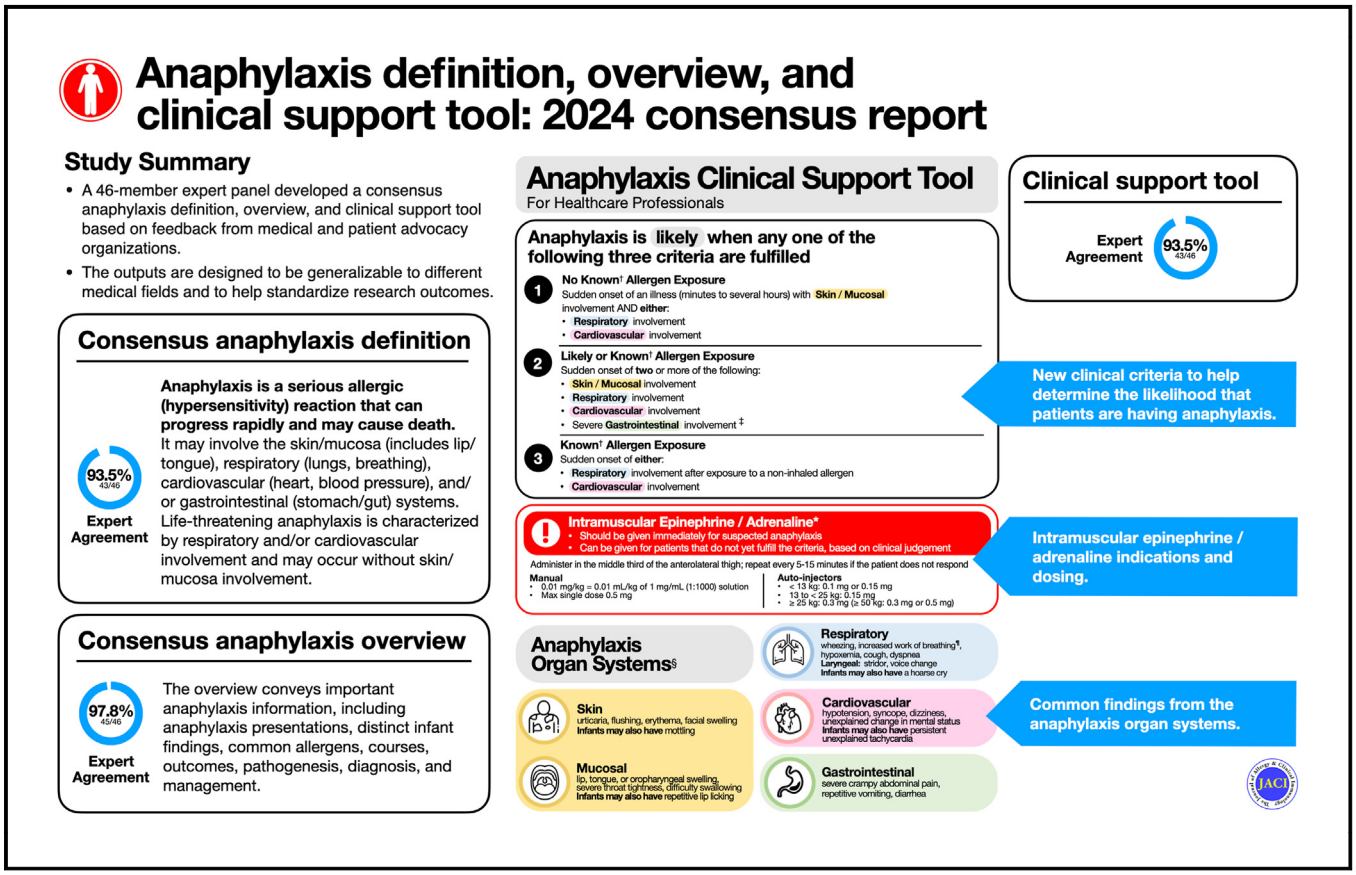
Anaphylaxis definition, overview, and clinical support tool: 2024 consensus report—a GA²LEN project

Timothy E. Dribin, MD, Antonella Muraro, MD, PhD, Carlos A. Camargo Jr, MD, DrPH, Paul J. Turner, FRCPCH, PhD, Julie Wang, MD, Graham Roberts, DM, et al

GRAPHICAL ABSTRACT



Capsule summary: The authors developed a consensus anaphylaxis definition, overview, and clinical support tool that includes clinical criteria, epinephrine (adrenaline) indications, and findings from the 4 organ systems. The support tool should facilitate improved care and standardize research outcomes.

J Allergy Clin Immunol 2025;■■■:■■■-■■■.

https://doi.org/10.1016/j.jaci.2025.01.021

Anaphylaxis definition, overview, and clinical support tool: 2024 consensus report—a GA²LEN project

Timothy E. Dribin, MD,[a,b] Antonella Muraro, MD, PhD,[c] Carlos A. Camargo, Jr, MD, DrPH,[d] Paul J. Turner, FRCPCH, PhD,[e] Julie Wang, MD,[f] Graham Roberts, DM,[g,h,i] Aikaterini Anagnostou, MD, PhD,[j,k] Susanne Halken, DM, DMSc,[l,m] Jay Liebermann, MD,[n] Margitta Worm, MD,[o] Torsten Zuberbier, MD,[p,q] and Hugh A. Sampson, MD,[f] on behalf of the GA²LEN Anaphylaxis Study Team* *Berlin, Germany; Boston, Mass; Cincinnati, Ohio; Houston, Tex; Newport (Isle of Wight), London, and Southampton, United Kingdom; Memphis, Tenn; New York, NY; Odense, Denmark; and Padua, Italy*

Background: The 2006 National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network anaphylaxis criteria are widely used in clinical care and research. In 2020, the World Allergy Organization published modified criteria that have not been uniformly adopted. Different criteria contribute to inconsistent care and research outcomes.

Objective: We sought to develop a consensus anaphylaxis definition, overview, and clinical support tool.

Methods: A 12-member writing group developed draft outputs modified with input from a 46-member international expert panel, 31 medical stakeholder organizations, and 15 patient advocacy organizations. The expert panel participated in a modified Delphi process to seek consensus for the outputs using a ≥80% consensus threshold.

Results: The first sentence of the definition reads, "Anaphylaxis is a serious allergic (hypersensitivity) reaction that can progress rapidly and may cause death." The definition also describes organ systems that may be involved and signs of life-threatening reactions. The overview includes details of anaphylaxis recognition and management. The clinical support tool incorporates new clinical criteria to help determine the likelihood that patients are having anaphylaxis, intramuscular epinephrine indications and dosing, and common findings from the anaphylaxis organ systems. In addition, 93.5% (43/46), 97.8% (45/46), and 93.5% (43/46) of experts agreed with the definition, overview, and clinical support tool, respectively.

Conclusion: The anaphylaxis overview is a novel educational tool conveying key elements of anaphylaxis recognition and management. We propose that the definition and clinical support tool should replace previous definitions and clinical criteria. The clinical support tool should facilitate improved anaphylaxis recognition and management across different clinical settings and standardize research outcomes. (J Allergy Clin Immunol 2025;■■■:■■■-■■■.)

Key words: *Adrenaline, anaphylaxis, clinical criteria, definition, epinephrine*

Abbreviations used
NIAID/FAAN: National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network
WAO: World Allergy Organization

Anaphylaxis is a potentially life-threatening hypersensitivity reaction with a rising incidence in many parts of the world.[1-5] There is no reference-standard diagnostic test for anaphylaxis; instead, clinicians must integrate details about potential triggers with presenting findings to determine the likelihood that a patient is having anaphylaxis and whether to administer the first-line therapy, epinephrine (adrenaline). Before 2006, there were no agreed-on anaphylaxis clinical criteria to support diagnostic and therapeutic decision-making, contributing to inconsistent and suboptimal patient care and research outcomes.[1]

In 2004, the National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) convened a meeting to develop a universally agreed-on definition and clinical criteria to accurately identify anaphylaxis. A 2005 symposium was organized to resolve outstanding issues from the first meeting. The landmark 2006 NIAID/FAAN criteria have been

From [a]the Division of Emergency Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati; [b]the Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati; [c]the Department of Woman and Child Health, Food Allergy Centre, Padua University Hospital, Padua; [d]the Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston; [e]the National Heart & Lung Institute, Imperial College London, London; [f]the Division of Allergy & Immunology, Icahn School of Medicine at Mount Sinai, New York; [g]the University of Southampton Faculty of Medicine, David Hide Asthma and Allergy Centre, Southampton; [h]St Mary's Hospital, Newport; [i]the National Institute for Health Research Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton; [j]the Department of Pediatrics, Division of Immunology, Allergy and Retrovirology, Texas Children's Hospital, Houston; [k]the Division of Allergy, Immunology & Retrovirology, Baylor College of Medicine, Houston; [l]the Hans Christian Andersen Children's Hospital, Odense; [m]the Denmark University of Southern Denmark, Odense; [n]The University of Tennessee Health Science Center, Memphis; [o]the Division of Allergy and Immunology, Department of Dermatology, Venerology and Allergy, Charite Univeritätsmedizin Berlin, Berlin; [p]the Fraunhofer Institute for Translational Medicine and Pharmacology (ITMP), Allergology and Immunology, Berlin; and [q]the Institute of Allergology, Charité–Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, and Humboldt-Universität zu Berlin, Berlin.

*GA²LEN Anaphylaxis Study Team members are listed in the Acknowledgments.

The first 2 authors contributed equally to this article, and both should be considered first author.

Received for publication September 20, 2024; revised December 13, 2024; accepted for publication January 6, 2025.

Corresponding author: Timothy E. Dribin, MD, Cincinnati Children's Hospital, 3244 Burnet Ave, Cincinnati, OH 45229. E-mail: Timothy.Dribin@cchmc.org.

0091-6749

https://doi.org/10.1016/j.jaci.2025.01.021

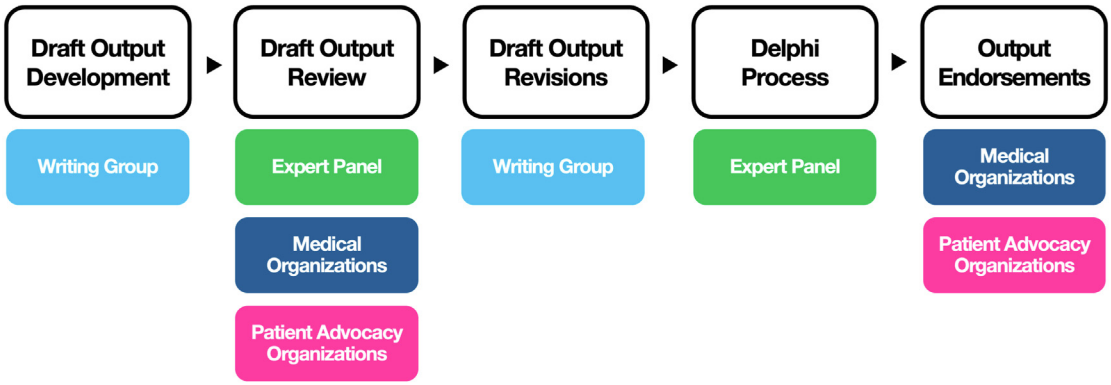


FIG 1. Study process.

widely adopted and used in clinical care and research (see Table E1 in the Online Repository available at www.jacionline.org).[1,6] In 2020, the World Allergy Organization (WAO) published modified anaphylaxis criteria that were based on emerging evidence as well as over a decade's worth of experience using the NIAID/FAAN criteria in clinical care and research.[7] The WAO approach reduced the number of criteria from 3 to 2, modified the gastrointestinal criterion to better align with definitions used in the United Kingdom and Australia, and incorporated isolated respiratory involvement after exposure to a known or highly probable allergen (excluding inhalant allergens) as likely anaphylaxis. The WAO criteria have not yet been validated or uniformly adopted in clinical care or research, and two sets of anaphylaxis criteria contribute to inconsistent patient care and research outcomes.

