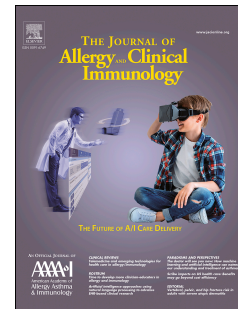


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Persistent, refractory, and biphasic anaphylaxis: a multidisciplinary Delphi study

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1 Persistent, refractory, and biphasic anaphylaxis: a multidisciplinary Delphi study

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Abstract**Background**

The use of inconsistent definitions for anaphylaxis outcomes limits our understanding of the natural history and epidemiology of anaphylaxis, hindering clinical practice and research efforts.

Objective

To develop consensus definitions for clinically relevant anaphylaxis outcomes utilizing a multidisciplinary group of clinical and research experts in anaphylaxis.

Methods

Using Delphi methodology, we developed agenda topics and drafted questions to review during monthly conference calls. Through online surveys, a 19-member panel, including experts in allergy/immunology and emergency medicine, rated their level of agreement with the appropriateness of statements on a 1 to 9 scale. A median value of 1.0 to 3.4 was considered “inappropriate;” 3.5 to 6.9, “uncertain;” and 7.0 to 9.0, “appropriate.” A disagreement index was then calculated, with values less than 1.0 categorized as “consensus reached.” If consensus was not reached after the initial survey, subsequent surveys were sent to panel members incorporating the aggregate de-identified responses from prior surveys. This process was repeated until consensus was reached or after 4 survey rounds, after which the question was categorized as “no consensus reached.”

Results

The panel developed outcome definitions for persistent, refractory and biphasic anaphylaxis, as well as persistent and biphasic non-anaphylactic reactions. There was also consensus among panel members regarding the need to develop an anaphylaxis severity grading system.

Conclusion

Dissemination and application of these definitions in clinical care and research will help standardize the terminology used to describe anaphylaxis outcomes, and serve as the foundation for future research, including the development of an anaphylaxis severity grading system.

Clinical Implication

The anaphylaxis outcome definitions proposed in this study have the potential to improve and standardize the care of, and research outcomes for patients with anaphylaxis.

Capsule Summary

We developed consensus anaphylaxis definitions for persistent, refractory, and biphasic anaphylaxis; dissemination and application of the definitions has the potential to standardize and improve clinical care and advance future research.

Keywords

Anaphylaxis; biphasic anaphylaxis; biphasic non-anaphylactic reactions; Delphi; emergency department; persistent anaphylaxis; persistent non-anaphylactic reactions; refractory anaphylaxis.

Abbreviations

DI: disagreement index

ED: emergency department

IM: intramuscular

IV: intravenous

NIAID/FAAN: National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network

NOS: not otherwise specified

Introduction

Anaphylaxis is a severe, systemic mast cell and/or basophil-mediated reaction that occurs after exposure with an allergy-causing substance (foods, medications, insect venom), while in other cases the etiology may be unknown or occur in relation to mast cell disorders.^{1,2} From 2008 to 2016 there were over 400,000 emergency department (ED) visits for anaphylaxis in the US. During this time period, ED visit rates for anaphylaxis doubled among all ages and tripled among children.³ These reactions impose a significant personal and financial burden on patients and families. In 2010 direct and indirect expenditures for anaphylaxis in the US were \$1.2 billion and \$609 million respectively, and these costs have likely increased during the past decade.⁴

Prompt recognition and treatment of anaphylaxis with intramuscular (IM) epinephrine are essential to mitigate reaction severity and to prevent complications, including respiratory failure, cardiovascular collapse, and death. In 2006, the National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network (NIAID/FAAN) developed a widely accepted definition of anaphylaxis for children and adults and established clinical diagnostic criteria (see Table 1).¹ The NIAID/FAAN guidelines have been instrumental in standardizing anaphylaxis diagnostic criteria, encouraging recognition and appropriate treatment, improving communication between healthcare providers and patients, and optimizing the care of patients with anaphylaxis across healthcare settings.²

Although most anaphylactic reactions resolve promptly after treatment with epinephrine, patients may experience persistent or recurrent symptoms necessitating additional interventions. However, there are no uniformly accepted consensus-based definitions to describe these disparate clinical outcomes, limiting our understanding of their epidemiology and risk factors as well as our ability to investigate or standardize their management.^{2,5} The lack of clear and objective definitions likely contributes to wide variability in reported rates of biphasic

anaphylaxis (between 1% to 19%) and inconsistent descriptions of predictors of biphasic anaphylaxis in recent studies.⁶⁻⁸

