchodilation and relief of urticaria, as listed in Table 7.[97–116]

The evidence base for prompt epinephrine injection in the initial treatment of anaphylaxis is stronger than the evidence base for the use of antihistamines and glucocorticoids in anaphylaxis.[14–16,20,97,101–116] It consists of: observational studies performed in anaphylaxis,[103–106] randomized, controlled clinical pharmacology studies in patients at risk for anaphylaxis but not experiencing it at the time of the investigation,[97–99] studies in animal models of anaphylaxis,[97–99,107] in vitro studies,[97,108] and retrospective studies, including epidemiologic studies,[14,97–99,109–116] and fatality studies.[8–10,13] The latter provide particularly compelling evidence for prompt epinephrine injection.[8–10,13] For example, in one study, only

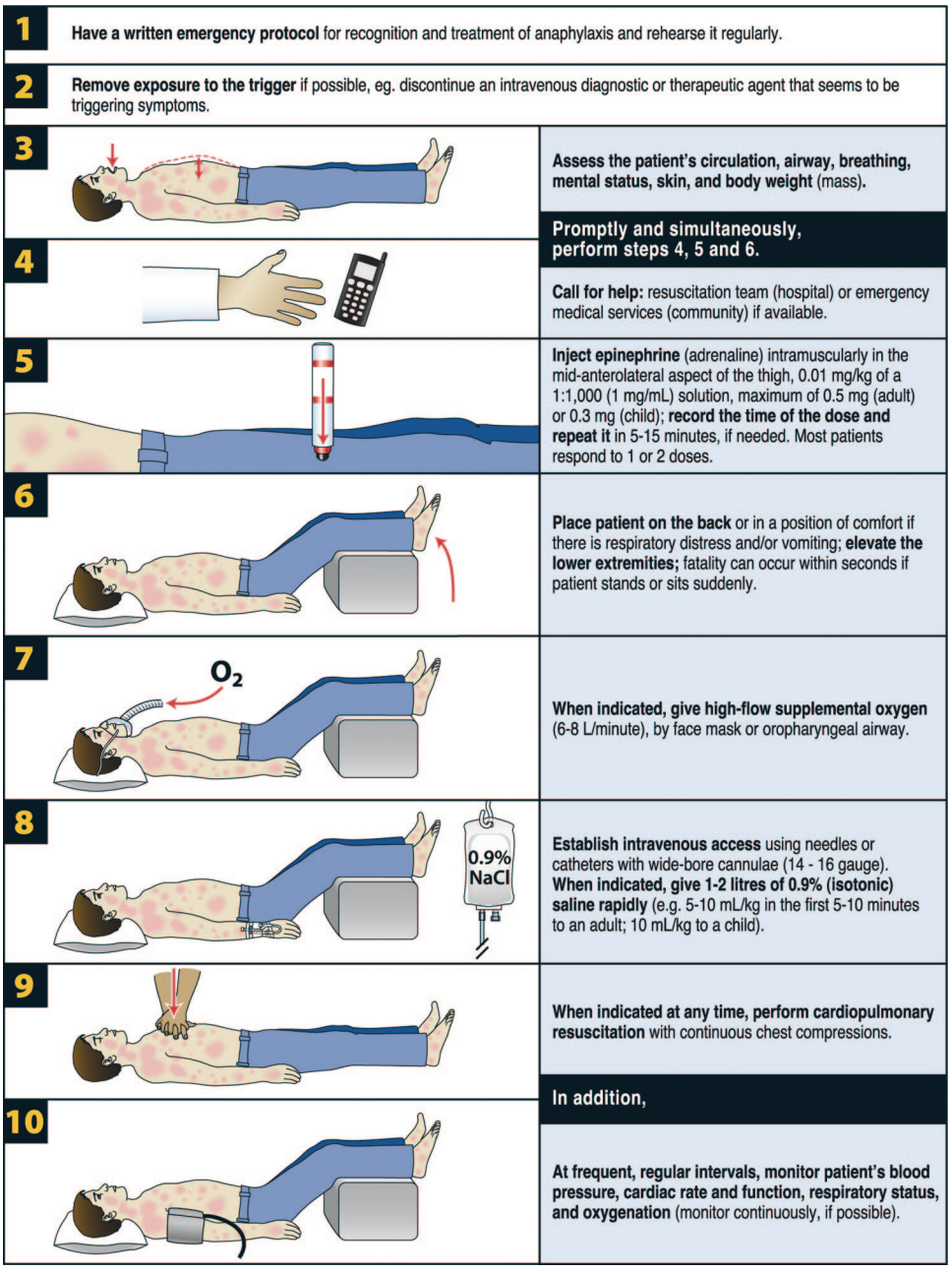

FIGURE 4. Basic management of anaphylaxis. This figure summarizes the basic initial treatment which is relatively inexpensive to implement and should be possible even in a low resource environment. Steps 4, 5 and 6 should be performed promptly and simultaneously as soon as anaphylaxis is diagnosed. Resuscitation guidelines recommend initiating cardiopulmonary resuscitation with chest compressions only (hands-only) before giving rescue breaths. In adults, chest compressions should be performed at a rate of 100–120/minute and a depth of 5–6 cm. In children, the rate should be at least 100 compressions/minute at a depth of 5 cm (4 cm in infants). If precious minutes are lost early in the treatment of an acute anaphylactic episode, subsequent management can become more difficult ([2,22–25,32,93–99]).

14% of 164 people with fatal anaphylaxis had received epinephrine before cardiorespiratory arrest.[13] The median times to cardiorespiratory arrest were 5 minutes after administration of a diagnostic or therapeutic intervention, 15 minutes after an insect sting, and 30 minutes after food ingestion.[13]

Epinephrine Dosing and Route of Administration

Epinephrine should be injected by the intramuscular route in the mid-anterolateral thigh as soon as anaphylaxis is diagnosed or strongly suspected, in a dose of 0.01 mg/kg of a 1:1,000 (1 mg/mL) solution, to a maximum of 0.5 mg in adults **(0.3 mg in children)**.[22–25,96–99] This achieves peak plasma and tissue concentrations rapidly. Depending on the severity of the episode and the response to the initial injection, the dose can be repeated every 5–15 minutes, as needed. Most patients respond to 1 or 2 doses of epinephrine injected intramuscularly promptly; however, more than 2 doses are occasionally required.[105,106,109,110]

Epinephrine is under-used in anaphylaxis treatment.[8–10,13,111,112] Failure to inject it promptly is potentially associated with fatality, encephalopathy because of hypoxia and/or ischemia, and biphasic anaphylaxis in which symptoms recur within 1–72 hours (usually within 8–10 hours) after the initial symptoms have resolved, despite no further exposure to the trigger.[106,107,117–120]

TABLE 5. Basic Management of Anaphylaxis[a]

Preliminary Steps

1) Have a posted, written emergency protocol for recognition and treatment of anaphylaxis and rehearse the protocol regularly[b]

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

3) Assess circulation, airway, breathing, mental status, skin, and body weight (mass)[c]

Promptly and simultaneously[d]

4) Call for help (resuscitation team in hospital or other healthcare setting, or emergency medical services in community setting), if available

5) 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, to a maximum of 0.5 mg (adult) or **0.3 mg (child[e])**; 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 a patient stands or sits suddenly

When indicated at any time during the episode

7) Give high flow supplemental oxygen (6-8 L/min) by face mask or oropharyngeal airway[f]

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

9) When indicated at any time, prepare to initiate cardiopulmonary resuscitation with continuous chest compressions[g].