Thus, in 2023, the Global Allergy and Asthma Excellence Network (GA^{2}LEN) convened an international expert panel to develop consensus anaphylaxis clinical criteria by resolving the differences between the NIAID/FAAN and WAO criteria. Here we report on the process and the 3 study outputs, which comprise an anaphylaxis definition; an anaphylaxis overview that includes essential details of anaphylaxis presentation, courses and outcomes, pathogenesis, diagnosis, and management; and an anaphylaxis clinical support tool that includes new clinical criteria, intramuscular epinephrine treatment indications and dosing, and clinical findings from the anaphylaxis organ systems.

METHODS

Participants

From August 2023 to June 2024, we convened a 46-member multidisciplinary panel of anaphylaxis experts. Experts were selected on the basis of having peer-reviewed anaphylaxis publications and/or serving in leadership roles in research or clinical organizations that guide anaphylaxis management. Table E2 in the Online Repository available at www.jacionline.org provides details of the countries and medical specialties represented. Twelve of the experts (T.D., A.M., C.C., P.T., J.W., G.W., A.A., S.H., J.L., M.W., T.Z., H.S.) served on a writing group tasked with developing and modifying the draft study outputs based on feedback from the expert panel as well as medical (n = 31) and patient advocacy organizations (n = 15) to ensure that the study outputs were generalizable to diverse end users in clinical care and research (Fig 1).

Medical organizations involved in the acute and long-term management of patients with or at risk of anaphylaxis were also selected. Patient advocacy organizations only provided feedback about the anaphylaxis definition because the overview and support tool are intended for health care professionals. Representatives from the US Food and Drug Administration, European Medicines Agency, Paul-Ehrlich Institut, and NIAID provided feedback about the study outputs but were not asked to endorse them. Table E3 in the Online Repository available at www.jacionline.org lists the participating organizations.

Study timeline

The first writing group meeting was in person in Padua, Italy (August 31, 2023), after which the writing group had monthly teleconference calls until the study's conclusion. After the writing group developed the draft study outputs, feedback about the outputs was solicited from the expert panel on a teleconference call (February 12, 2024). An electronic REDCap survey was also sent to the expert panel for additional feedback. The writing group modified the study outputs, after which a second teleconference call (April 16, 2024) was conducted with the expert panel to review the modified outputs and seek additional feedback. Feedback from patient advocacy organizations was solicited during two teleconference calls on April 1 and 3, 2024, and from medical organizations on a teleconference call on May 14, 2024.

Delphi process

The expert panel then participated in a modified Delphi process (see the Methods section in the Online Repository available at www.jacionline.org) using an *a priori* ≥80% agreement threshold with a maximum of 3 voting rounds to seek consensus for the study outputs. After the Delphi process, participating organizations were sent an electronic survey to determine whether they endorsed the outputs.

RESULTS

The writing group identified the following themes through open discussion, which served as a framework for the 3 anaphylaxis outputs: definition, overview, and clinical support tool. The themes were refined during the study and were based on feedback from the expert panel and participating organizations.

Definition

Theme: The definition is designed for health care professionals and laypersons. It conveys that anaphylaxis may cause death, describes potential organ system involvement,

and includes signs of life-threatening reactions. Patient advocacy groups recommended including "may cause death" in the first sentence to address the concern that some people may be unaware that anaphylaxis can be fatal and is therefore an important public health concern.[8,9] Additionally, advocacy groups recommended including easy-to-understand organ system descriptors.

Theme: The definition does not include details of anaphylaxis courses, outcomes, pathogenesis, management, or therapies.

Theme: There was disagreement about the use of the ABC mneumonic. Although experts thought it beneficial to include airway, breathing, and/or cardiovascular (ABC) involvement to denote signs of life-threatening reactions, advocacy organizations thought this mnemonic was not value added to laypersons, especially because it does not translate well to non-English languages.

Theme: Whether the definition should include epinephrine. Advocacy organizations thought the definition should include wording about treatment with epinephrine to educate patients, caregivers, and clinicians about the importance of treating anaphylaxis with epinephrine. However, experts felt that the definition should not include therapies, consistent with other medical definitions, including the NIAID/FAAN and WAO anaphylaxis definitions.

Overview

Theme: The overview conveys important anaphylaxis information not included in the definition and support tool. Such information includes anaphylaxis presentations, distinct infant findings, common allergens, courses, outcomes, pathogenesis, diagnosis, and management.

Theme: It is not a systematic review or practice parameter. The overview refers to the best available evidence when there are insufficient data to support specific evaluation (eg, tryptase) or management strategies. Experts agreed that the overview should be concise and only provide the most salient information when describing anaphylaxis pathogenesis, diagnosis, and adjunctive therapies because this information has been well described in systematic reviews and practice parameters.[7,10-12]

Clinical support tool

Theme: The support tool is designed for health care professionals trained to recognize anaphylaxis findings, apply the clinical criteria, and decide whether to administer epinephrine. Experts recognized that the support tool is too complex to be reliably used by laypersons because it is based on the need to account for the allergen exposure (no known, likely, known) and combinations of findings from 4 organ systems. Furthermore, patient advocacy organizations told us that the central question facing patients/caregivers is not whether someone is having anaphylaxis but whether to administer epinephrine. Future research is needed to develop an easy-to-use and readily accessible decision support aid to promote appropriate and timely epinephrine use for patients/caregivers by linking reaction signs/symptoms with prescriptive epinephrine treatment advice.[13-15]

Theme: The NIAID/FAAN and WAO clinical criteria have been misinterpreted and misapplied in clinical care as diagnostic criteria. The support tool clinical criteria are not diagnostic criteria because there is no reference-standard anaphylaxis diagnostic test. Instead, the criteria should be used to determine the likelihood that a patient is having anaphylaxis in clinical care and research.

Theme: The criteria will not have perfect test characteristics for sensitivity, specificity, positive predictive value, and negative predictive value. Experts agreed that the criteria should have higher sensitivity while accepting lower specificity to avoid anaphylaxis underrecognition and potential underuse of epinephrine.

Theme: The positive predictive value of the support tool will vary according to setting. The prevalence of anaphylaxis/acute allergic reactions is different depending on the setting. It is higher in the allergy clinic, where findings are almost always attributed to an allergic reaction, versus in the prehospital, emergency department, inpatient, or perioperative settings, where the symptoms may be secondary to a nonallergic diagnosis. Thus, the positive predictive value of the criteria will be higher in allergy clinics than in other settings.

Theme: The clinical criteria are stratified according to type of allergen exposure as not known, likely, or known, and the term *allergen* broadly includes any anaphylaxis trigger (eg, foods, insect stings, medications, exercise), irrespective of the underlying mechanism. Including these categories directs providers to use the first criterion if there is no known allergen exposure, the second criterion if the allergen is likely, and the second or third criterion if the allergen is known. *No known allergen exposure* is defined as scenarios in which one cannot determine whether there was an allergen exposure or cannot identify a likely allergen, whereas known allergens do not require confirmatory testing—as, for example, when suspicious symptoms develop after an insect sting in someone without an existing diagnosis.

Theme: Whether there is no known, likely, or known allergen exposure affects the pre- and posttest probability of having anaphylaxis. To fulfill the first criterion, patients must have skin/mucosa and either respiratory or cardiovascular involvement, given that the pretest probability of having anaphylaxis with no known allergen exposure is lower than in patients exposed to likely or known allergens. When there is no known allergen exposure, providers must maintain a broad differential of conditions that may mimic anaphylaxis.[16-18] The first criterion does not include gastrointestinal involvement because nonallergic diagnoses may present with skin/mucosa and gastrointestinal features. The pretest probability of the second criterion is higher than the first because patients must be exposed to likely or known allergens. Anaphylaxis typically, but not always, involves multiple systems. As a result, this criterion classifies a patient as likely having anaphylaxis with any multisystem involvement, including skin/mucosa and severe gastrointestinal involvement. The third criterion accounts for the less common scenario where a patient presents with isolated respiratory or cardiovascular involvement. Because this is the only criterion not requiring multisystem involvement, patients must be exposed to known allergens (highest pretest probability) to avoid possible misdiagnosis by excluding other serious cardiopulmonary conditions.

Theme: The new clinical criteria define gastrointestinal involvement as "severe" rather than "persistent." Consistent with the WAO and Australasian Society of Clinical Immunology and Allergy definitions, the new clinical criteria define gastrointestinal involvement as "severe," whereas

the NIAID/FAAN criteria included "persistent" gastrointestinal features, which could, by definition, be mild.[1,7] Importantly, gastrointestinal involvement after noningested allergen exposure suggests anaphylaxis. Gastrointestinal involvement after ingested allergen exposure may be due to local and/or systemic reactions—a distinction that may be difficult to make in clinical practice.

Theme: Anaphylaxis is likely in patients who develop isolated respiratory involvement after exposure to a known noninhaled allergen. Consistent with the WAO criteria, experts agreed that anaphylaxis was likely in patients who develop isolated respiratory involvement after exposure to a known noninhaled allergen.[7] The distinction of "noninhaled allergen" was included to raise awareness that isolated respiratory involvement after exposure to inhaled allergens does not constitute anaphylaxis. Although patients can develop inhalant-induced anaphylaxis, multisystem involvement is required for inhaled allergens.

Theme: Treatment with epinephrine should not be linked to anaphylaxis diagnosis. There will be patients who receive epinephrine whose presentation does not fulfill anaphylaxis criteria, and there will be patients who do not receive epinephrine whose presentation fulfills the criteria. The support tool states that epinephrine "should be given immediately for suspected anaphylaxis" and "can be given for patients that do not yet fulfill clinical criteria, based on clinical judgment." This concept is not novel, and it addresses the significant underuse of epinephrine to treat anaphylaxis in both prehospital and hospital settings.[1,13,19]

Theme: Intramuscular epinephrine treatment indications and dosing should be included in the support tool. In contrast to the NIAID/FAAN and WAO criteria, the support tool includes intramuscular epinephrine (adrenaline) treatment indications and dosing.[1,7] The support tool states that epinephrine can be given every 5 to 15 minutes; however, clinicians are free to use their judgment to liberalize the dosing frequency to less than 5 minutes.[1] Autoinjector dosing in the support tool is based on published anaphylaxis guidelines and may not reflect manufacturer recommendations.[7,11,12,20,21] Alternative age-based epinephrine dosing is provided because weight-based dosing in the prehospital setting has been associated with dosing errors and delays in administration.[20,22-29] Additionally, the support tool includes dosing for Neffy (ARS Pharmaceuticals), the first noninjectable epinephrine delivery device approved by the US Food and Drug Administration and the European Medicines Agency in 2024.

Theme: Intravenous epinephrine dosing should not be included in the support tool. Experts agreed that most providers provide epinephrine intramuscularly, and specialties that use continuous epinephrine infusions (emergency medicine, intensive care, anesthesia) have reliable dosing resources.

Theme: When new noninjectable epinephrine delivery devices receive regulatory agency approval, the support tool will need to be modified to include them.

Theme: The support tool focuses on common or serious signs/symptoms, favoring signs over symptoms. The support tool's section on anaphylaxis organ systems includes organ system–specific signs/symptoms that are common and/or serious. It favors signs over symptoms because it is unclear how patient-reported symptoms should affect clinical decision-making.