This gap presents a need to develop consensus definitions of anaphylaxis outcomes for application in clinical care and research, including persistent, refractory, and biphasic anaphylaxis as well as persistent and biphasic non-anaphylactic reactions. Such definitions will be instrumental when reporting outcomes in population and patient level studies, including trials comparing the efficacy of adjunctive and novel therapeutics. Therefore, the objective of the study was to develop consensus definitions for specific, clinically relevant anaphylaxis outcomes utilizing a multidisciplinary group of clinical and research experts in anaphylaxis.

Methods

Delphi group panel members

We convened a Delphi group consisting of a 19-member panel of experts in the field of anaphylaxis, including allergists/immunologists and general and pediatric emergency medicine specialists. Panel members were selected based on their clinical expertise, prior published research, expert recommendations, and membership in national research networks and anaphylaxis interest groups. Three experts in qualitative and Delphi methodology were also included. Panel members engaged in monthly conference calls and surveys from September 2019 through March 2020 to develop consensus anaphylaxis outcome definitions. The institutional review board at Cincinnati Children's Hospital Medical Center approved this study.

Literature search

We performed a literature review of Embase, PubMed, Cochrane and Scopus databases for English articles from 1997 to August 2019 using the following search terms: anaphylaxis severity, anaphylaxis grading system, anaphylaxis grading scale, anaphylaxis grade, biphasic anaphylaxis, persistent anaphylaxis, refractory anaphylaxis, and protracted anaphylaxis. Articles published prior to 1997 were also included if they were cited at least 5 times in references from the literature search. The primary investigator (TD) reviewed the literature search and excluded duplicate articles and articles not related to the study aims. Study panel members had access to relevant articles and were asked to review them prior to conference calls and before responding to survey questions. If a panel member felt an important article was omitted from the literature search, the article was disseminated to all panel members and made available in a common online study folder that included all articles from the search.

Delphi surveys

The Delphi method is a structured group consensus technique with identified subject-matter experts answering survey questions in iterative rounds. We used the approach by Fitch and colleagues (the RAND/UCLA appropriateness method)⁹ which has been used in similar studies.^{10,11} In each survey round, panel members were asked to rate each statement on level of agreement (1 extremely inappropriate to 9 extremely appropriate), or not applicable if panel members did not feel they had the necessary expertise or background knowledge to rank a particular statement.^{10,11} Additionally, panel members were encouraged to submit free text comments to clarify their response to every question, suggest additional questions, or recommend modifications to existing questions. A median appropriateness value of 1.0 to 3.4 was considered “inappropriate;” 3.5 to 6.9, “uncertain;” and 7.0 to 9.0, “appropriate.”^{10,11} A disagreement index (DI) was then calculated (see table E2 in the Online Repository), and, a value less than 1.0 indicated “consensus reached” regarding the statement.^{10,11}

If consensus for a question was not reached after the initial survey, subsequent surveys were sent to panel members incorporating the aggregate de-identified responses from prior surveys with the goal of narrowing responses to reach consensus. This process was repeated until consensus was reached for each statement or after 4 survey rounds. If no consensus was reached by the fourth round, the question was categorized as “no consensus reached.” After consensus was reached for individual questions pertaining to a topic (e.g. biphasic anaphylaxis), a composite definition was created based on the responses from questions pertaining to the study topic. For an explanation of questions that the group considered when determining the need for and developing consensus outcome definitions, see the supplemental document in the Online Repository.

216 *Conference calls*

217 Three panel members (TD, HS, DS) developed agenda topics and drafted questions to
218 review during conference calls. Monthly conference calls with the full Delphi panel were
219 designed to answer logistical questions related to study execution, review results from the prior
220 survey rounds including questions for which the group did not reach consensus, and review and
221 clarify questions. During calls, panel members also discussed relevant research and clinical
222 experiences related to the questions. Audio recordings of the calls were made available to panel
223 members who could not join the live calls. Qualitative themes discussed during calls related to
224 specific questions and topics are presented in the results section to provide a contextual
225 framework for the definitions. Following conference calls, panel members were asked to
226 review/revise questions, and the primary investigator compiled revisions and incorporated them
227 into a secure, anonymous online survey (Research Electronic Data Capture, Nashville, TN).¹²

228

229

Results

All panel members (n=19) participated in each Delphi round. An overview of questions related to each Delphi topic, including the median score, DI, number of survey rounds to reach (DI < 1.0) or not reach consensus (DI ≥ 1.0) on questions, and number of panel members for each round are listed in Table E3 in the Online Repository.