In addition

10) At frequent and regular intervals, monitor patient's blood pressure, cardiac rate and function, respiratory status and oxygenation and obtain electrocardiograms; start continuous non-invasive monitoring, if possible[h]

[a]These Guidelines are primarily intended to summarize the basic initial management of anaphylaxis for allergy/immunology specialists; however, they will likely also be of interest to a broader group of healthcare professionals.

[b]The written emergency protocol for anaphylaxis assessment and treatment should include drug dosages for adults and children, and telephone numbers and contact details for resuscitation team, emergency medical services, emergency department, etc. The protocol should also include flow charts (examples given in reference 24) for recording the times of clinical observations and events, vital signs measurements, medications/doses administered, details of oxygen and intravenous fluid treatment, and times at which observations were made and interventions took place.

[c]Body weight should be measured or estimated so that medication doses and intravenous fluid resuscitation can be calculated accurately.

[d]Steps 4, 5, and 6 should be performed promptly and simultaneously as soon as anaphylaxis is diagnosed or strongly suspected. If precious minutes are lost early in the treatment of an acute anaphylactic episode, subsequent management can become more difficult.

[e]Child is defined as a pre-pubertal patient weighing less than 35–40 kg; not defined by age.

[f]Supplemental oxygen should be given to all patients with respiratory distress and those receiving repeated doses of epinephrine. It should also be considered for any patients with anaphylaxis who have concomitant asthma, other chronic respiratory disease, or cardiovascular disease.

[g]Initiate cardiopulmonary resuscitation with chest compressions only (hands-only) before giving rescue breaths. In adults, chest compressions should be performed at a rate of 100–120/minute, and a depth of 5–6 cm. In children, the rate should be at least 100 compressions/minute at a depth of 5 cm (4 cm in infants). The compression/ventilation ratio performed by one rescuer should be 30:2.

[h]Duration of monitoring should be individualized; for example, patients with moderate respiratory or cardiovascular compromise should be monitored in a medically supervised setting for at least 4 hours and if indicated, 8–10 hours or longer, and patients with severe or protracted anaphylaxis might require monitoring and interventions for days.

Adapted from references 2, 22–25, 32, 93–99.

Epinephrine in a dose of 0.01 mg/kg of a 1:1,000 (1 mg/mL) solution injected promptly by the intramuscular route is effective and safe in the **initial** treatment of anaphylaxis. In other anaphylaxis scenarios, this low first-aid dose is unlikely to be effective. For example, if shock is imminent or has already developed, epinephrine needs to be given by slow intravenous infusion, ideally with the dose titrated according to noninvasive continuous monitoring of cardiac rate and function. If cardiac arrest is imminent or has already occurred, an intravenous bolus dose of epinephrine is indicated; however, in other anaphylaxis scenarios, this route of administration should be avoided, for the reasons listed below.[116]

Adverse Effects of Epinephrine

Transient pharmacologic effects after a **recommended** dose of epinephrine by any route of administration include pallor, tremor, anxiety, palpitations, dizziness, and headache.[97–99,105] These symptoms indicate that a therapeutic dose has been given.[97–99,104] Serious adverse effects such as ventricular arrhythmias, hypertensive crisis, and pulmonary edema potentially occur after an **overdose** of epinephrine by any route of administration. Typically, they are reported after intravenous epinephrine dosing[13]; for example, overly rapid intravenous infusion, bolus administration, and dosing error because of intravenous infusion or intravenous injection of the 1:1,000 (1 mg/mL) solution appropriate for intramuscular injection, instead of the dilute solutions appropriate for intravenous administration (1:10,000 [0.1 mg/mL] or 1:100,000 [0.01 mg/mL]). Physician confusion about the correct epinephrine dose and route of administration for the **initial** treatment of anaphylaxis versus the correct epinephrine doses and routes of infusion for shock and cardiac arrest can lead to anaphylaxis fatality from epinephrine overdose.[116]

Epinephrine and the Heart

As noted on pages 19–20, the heart is a potential target organ in anaphylaxis.[39] ACS can occur in anaphylaxis in the absence of epinephrine injection[40,88,89] in patients with known

TABLE 6. Medications, Supplies, and Equipment for Anaphylaxis Treatment

- Medications[a,b]
  - First line (priority medication)
    - Epinephrine (adrenaline) 1:1,000 (1 mg/mL)for intramuscular injection 0.01 mg/kg, to a maximum of 0.5 mg (adult), **0.3 mg (child[c])**
  - Second line medications
    - H_1-antihistamine for intravenous infusion eg. chlorpheniramine 10 mg (adult), **2.5-5 mg (child)[c]** or diphenhydramine 25-50 mg (adult) **(1 mg/kg, maximum 50 mg [child[c]])**
    - ß$_2$-adrenergic agonist, eg. salbutamol (albuterol) solution, 2.5 mg/3 mL or 5 mg/3 mL (adult), **(2.5 mg/3 mL [child[c]])** given by nebulizer and face mask
    - glucocorticoid for intravenous infusion, eg. hydrocortisone 200 mg (adult), maximum **100 mg (child[c])**; or methylprednisolone 50-100 mg (adult); **1 mg/kg, maximum 50 mg (child[c])**
    - H_2-antihistamine for intravenous infusion,[d] for example, ranitidine 50 mg (adult) or **1 mg/kg, maximum 50 mg (child[c])**
- Supplies
  - Management of the airway
    - Supplemental oxygen (oxygen tank,[b] valve with flow-meter, and extension tubing)
    - Ambu bag/valve/mask, self-inflating with reservoir (volume 700–1,000 mL [adult]; **100–700 mL [child[c]])**
    - Disposable face masks (infant, toddler, child, adult)
    - Oropharyngeal airway: 6 cm, 7 cm, 8 cm, 9 cm, 10 cm
    - Pocket masks, nasal cannulae,[e] laryngeal mask airways[e]
    - Supplies for suctioning
    - Supplies for intubation
  - Management of hypotension and shock
    - Supplies for giving large volumes of intravenous fluids rapidly, eg. 0.9% (isotonic) saline, 1 L bags
    - Alcohol swabs
    - Tourniquet
    - Indwelling intravenous catheters (gauge 14, 16, 18, 20, 22)
    - Intravenous butterfly needles (gauge 19, 21, 23, 25)
    - Syringes with needles (1 mL, 10 mL, 20 mL)
    - Macro-drip administration sets
    - Extension tubing
    - T-connectors
    - 3-way stopcock
    - Arm boards (4 sizes)
  - Other supplies
    - Written emergency protocol for anaphylaxis treatment[f]
    - Flow chart for recording times and events
    - Synthetic tape
    - Gloves, preferably latex-free
- Equipment
  - Essential
    - Stethoscope
    - Sphygmomanometer, blood pressure cuffs (infant, child, adult, obese adult)
    - Watch or clock
    - Cardiac arrest backboard or any flat, hard surface for use in cardiopulmonary resuscitation
    - Equipment for suctioning
    - Equipment for intubation
    - Equipment for giving large volumes of intravenous fluids rapidly
  - Desirable
    - Electrocardiogram machine and supplies
    - Equipment for continuous noninvasive blood pressure monitoring[g]
    - Equipment for continuous noninvasive cardiac monitoring[g]
    - Pulse oximeter
    - Defibrillator

[a]Second line medication, for example, H_1-antihistamine or glucocorticoid should be given by slow intravenous infusion over 10–15 minutes. Do not delay the administration of epinephrine, supplemental oxygen, or IV fluid resuscitation by taking time to draw up and administer a second-line medication.

[b]The expiry dates of all medications should be reviewed regularly, for example, after use and at monthly intervals, followed by restocking as needed. Oxygen tanks should also be checked regularly.