Theme: The support tool includes distinct findings in infants and young children. The NIAID/FAAN and WAO criteria do not include signs of anaphylaxis sometimes seen in infants and young children. The support tool's section on anaphylaxis organ systems includes some of these distinct findings. Recognizing anaphylaxis in infants and young children is challenging because they are nonverbal, and potential findings of allergic reactions (eg, crying, fussiness) in this age may overlap with normal behavior.[30-32] Additionally, providers may lack pediatric training or experience. The support tool will thus help improve anaphylaxis recognition and management in early childhood.

Theme: The support tool should be formatted to promote ease of use in clinical care. This includes assigning different colors to organ systems, removing the example signs/symptoms for different organ systems from the clinical criteria, and moving them to the section on anaphylaxis organ systems. Additionally, although skin and mucosal involvement are not treated as two organ systems in the NIAID/FAAN and WAO criteria, experts thought it was important to clearly show that skin and mucosa are treated as one organ system.

Box 1. Consensus anaphylaxis definition

> **Anaphylaxis is a serious allergic (hypersensitivity) reaction that can progress rapidly and may cause death.** It may involve the skin/mucosa (includes lip/tongue), respiratory (lungs, breathing), cardiovascular (heart, blood pressure), and/or gastrointestinal (stomach/gut) systems. Life-threatening anaphylaxis is characterized by respiratory and/or cardiovascular involvement and may occur without skin/mucosa involvement.

Delphi results and output endorsements

The 3 study outputs achieved consensus agreement after one round, with 93.5% (43/46), 97.8% (45/46), and 93.5% (43/46) of experts agreeing with the anaphylaxis definition (Box 1), overview (Box 2), and clinical support tool (Fig 2), respectively. The support tool references a more complete list of potential signs/symptoms that may occur before or during anaphylaxis (Table I), which providers can reference to account for less common and nonspecific presentations (eg, "sense of impending doom") that do not align with a specific organ system.

The 36 organizations that endorsed the study outputs are listed in Box 3, and Table E4 in the Online Repository available at www.jacionline.org provides comments from the Delphi and output endorsement phases of the study.

DISCUSSION

We developed international consensus on 3 anaphylaxis documents: definition, overview, and clinical support tool. The 3 outputs are designed to be generalizable to different medical fields, including allergy, anesthesia, emergency medicine, emergency medical services, hospital medicine, intensive care, and primary care. The anaphylaxis overview is a novel educational tool to teach health care providers about key facets of anaphylaxis recognition and management. We propose that the anaphylaxis definition and clinical support tool should replace prior definitions and clinical criteria.[1,7] The application of the support tool in clinical care and research should facilitate improved anaphylaxis recognition and management, enhance epidemiologic surveillance, and standardize outcomes in observational and interventional studies.

Box 2. Consensus anaphylaxis overview

Please reference anaphylaxis practice parameters and systematic reviews for an in-depth appraisal of the most up-to-date evidence and care guidelines.

Anaphylaxis is a serious allergic (hypersensitivity) reaction that can progress rapidly and may cause death

It may involve the skin/mucosa (eg, urticaria, flushing, angioedema), respiratory system (eg, upper airway obstruction, bronchospasm, cough), cardiovascular system (eg, syncope, hypotension, shock), and/or gastrointestinal system (eg, severe abdominal pain, repetitive vomiting, diarrhea). Life-threatening anaphylaxis is characterized by airway, breathing, and/or cardiovascular compromise and may occur without skin/mucosa involvement.

Infants with anaphylaxis may have distinct signs such as a hoarse cry (laryngeal involvement), repetitive lip licking (mucosal involvement), or abrupt nonspecific behavioral changes (eg, irritability, persistent crying).

The most common allergens inducing anaphylaxis are foods, medications, and insect stings; in some cases, the precise etiology may be unknown. Anaphylaxis is a systemic reaction not just limited to the skin/mucosa, where symptoms/signs occur beyond the site of allergen exposure. Anaphylaxis usually occurs with multisystem involvement but can present with isolated cardiovascular or respiratory compromise. Skin/mucosa signs may be absent in up to 20% of presentations. For ingested allergens such as foods, gastrointestinal involvement may be due to local effects rather than a systemic reaction, a distinction that may be difficult to make in clinical practice.

Reactions occur along a severity spectrum including life-threatening anaphylaxis, which is characterized by airway, breathing, and/or cardiovascular (ABC) compromise. Anaphylaxis is dynamic; reactions may initially appear mild and then become severe. Although uncommon, patients may have persistent or biphasic reactions (characterized by initial symptom resolution followed by symptom recurrence).

Anaphylaxis is classically described as a type 1 hypersensitivity reaction driven by IgE-mediated release of histamine and other mediators from effector cells (such as mast cells) after allergen exposure. Non-IgE-mediated anaphylaxis is also well described, particularly to some drugs and certain types of exercise-induced anaphylaxis; symptoms/signs are indistinguishable from IgE-mediated anaphylaxis.

There is no gold-standard diagnostic test for anaphylaxis. Tryptase may be helpful to obtain, depending on the clinical scenario, for later supporting the diagnosis. Until better diagnostic tests are developed, anaphylaxis remains a clinical diagnosis.

Initial anaphylaxis management strategies include removing the offending allergen and placing patients in the supine position with their legs elevated to promote venous return. For patients with respiratory involvement, every effort should be made to ensure patient positioning does not worsen symptoms. There have been no randomized controlled trials of anaphylaxis therapies, and thus therapeutic recommendations are based on clinical experience, observational studies,

(Continued)

Box 2. *(Continued)*

animal models, or extrapolation from conditions with similar presentations.

Intramuscular epinephrine (adrenaline) administered in the anterolateral thigh is the first-line treatment for anaphylaxis. Intravenous epinephrine is the preferred route for anaphylaxis during general anesthesia, but this requires appropriate cardiac monitoring and clinical expertise. Repeat epinephrine is indicated when patients do not respond to initial dosing.

Most anaphylaxis reactions respond to 1-2 epinephrine doses. Failure to respond to 2 doses implies the possibility of a life-threatening reaction and must prompt urgent escalation including intravascular fluid resuscitation. Refractory anaphylaxis is categorized as the need for 3 or more epinephrine doses and may warrant treatment with a continuous epinephrine infusion, intravenous fluids, and other resuscitative interventions. Patients with anaphylaxis are at risk of "anaphylactic shock," which is a form of distributive shock resulting in end-organ hypoperfusion. Management includes aggressive fluid resuscitation and if not responsive to intramuscular epinephrine, initiation of a continuous epinephrine infusion.

Adjunctive anaphylaxis therapies include H-1 and H-2 receptor antagonists, inhaled bronchodilators, supplemental oxygen, inhaled epinephrine, intravenous fluids, and systemic corticosteroids. The use of these therapies must never delay or supplant treatment with intramuscular epinephrine and should be guided by the best available evidence and clinical judgment.

We designed and executed the study to ensure that the study outputs had face validity and were generalizable to different specialties to promote their broad dissemination and implementation in clinical care and research. The 46-member expert panel included individuals from 14 countries and 7 specialties, and 36 medical and patient advocacy organizations endorsed the study outputs. Additionally, we used a high consensus threshold of ≥80% and surpassed this threshold for the definition (93.5%), overview (97.8%), and (93.5%) support tool after only one Delphi round.

The consensus anaphylaxis definition balances the shared (and sometimes divergent) priorities of health care providers and patient advocacy organizations. The definition would be worded differently if intended only for health care providers—specifically, by not including that anaphylaxis "may cause death," which is an uncommon event. However, patient advocacy organizations reinforced that some patients/caregivers are not aware that anaphylaxis may be fatal and thus thought strongly that the inclusion of "may cause death" was essential for educational purposes. Although there are potential downsides of including "may cause death," such as overemphasizing the true risk of fatalities, thereby causing undue stress for patients/caregivers, the expert panel, in collaboration with patient advocacy organizations, thought the potential benefit, particularly increased awareness by both patients and providers about the seriousness of anaphylaxis, outweighed the downsides, especially because it is not yet possible to predict anaphylaxis fatalities. Including "may cause death" also reinforces to providers, especially nonallergists, that any systemic allergic reaction has the potential to progress to a fatal outcome, and therefore epinephrine should always be the first-line therapy. The definition also includes easy-to-understand descriptions of organ systems to optimize

Anaphylaxis Clinical Support Tool

For Healthcare Professionals

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

1 No Known† Allergen Exposure

Sudden onset of an illness (minutes to several hours) with **Skin / Mucosal** involvement AND **either**:

- **Respiratory** involvement
- **Cardiovascular** involvement

2 Likely or Known† Allergen Exposure

Sudden onset of **two** or more of the following:

- **Skin / Mucosal** involvement
- **Respiratory** involvement
- **Cardiovascular** involvement
- Severe **Gastrointestinal** involvement ‡

3 Known† Allergen Exposure

Sudden onset of **either**:

- **Respiratory** involvement after exposure to a non-inhaled allergen
- **Cardiovascular** involvement

Intramuscular Epinephrine / Adrenaline*

- Should be given immediately for suspected anaphylaxis
- Can be given for patients that do not yet fulfill the criteria, based on clinical judgement

Administer in the middle third of the anterolateral thigh; repeat every 5-15 minutes if the patient does not respond

Manual

- 0.01 mg/kg = 0.01 mL/kg of 1 mg/mL (1:1000) solution
- Max single dose 0.5 mg

Auto-injectors

- < 13 kg: 0.1 mg or 0.15 mg
- 13 to < 25 kg: 0.15 mg
- ≥ 25 kg: 0.3 mg (≥ 50 kg: 0.3 mg or 0.5 mg)

Anaphylaxis Organ Systems§

Respiratory
wheezing, increased work of breathing¶, hypoxemia, cough, dyspnea
Laryngeal: stridor, voice change
Infants may also have a hoarse cry

Skin
urticaria, flushing, erythema, facial swelling
Infants may also have mottling

Cardiovascular
hypotension, syncope, dizziness, unexplained change in mental status
Infants may also have persistent unexplained tachycardia

Mucosal
lip, tongue, or oropharyngeal swelling, severe throat tightness, difficulty swallowing
Infants may also have repetitive lip licking

Gastrointestinal
severe crampy abdominal pain, repetitive vomiting, diarrhea

FIG 2. Anaphylaxis clinical support tool. *Recommendations from AAAAI, ACAAI, AAP, CSACI, and EAACI. Autoinjector dosing recommendations may not be in accordance with manufacturer recommendations. ASCIA recommends transitioning to 0.3 mg autoinjector for children weighing >20 kg. Some organizations recommend age-based dosing,[20,23,24,26] as follows: <12 months, 0.1 mg; <6 years, 0.15 mg; ≥6 years, 0.3 mg; and adolescents/adults, 0.5 mg. Intranasal epinephrine (Neffy) can be provided to patients weighing ≥30 kg. Administer one spray (2 mg epinephrine) in one nostril. If symptoms do not improve or worsen after initial treatment, administer second dose in same nostril with new nasal spray starting 5 minutes after first dose. †*Allergen* broadly includes any anaphylaxis trigger (eg, foods, insect stings, medications, exercise), irrespective of underlying mechanism. *No known allergen exposure* means the provider cannot determine whether there was allergen exposure or cannot identify likely allergens. Known allergens do not require confirmatory testing, as when suspicious symptoms develop after insect sting in someone without existing diagnosis. ‡Gastrointestinal involvement after noningested allergen exposure suggests anaphylaxis. Gastrointestinal involvement after ingested allergen exposure may be due to local and/or systemic reactions, a distinction that may be difficult to make in clinical practice. §Table I lists possible anaphylaxis signs/symptoms, including additional organ systems and nonspecific presentations. ¶"Increased work of breathing" refers to age-defined tachypnea that is not brief or self-resolving, use of accessory muscles, retractions, nasal flaring, or grunting (infants). *AAAAI,* American Academy of Allergy, Asthma & Immunology; *AAP,* American Academy of Pediatrics; *ACAAI,* American College of Allergy Asthma and Immunology; *ASCIA,* Australasian Society of Clinical Immunology and Allergy; *CSACI,* Canadian Society of Allergy and Clinical Immunology; *EAACI,* European Academy of Allergy and Clinical Immunology.