There was consensus that the 2006 NIAID/FAAN anaphylaxis criteria should be used to categorize anaphylaxis in all outcome definitions, and that the definitions developed by the expert panel would apply to all ages, including infants, children, and adults. Consensus was also reached that anaphylaxis is a clinical diagnosis, and thus the definitions can apply to all cases of anaphylaxis that fulfill NIAID/FAAN criteria no matter the allergen, pathophysiologic response (e.g. IgE mediated vs. non-IgE mediated), underlying conditions, or comorbidities. There was consensus that the panel should develop outcome definitions for persistent anaphylaxis, refractory anaphylaxis, biphasic anaphylaxis, as well as persistent non-anaphylactic reactions, biphasic non-anaphylactic reactions, and an anaphylaxis severity grading system (see Table E3 in the Online Repository for question specific median appropriateness values and DI).

Consensus was also reached regarding the need to develop separate diagnostic criteria (other than the NIAID/FAAN anaphylaxis criteria¹) for infant anaphylaxis given the NIAID/FAAN criteria may lack adequate sensitivity for diagnosing anaphylaxis in this age group. However, in the free text option for this question, panel members responded that rather than developing separate criteria for infant anaphylaxis, the NIAID/FAAN criteria could be modified to include clinical features that are more sensitive for diagnosing anaphylaxis in infants.

Definition of persistent anaphylaxis

The definition for persistent anaphylaxis is shown in Table II. Panel members acknowledged that there is minimal data supporting a time threshold for classifying reactions as persistent, and thus the proposed time threshold is based on expert opinion, clinical expertise, and an extensive review of the literature. To account for this, panel members were asked to suggest time thresholds based on their review of the literature and clinical experience. Suggested time thresholds were 1, 2, 4, 6, 12, and 24 hours. After two Delphi rounds, there was consensus that to be categorized as persistent anaphylaxis, persistent symptoms must fulfill NIAID/FAAN anaphylaxis criteria and must last ≥ 4 hours.¹ Additionally, there was agreement that the definition of persistent anaphylaxis was independent of the management of the initial reaction.

Definition of refractory anaphylaxis

The definition of refractory anaphylaxis is shown in Table II. It took three Delphi rounds to determine whether reactions must be treated with 2 or 3 epinephrine doses to be categorized as refractory anaphylaxis. Consensus was reached that to be categorized as refractory anaphylaxis, the initial reaction must be treated with 3 or more appropriate doses of epinephrine (or initiation of an intravenous [IV] epinephrine infusion) in addition to symptom-directed medical management, such as an IV fluid bolus for hypotension or supplemental oxygen for hypoxia or shock. For this question, we intentionally did not include every possible symptom/therapy combination, but instead included a general statement to reflect the need for patients to receive appropriate resuscitative/supportive therapies in addition to treatment with epinephrine. The group reinforced that this statement does not mean clinicians should delay or substitute treatment with epinephrine to administer other therapies (e.g. inhaled beta agonists, IV fluid boluses); instead, it reflects the importance of ensuring patients receive appropriate resuscitative efforts before classifying reactions as refractory. There was also agreement that the definition of

refractory anaphylaxis was not dependent on the duration of symptoms/exam findings, but instead the persistence of anaphylaxis following appropriate epinephrine administration and medical management of specific symptoms/exam findings.

Definition of biphasic anaphylaxis

The composite definition of biphasic anaphylaxis is outlined in Table II. Panel members reached consensus that initial symptoms need to completely resolve prior to the onset of recurrent symptoms and that recurrent symptoms must fulfill NIAID/FAAN anaphylaxis criteria¹. Furthermore, there was agreement that the definition of biphasic anaphylaxis is independent of the management of the initial reaction. Thus, initial reactions do not have to be treated with epinephrine for recurrent symptoms to be categorized as a biphasic anaphylaxis. During dialogue about this question, panel members agreed that anaphylactic reactions may resolve without treatment with epinephrine prior to medical provider evaluation. Thus, there would be no indication to administer epinephrine at the time of provider evaluation. If patients then developed recurrent symptoms that fulfilled biphasic anaphylaxis criteria, the reaction would appropriately be categorized as biphasic.