[c]Child is defined as a prepubertal patient weighing less than 35–40 kg (not defined by age).

[d]H_2-antihistamines are sometimes used for anaphylaxis treatment in the US and Canada.

[e]Nasal cannulae deliver oxygen at a flow rate of 2–6 L/m; laryngeal mask airways do not protect the airway against aspiration and present a hazard in patients who are vomiting or at risk of vomiting.

[f]A written emergency protocol for anaphylaxis treatment should be posted in a prominent place and rehearsed regularly. It should include drug dosages for adults and children, as well as telephone numbers and contact details for resuscitation team, emergency medical services, emergency department, etc.

[g]Needed if administering intravenous epinephrine or another intravenous vasopressor.

Adapted from references 3, 21–25.

TABLE 7. Epinephrine (Adrenaline): First-Line Medication for Anaphylaxis Treatment

Strength of Recommendations[a]	B-C (As Defined in Footnote)[a]
Pharmacologic effects when given by injection[b]	At alpha-1 adrenergic receptor
	Increases vasoconstriction and increases vascular resistance (in most body organ systems)[c]
	Increases blood pressure
	Decreases mucosal edema in the airways
	At beta-1 adrenergic receptor
	Increases cardiac contraction force
	Increases heart rate
	At beta-2 adrenergic receptor
	Decreases mediator release
	Increases bronchodilation
Clinical relevance	Increases blood pressure and prevents and relieves hypotension and shock
	Decreases upper airway obstruction, eg. in larynx
	Decreases urticaria and angioedema
	Decreases wheezing
Potential adverse effects after the usual epinephrine dose of 0.01 mg/kg of a 1:1,000 (1 mg/mL) solution intramuscularly[d] (to a maximum of 0.5 mg [adult] or **0.3 mg** [**child**])	Pallor, tremor, anxiety, palpitations, dizziness, headache; these symptoms indicate that a pharmacologic dose has been injected
Potential adverse effects after epinephrine overdose (eg. overly rapid intravenous infusion, intravenous bolus dose, or dosing error, eg. intravenous administration of an undiluted 1:1,000 (1 mg/mL) solution[e])	Ventricular arrhythmias, hypertension, pulmonary edema; note that the heart itself is a potential **target organ** in anaphylaxis; therefore, acute coronary syndromes (angina, myocardial infarction, arrhythmias) can also occur in untreated anaphylaxis in patients with known coronary artery disease, in those in whom subclinical coronary artery disease is unmasked, and even in patients (including children) without coronary artery disease in whom the symptoms are due to transient vasospasm
Reasons why the intramuscular route is preferred over the subcutaneous route for initial treatment of anaphylaxis	Epinephrine has a vasodilator effect in skeletal muscle[c]; skeletal muscle is well-vascularized; after intramuscular injection into the vastus lateralis (mid-anterolateral thigh), absorption is rapid and epinephrine reaches the central circulation rapidly; rapid absorption is important in anaphylaxis, in which the median times to cardiorespiratory arrest are reported as 5 minutes (iatrogenic, eg. injected medication), 15 minutes (stinging insect venom), 30 minutes (food)
Reasons for apparent lack of response to epinephrine	Error in diagnosis, patient suddenly stands or sits (or is placed in the upright position) after epinephrine injection; rapid anaphylaxis progression; patient taking a beta-adrenergic blocker or other medication that interferes with epinephrine effect; epinephrine injected too late; dose too low on mg/kg basis; dose too low because epinephrine is past expiry date[f]; not enough injection force used; route not optimal; injection site not optimal; other

[a]Levels of evidence are defined as: A: directly based on meta-analysis of randomized controlled trials or evidence from at least one randomized controlled trial; B: directly based on at least one controlled study without randomization or one other type of quasi-experimental study, or extrapolated from such studies; C: directly based on evidence from non-experimental descriptive studies such as comparative studies, or extrapolated from randomized controlled trials or quasi-experimental studies.

[b]Intramuscular epinephrine injection is preferred in the initial treatment of anaphylaxis for the reasons listed above. Subcutaneous epinephrine injection causes local vasoconstriction that potentially leads to delayed absorption. If epinephrine is given by metered-dose inhaler, it is difficult to inhale the 20–30 puffs needed to achieve high plasma/tissue epinephrine concentrations and systemic effects. Epinephrine is occasionally administered through an endotracheal tube, or by face mask and compressor, or topically for mucosal edema and obstruction in the oropharynx and larynx. Epinephrine given orally is ineffective because of rapid metabolism in the gastrointestinal tract.

[c]Epinephrine has a **vasodilator** effect in skeletal muscle. It also enhances blood flow in coronary arteries due to increased myocardial contractility and increased duration of diastole. These actions are well-recognized effects of **endogenous** epinephrine in the "fight or flight" response.

[d]The maximum initial intramuscular dose of epinephrine in anaphylaxis (0.3–0.5 mg) of a 1:1,000 (1 mg/mL) solution is lower than the 1 mg dose recommended for initial use in cardiopulmonary resuscitation. The intramuscular dose is unlikely to be effective if anaphylaxis has progressed to shock or cardiac arrest.

[e]Ideally, epinephrine should be administered intravenously only by physicians who are trained, experienced and equipped to give vasopressors through infusion pump and titrate the dose frequently, based on continuous monitoring of blood pressure and cardiac rate and function.

[f]Epinephrine in solution potentially degrades rapidly if exposed to heat and light.

Adapted from references 2, 3, 13, 14, 22, 23, 30–32, 39–41, 88, 89, 97–99, 104, 116.

coronary artery disease, and those in whom subclinical coronary artery disease is unmasked by the anaphylactic episode. ACS can also occur in those of any age, including children, who have no cardiovascular abnormalities as determined by electrocardiogram and echocardiography after complete recovery from the anaphylactic episode in which the ACS developed.[88,89] Although caution is necessary and dosing errors need to be avoided, epinephrine is not contraindicated in the treatment of anaphylaxis in patients with known or suspected cardiovascular disease, or in middle-aged or elderly patients without any history of coronary artery disease who are at increased risk of ACS only because of their age.[40,97] Through its beta-1 adrenergic effects, epinephrine actually increases coronary artery blood flow because of an increase in myocardial contractility and in the duration of diastole relative to systole.[40] Concerns about the potential adverse cardiac effects of epinephrine therefore need to

be weighed against concerns about the cardiac 8 of untreated anaphylaxis.[39–41,46,47,97]

Positioning the Patient

Patients with anaphylaxis should not suddenly sit, stand, or be placed in the upright position. Instead, they should be placed on the back with their lower extremities elevated or, if they are experiencing respiratory distress or vomiting, they should be placed in a position of comfort with their lower extremities elevated. This accomplishes 2 therapeutic goals: 1) preservation of fluid in the circulation (the central vascular compartment), an important step in managing distributive shock; and 2) prevention of the empty vena cava/empty ventricle syndrome, which can occur within seconds when patients with anaphylaxis suddenly assume or are placed in an upright position. Patients with this syndrome are at high risk for sudden death. They are unlikely to respond to epinephrine regardless of route of administration, because it does not reach the heart and therefore cannot be circulated throughout the body.[93]

Management of Respiratory Distress

Supplemental oxygen should be administered by face mask or by oropharyngeal airway at a flow rate of 6–8 L/min to all patients with respiratory distress and those receiving repeated doses of epinephrine[2,22–25,32,96] (Table 5). It should also be considered for any patient with anaphylaxis who has concomitant asthma, other chronic respiratory disease, or cardiovascular disease.[96] Continuous monitoring of oxygenation by pulse oximetry is desirable, if possible.