TABLE I. Potential anaphylaxis signs/symptoms

Organ system	Symptom	Sign	Infant
Skin/mucosa			
Skin	Pruritus, skin discomfort	Urticaria, erythema, flushing	Mottling
Mucosa	Mouth tingling, itchy mouth or throat, throat tightness,* discomfort	Facial swelling, conjunctival injection, chemosis, nasal congestion, rhinorrhea, throat clearing, lip swelling, tongue, soft palate, uvula swelling	Tongue thrusting or pulling, repetitive lip licking, ear tugging, eye rubbing
Respiratory			
General	Chest tightness, dyspnea	Cough, increased work of breathing, wheezing or bronchospasm, hypoxemia, apnea, cyanosis, pallor, reduced peak expiratory flow	—
Laryngeal	Throat tightness or discomfort	Voice change, hoarseness, stridor	Hoarse cry
Cardiovascular	Weak, dizzy, light-headed, palpitations, chest pain, blurred vision, difficulty hearing	Weak pulse, wide pulse pressure, syncope (collapse), cyanosis, pallor, arrhythmia, incontinence, bradycardia may occur in elderly and/or those in shock, hypotension,† shock, cardiac arrest	Persistent unexplained tachycardia, cyanosis
Gastrointestinal	Nausea, persistent crampy abdominal pain, dysphagia	Emesis, diarrhea, abdominal pain	Spitting up, hiccups, back arching
Neurologic‡	Confusion, drowsy, headache	Unexplained change in mental status, lethargy, somnolence, seizure	Hypotonia, persistent and unexplained irritability, inconsolability, crying, decreased activity
Other	Lower back pain in women due to uterine cramping, sense of impending doom, metallic taste, anxiety	—	—

Signs/symptoms may occur before or during anaphylaxis. Modified from severity subgrading system for acute allergic reactions.[32]
*Patient-reported throat tightness may indicate mucosal and/or laryngeal involvement—a distinction that is difficult to make in clinical practice without direct visualization of the laryngeal space.
†Hypotension was as previously defined:[1,32] infants aged 1 month to <12 months, systolic blood pressure (SBP) <70 mm Hg; children aged 1-10 years, SBP less than [70 mm Hg + (2 × age in years)]; adults and children aged >10 years, SBP <90 mm Hg; or decrease in SBP >30% from individual baseline.
‡May be secondary to other organ system involvement.

layperson comprehension. Additionally, some phrases favored by patient advocacy groups were omitted because they did not align with the framework of other medical definitions, namely that the definition should not include therapies (epinephrine).[1,7,12,33]

The anaphylaxis overview is the first summary document developed on the basis of input from an international expert panel and medical stakeholders. It is an invaluable educational tool to teach health care providers from different specialties and experience levels about crucial facets of anaphylaxis recognition and management. The overview provides clear recommendations when there is sound evidence supporting management practices but avoids making strong recommendations when there is insufficient evidence (eg, adjunctive therapies) and instead provides information about the best available evidence, including guidelines, systematic reviews, and practice parameters.[7,10-12]

The clinical support tool is a significant advancement in anaphylaxis care by incorporating key facets of anaphylaxis recognition and management—clinical criteria, epinephrine treatment indications and dosing, and common and serious findings, including in infants and young children—into one easy-to-use document. This will allow providers who may not have experience managing anaphylaxis an all-in-one reference to support both recognition and management decisions for patients across the age spectrum and in different clinical settings. Furthermore, developing widely agreed-on anaphylaxis criteria that build on the strong foundations of the NIAID/FAAN and WAO criteria and that attempt to resolve their limitations will help standardize clinical care and research to improve patient outcomes. Additional strengths of the support tool include reiterating that the clinical criteria are designed to determine the "likelihood" that a patient is having anaphylaxis, incorporating intramuscular epinephrine indications and dosing, emphasizing that epinephrine can be provided to patients whose disease does not yet fulfill the criteria according to clinical judgment, and summarizing common and serious anaphylaxis findings, including distinct infant signs, with user-friendly design features (organ system colors and graphics). Epinephrine is the only therapy included in the support tool, which is intentional. We want to reinforce to providers across disciplines that epinephrine is the first-line anaphylaxis therapy and should always be administered over adjunctive therapies.

The clinical support tool is not a substitute for provider judgment and experience because some elements, such as "severe" gastrointestinal involvement, cannot be easily defined or quantified. Ultimately, providers are responsible for incorporating information from the medical history (allergy history, allergen status) with presenting findings to determine the likelihood of anaphylaxis and whether to administer epinephrine. Although many clinical presentations are unquestionably anaphylaxis or not, the diagnosis may be uncertain, especially when the allergen is unknown, in infants and young children, or in patients who are predominantly experiencing subjective symptoms.

Limitations and future research priorities

First, the clinical support tool was developed on the bases of the best available evidence, clinical experience, and input from a large multidisciplinary expert panel using rigorous Delphi methodology.[32,34-36] However, there is a lack of basic or translational science to support the criteria.[37] Although there have been

Box 3. Organizations that endorsed study outputs

Medical
American Academy of Allergy, Asthma & Immunology (AAAAI)
American Academy of Pediatrics (AAP)
American Association of Nurse Anesthesiology (AANA)
American Association of Nurse Practitioners (AANP)
American College of Asthma, Allergy & Immunology (ACAAI)
Asia Pacific Association for Adult Allergy and Clinical Immunology (APAACI)
Asia Pacific Academy of Pediatric Allergy, Respirology and Immunology (APAPARI)
Australasian Society for Allergy and Clinical Immunology (ASCIA)
British Society for Allergy & Clinical Immunology (BSCAI)
Canadian Society for Allergy and Clinical Immunology (CSACI)
Chinese Society of Allergy
Emergency Nurses Association (ENA)
European Society for Emergency Medicine (EuSEM)
European Society of Anaesthesiology and Intensive Care (ESAIC)
German Society for Allergology and Clinical Immunology (DGAKI) Deutsche Gesellschaft für Allergologie und klinische Immunologie
National Association of Emergency Medical Technicians (NAEMT)
National Association of EMS Physicians (NAEMSP)
National Association of State EMS Officials (NASEMSO)
Polish Society of Allergology
Society of Critical Care Medicine (SCCM)
Society of Emergency Medicine PAs
Patient advocacy*
Allergy & Anaphylaxis Australia
Allergy Foundation of South Africa
Allergy UK
Anaphylaxis UK
Asociación Española de Personas con Alergia a Alimentos y Látex (AEPNAA)
Association Française pour la Prévention des Allergies (AFPRAL)
Asthma and Allergy Association
Asthma and Allergy Foundation of America (AAFA)
Deutscher Allergie- und Asthmabund (DAAB)
Food Allergy & Anaphylaxis Connection Team (FAACT)
Food Allergy Canada
Food Allergy Italia/European Federation of Allergy and Airways Diseases Patients' Associations
Food Allergy Research & Education (FARE)
ATOPICCO Network for Children of the Earth
S.O.S. Alergia

*Patient advocacy organizations were only asked whether they endorsed the anaphylaxis definition.

advances in identifying diagnostic and predictive anaphylaxis biomarkers, anaphylaxis remains a clinical diagnosis, and research is needed to identify and develop biomarker assays to support diagnostic and management decision-making.[11,37] Second, the new clinical criteria have not been validated. Although prospective research is needed to evaluate their utility and test characteristics in different clinical settings, these studies are challenging because there is no reference-standard comparator.[38,39]

Third, although in its present form the clinical support tool is static, future work is needed to develop smartphone, web-based, or electronic medical record applications embedded with the support tool to enhance its functionality, implementation, and dissemination.[40,41] Algorithms would take user input and determine whether patients are likely having anaphylaxis by asking users about the type of allergen exposure and automatically selecting the appropriate criterion and criterion-specific organ system. The applications would include interactive epinephrine dosing instructions, which would have the positive impact of limiting dosing errors and delays, especially in the prehospital setting and in low-resource environments. These features could be easily modified when new epinephrine delivery devices receive regulatory agency approval.[42-44]

Fourth, an important priority is to develop a patient-oriented decision support aid that is easy to use and readily accessible. This aid should promote appropriate and timely epinephrine receipt for patients/caregivers in the community by linking reaction findings with prescription epinephrine treatment advice.[13-15] Finally, the study outputs will need to be modified based on emerging evidence and experience using them in clinical care and research.

Conclusions

In this international anaphylaxis study, we developed a consensus anaphylaxis definition, overview, and clinical support tool. The anaphylaxis overview is a novel educational tool to teach health care providers about key facets of anaphylaxis care. We propose that the anaphylaxis definition and clinical support tool should replace previous definitions and criteria. The clinical support tool should facilitate improved anaphylaxis recognition and management, enhance epidemiologic surveillance, and standardize outcomes in observational and interventional studies. Future research is needed to disseminate and implement the clinical support tool into clinical care, validate its performance in different clinical settings, and develop a patient-oriented support tool to promote appropriate and timely epinephrine use in the community. The study outputs will require future refinement based on emerging evidence.

DISCLOSURE STATEMENT

Supported by the Global Allergy and Asthma Excellence Network, GA^{2}LEN Anaphylaxis Core, Division of Emergency Medicine, Cincinnati Children's Hospital Medical Center; the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) under award K23AI175525; the National Center for Advancing Translational Sciences, NIH, under award 2UL1TR001425-05A1; and the National Center for Advancing Translational Sciences, NIH, under award 2KL2TR001426-05A1. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Disclosure of potential conflict of interest: T. E. Dribin reports grant support from the National Institutes of Health, Cincinnati Children's Hospital Research Foundation, and the Center for Clinical & Translational Science & Training. A. Muraro reports speaker fees for Aimmune, Nestlé Health Science, Nestlé Purina, DVB Technologies, and Sanofi; and advisory boards for Sanofi, DVB Technologies, Nestlé Health Science, Novartis, and Regeneron. C. A. Camargo Jr has served on the scientific advisory boards of ARS Pharma, Aquestive, and Bryn. P. J. Turner reports service as chairperson for the World Allergy Organization (WAO) Anaphylaxis Committee and colead for the Resuscitation Council UK Anaphylaxis Guideline Group. J. Wang reports institutional clinical trial support from the NIH, Aimmune, DBV Technologies, and Siolta; consulting fees from DBV Technologies and Novartis; and royalties from UpToDate. G. Roberts is author of the EAACI Anaphylaxis Guidelines and president of the British Society for Allergy and Clinical Immunology. A. Anagnostou reports institutional funding from Novartis; advisory board member for

Ready, Set, Food, Novartis, Genentech, and Bryn; and consultation/speaker fees from ALK, EPG Health, MJH, Adelphi, Aimmune Therapeutics, Genentech, FARE, Medscape, and Innovation Horizons. S. Halken reports personal speaker fees from ALK Nordic, Viatris, Meadjohnson Europe, and Abigo; and personal fee from Stallergenes for being a member of IDMC for an allergen immunotherapy trial during the conduct of the study. J. Liebermann reports institutional funding from DBV and Novartis; advisor/consultant for ALK, Aquestive, ARS, Bryn, Genentech, Novartis Adjudication, AbbVie, Amgen, and Celldex; cochairship of Joint Task Force for Practice Parameters; and board member of the American Board of Allergy and Immunology. M. Worm reports honoraria and/or consulting fees from AbbVie, Aimmune Therapeutics, ALK-Abelló, Allergopharma, Almirall, Amgen, Biotest, Boehringer Ingelheim, DBV Technologies, Genzyme, Kymab, LEO Pharma, Eli Lilly, Mylan, Novartis, Pfizer, Regeneron Pharmaceuticals, Sanofi, Stallergenes Greer, and Worg Pharmaceutics. T. Zuberbier reports institutional funding for research, lecture honoria, and/or consulting from Amgen, AstraZeneca, AbbVie, ALK, Almirall, Astellas, Bayer Health Care, Bencard, Berlin Chemie, FAES, HAL, Henkel, Kryolan, Leti, L'Oreal, Meda, Menarini, Merck, MSD, Novartis, Pfizer, Sanofi, Stallergenes, Takeda, Teva, UCB, and Uriach; and is a member of Allergic Rhinitis and Its Impact on Asthma (ARIA)/World Health Organization, German Society for Allergology and Clinical Immunology, European Centre for Allergy Research Foundation, GA^{2}LEN, and WAO. H. A. Sampson reports funding to his institution for grants from the NIAID, NIH; consulting fees from DBV Technologies, N-Fold Therapeutics, and Siolta; and stock options from DBV Technologies and N-Fold Therapeutics.