Consensus was reached that there should be a minimum and maximum time threshold from the complete resolution of initial symptoms to the onset of recurrent symptoms. Panel members noted that reducing the minimum time threshold (the threshold before which the presence of new/recurrent symptoms/exam findings would not be categorized as biphasic anaphylaxis) would increase the definition's sensitivity while expanding the threshold would increase the definition's specificity. In contrast, if the upper time threshold (the threshold after which the presence of new/recurrent symptoms/exam findings would not be categorized as biphasic anaphylaxis) was excessively long (e.g. 1 week), it would decrease the definition's

specificity by including reactions that may not be related to the initial reaction but instead represent discrete reactions. Panel members suggested lower (30, 60, 120, and 240 minutes) and upper time thresholds (24, 36, 48, and 72 hours) for classifying biphasic reactions based on their review of the literature and clinical expertise. The final lower and upper time thresholds developed by the group were ≥ 1 hour (required two Delphi rounds to reach consensus) and ≤ 48 hours (required three Delphi rounds to reach consensus) respectively.

Definitions of persistent and biphasic non-anaphylactic reactions

The definitions of persistent and biphasic non-anaphylactic reactions are listed in Tables III. The only difference between the definitions of persistent and biphasic non-anaphylactic reactions and persistent and biphasic anaphylaxis is that for the former definitions, persistent and recurrent symptoms do not fulfill NIAID/FAAN anaphylaxis criteria.¹

Definition of anaphylaxis not otherwise specified (NOS)

Consensus was reached that anaphylaxis NOS is defined as anaphylactic reactions that do not fulfill the following clinical outcomes: fatal anaphylaxis, persistent anaphylaxis, biphasic anaphylaxis, persistent non-anaphylactic reactions, or biphasic non-anaphylactic reactions. However, the panel recognized that there is a spectrum of severity among patients with this label and that the definition can only be applied after 48 hours (the time at which reactions can no longer be classified as biphasic).

The outcome definitions shown in Figure 1 are not mutually exclusive and a patient may fulfill more than one outcome through their clinical course; however, one outcome must always precede another. For example, a patient may have refractory anaphylaxis (for which symptoms completely resolve after treatment with 3 doses of IM epinephrine) and if the initial reaction lasts

321 4 hours it would then fulfill persistent anaphylaxis criteria (this example would be categorized as
322 refractory, persistent anaphylaxis).

323

324

Discussion

We convened a multidisciplinary panel of anaphylaxis experts to develop consensus anaphylaxis outcome definitions for persistent, refractory, and biphasic anaphylaxis, as well as persistent and biphasic non-anaphylactic reactions. Although there was agreement that there is also a need to develop an anaphylaxis severity grading system and separate criteria for diagnosing infant anaphylaxis (or modify existing NIAID/FAAN criteria to include symptoms more specific for infant anaphylaxis)¹, we felt these topics were beyond the scope of this study and would be better addressed through future investigation which could expand upon or incorporate components of the definitions outlined in this study.

The study was conducted using rigorous Delphi methodology previously applied in other clinical fields of medicine,⁹⁻¹¹ and we included clinicians and researchers with expertise in Delphi methodology and qualitative research to ensure the appropriateness of methods and study procedures. This is the first study to evaluate the need for anaphylaxis outcome definitions based on input from a multidisciplinary group of anaphylaxis experts, including allergists/immunologists and ED providers who care for children and adults.

This study advances the classification of anaphylaxis outcomes by defining not only persistent, refractory, and biphasic anaphylaxis, but also persistent and biphasic allergic reactions that do not fulfill NIAID/FAAN anaphylaxis criteria.¹ We felt these were necessary designations given that prior studies have categorized all biphasic reactions, no matter whether they fulfill NIAID/FAAN criteria, as biphasic anaphylaxis.^{6,13-15} This distinction is important to harmonize data about the prevalence and risk factors for biphasic anaphylaxis in clinical practice, given clinicians may make different management decisions based on the risk of biphasic anaphylaxis versus biphasic non-anaphylactic reactions. Additionally, the outcome definitions only apply to

anaphylactic reactions and thus cannot be used to describe clinical courses following non-anaphylactic reactions. For example, if a patient has a non-anaphylactic reaction and then develops recurrent symptoms that fulfill anaphylaxis criteria, the recurrent symptoms cannot be classified as biphasic anaphylaxis.