Management of Hypotension and Shock

During anaphylaxis, large volumes of fluids potentially leave the patient's circulation and enter the interstitial tissue; therefore, rapid intravenous infusion of 0.9% saline (isotonic saline or normal saline) should be commenced as soon as the need for it is recognized (Table 5). The rate of administration should be titrated according to the blood pressure, cardiac rate and function, and urine output. All patients receiving such treatment should be monitored for volume overload.[2,22–25,32,96]

Second-Line Medications

Anaphylaxis guidelines published to date in indexed, peer-reviewed journals differ in their recommendations for administration of second-line medications such as antihistamines, beta-2 adrenergic agonists, and glucocorticoids. The evidence base for use of these medications in the initial management of anaphylaxis, including doses and dose regimens, is extrapolated mainly from their use in treatment of other diseases such as urticaria (antihistamines) or acute asthma (beta-2 adrenergic agonists and glucocorticoids). Concerns have been raised that administering one or more second-line medications potentially delays prompt injection of epinephrine, the first-line treatment. Additional information about the second-line medications is provided in the after paragraphs and in Table 5, 6, and 8.[2,3,15,16,21–25,32,121–127]

H_1-Antihistamines

In anaphylaxis, H_1-antihistamines relieve itching, flushing, urticaria, angioedema, and nasal and eye symptoms[111]; however, they should not be substituted for epinephrine because they are not life-saving; that is, they do not prevent or relieve upper airway obstruction, hypotension, or shock[2,15,22,23,32,96,121] (Table 8). Some guidelines do not recommend H_1-antihistamine treatment in anaphylaxis,[23] citing lack of supporting evidence from randomized controlled trials that meet current standards. Others recommend various H_1-antihistamines in various intravenous and oral dosing regimens.[21,22,24,25] In a Cochrane systematic review, no high quality evidence from randomized, controlled trials was found to support the use of H_1-antihistamines in treatment of anaphylaxis.[15] There are concerns about their slow onset of action relative to epinephrine, and about potential harmful central nervous system effects, for example, somnolence and impairment of cognitive function caused by first-generation H_1-antihistamines given in usual doses.[15,121–124]

Beta-2 Adrenergic Agonists

Extrapolating from their use in acute asthma, selective beta-2 adrenergic agonists such as salbutamol (albuterol) are sometimes given in anaphylaxis as additional treatment for wheezing, coughing, and shortness of breath not relieved by epinephrine. Although this is helpful for lower respiratory tract symptoms, these medications should not be substituted for epinephrine because they have minimal alpha-1 adrenergic agonist vasoconstrictor effects and do not prevent or relieve laryngeal edema and upper airway obstruction, hypotension, or shock[2,22,23,25,32] (Table 8).

Glucocorticoids

Glucocorticoids switch off transcription of a multitude of activated genes that encode proinflammatory proteins. Extrapolating from their use in acute asthma, the onset of action of systemic glucocorticoids takes several hours.[125,126] Although they potentially relieve protracted anaphylaxis symptoms and prevent biphasic anaphylaxis,[2,16,22,24,25,32,111] these effects have never been proven (Table 8). A Cochrane systematic review failed to identify any evidence from randomized, controlled trials to confirm the effectiveness of glucocorticoids in the treatment of anaphylaxis, and raised concerns that they are often inappropriately used as first-line medications in place of epinephrine.[16]

H_2-Antihistamines

An H_2-antihistamine, administered concurrently with an H_1-antihistamine, potentially contributes to decrease in flushing, headache, and other symptoms[121]; however, H_2-antihistamines are recommended in only a few anaphylaxis guidelines.[24,58] Rapid intravenous administration of cimetidine has been reported to increase hypotension.[2,24,32] Anaphylaxis to ranitidine has been reported.[12,127] Although H_2-antihistamines have been studied in anaphylaxis,[122,123] no evidence from randomized placebo-controlled trials that are free from methodological problems supports their use in treatment of this disease.

TABLE 8. Second-Line Medications for Anaphylaxis Treatment

Medication	H_1-Antihistamines[a] (eg. Intravenous Chlorpheniramine or Diphenhydramine; Oral Cetirizine)	Beta-2 Adrenergic Agonists[a] (eg. Salbutamol [Albuterol] by Inhalation)	Glucocorticoids[a] (eg. Intravenous Hydrocortisone or Methylprednisolone; Oral Prednisone or Prednisolone)
Strength of recommendation for use in anaphylaxis[b]	C	C	C
Pharmacologic effects	At H_1-receptor, inverse agonist effect; stabilize receptors in inactive conformation; decrease skin and mucosal symptoms	At beta-2 receptor, increase bronchodilation	Switch off transcription of activated genes that encode pro-inflammatory proteins; decrease late phase allergic response
Clinical relevance	Decrease itch, flush, urticaria, sneezing, and rhinorrhea, but are not life-saving because they do not prevent or relieve obstruction to airflow or hypotension/shock	Decrease wheeze, cough and shortness of breath but are not life-saving because they do not prevent or relieve upper airway obstruction or hypotension/shock	Onset of action takes several hours; therefore, are not life-saving in initial hours of an anaphylactic episode; used to prevent and relieve protracted or biphasic anaphylaxis; however, these effects have not been proven
Potential adverse effects (usual dose)	First-generation drugs cause drowsiness, somnolence, and impaired cognitive function[c]	Tremor, tachycardia, dizziness, jitteriness	Unlikely during a short course
Potential adverse effects (overdose)	Extreme drowsiness, confusion, coma, respiratory depression, and paradoxical central nervous system stimulation, eg. seizures in infants and children	Headache, hypokalemia, vasodilation	Unlikely
Comment	From 0 to 14 different H_1-antihistamines[c] and different dose regimens are listed as adjunctive medications in anaphylaxis guidelines; role not proven	Use in anaphylaxis is extrapolated from use in acute asthma; if given as adjunctive treatment for bronchospasm not relieved by epinephrine, should optimally be delivered by face mask and nebulization	From 0 to 3 different glucocorticoids[d] and different dose regimens[d] are listed as adjunctive medications in anaphylaxis guidelines; role not proven

[a]H_1-antihistamines, beta-2 adrenergic agonists, and glucocorticoids are considered to be second line (adjunctive or ancillary) medications relative to epinephrine, the first-line medication. There are no randomized placebo-controlled trials of any of these medications in the treatment of acute anaphylactic episodes.

[b]Levels of evidence are defined as: A: directly based on meta-analysis of randomized controlled trials or evidence from at least one randomized controlled trial; B: directly based on at least one controlled study without randomization or one other type of quasi-experimental study, or extrapolated from such studies; C: directly based on evidence from non-experimental descriptive studies such as comparative studies, or extrapolated from randomized controlled trials or quasi-experimental studies.

[c]H_1-antihistamine use and dosing in anaphylaxis are extrapolated from urticaria treatment. The route of administration depends on the severity of the episode. Only first-generation H_1-antihistamines are available for intravenous use. They potentially increase vasodilation and hypotension if given rapidly. If an oral H_1-antihistamine is given, a low sedating medication such as cetirizine, which is available generically and absorbed rapidly, is preferable to a sedating H_1-antihistamine such as chlorpheniramine or diphenhydramine.

[d]Glucocorticoid use and dosing in anaphylaxis are extrapolated from acute asthma treatment. The route of administration depends on the severity of the episode.

Adapted from references 2, 3, 15, 16, 21–25, 30–32, 121–126.