Group authors: Montserrat Alvaro-Lozano, MD, MsC, PhD (1); Stefania Arasi, MD, PhD (2); Moshe Ben-Shoshan MD, MSc (3); Kirsten Beyer, MD (4); Dianne E. Campbell, MD, PhD (5); Ronna L. Campbell, MD, PhD (6); Victoria Cardona, MD, PhD (7); R. Sharon Chinthrajah, MD (8); Antoine Deschildre, MD (9); Motohiro Ebisawa, MD, PhD (10); Montserrat Fernandez-Rivas, MD, PhD (11); Alessandro Fiocchi MD (12); David M. Fleischer, MD (13); Adam T. Fox MD, FRCPCH (14); Katie Frith, MBBS (15,16); Lene H. Garvey, MD, PhD (17,18); R. Maximiliano Gómez, MD, PhD (19); Matthew Greenhawt, MD, MBA, MSc (13); Ruchi Gupta, MD, MPH (20,21); Douglas P. Mack, MSc, MD (22); Kenneth A. Michelson, MD, MPH (23); Caroline Nilsson MD, PhD (24); Anna Nowak-Wegrzyn, MD, PhD (25); Hanneke N. G. Oude Elberink, MD, PhD (26,27); Ruby Pawankar, MD, PhD (28); Guillaume Pouessel, MD (9); Pablo Rodriguez del Rio, MD, PhD (29); Nicholas Henry Sargant, MBBS, MRCPCH, MSc (30); Amy M. Scurlock, MD (31); Marcus S. Shaker, MD, MS (32,33); Peter Smith, MBBS, PhD (34,35); Jasmeet Soar, MB, BChir, FRCA, FFICM, FRCP (36); Brad Sobolewski, MD, MEd (37,38); Luciana Kase Tanno, MD, PhD (39,40,41); and Gary Wing-Kin Wong, MD (42).

Group author affiliations: (1) Allergology and Clinical Immunology Department, Hospital Sant Joan de Déu, Barcelona, Institut de Recerca Sant Joan de Déu, Universitat de Barcelona, Barcelona, Spain; (2) Translational Research in Pediatric Specialties Area, Division of Allergy, Bambino Gesù Children's Hospital, Rome, Italy; (3) Division of Allergy, Immunology, and Dermatology, Department of Pediatrics, McGill University Health Centre, Montreal, Quebec, Canada; (4) Department of Pediatric Respiratory Medicine, Immunology and Critical Care Medicine, Charité Universitätsmedizin Berlin, Berlin, Germany; (5) Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia; (6) Department of Emergency Medicine, Mayo Clinic, Rochester, Minn; (7) Department of Allergy, Hospital Universitari Vall d'Hebron, Barcelona, Spain; (8) Sean N Parker Center for Allergy and Asthma Research, Stanford University, Stanford, Calif; (9) CHU Lille, University of Lille, Pediatric Pulmonology and Allergy Unit, Hôpital Jeanne de Flandre, Lille, France; (10) Clinical Research Center for Allergy and Rheumatology, NHO Sagamihara National Hospital, Sagamihara, Japan; (11) Allergy Department, Hospital Clinico San Carlos, Facultad de Medicina, Universidad Complutense, IdISSC, Madrid, Spain; (12) Pediatric Hospital Bambino Gesù IRCCS, Rome, Italy; (13) University of Colorado School of Medicine and Children's Hospital Colorado, Aurora, Colo; (14) Guy's & St Thomas' Hospitals NHS Foundation Trust, London, England, United Kingdom; (15) Department of Immunology, Sydney Children's Hospital, Randwick, New South Wales, Australia; (16) School of Clinical Medicine, University of New South Wales, Sydney, New South Wales, Australia; (17) Allergy Clinic, Department of Dermatology and Allergy, Copenhagen University Hospital Gentofte, Copenhagen, Denmark; (18) Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; (19) Faculty of Health Sciences, Catholic University of Salta, Salta, Argentina; (20) Center for Food Allergy & Asthma Research, Institute for Public Health and Medicine, Northwestern University Feinberg School of Medicine, Chicago, Ill; (21) Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Ull; (22) Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada; (23) Division of Emergency Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Ill; (24) Department of Clinical Science and Education, Karolinska Institutet, Stockholm, Sweden; (25) New York University Grossman School of Medicine, New York, NY; (26) Department of Allergology, Internal Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; (27) Groningen Research Institute of Asthma and COPD, University of Groningen, Groningen, The Netherlands; (28) Department of Pediatrics, Nippon Medical School, Sendagi, Bunkyo-ku, Tokyo, Japan; (29) Servicio de Alergia, Hospital Universitario Niño Jesús, Madrid, Spain; (30) Bristol Royal Hospital for Children, Bristol, England, United Kingdom; (31) University of Arkansas for Medical Sciences Arkansas Children's Hospital and Research Institute, Little Rock, Ark; (32) Departments of Medicine and Pediatrics, Geisel School of Medicine at Dartmouth, Hanover, NH; (33) and Dartmouth-Hitchcock Medical Center, Section of Allergy and Clinical Immunology, Lebanon, NH; (34) Clinical Medicine, Griffith University, Southport, Queensland, Australia; (35) Queensland Allergy Services Private Practice, Queensland, Southport, Australia; (36) Southmead Hospital, North Bristol NHS Trust, Bristol, England, United Kingdom; (37) Division of Emergency Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; (38) Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio; (39) Division of Allergy, University of Montpellier, Montpellier, France; (40) Desbrest Institute of Epidemiology and Public Health, INSERM, University of Montpellier, Montpellier, France; (41) Montpellier WHO Collaborating Centre on Scientific Support of Classifications, Montpellier, France; and (42) Department of Paediatrics, Chinese University of Hong Kong, Hong Kong.

Group author disclosures of potential conflict of interest (those not listed here report no relevant conflict of interest): S. Arasi reports participation as advisory board member, consultant, and/or speaker for DBV, Novartis, Aimmune, and Ulrich outside the submitted work. M. Ben-Shoshan reports participation as consultant for Sanofi and Novartis. K. Beyer reports grants from the German Research Foundation, the Federal Ministry of Education and Research, and the Federal Ministry of Food and Agriculture, as well as from Aimmune, Danone/Nutricia, DBV, Hipp, Hycor, Infectopharm, and Novartis; personal fees from Aimmune, Akademie Fresenius, Allergy Therapeutics, ALK, Danone/Nutricia, Hipp, Hycor, Infectopharm, Kantar Health, Limbach Gruppe, Mylan/Meda/Mice, Nestlé, Novartis, Sonic Health Care, and ThermoFisher. D. E. Campbell reports part-time employment at DBV; receipt of technology research grants to institution; and National Health and Medical Research Council of Australia and Food Allergy Research and Education executive member and training and innovation lead, National Allergy Centre of Excellence, Australia Member Clinical Governance Committee, Westhead Fertility Centre, University of Sydney, Australia. R. L. Campbell reports participation as consultant for Bryn Pharma Author for UpToDate. V. Cardona reports funding for services as advisor, speaker and/or researcher for Allergy Therapeutics and Thermo Fisher. R. S. Chinthrajah reports grant support from the Consortium for Food Allergy Research (CoFAR), National Institute of Allergy and Infectious Disease (NIAID), and Food Allergy Research. A. Deschildre reports fees for lectures and honoraria for attending advisory

boards from Novartis, GSK, Sanofi, Regeneron, AstraZeneca, Aimmune, Viatris, ALK, and Stallergenes-Greer outside the submitted work. M. Ebisawa reports receipt of lecture fees from Viatris, SAB, ARS-Pharmaceuticals, Novartis, and Sanofi. A. Fiocchi reports research grants from Ferrero, Hipp, Sanofi, Novartis, AstraZeneca, and DBV; and fees for presentations and advisory boards for Danone, Abbott, Ferrero, Stallergenes, and Novartis. D. M. Fleischer reports research grants to institution from ARS Pharmaceuticals and DBV Technologies; unpaid advisory board member for Food Allergy & Anaphylaxis Connection Team and the National Peanut Board; royalties from UpToDate; consultation fees as a member of physician/medical advisory boards to Aquestive, ARS Pharmaceuticals, Bryn Pharma, DBV Technologies, Genentech, and Nasus; and speaker fees from Genentech outside the submitted work. A. T. Fox reports participation as chair, UK National Allergy Strategy Group; chair, Allergy UK Health Advisory Board; previous trustee of British Society for Allergy & Clinical Immunology; safety monitor for commercial clinical trials for ALK-Abelló; and lecture fees from Aimmune. L. H. Garvey reports personal speaker fees from ALK Nordic, Viatris, and Thermo Fisher; and adjudication committee member Merck and Biomarin. M. Greenhawt is a consultant for Aquestive; and is a member of physician/medical advisory boards for DBV Technologies, Takeda, Griffols, Nutricia, Novartis, Aquestive, and Allergy. R. Gupta receives research support from the National Institutes of Health (NIH), Food Allergy Research & Education, Melchiorre Family Foundation, Sunshine Charitable Foundation, Novartis, and Genentech; serves as medical consultant/advisor for Genentech, Novartis, Food Allergy Research & Education, OWYN, Kaléo, Aquestive Therapeutics, and Byrn Pharma; and holds an ownership interest in Yobee Care. D. P. Mack reports consulting for ALK-Abelló, DBV, Alladapt, Bausch Health, and Pfizer; and is an investigator for ALK-Abelló and DBV. C. Nilsson reports grants to institution from Aimmune Therapeutics, a Nestlé Company; and lecture fees from ALK, Themofisher, and GSK. H. N. Oude Elberink reports consultancy fees to instituiuon from ALK-Abelló; has received fees for delivering lectures from ALK-Abelló, Mylan, Sanofi-Genzyme, and Novartis; has received consultancy fees from ALK-Abelló, Novarti, Blueprint, and Cogent; has received research support from Novartis, Mylan, ALK-Abelló, Aimmune, Cogent and Blueprint; and has received payment for developing educational presentations from ALK-Abelló and Mylan. G. Pouessel has provided consultation and speaker services for AI Therapeutics, Bausch+Lomb, Stallergenes, Novartis, DVB Technology, ALK-Abelló, Theravia, and Bioprojet; and serves as medical consultant/advisor for Theravia and Bioprojet. P. Rodriguez del Rio reports service as speaker for GSK, FAES, Novartis, ALK-Abelló, LETI, Sanofi, Stallergenes, DBV, EPG-Health, Roxall, Diater, and AstraZeneca. A. M. Scurlock reports grant funding from NIAID-NIH/CoFAR; grant funding from Food Allergy Research and Education (FARE); and clinical trial funding from Aravax, Novartis, Siolta Therapeutics, Genentech, and ALK. M. S. Shaker reports membership in the Joint Task Force on Practice Parameters; serves on the editorial boards of *The Journal of Allergy and Clinical Immunology In Practice* and *Journal of Food Allergy;* is associate editor of *Annals of Allergy, Asthma & Immunology;* and serves on the board of directors of the American Academy of Allergy, Asthma & Immunology (views expressed are his own). J. Soar reports editorship of *Resuscitation;* receipt of payment from Elsevier; and cochairship of the Resuscitation Council UK Anaphylaxis Working Group. G. W. Wong reports consultancy for Nestlé Nutrition Institution and Haleon.