The definitions are designed to apply to both clinical care and research, and are based on best available, although limited evidence. Nonetheless, we believe the definitions are pragmatic and also provide a nuanced approach for evaluating distinct, clinically important outcomes of patients with anaphylaxis. Thus, we do not anticipate significant barriers when applying the definitions to bedside care because they are based on important clinical questions and they incorporate reaction features that are easily ascertained during medical evaluation (e.g. duration of symptoms, resolution of initial symptoms/exam findings).

During conference calls, panel members routinely stated that there is a lack of validated data to inform responses to many of the questions. Still, this study is a practical, necessary first step in standardizing the outcomes of patients with anaphylaxis. Applications of the definitions in clinical care and research has the potential to improve communication among clinicians and patients/families and to standardize research outcomes. For example, if a patient develops isolated urticaria 2 hours after complete resolution of initial anaphylaxis symptoms, the reaction would be classified as “anaphylaxis with a biphasic non-anaphylactic reaction,” while a patient with anaphylaxis who requires 3 doses of epinephrine and who receives symptom-directed therapy would be described as having “refractory anaphylaxis.” These efforts may help better elucidate the true prevalence of persistent, refractory, and biphasic anaphylaxis and may be incorporated in study protocols to evaluate the efficacy of adjunctive anaphylaxis medications (e.g. systemic steroids, antihistamines) and novel therapeutics.

There was robust discussion about whether definitions should apply to broad categories of patient ages and allergens, or instead should be limited in scope. These were important questions given that reactions may be caused by allergens involving different pathophysiologic pathways that necessitate tailored short- and long-term management decisions. Although there was uncertainty as to whether the definitions should apply to infants, consensus was ultimately reached that infants should be included; however, it is important to acknowledge that the sensitivity of these definitions may be lower in infancy because symptoms are more difficult to detect in this age group. Thus, these criteria should not dictate management decisions across all settings and contextual clinical management remains paramount. Instead, the definitions are designed to standardize the terminology used to describe patient outcomes following anaphylactic reactions. This statement was instrumental to the study given we sought to develop definitions that clinicians and researchers alike will support to advance patient care and research, and thus we believe will lead to their widespread dissemination and application.

Panel members repeatedly emphasized that the definitions are not intended to dictate clinical care given there may be unique diagnostic and therapeutic decisions for specific allergens and patient presentations. Additionally, the definitions are not prescriptive to decision making about observation periods or need for hospitalization. For example, it may be reasonable for a patient with isolated oropharyngeal edema to have an extended observation period to ensure she does not develop upper airway obstruction despite the patient not fulfilling persistent or refractory anaphylaxis criteria. Similarly, a patient with anaphylaxis that lasts 3 hours may require hospitalization despite the reaction not fulfilling persistent anaphylaxis criteria.

When developing the outcome definitions, a key concept was whether definitions were independent of the management of the initial reaction. The group reached consensus that for

394 persistent and biphasic reactions, the diagnosis was not dependent on the management of the
395 initial reaction given the definitions are intended to classify the presence/absence of symptoms in
396 relation to the initial reaction. However, there was recognition that there is a subset of patients
397 who have persistent anaphylactic reactions despite treatment with multiple doses of epinephrine
398 and symptom-directed medical management, and thus we developed a definition for refractory
399 anaphylaxis. Although the definition introduces subjective elements such as treatment decisions,
400 we believe this is an important clinical and research distinction given there is no precise estimate
401 in the literature about the prevalence and risk factors for refractory or fatal anaphylaxis, nor how
402 to optimize treatment strategies in this high-risk cohort.¹⁶

403 A fundamental theme of the definitions is the timing of new/recurrent symptoms and the
404 duration of *persistent* anaphylaxis. Although there was agreement that definitions should include
405 clear time delineations, there was acknowledgment that there are insufficient data to inform these
406 time periods. It was underscored that reducing or extending time thresholds would affect the
407 prevalence of outcomes and the sensitivity/specificity of definitions. Similarly, shortening the
408 asymptomatic period for *biphasic* anaphylaxis would be associated with an increased prevalence
409 of these reactions and would also increase the definition's sensitivity. In contrast, an excessively
410 short asymptomatic period (e.g. one minute) would not be clinically or biologically plausible and
411 would reduce the definition's specificity while an excessively long minimal asymptomatic period
412 (e.g. 12 hours) would not have face validity for clinicians who would be reluctant to not
413 categorize symptoms that recur after 4 or 6 hours as biphasic. To account for these scenarios, the
414 group made a concerted effort to ensure time thresholds were clinically and biologically
415 plausible to ensure buy-in from clinicians and researchers alike and agreed that for persistent

anaphylaxis symptoms/exam findings must last ≥ 4 hours and for biphasic anaphylaxis the asymptomatic period must be from 1 to 48 hours.