Treatment of Refractory Anaphylaxis

A minority of patients do not respond to timely, basic initial anaphylaxis treatment with epinephrine by intramuscular injection(s), positioning on the back with lower extremities elevated, supplemental oxygen, intravenous fluid resuscitation, and second-line medications. If possible, such patients should be transferred promptly to the care of a specialist team in emergency medicine, critical care medicine, or anesthesiology.[2,22–25,32,96] These physicians, nurses, and technicians are typically trained, experienced, and equipped to provide skilled management of the airway and mechanical ventilation, and to provide optimal shock management by safely administering vasopressors through an infusion pump with frequent dose titration based on continuous noninvasive monitoring of cardiovascular and respiratory outcomes[128–131] (Table 6).

Physicians working in areas where such support is not readily available should, if possible, receive extra training in the management of anaphylaxis refractory to the initial intramuscular injection of epinephrine, supplemental oxygen, and intravenous fluid resuscitation. Ideally, they should also have up-to-date cardiopulmonary resuscitation skills, including experience with initiating cardiopulmonary resuscitation with chest compressions before giving rescue breaths.[94,95]

Intubation

When intubation is indicated in a patient with anaphylaxis, it should be performed by the most experienced healthcare professional available, because it can be difficult to insert an endotracheal tube if the patient's tongue and pharyngeal mucosa are swollen, and if angioedema and copious mucus obscure the larynx and other anatomic landmarks in the upper airway. The patient should be pre-oxygenated for 3–4 minutes before intubation. Supplies and equipment for optimal management of the airway are outlined in Table 6.[24,96] When mechanical ventilation

is not available, prolonged attempts at ventilation using a self-inflating bag with reservoir, mask, and supplemental oxygen for several hours are often successful in anaphylaxis treatment.[96]

Intravenous Vasopressors

Patients experiencing hypotension or shock refractory to basic initial treatment, including intravenous fluid resuscitation, require intravenous epinephrine and, sometimes, an additional intravenous vasopressor or other medication. No clear superiority of dopamine, dobutamine, norepinephrine, phenylephrine, or vasopressin (either added to epinephrine alone, or compared with one another), has been demonstrated in clinical trials. Although recommendations are given for initial doses, there are no established dosing regimens, as such, for any of these medications, because the dose is titrated according to the clinical response.[128–130]

Vasopressors and the supplies, equipment and skills necessary for the optimal administration of these medications and for monitoring of patients receiving them are not universally available.[3] Even under optimal circumstances, the mortality rate in patients receiving these medications is high. Potentially fatal dose errors leading to ventricular arrhythmias, hypertensive crisis, and pulmonary edema can occur when an intravenous vasopressor is not given through an infusion pump and/or when blood pressure, cardiac rate and function, and oxygenation are not continuously monitored to guide dose titration.[116,128–130]

Glucagon, a polpypeptide with noncatecholamine-dependent inotropic and chronotropic cardiac effects, is sometimes needed in patients taking a beta-adrenergic blocker who have hypotension and bradycardia and who do not respond optimally to epinephrine.[24,131] Anticholinergic agents are sometimes needed in beta-blocked patients, for example, atropine in those with persistent bradycardia or ipratropium in those with epinephrine-resistant bronchospasm.[2,22–24,32,96]

Vulnerable Patients

Medical management of anaphylaxis during pregnancy is similar to management in the nonpregnant patient. Epinephrine given promptly by intramuscular injection is the first-line medication of choice; there is little evidence to support the use of ephedrine, a less potent bronchodilator and vasoconstrictor. Supplemental oxygen and appropriate management of hypotension are critically important. The pregnant patient should be placed semi-recumbent on her left side with the lower extremities elevated, to prevent positional hypotension resulting from compression of the inferior vena cava by the gravid uterus. In addition to frequent or continuous monitoring of maternal oxygenation, blood pressure, and cardiac rate and function, regular fetal heart monitoring (continuous electronic monitoring, if possible) is recommended for women with anaphylaxis who are more than 24 weeks pregnant. Fetal distress should be relieved by correcting maternal hypoxia and/or hypotension with appropriate medical management; however, if the distress persists, emergency cesarean section should be considered.[36]

Management of anaphylaxis in infants is similar to management in older patients. Extreme care should be taken in calculating and drawing up the epinephrine intramuscular dose, which is 0.01 mg/kg of a 1:1,000 (1 mg/mL) solution; for example, the correct dose for a 5 kg infant is 0.05 mg. Infants cannot describe symptoms of epinephrine overdose; signs include hypertension that is based on different (lower) normal values for blood pressure than in children and adults, and pulmonary edema that, like anaphylaxis itself, can be manifest by cough and respiratory distress.[34]

Management of anaphylaxis in the elderly can be complicated by concomitant cardiovascular disease and limited cardiac reserve, and by concurrent medications such as beta-adrenergic blockers. As noted on pages 23, 25, and 26, there is no absolute contraindication to treatment with epinephrine in such patients, although the benefits and risks need to be carefully weighed.[24,40,41,98]

Duration of Monitoring in the Healthcare Setting

Protracted uniphasic anaphylaxis is uncommon, but can last for days. Biphasic anaphylaxis, as defined on page 22 occurs in up to 23% of adults and up to 11% of children with anaphylaxis.[105,106,118–120] After apparent resolution of symptoms, duration of monitoring in a medically supervised setting should be individualized. For example, patients with moderate respiratory or cardiovascular compromise should be monitored for at least 4 hours, and if indicated, for 8–10 hours or longer, and patients with severe or protracted anaphylaxis might require monitoring and interventions for days. In reality, local conditions including availability of trained and experienced staff and Emergency Department beds or hospital beds often determine the duration of monitoring that is possible.[2,3,96,99]

MANAGEMENT OF ANAPHYLAXIS AT TIME OF DISCHARGE FROM A HEALTHCARE SETTING

Treatment of anaphylaxis does not end with resolution of the acute episode in a healthcare setting. In this section of the Guidelines, we discuss the long-term management of patients discharged after anaphylaxis treatment, who should be prepared and equipped to treat symptom recurrence regardless of whether this occurs during the same episode or in a future episode. In addition, they should be advised that, if possible, their specific anaphylaxis trigger(s) need to be confirmed, because the key to long-term prevention of recurrence is trigger avoidance and, if relevant, immunomodulation, including allergen immunotherapy.

Preparation for Self-Treatment of Anaphylaxis Recurrence in the Community

Preparation for self-treatment of anaphylaxis recurrences in the community is outlined in Figure 5 and Table 9.[2,22–25,32,59,68,69,72,73,87,96,97,99,132–139] Patients should be discharged with epinephrine or a prescription for epinephrine, preferably in the form of one or more epinephrine autoinjectors. They should be taught why, when, and how to inject epinephrine and equipped with a personalized written anaphylaxis emergency action plan that helps them to recog-

FIGURE 5. Discharge management and prevention of future anaphylaxis recurrences in the community. Panel 1 describes management at the time of discharge after treatment of an acute anaphylactic episode in a healthcare setting. Panel 2: Anaphylaxis triggers suggested by the history of the acute episode should be confirmed by measurement of allergen-specific IgE levels (sometimes performed before discharge) and by allergen skin tests (generally performed 3–4 weeks after the acute anaphylactic episode); however, for most allergens, this time interval has not been definitively established in prospective studies. Patients with a convincing history of anaphylaxis and negative tests should therefore be retested weeks or months later. Panel 3 summarizes long-term risk reduction through avoidance of known confirmed triggers and where relevant, immunomodulation, for example, medication desensitization according to published protocols, or immunotherapy with appropriate standardized venom to prevent anaphylaxis recurrences from insect (Hymenoptera) stings ([2,22–25,32,59,68,69,72,73,76,77,87,96,97,99,132–139]).