We acknowledge the following at the Division of Emergency Medicine, Cincinnati Children's Hospital Medical Center, for their contributions to the study: Selena McKean (project management); Lillian Klein, BS (project management); and Stephanie Boyd, PhD (data management).

We acknowledge the following for reviewing and/or endorsing study outputs and definitions: Moshe Ben-Shoshan, MD, MSc, for the Canadian Society of Allergy and Clinical Immunology (CSACI), reviewed and endorsed the study outputs; Gailen D. Marshall Jr, MD, PhD, reviewed and endorsed the study outputs on behalf of the American College of Allergy, Asthma & Immunology (ACAAI); Timothy P. Chizmar, MD, for the National Association of State EMS Officials (NASEMSO), reviewed and endorsed the study outputs; James "Tripp" E. Winslow, MD, MPH, for the National Association of State EMS Officials (NASEMSO), reviewed and endorsed the study outputs; Angel Sánchez Sanz, for the Asociación Española de Personas con Alergia a Alimentos y Látex (AEPNAA), reviewed and endorsed the anaphylaxis definition; Michael Levin, MBChB, PhD, for the Allergy Foundation of South Africa, reviewed and endorsed the anaphylaxis definition; Katie Frith, MBBS, for the Australasian Society of Clinical Immunology and Allergy (ASCIA), reviewed and endorsed the study outputs; Sophie Vallis, for Anaphylaxis UK, reviewed and endorsed the anaphylaxis definition; Mary Kelly, for Anaphylaxis UK, reviewed and endorsed the anaphylaxis definition; the European Society for Emergency Medicine (EuSEM) reviewed and endorsed the study outputs; Jacob Miller, for the Emergency Nurses Association, reviewed and endorsed the study outputs; Alicia Valerio, for the American Association of Critical Care Nurses, reviewed the study outputs; Gustavo Andres Marino, for S.O.S. Alergia, reviewed and endorsed the anaphylaxis definition; Céline Demoulin, for the Association Française pour la Prévention des Allergies (AFPRAL), reviewed and endorsed the anaphylaxis definition; Emma E. Cook and Tomomi Akagi, for ATOPICCO Network for Children of the Earth, reviewed and endorsed the anaphylaxis definition; Dobromir Penkov, for the European Medicines Agency, reviewed and provided feedback about the study outputs; Melanie Carver, for the Asthma and Allergy Foundation of America, reviewed and endorsed the anaphylaxis definition; Michael Gooch, for the American Association of Nurse Practitioners, reviewed and endorsed the study outputs; Johnnie Sue Wijewardane, for the American Association of Nurse Practitioners, reviewed and endorsed the study outputs; Ruby Pawankar, MD, PhD, for the Asia Pacific Association for Adult Allergy and Clinical Immunology (APAACI), reviewed and endorsed the study outputs; Mikaela Odemyr, for the Asthma and Allergy Association, reviewed and endorsed the anaphylaxis definition; Jennifer Gerdts, for Food Allergy Canada, reviewed and endorsed the anaphylaxis definition; Amy M. Scurlock, MD, for the American Academy of Pediatrics, reviewed the study outputs; Jose G. Cabanas, MD, MPH, president of the National Association of EMS Physicians (NAEMSP), reviewed and endorsed the study outputs; the American College of Emergency Physicians (ACEP) reviewed the study outputs; the Australasian College for Emergency Medicine (ACEM) reviewed the study outputs; Kevin Driscoll, DNP, MSN, CRNA, and Paula Belson, PhD, CRNA, FAANA, for the American Association of Nurse Anesthesiology (AANA), reviewed and endorsed the study outputs; Radmilo Jankovic, MD, PhD, and Carolina S. Romero, MD, MStat, PhD, and Arash Afshari, MD, PhD, for the European Society of Anaesthesiology and Intensive Care (ESAIC), reviewed and endorsed the study outputs; Wolfgang Buhre, president of ESAIC, reviewed and endorsed the study outputs; Heatherlee Bailey, MD, MCCM, for the Society of Critical Care Medicine (SCCM), reviewed and endorsed the study outputs; Marcus S. Shaker, MD, MS, FAAAAI, for the American Academy of Allergy, Asthma & Immunology (AAAAI), reviewed and endorsed the study outputs; Motohiro Ebisawa, MD, PhD, and Gary Wing-Kin Wong, MD, for the Asia Pacific Academy of Pediatric Allergy, Respirology and Immunology (APAPARI), reviewed and endorsed the study outputs; Graham Roberts, DM, for the British Society of Allergy and Clinical Immunology, reviewed and endorsed the study outputs; Jeffrey L. Jarvis, MD, EMT-P, for the National Association of Emergency Medical Technicians (NAEMT), reviewed and endorsed the study outputs; Ronald Rabin, Joohee Lee, MD, Kathleen Hise, MD, and Anubha Tripathi, MD, for the US Food and Drug Administration (FDA), reviewed and provided feedback about the study outputs; Alkis Togias, MD, and Patricia Fulkerson, MD, PhD, for NIAID, reviewed and provided feedback about the study outputs; Vera Mahler, MD, for the Paul-Ehrlich Institut, reviewed and provided feedback about the study outputs; Marcia Podestà, for the Food Allergy Italia/European Federation of Allergy and Airways Diseases Patients' Associations, reviewed and endorsed the anaphylaxis definition; Sabine Schnadt, for the Deutscher Allergie- und Asthmabund (DAAB), reviewed and endorsed the anaphylaxis definition; Simone Miles, CEO of Allergy UK, endorsed the anaphylaxis definition; Margaret Kelman, for Allergy UK, reviewed and endorsed the anaphylaxis definition; Maria Said, AM, for Allergy and Anaphylaxis Australia, reviewed and endorsed the anaphylaxis definition; Eleanor Garrow-Holding, president and CEO of the Food Allergy & Anaphylaxis Connection Team (FAACT), reviewed and endorsed the anaphylaxis definition; Anita Roach, for FARE, reviewed and endorsed the anaphylaxis definition; Michael J. Parr, MBBS, for the Australian Resuscitation Council, reviewed the study outputs; Maciej Kupczyk, MD, PhD, for the Polish Society of Allergology, reviewed and endorsed the study outputs; the German Society for Allergology and Clinical Immunology

(DGAKI) reviewed the study outputs; the French Allergy Society reviewed the study outputs; the Spanish Society of Allergology and Clinical Immunology (SEAIC) reviewed the study outputs; and Tom McNally, PA-C, for the Society of Emergency Medicine PAs, reviewed and endorsed the study outputs.

Key messages

- **The anaphylaxis overview is a novel educational tool, and we propose that the definition should replace previous definitions.**
- **The clinical support tool should facilitate improved anaphylaxis recognition and management and standardize research outcomes.**

REFERENCES

1. Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391-7.
2. Michelson KA, Dribin TE, Vyles D, Neuman MI. Trends in emergency care for anaphylaxis. J Allergy Clin Immunol Pract 2020;8:767-8.e2.
3. Dribin TE, Neuman MI, Schnadower D, Sampson HA, Porter JJ, Michelson KA. Trends and variation in pediatric anaphylaxis care from 2016-2022. J Allergy Clin Immunol Pract 2023;11:1184-9.
4. Turner PJ, Campbell DE, Motosue MS, Campbell RL. Global trends in anaphylaxis epidemiology and clinical implications. J Allergy Clin Immunol Pract 2020;8:1169-76.
5. Motosue MS, Bellolio MF, Van Houten HK, Shah ND, Campbell RL. Increasing emergency department visits for anaphylaxis, 2005-2014. J Allergy Clin Immunol Pract 2017;5:171-5.e3.
6. Pumphrey RSH, Stanworth SJ. The clinical spectrum of anaphylaxis in north-west England. Clin Exp Allergy 1996;26:1364-70.
7. Cardona V, Ansotegui IJ, Ebisawa M, El-Gamal Y, Fernandez Rivas M, Fineman S, et al. World Allergy Organization anaphylaxis guidance, 2020. World Allergy Organ J 2020;13:100472.
8. Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. N Engl J Med 1992;327:380-4.
9. Turner PJ, Jerschow E, Umasunthar T, Lin R, Campbell DE, Boyle RJ. Fatal anaphylaxis: mortality rate and risk factors. J Allergy Clin Immunol Pract 2017;5:1169-78.
10. Shaker MS, Wallace DV, Golden DBK, Oppenheimer J, Bernstein JA, Campbell RL, et al. Anaphylaxis—a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. J Allergy Clin Immunol 2020;145:1082-123.
11. Golden DBK, Wang J, Waserman S, Akin C, Campbell RL, Ellis AK, et al. Anaphylaxis: a 2023 practice parameter update. Ann Allergy Asthma Immunol 2024;132:124-76.
12. Muraro A, Worm M, Alviani C, Cardona V, DunnGalvin A, Garvey LH, et al. EAACI guidelines: anaphylaxis (2021 update). Allergy 2022;77:357-77.
13. Dribin TE, Waserman S, Turner PJ. Who needs epinephrine? Anaphylaxis, autoinjectors, and parachutes. J Allergy Clin Immunol Pract 2023;11:1036-46.
14. Dribin TE. The need to link anaphylaxis signs and symptoms with targeted therapeutic strategies. Ann Allergy Asthma Immunol 2023;131:135-6.
15. Greenhawt M, Lieberman JA, Dribin TE, Shaker MS, Spergel J. Retire the advice to send patients to the emergency room after epinephrine use for observation. Ann Allergy Asthma Immunol 2023;130:697-8.
16. Uy EJB. Key concepts in clinical epidemiology: estimating pre-test probability. J Clin Epidemiol 2022;144:198-202.
17. Motosue MS, Li JT, Campbell RL. Anaphylaxis: epidemiology and differential diagnosis. Immunol Allergy Clin North Am 2022;42:13-25.
18. Dribin TE, Motosue MS, Campbell RL. Overview of allergy and anaphylaxis. Emerg Med Clin North Am 2022;40:1-17.
19. Gabrielli S, Clarke A, Morris J, Eisman H, Gravel J, Enarson P, et al. Evaluation of prehospital management in a canadian emergency department anaphylaxis cohort. J Allergy Clin Immunol Pract 2019;7:2232-8.e3.
20. Resuscitation Council UK (RCUK). Emergency treatment of anaphylaxis: guidelines for healthcare providers. London (United Kingdom): RCUK; 2021:1-61.
21. Frith K, Smith J, Joshi P, Ford LS, Vale S. Updated anaphylaxis guidelines: management in infants and children. Aust Prescr 2021;44:91-5.
22. Shah MI, Ostermayer DG, Browne LR, Studnek JR, Carey JM, Stanford C, et al. Multicenter evaluation of prehospital seizure management in children. Prehosp Emerg Care 2021;25:475-86.
23. Australia New Zealand Committee on Resuscitation (ANZCOR). ANZCOR guideline 9.2.7—first aid management of anaphylaxis. 2019. Available at: https://www.anzcor.org/home/new-guideline-page-2/guideline-9-2-7-first-aid-management-of-anaphylaxis/.
24. Whyte AF, Soar J, Dodd A, Hughes A, Sargant N, Turner PJ. Emergency treatment of anaphylaxis: concise clinical guidance. Clin Med 2022;22:332-9.
25. Pediatric dose optimization for seizures in EMS (PediDOSE). NIH RePORTER. August 1, 2021. Available at: https://reporter.nih.gov/search/lItIcqf_akqg5-ddzyLc9A/project-details/10211793#details. Accessed June 3, 2024.
26. National Association of State Emergency Medical Services Officials (NASEMSO). National model EMS clinical guidelines. 2022. Available at: https://nasemso.org/docs.ashx?id=1444322.
27. Hoyle JD Jr, Ekblad G, Hover T, Woodwyk A, Brandt R, Fales B, et al. Dosing errors made by paramedics during pediatric patient simulations after implementation of a state-wide pediatric drug dosing reference. Prehosp Emerg Care 2020;24:204-13.
28. Kazi R, Hoyle JD Jr, Huffman C, Ekblad G, Ruffing R, Dunwoody S, et al. An analysis of prehospital pediatric medication dosing errors after implementation of a state-wide EMS pediatric drug dosing reference. Prehosp Emerg Care 2024;28:43-9.
29. Lim CAE, Kaufman BJ, O'Connor J, Cunningham SJ. Accuracy of weight estimates in pediatric patients by prehospital emergency medical services personnel. Am J Emerg Med 2013;31:1108-12.
30. Handorf A, Roy IR, Cohen A, Camargo CA, Dribin TE, Pistiner M. Development and evaluation of modified criteria for infant and toddler anaphylaxis. J Allergy Clin Immunol Pract 2024.
31. Greenhawt M, Gupta RS, Meadows JA, Pistiner M, Spergel JM, Camargo CA, et al. Guiding principles for the recognition, diagnosis, and management of infants with anaphylaxis: an expert panel consensus. J Allergy Clin Immunol Pract 2019;7:1148-56.e5.
32. Dribin TE, Schnadower D, Spergel JM, Campbell RL, Shaker M, Neuman MI, et al. Severity grading system for acute allergic reactions: a multidisciplinary Delphi study. J Allergy Clin Immunol 2021;148:173-81.
33. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:801-10.
34. Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, et al. Developing a new definition and assessing new clinical criteria for septic shock: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:775-87.
35. Greenhawt M, Dribin TE, Abrams EM, Shaker M, Chu DK, Golden DBK, et al. Updated guidance regarding the risk of allergic reactions to COVID-19 vaccines and recommended evaluation and management: a GRADE assessment and international consensus approach. J Allergy Clin Immunol 2023;152:309-25.
36. Mack DP, Dribin TE, Turner PJ, Wasserman RL, Hanna MA, Shaker M, et al. Preparing patients for oral immunotherapy (PPOINT): international Delphi consensus for procedural preparation and consent. J Allergy Clin Immunol 2024;153:1621-33.
37. Dribin TE, Schnadower D, Wang J, Camargo CA Jr, Michelson KA, Shaker M, et al. Anaphylaxis knowledge gaps and future research priorities: a consensus report. J Allergy Clin Immunol 2022;149:999-1009.
38. Campbell RL, Hagan JB, Manivannan V, Decker WW, Kanthala AR, Bellolio MF, et al. Evaluation of National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network criteria for the diagnosis of anaphylaxis in emergency department patients. J Allergy Clin Immunol 2012;129:748-52.
39. Loprinzi Brauer CE, Motosue MS, Li JT, Hagan JB, Bellolio MF, Lee S, et al. Prospective validation of the NIAID/FAAN criteria for emergency department diagnosis of anaphylaxis. J Allergy Clin Immunol Pract 2016;4:1220-6.
40. Agarwal S, Glenton C, Tamrat T, Henschke N, Maayan N, Fønhus MS, et al. Decision-support tools via mobile devices to improve quality of care in primary healthcare settings. Cochrane Database Syst Rev 2021;(7):CD012944.
41. Sutton RT, Pincock D, Baumgart DC, Sadowski DC, Fedorak RN, Kroeker KI. An overview of clinical decision support systems: benefits, risks, and strategies for success. NPJ Digit Med 2020;3:17.
42. Casale TB, Ellis AK, Nowak-Wegrzyn A, Kaliner M, Lowenthal R, Tanimoto S. Pharmacokinetics/pharmacodynamics of epinephrine after single and repeat administration of neffy, EpiPen, and manual intramuscular injection. J Allergy Clin Immunol 2023;152:1587-96.
43. Dworaczyk DA, Hunt A, Di Spirito M, Lor M, Rance K, van Haarst AD. Randomized trial of pharmacokinetic and pharmacodynamic effects of 13.2 mg intranasal epinephrine treatment in congestion. Ann Allergy Asthma Immunol 2024;133:186-93.e2.
44. Bernstein D, Oppenheimer J, Golden D, Camargo C, Greenhawt M, Fleischer D, et al. Pharmacokinetics of epinephrine sublingual film following three different administration procedures. J Allergy Clin Immunol 2023;151:abstract 6.

METHODS

A modified Delphi process was conducted to achieve consensus for the study outputs.[E1-E4] Consensus was defined as ≥80% agreement for the study outputs, with a minimum of 80% of experts having to complete each survey round. An anonymous electronic REDCap survey was sent to experts (May 28, 2024) asking them to rate their level of agreement on a 4-point scale for each output, statement, or question, as follows: 1 = strongly disagree; 2 = disagree; 3 = agree; and 4 = strongly agree. "Strongly agree" and "agree" were grouped as "agree," and "strongly disagree" and "disagree" were grouped as "disagree." If consensus was not achieved after the first Delphi round, up to 2 additional rounds were conducted to seek consensus. In the subsequent survey rounds, panelists were provided with the results from the previous rounds, including free-text comments to inform their responses. If consensus was not achieved after the third round, the outputs were categorized as "consensus not achieved."

This study was approved by the institutional review board at Cincinnati Children's Hospital Medical Center.

REFERENCES

E1. Dribin TE, Sampson HA, Camargo CA Jr, Brousseau DC, Spergel JM, Neuman MI, et al. Persistent, refractory, and biphasic anaphylaxis: a multidisciplinary Delphi study. J Allergy Clin Immunol 2020;146:1089-96.

E2. Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, et al. Developing a new definition and assessing new clinical criteria for septic shock: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:775-87.

E3. Mack DP, Dribin TE, Turner PJ, Wasserman RL, Hanna MA, Shaker M, et al. Preparing patients for oral immunotherapy (PPOINT): international Delphi consensus for procedural preparation and consent. J Allergy Clin Immunol 2024;153:1621-33.

E4. Dribin TE, Schnadower D, Spergel JM, Campbell RL, Shaker M, Neuman MI, et al. Severity grading system for acute allergic reactions: a multidisciplinary Delphi study. J Allergy Clin Immunol 2021;148:173-81.

E5. Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391-7.

TABLE E1. NIAID/FAAN clinical criteria for diagnosing anaphylaxis

1. Acute onset of illness (minutes to several hours) with involvement of skin and/or mucosal tissue (eg, generalized hives; pruritus or flushing; swollen lips, tongue, uvula) and at least *one* of:
   a. Respiratory compromise (eg, dyspnea, wheeze–bronchospasm, stridor, reduced PEF, hypoxemia).
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence).
2. Two or more of the following that occur rapidly after exposure to *likely* allergen for that patient (minutes to several hours):
   a. Involvement of skin/mucosa tissue (eg, generalized hives; itch–flush; swollen lips, tongue, uvula).
   b. Respiratory compromise (eg, dyspnea, wheeze–bronchospasm, stridor, reduced PEF, hypoxemia).
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting).
3. Reduced BP after exposure to *known* allergen for that patient (minutes to several hours):
   a. Infants and children: low SBP (age specific) or >30% decrease in SBP.*
   b. Adults: SBP <90 mm Hg or >30% decrease from individual baseline.

Anaphylaxis is highly likely when any one of the 3 criteria are fulfilled.[E5]

BP, Blood pressure; *PEF,* peak expiratory flow; *SBP,* systolic BP.

*Low SBP for children is defined as <70 mm Hg from 1 month to 1 year; less than [70 mm Hg + (2 × age)] from 1 to 10 years; and <90 mm Hg from 11 to 17 years.

TABLE E2. Expert panel characteristics

Characteristic	No. (%)
Medical specialty*	
Allergy/immunology	40 (87.0)
Anesthesia	2 (4.3)
Emergency medicine	5 (10.9)
Epidemiology, public health	1 (2.2)
Intensive care	2 (4.3)
Primary care	1 (2.2)
Pulmonary	1 (2.2)
Patient population	
Pediatric	27 (58.7)
Adult	4 (8.7)
Pediatric and adult	15 (32.6)
Country of practice/work	
Argentina	1 (2.2)
Australia	3 (6.5)
Canada	2 (4.3)
China	1 (2.2)
Denmark	2 (4.3)
France	3 (6.5)
Germany	3 (6.5)
Italy	3 (6.5)
Japan	2 (4.3)
The Netherlands	1 (2.2)
Spain	4 (8.7)
Sweden	1 (2.2)
United Kingdom	5 (10.9)
United States	15 (32.6)

*Experts may be trained in more than one specialty.

TABLE E3. Participating organizations

Organization name (abbreviation)	Country/region	Organization type
Medical		
American Academy of Allergy, Asthma & Immunology (AAAAI)	United States	Allergy/immunology
American Academy of Pediatrics (AAP)	United States	Allergy/immunology, pediatrics
American Association of Critical Care Nurses (AACN)	United States	Critical care, nursing
American Association of Nurse Anesthesiology (AANA)	United States	Nurse anesthetists
American Association of Nurse Practitioners (AANP)	United States	Nurse practitioners
American College of Asthma, Allergy & Immunology (ACAAI)	United States	Allergy/immunology
American College of Emergency Physicians (ACEP)	United States	Emergency medicine
Asia Pacific Association for Adult Allergy and Clinical Immunology (APAACI)	Asia Pacific	Allergy/immunology
Asia Pacific Academy of Pediatric Allergy, Respirology and Immunology (APAPARI)	Asia Pacific	Allergy/immunology, pediatrics
Australasian College for Emergency Medicine (ACEM)	Australia/New Zealand	Emergency medicine
Australian Resuscitation Council	Australia	Represents all major groups involved in teaching and practice of resuscitation
Australasian Society for Allergy and Clinical Immunology (ASCIA)	Australia/New Zealand	Allergy/immunology
British Society for Allergy & Clinical Immunology (BSCAI)	United Kingdom	Allergy/immunology
Canadian Society for Allergy and Clinical Immunology (CSACI)	Canada	Allergy/immunology
Chinese Society of Allergy	China	Allergy/immunology
Emergency Nurses Association (ENA)	United States	Emergency medicine, advanced practice registered nurses, nursing
European Medicines Agency (EMA)*	European Union	Regulatory
European Society of Anaesthesiology and Intensive Care (ESAIC)	European Union	Anesthesiology, critical care
European Society for Emergency Medicine (EuSEM)	European Union	Emergency medicine, emergency medical services, nursing, pediatrics, scientific/research
French Allergy Society	France	Allergy/immunology
German Society for Allergology and Clinical Immunology/Deutsche Gesellschaft für Allergologie und klinische Immunologie (DGAKI)	Germany	Allergy/immunology
National Association of Emergency Medical Technicians (NAEMT)	United States	Emergency medical services
National Association of EMS Physicians (NAEMSP)	United States	Emergency medical services
National Association of State EMS Officials (NASEMSO)	United States	Emergency medical services
National Institute of Allergy and Infectious Diseases (NIAID)†	United States	Research agency
Paul-Ehrlich Institut‡	Germany	Regulatory
Polish Society of Allergology	Poland	Allergy/immunology
Society of Critical Care Medicine (SCCM)	United States	Critical care
Society of Emergency Medicine PAs	United States	Emergency medicine
Spanish Society of Allergology and Clinical Immunology (SEAIC)	Spain	Allergy/immunology
US Food and Drug Administration (FDA)§	United States	Regulatory
Patient advocacy		
Allergy & Anaphylaxis Australia	Australia	Patient advocacy
Allergy Foundation of South Africa	South Africa	Patient advocacy
Allergy UK	United Kingdom	Patient advocacy
Anaphylaxis UK	United Kingdom	Patient advocacy
Asociación Española de Personas con Alergia a Alimentos y Látex (AEPNAA)	Spain	Patient advocacy
Association Française pour la Prévention des Allergies (AFPRAL)	France	Patient advocacy
Asthma and Allergy Association	Sweden	Patient advocacy
Asthma and Allergy Foundation of America (AAFA)	United States	Patient advocacy
Deutscher Allergie- und Asthmabund (DAAB)	Germany	Patient advocacy
Food Allergy & Anaphylaxis Connection Team (FAACT)	United States	Patient advocacy
Food Allergy Canada	Canada	Patient advocacy
Food Allergy Italia/European Federation of Allergy and Airways Diseases Patients' Associations	European Union/Italy	Patient advocacy
Food Allergy Research & Education (FARE)	United States	Patient advocacy
ATOPICCO Network for Children of the Earth	Japan	Patient advocacy
S.O.S. Alergia	Argentina	Patient advocacy

*The views expressed during the study are the personal views of the EMA participant and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA.