nize anaphylaxis symptoms, and instructs them to inject epinephrine promptly, then seek medical assistance.[132–134]

If epinephrine auto-injectors are not available or affordable, a substitute epinephrine formulation should be recommended, such as a prefilled 1 mL syringe containing the patient's correct epinephrine dose, or an ampule of epinephrine, a 1 mL syringe, and written instructions about drawing up the correct dose.[97,108] These alternative, but not preferred, approaches have major limitations, as described in Table 7. An epinephrine metered-dose inhaler should not be substituted for injectable epinephrine.[97,101,102]

Currently available epinephrine auto-injectors also have some limitations. These include the lack of an optimal range of doses; for example, a 0.1 mg dose for use in infants and young children weighing less than 15 kg, uncertainties about appropriate needle length required for intramuscular dosing in patients who are overweight or obese, intrinsic safety hazards, and limited shelf-life of only 12–18 months.[97]

Anaphylaxis education should ideally begin before patients are discharged from the emergency department or other healthcare facility where their anaphylaxis was treated. Patients should be advised that they have experienced a potentially life-threatening medical emergency ("killer allergy"), and that if their symptoms recur within the next 72 hours, they should inject epinephrine and call emergency medical services or be taken to the nearest emergency facility by family or caregivers.[132,133] They should also be advised that they are at increased risk for future episodes of anaphylaxis, and that they need follow-up, preferably assessment or reassessment by an allergy/immunology specialist. Medical identification (for example, bracelet or wallet card) stating their diagnosis of anaphylaxis, relevant concomitant diseases, and concurrent medications should be recommended.

Anaphylaxis education should be personalized according to the needs of the individual patient, taking into consideration their age, concomitant diseases, concurrent medications, relevant anaphylaxis trigger(s), and likelihood of encountering such trigger(s) in the community.[132,133]

Confirmation of Anaphylaxis Trigger(s)

Anaphylaxis trigger(s) should be identified by obtaining a detailed history of the acute episode.[2,24,31,32] Sensitization to the trigger(s) suggested by the history should be confirmed by using allergen skin tests and/or measurement of allergen-specific IgE levels in serum[59,69,135–138] (Fig. 5, Table 9). The optimal time for testing is generally stated to be 3–4

TABLE 9. Recommendations at Time of Discharge From the Healthcare Setting

Medication
Epinephrine/adrenaline auto-injector[a]
Epinephrine from an ampule/syringe[b] or prefilled syringe[c] (alternative but not preferred formulations)
Other aspects of discharge management
Anaphylaxis emergency action plan (personalized, written)
Medical identification (eg, bracelet, wallet card)
Medical record electronic flag (or chart sticker)
Emphasize the importance of follow-up, preferably with an allergy/immunology specialist
Assessment of sensitization to allergen
Before discharge, consider assessing sensitization to allergens suggested in the history of the acute episode, by measuring serum IgE levels to relevant allergen(s), if the test is available[d]
3-4 weeks after the episode, confirm allergen sensitization using skin tests[e]
Challenge/provocation tests might be needed in some patients, for example, with food or medication allergy, in order to assess risk of future anaphylactic episodes further[f]
Long-term risk reduction: avoidance and/or immunomodulation
Food-triggered anaphylaxis: avoidance of relevant food(s)
Stinging insect-triggered anaphylaxis: avoidance of stinging insects; subcutaneous venom immunotherapy (protects up to 80–90% of adults and 98% of children)
Medication-triggered anaphylaxis: avoidance of relevant medications; if indicated, medically supervised desensitization in a healthcare setting according to published protocols
Idiopathic anaphylaxis: for frequent episodes, consider glucocorticoid and H_1-antihistamine prophylaxis for 2-3 months
Optimal management of asthma and other concomitant diseases

[a]Some formulation of injectable epinephrine should be carried at all times by patients at risk of recurrence; only 3 fixed doses are available in auto-injectors (0.1 mg, 0.3 mg, and 0.5); more than one epinephrine injection is needed in up to 23% of adults receiving an epinephrine injection for anaphylaxis; therefore, consider prescribing more than one epinephrine auto-injector.

[b]Recommended for use in community settings if epinephrine (adrenaline) auto-injectors are not available or affordable; even when training and written instructions are provided, people without a medical background find it hard to draw up an epinephrine dose accurately and rapidly from an ampule by using a 1 mL syringe.

[c]Recommend only if epinephrine (adrenaline) auto-injectors are not available or affordable; unsealed, prefilled syringes containing epinephrine should be replaced regularly every 3–4 months because epinephrine degrades rapidly on exposure to air.

[d]If allergen-specific IgE levels are measured in a blood sample obtained during or shortly after the episode, neutralization or consumption of serum IgE may have occurred; also in patients who have received intravenous fluid resuscitation, levels can be falsely low or absent/undetectable due to the dilutional effect on circulating IgE.

[e]Skin prick tests should be performed to assess sensitization to foods, venoms, and medications; intradermal tests are useful in venom and medication allergy, but are generally contraindicated in food allergy.

[f]Should be conducted only in appropriately equipped healthcare facilities staffed by professionals who are trained and experienced in patient selection, performing challenges according to protocol, and diagnosing and treating anaphylaxis. Before a challenge is performed, the potential risk versus the potential benefit should be discussed with the patient and documented in the medical record. In many countries, written informed consent is obtained before challenge/provocation tests.

Adapted from references 2, 22–25, 32, 59, 68, 69, 72, 73, 87, 96, 97, 99, 132–139.

weeks after an acute anaphylactic episode; however, for most allergens, this time interval has not been definitively established in prospective studies.[32] Patients with a convincing history of anaphylaxis and negative tests should therefore be retested weeks or months later.[32,137]

A medically supervised, graded challenge/provocation test conducted in an appropriately equipped healthcare setting staffed by trained and experienced healthcare professionals is sometimes necessary to determine the risk of anaphylaxis recurrence.[138,139] Examples of this situation include: 1) selected patients with an unclear history of food-induced anaphylaxis who have little or no evidence of sensitization to the implicated food or to any potentially relevant hidden, substituted or cross-reacting allergen; 2) selected patients with food-dependent exercise-induced anaphylaxis, although this can be difficult to reproduce in a laboratory setting[139]; and 3) selected patients with anaphylaxis to a medication or biologic agent. For some therapeutic agents, challenge tests are the diagnostic approach of choice because the relevant pro-drugs, haptens, immunogenic degradation products, and metabolites are unknown and therefore unavailable for use in skin tests or in vitro tests.[72,73]

In vitro tests that are currently used in research might, in the future, possibly be used to predict increased clinical risk of anaphylaxis.[140,141]

Prevention of Anaphylaxis Recurrences

Most recommendations for preventing recurrences of anaphylaxis, either by strict avoidance of the specific trigger(s) or relevant immunomodulation are based on expert opinion and consensus, rather than on rigorous, randomized, placebo-controlled, double-blind trials.[2,22–25,32,59,72,73] An important exception to this statement is the use of subcutaneous immunotherapy with the relevant insect venom(s) to prevent recurrence of stinging insect anaphylaxis.[68–70,135–137]

Management of Relevant Concomitant Diseases

Regular follow-up of all patients at risk for anaphylaxis recurrences is an important aspect of long-term risk reduction and prevention of future episodes[2,32] (Fig. 5, Table 9). Optimal management of concomitant diseases is a major therapeutic goal in patients with asthma, cardiovascular diseases, mastocytosis, clonal mast cell disorders, or other health issues that place them at increased risk of severe or fatal anaphy-

laxis.[8–10,13,37–44] The relevant benefits and risks of medications such as beta-blockers or ACE inhibitors should be discussed with these patients and with other physicians involved in their care, and the discussions should be documented in the patients' medical records.[39–41,46–48]