†The views expressed during the study are the personal views of the NIAID participants and may not be understood or quoted as being made on behalf of or reflecting the position of the NIAID.

‡The views expressed during the study are the personal views of the PEI participant and may not be understood or quoted as being made on behalf of or reflecting the position of the PEI.

§The views expressed during the study are the personal views of the FDA representatives and may not be understood or quoted as being made on behalf of or reflecting the position of the FDA.

TABLE E4. Delphi and study output endorsement comments

Domain	Delphi comments
Definition	● I would prefer more objective criteria for definition combining the NIAID/WAO (2 organ systems or hypotension/Resp distress after potential allergen). ● Too long and too much detail about organ involvement. I am missing the ABC as this is what makes the definition operational. I wonder if the last sentence could read "Life-threatening anaphylaxis is characterized by involvement of airway/breathing and/or cardiovascular system and may occur without skin/mucosa involvement. ● The multiple parentheticals are distracting, but ultimately I can live with this. If the definition is for clinicians, the parentheticals can be removed. If it's for families, the parentheticals should be there. It's hard to serve both groups well at the same time. ● Very minor edit but perhaps write "lungs" (plural) ● I don't love the "may cause death." So can asthma. Is that how we define asthma? ● I don't like the specific reference to lip involvement as an example of skin/mucosa symptoms. Otherwise, I'm happy with the suggested definition. ● Anaphylaxis is a serious allergic reaction (hypersensitivity) that can progress rapidly and may cause death. It may involve the skin/mucosa (includes lip/tongue), respiratory (lung, breathing), cardiovascular (heart, blood pressure), and/or gastrointestinal (stomach/gut) systems. Potentially life-threatening anaphylaxis is characterized by respiratory and/or cardiovascular involvement and may occur without skin/mucosa involvement.
Overview	● The sentence about "anaphylaxis triggers" should be placed after the clinical symptoms and presentation. Regarding anaphylaxis treatment, one sentence seems to be repeated twice. "Management includes aggressive fluid resuscitation and if not responsive to intramuscular epinephrine, initiation of a continuous epinephrine infusion." In all guidelines, O_2 therapy is required as soon as there is no improvement after the first adrenaline doses in particular in case of respiratory and/or cardiovascular involvement. O_2 therapy should not be considered as an additional therapy on the same line as H_1-H_2 antagonists. This should be highlighted. "Management includes aggressive fluid resuscitation and if not responsive to intramuscular epinephrine, initiation of a continuous epinephrine infusion." I would add "under the strict supervision of experienced physicians and close monitoring." "There have been no randomized controlled trials of anaphylaxis therapies, and thus therapeutic recommendations are based on clinical experience, observational studies, animal models, or extrapolation from conditions with similar presentations." I would delete this sentence as it could send a confusing message about the need for adrenaline to treat anaphylaxis. ● Concise overview. Nice that ABC approach is included. Would like a bit more information about how to interpret tryptase. Still feel that fluids should be introduced earlier ie when there is no response to the first adrenaline dose. I suggest the sentence should be Repeat epinephrine is indicated when patients do not respond to initial dosing and fluids. ● I think it would be useful to stress that symptoms appear more or less simultaneously or in a short period of time. ● Each statement is fair and well written, but they don't flow all that well from one to another and there is a bit of duplication. I would add to the Tryptase statement "Tryptase may be helpful to obtain, depending on the clinical scenario, for later supporting the diagnosis." That a negative or low serum Tryptase does not rule out anaphylaxis—it has a poor negative predictive value. "Adjunctive therapies include"—the role of and evidence for use of corticosteroids is anaphylaxis is very limited. I would be in favor of caveating the corticosteroid mention—perhaps—limited evidence for the effectiveness of corticosteroids in the management of anaphylaxis outside biphasic and refractory anaphylaxis. ● In reality—most anaphylaxis self resolves. ● My only suggested edit would be to move the sentence about indications for repeat adrenaline doses to immediately after the sentence about IM adrenaline administered in the anterolateral thigh being the first line treatment for anaphylaxis. This can then be followed with the line about IV adrenaline being the preferred route for anaphylaxis during general anesthesia. ● Grammar. . . . Infants may have a hoarse cry. It is missing "a." ● One additional remark: If two injections of epinephrine do not work, it could obviously indicate refractory anaphylaxis. However, one should also consider another diagnosis. For this reason, my suggestion would be to consider adding the following sentence after line 2 in this paragraph ending with "including intravascular fluid resuscitation." "On the other hand, the differential diagnosis (DD) should also be carefully considered, and there may be another diagnosis, such as vocal cord dysfunction, etc." ● (1) Would better delineate that the infant symptoms you call out are in *addition* and not as isolated features of a reaction, so that every time an infant licks their lips, they aren't given epi. This still, at some level, lacks the context in the setting of a known or likely ingestion. . . . Also, just the recent AAFA paper isn't anywhere near enough valid data to really anchor these presentations per se. (2) Anytime the word "life-threatening" must appear, just say "potentially life threatening" which still makes the same point but more appropriately places the hedge of the exceptional rarity of the event. This does not diminish any of advocacy's claims to whatever insane reason they want to keep anchoring death to this. ● Nasal spray epinephrine will soon be approved (FDA and EMA). Depending on how soon our document will be released, we may have to amend the part on the use of epinephrine.
Clinical support tool	● Legend: I would not mention the adrenaline doses recommended in the ASCIA guidelines because they differ from those recommended here, it could be confusing. ● Good that adrenaline dosage is now included. However, it is very complicated for people not used to treating anaphylaxis and this is likely to lead to delays in treatment. An effective algorithm for acute management has to be as simple as possible with a clear flow through the algorithm and few choices, as every choice will lead to pausing and delay in

(Continued)

TABLE E4. *(Continued)*

Domain	Delphi comments
	treatment. Here there are three choices for diagnosis, some of which may be unfamiliar to those not used to treating anaphylaxis. The dosing is also very detailed and considering the relatively rare occurrence of anaphylaxis in children below 13 kg perhaps over and under 25 kg would be sufficient. Footnotes are unlikely to be noticed in the acute setting. I have tried the tool on several anesthetists who all get confused by the three options and by the symptoms being at the bottom of the page so you have to move your gaze up and down. It took them >5 min to familiarize themselves with the algorithm which in my mind is too long and reflects the complexity of the support tool. ● I do not find the 3 levels of allergen exposure helpful. Waiting 15 minutes before a further dose of IM adrenaline is too long. ● Where does 13kg as the lower/upper limit of weight for 150ug/100ug come from?? possibly needs a footnote in the support tool legend. Usually either 10 or 15kg by most guidance. Persistent tachycardia may be a sign of anaphylaxis in infants/young children- but it is more often a consequence of epi treatment- and the risk of highlighting it here is that isolated tachycardia may give rise to the administration of multiple doses of epi chasing a tachycardia which is caused by the epi administration itself. ● Agreement on weight or age for dosing is mandatory. ● A known allergen is sometimes interpreted as a generally well-known allergen among the population (such as peanuts) instead of as an allergen known specifically for that particular patient. My suggestion is to slightly modify the legend to: "Known allergen for the particular patient" ● Clinical support still tool does not say anything (in the main text or in the footnotes) about assessment and exclusion of conditions, such as a viral illness, that must be considered and ruled out before a child is simply presumed to have anaphylaxis where there is "no known allergen exposure." This is still not sufficient and will continue to lead to perpetuation of "any 2 organ symptoms" including those seen in HSP or other viral conditions, being presumed (wrongly) to be anaphylaxis because of people refusing to think who will continue to presume every rash and cough is anaphylaxis by default. Other things can present with skin/mucosal and respiratory involvement that have nothing to do with anaphylaxis, and anaphylaxis would not nor should be the first thought in this situation. Add a footnote to say "have considered other similar presentations such as acute viral illness" or something. If you are going to cede the fatality thing, at least add this as well. Or, this won't end up evolving the definition over the current one . . . Instead of "should be given immediately" consider "recommend immediate administration." ● Age-based dosing is one suggestion, but if we include this, should we also include weight-based dosing algorithms? ● Again, this part will need to be updated when nasal epinephrine is available.
Endorsement comments	● During participation in the ANACARE study I supported the inclusion of "Skin/Mucosal involvement" under "3. Known† Allergen Exposure" of the Anaphylaxis Clinical Support Tool For Healthcare Professionals. ● Thank you for involving our organization. ● I have noticed that the use of adrenaline/epinephrine as the first-line treatment of anaphylaxis has been removed from the definition you proposed some time ago. The name of the first-line treatment remains an issue: epinephrine or adrenaline. Given the consensus of the definition, perhaps it would be appropriate to address this aspect in an attempt to have a unified term. Currently, the situation is quite diverse and creates confusion, mainly because the acronyms (EAI or AAI) do not coincide. This can depend on the region where you live. ● Thank you for collaborating with patient advocacy groups. ● The clinical support tool—I note you don't use A, B, C Airways, Breathing, Circulation which is well known first aid response management tool used amongst Health care professionals UK and Eu wide—mentioned in the EAACI guidance for anaphylaxis and in the anaphylaxis summary provided—should the tool not reflect this summary and use the same language? I also feel that skin and GI should sit together in number 2 of the clinical support tool and that Airways, breathing and circulation should be the diagnostic criteria—I appreciate your rationale in the summary that it can be difficult to distinguish but EAACI and UK guidance put them together. Is there agreement that skin and GI symptoms alone are markers of severe enough disease to diagnose anaphylaxis without respiratory or cardiovascular symptoms? ● Feedback from NASEMSO:—We believe that the definition, overview and clinical support tool are valuable additions to assist a broad audience with the identification and treatment of individuals experiencing anaphylaxis.—We do not see any significant conflicts with our National Model EMS Clinical Guidelines v.3.0 (https://nasemso.org/wp-content/uploads/National-Model-EMS-Clinical-Guidelines_2022.pdf). Members of our Board asked that "anaphylactoid reactions" also be considered in the educational material. ● Great work! ● Likely that it will used as a reference in future revisions of our guideline documents. Reservations regarding the recommendation of H_2 blocker.