Avoidance and Immunomodulation, Including Allergen Immunotherapy

Anaphylaxis trigger(s) should be flagged appropriately in the medical records. Personalized written instructions for avoidance of the confirmed specific trigger (food, insect, medication, NRL, or other allergen) should be provided and discussed at regular intervals (Fig. 5, Table 9). Patients should be directed to reliable Websites or other sources of information that consistently provide accurate, up-to-date information, preferably in their own language. The WAO has established patient information links to various allergist-recommended educational resources categorized by language and geographical region at www.worldallergy.org/links/patient_links.php. Examples of some useful English language sites are www.anaphylaxis.org.uk/home.aspx, www.foodallergy.org, and www.latexallergyresources.org.[2,22–25,31,32,96,132,133]

Foods. Patients with a history of food-triggered anaphylaxis should avoid the food(s) that caused the reaction. This can be difficult because of hidden, substituted, and cross-reacting foods or foods that are "contaminated" because of cross-contact with the relevant allergen. Lack of labeling or confusing labels on packaged foods can also be problematic. Written lists of alternative names for the allergens, for example, "casein" for milk, likely sources of this allergen (eg, candies, cookies, cereal bars), and cross-reacting allergens (eg, cow's milk with goat's and sheep's milk) should be provided. Vigilant food avoidance measures potentially decrease the quality of life for those at risk for anaphylaxis and for their families and caregivers. Strict avoidance of many foods potentially leads to nutritional deficiencies; to prevent this, consultation with a dietician should be considered and in children, gains in height and weight (mass) should be monitored.[58,59,142–146]

Future therapeutic options to prevent food-induced anaphylaxis include strategies that target specific foods and those that are not food-specific.[58,59] In carefully selected patients, randomized placebo-controlled trials of oral immunotherapy with a food such as milk, egg, peanut, or tree nut confirm that incremental dosing leads to clinical desensitization and possibly to development of immune tolerance; however, adverse effects are common, especially on the initial dose escalation day and on subsequent dose build-up days.[147,148] Novel approaches to allergen nonspecific immunomodulation include regular subcutaneous injections of anti-IgE antibody and oral administration of Food Allergy Herbal Formula-2, a well-characterized Chinese herbal formulation.[59] Research in progress appears promising, however, the WAO does not currently recommend oral food allergen immunotherapy or other immunomodulatory approaches to prevent anaphylaxis triggered by foods.

Insect Stings. Patients with a history of stinging insect venom-triggered anaphylaxis should ideally avoid subsequent exposure to such insects; however, beekeepers, gardeners, forestry workers, and others with occupational exposure may find it difficult to follow this advice.[24]

Patients with anaphylaxis triggered by venom from honey bees, yellow jackets, yellow hornets, white-faced hornets, paper wasps, and some species of ants should receive subcutaneous immunotherapy with the relevant standardized insect venom(s) for at least 3–5 years. Protection can be achieved in up to 80–90% of adults and 98% of children, in whom it lasts for decades.[68–70,135–137] Those with fire ant triggered anaphylaxis should receive subcutaneous immunotherapy with fire ant whole body extract.[71,135]

Medications. Patients with a history of anaphylaxis triggered by a medication should not be given that medication. A safe and effective non-cross-reacting medication, preferably from a different pharmacologic class, should be substituted, if available.[2,24,32,72–74] A written list containing the name of the medication that triggered the anaphylaxis and the names of related and cross-reacting medications should be provided.[2,24,32,72–74]

Those who require a drug for which no safe and effective substitute is available should undergo desensitization, defined as induction of a temporary state of tolerance to the relevant medication for one uninterrupted course of treatment. It should be conducted in a healthcare setting, according to an established protocol, by healthcare professionals trained and experienced in such procedures and in management of anaphylaxis if it occurs during the desensitization procedure.[72,73,76,77] Desensitization protocols are available for many agents, including antimicrobials, anti-fungals, anti-virals, NSAIDs, biologics, and chemotherapeutics.[77]

For patients at increased risk of anaphylaxis from RCM, a nonionic RCM should be administered and premedication with a corticosteroid and an antihistamine should be considered[24]; however, use of premedication is controversial and does not prevent all future reactions.[80]

Other Triggers. For prevention of exercise-induced anaphylaxis, strict avoidance of the relevant co-trigger such as food(s), ethanol, and NSAID(s) should be recommended. Exercise under ambient conditions of high humidity, extreme heat or cold, or high pollen counts should be avoided, if relevant. Additional precautions should include never exercising alone, discontinuing exertion immediately when the first symptom of anaphylaxis occurs, and carrying a mobile phone and epinephrine auto-injector.[53–57]

For anaphylaxis from NRL, avoidance of latex in healthcare settings and community settings is the treatment of choice. Additionally, if relevant, such patients should avoid cross-reacting fruits and vegetables such as avocado, kiwi, banana, potato, tomato, chestnut, and papaya.[24] For anaphylaxis to seminal fluid, condom use by the patient's partner and, if available, desensitization to seminal fluid, are recommended.[24,86] For anaphylaxis induced by some nonimmune triggers such as cold, heat, sunlight, ultraviolet radiation, or ethanol, avoidance of the trigger is the key to prevention of recurrences.[2,32]

Idiopathic Anaphylaxis. There are no randomized controlled trials of pharmacologic prophylaxis of idiopathic anaphylac-

tic episodes; however, patients with frequent episodes, that is, more than 6 in 1 year or more than 2 in 2 months, are reported to benefit from prophylactic treatment with a systemic glucocorticoid and an H_1-antihistamine.[24,87] Prophylactic omalizumab injections are also reported to reduce the number of episodes.[149] Most patients with idiopathic anaphylaxis go into remission within a few years.

Long-Term Follow-Up

For patients at risk for anaphylaxis recurrences in the community, regular follow-up visits, for example, at yearly intervals, are desirable to review self-injection of epinephrine, to discuss allergen avoidance techniques and potential immunomodulation, and to help patients achieve optimal control of concomitant diseases (Table 9).

WAO ANAPHYLAXIS GUIDELINES DISSEMINATION AND IMPLEMENTATION

The WAO Anaphylaxis Guidelines are being published concurrently in the *World Allergy Organization Journal* (*WAO Journal*) at www.WAOJournal.org to facilitate rapid access by all 30,000 WAO members and in *The Journal of Allergy and Clinical Immunology* to facilitate retrieval by all healthcare professionals worldwide through PubMed and other search engines. The recommendations for anaphylaxis assessment and basic initial management as discussed in the Guidelines are also being disseminated through posters, pocket cards, and applications (apps) for mobile devices.

The main barriers to implementation of the recommendations in the Guidelines include the erroneous perception that anaphylaxis is a rare disease, and the lack of universal availability of essential medications, supplies and equipment for its assessment and management worldwide. Additional barriers include lack of awareness that hypotension and shock are often absent in anaphylaxis, that tryptase or histamine levels are not necessarily elevated, that death can occur within a few minutes, and that prompt basic initial treatment can be life-saving.[3,4,13,90,94–97,99,101,102]

The WAO member societies were extensively involved in development of the Guidelines. Their ongoing contributions through e-mail discussions and dialogue at national and international meetings will help to facilitate Guidelines dissemination and implementation. At the request of WAO member societies, the WAO Secretariat is available to assist with translation of Guidelines-related materials such as posters and pocket cards.

WAO ANAPHYLAXIS GUIDELINES UPDATES

At regular 2–4 year intervals, the WAO Anaphylaxis Special Committee will formally reassess the evidence supporting the Guidelines, update them in the event of substantial new evidence emerging, and revise the strategies for their dissemination and implementation.

Global Agenda for Anaphylaxis Research

A global research agenda to address uncertainties in the assessment and management of anaphylaxis is proposed. Potential areas of investigation with regard to anaphylaxis assessment might include: development of an instrument for quantification of patient-specific risk factors, development of rapid, specific, sensitive in vitro tests or a panel of such tests to confirm the clinical diagnosis, and development of in vitro tests to distinguish allergen sensitization from clinical risk of anaphylaxis and reduce the need for challenge/provocation tests. Potential areas of investigation with regard to management include randomized, placebo-controlled trials of interventions to prevent anaphylaxis, and (with appropriate precautions including epinephrine injection, supine positioning, supplemental oxygen, and intravenous fluid resuscitation), randomized placebo-controlled trials of second-line pharmacologic agents, for example, glucocorticoids, in the treatment of anaphylaxis. Although randomized controlled trials of the first-line medication, epinephrine, are not ethical to perform, other types of studies of this life-saving drug, for example, clinical pharmacology studies, investigations in animal models, in vitro studies, and retrospective studies, including epidemiologic studies, should continue in order to improve the evidence base for treatment and guide clinical decision-making.[2,150]

SUMMARY

The WAO Guidelines focus on recommendations for the basic initial treatment of anaphylaxis, as summarized below.

Prepare for anaphylaxis assessment and management of anaphylaxis in healthcare settings. Have a posted, written emergency protocol and rehearse it regularly. As soon as the clinical diagnosis of anaphylaxis is made, discontinue exposure to the trigger, if possible; for example, discontinue an intravenously administered diagnostic or therapeutic agent. Assess the patient rapidly (circulation, airway, breathing, mental status, and skin). Simultaneously and promptly: call for help; inject epinephrine (adrenaline) by the intramuscular route in the mid-anterolateral aspect of the thigh; and place the patient on the back or in a position of comfort with the lower extremities elevated.

When indicated at any time during the anaphylactic episode, administer supplemental oxygen, give intravenous fluid resuscitation, and initiate cardiopulmonary resuscitation with continuous chest compressions. At frequent and regular intervals, monitor the patient's blood pressure, cardiac rate and function, respiratory status and oxygenation and obtain electrocardiograms; start continuous noninvasive monitoring, if possible.

Patients with anaphylaxis refractory to the above measures, for example, those requiring intubation and mechanical ventilation and those requiring intravenous epinephrine or another vasopressor should, if possible, be transferred to a healthcare facility where additional support is available. Ideally, this includes specialists in emergency medicine, critical care medicine and/or anesthesiology, trained and experienced nurses and technicians, and appropriate medications, supplies, and equipment. Where such skilled support is not available, physicians should, if possible, obtain additional training and experience in the management of refractory anaphylaxis and additional training in life-support measures.

At the time of their discharge from the healthcare setting, equip patients with epinephrine for self-administra-

tion, an anaphylaxis emergency action plan, and medical identification to facilitate prompt recognition and treatment of anaphylaxis recurrences in the community. Advise patients that they need follow-up visits with a physician, preferably an allergy/immunology specialist, to confirm their specific anaphylaxis trigger(s), prevent recurrences by avoiding specific trigger(s), and receive immunomodulation, if relevant.

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Member Society

Albanian Society of Allergology and Clinical Immunology
American Academy of Allergy, Asthma and Immunology
American College of Allergy, Asthma and Immunology
Argentine Association of Allergy and Clinical Immunology
Argentine Society of Allergy and Immunopathology
Australasian Society of Clinical Immunology and Allergy
Austrian Society of Allergology and Immunology
Azerbaijan Society for Asthma, Allergy and Clinical Immunology
Bangladesh Society of Allergy and Immunology
Belgian Society of Allergology and Immunology
Brazilian Society of Allergy and Immunopathology
British Society for Allergy and Clinical Immunology
Bulgarian National Society of Allergology
Canadian Society of Allergy and Clinical Immunology
Chilean Society of Allergy and Immunology
China Allergology Society and Chinese Allergists
Colombian Allergy, Asthma, and Immunology Association
Croatian Society of Allergology and Clinical Immunology
Cuban Society of Allergology
Czech Society of Allergology and Clinical Immunology
Danish Society for Allergology
Dutch Society of Allergology
Egyptian Society of Allergy and Clinical Immunology
Egyptian Society of Pediatric Allergy and Immunology
Finnish Society of Allergology and Clinical Immunology
French Society of Allergology
Georgian Association of Allergology and Clinical Immunology
German Society for Allergology and Clinical Immunology
Hellenic Society of Allergology and Clinical Immunology
Honduran Society of Allergy and Clinical Immunology
Hong Kong Institute of Allergy
Hungarian Society of Allergology and Clinical Immunology
Icelandic Society of Allergy and Immunology
Indian College of Allergy, Asthma and Applied Immunology
Indonesian Society for Allergy and Immunology
Israel Association of Allergy and Clinical Immunology
Italian Association of Territorial and Hospital Allergists
Italian Society for Allergology and Clinical Immunology
Japanese Society of Allergology
Korean Academy of Allergy, Asthma and Clinical Immunology
Latvian Association of Allergists
Lebanese Society of Allergy and Immunology
Malaysian Society of Allergy and Immunology
Mexican College of Allergy, Asthma and Clinical Immunology
Mexican College of Pediatricians Specialized in Allergy and Clinical Immunology
Mongolian Society of Allergology
Norwegian Society of Allergology and Immunopathology
Panamanian Association of Allergology and Clinical Immunology
Paraguayan Society of Immunology and Allergy
Peruvian Society of Allergy and Immunology
Philippine Society of Allergy, Asthma and Immunology
Polish Society of Allergology
Portuguese Society of Allergology and Clinical Immunology
Romanian Society of Allergology and Clinical Immunology
Russian Association of Allergology and Clinical Immunology
Serbian Association of Allergologists and Clinical Immunologists
Allergy and Clinical Immunology Society (Singapore)
Slovenian Association for Allergology and Clinical Immunology
Allergy Society of South Africa
Spanish Society of Allergology and Clinical Immunology
Allergy & Immunology Society of Sri Lanka
Swiss Society of Allergology and Immunology
Allergy, Asthma and Immunology Society of Thailand
Turkish National Society of Allergy and Clinical Immunology
Ukrainian Association of Allergologists and Clinical Immunologists
Uruguayan Society of Allergology
Venezuelan Society of Allergy and Immunology
Vietnam Association of Allergy, Asthma and Clinical Immunology
Zimbabwe Allergy Society

Member Societies-Regional Organizations

Asia Pacific Association of Allergology and Clinical Immunology
Commonwealth of Independent States (CIS Society)
European Academy of Allergy and Clinical Immunology
Latin American Society of Allergy, Asthma and Immunology

Affiliate Members

GA2LEN
International Primary Care Respiratory Group (IPCRG)
International Association of Asthmology
Southern European Allergy Societies (SEAS)

Associate Members

National Association for Private Algerian Allergists
Ecuadorian Society of Allergology and Affiliated Sciences
Ecuadorian Society of Allergy and Immunology
Jordanian Society for Allergy and Clinical Immunology
Kuwait Society of Allergy and Clinical Immunology
Moroccan Society of Allergology and Clinical Immunology
Swedish Association for Allergology

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