Limitations and future areas for research

This study is subject to limitations, mainly related to the paucity of validated clinical or basic science research to support the criteria upon which the definitions are based. We recognize that consensus was reached for definitions and time thresholds based on expert opinion using best available evidence, and not objective data such as trends in the level of anaphylaxis biomarkers (e.g. tryptase) over time. This was required, as there are currently no biomarkers that are routinely used in clinical practice that correlate well to symptoms or clinical courses.¹⁶ Additionally, for the definitions of persistent and biphasic anaphylaxis, we were not able to provide an explanation for how the route of allergen exposure may elicit persistent or recurrent/new symptoms (e.g. persistent allergen exposure in the gastrointestinal tract), or the effect of medications and their half-lives on symptom duration or recurrence. Although the definitions rely on the 2006 NIAID/FAAN anaphylaxis criteria,¹ we recognize that there are new proposed anaphylaxis diagnostic criteria in the literature.¹⁷ The group reached consensus that the 2006 NIAID/FAAN criteria should be used given they are broadly applied in clinical practice and research, have been validated in both retrospective and prospective studies, and have withstood the test of time since their inception.^{1,18,19} We believe the definitions proposed in this study could be easily adopted based on modifications to the NIAID/FAAN criteria or new diagnostic criteria.

Despite these limitations, we believe this study is foundational because it proposes definitions that have the potential to advance clinical care and research, including prospective cohort studies to evaluate the feasibility of applying the definitions in clinical and research

settings and thereby determining the true prevalence of these reactions. Although we based definitions on symptoms and exam findings, we are optimistic this work reinforces the need to transition current clinical practice to a precision medicine model of care.^{20,21} Such a model would incorporate biomarkers, genetics, and epigenetics to enhance clinicians' ability to accurately diagnose anaphylaxis, predict treatment responses as well as patient specific risks of persistent or biphasic reactions, and develop targeted therapies to treat and prevent anaphylaxis among high risk individuals.

Finally, there is a need for a consensus anaphylaxis severity grading system for application in clinical care and research. Limitations of prior grading systems include the use of non-specific terms to denote reaction severity and the inability to differentiate between clinically important phenotypes. Additionally, some grading systems are complex and difficult to remember (which precludes their use in clinical care), while others have limited relevance in research because they lack granularity or do not account for the totality of symptoms during the course of reactions.²²⁻³² Thus, a consensus grading system must be clinically relevant for patients and families and enable researchers to accurately categorize reaction severity when assessing the efficacy of current and novel therapies in clinical trials. Such a severity system could be incorporated into the outcome definitions outlined in this study to categorize the severity of persistent and biphasic anaphylaxis.

Conclusion

We developed consensus definitions of persistent, refractory, and biphasic anaphylaxis, as well as persistent and biphasic non-anaphylactic reactions. Successful dissemination and application of these definitions in clinical care and research has the potential to standardize the terminology used to describe anaphylaxis outcomes among clinicians and patients. They can

serve as a foundation for future research to evaluate the epidemiology of anaphylaxis, transform current clinical practice to a precision medicine model of care, and determine the efficacy of current and novel therapeutics. Additionally, this study supports the need to develop a consensus anaphylaxis severity grading system for application in clinical care and research.

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Table I: Clinical criteria for diagnosing anaphylaxis[†]***Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:***

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING
 - a. Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
 - b. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
 - a. Involvement of the skin-mucosal tissue (e.g. generalized hives, itch-flush, swollen lips-tongue-uvula)
 - b. Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
 - c. Reduced blood pressure or associated symptoms (e.g. hypotonia [collapse], syncope, incontinence)
 - d. Persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
 - a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP[†]
 - b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

[†]Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 x age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years. Used with permission.

Table II: Clinical criteria for diagnosing persistent, refractory, and biphasic anaphylaxis***Persistent anaphylaxis is highly likely when the following criterion is fulfilled: ^a***

Presence of symptoms/exam findings that fulfill the 2006 NIAID/FAAN anaphylaxis criteria that persist for at least 4 hours.¹

Refractory anaphylaxis is highly likely when both of the following 2 criteria are fulfilled: ^b

-
1. Presence of anaphylaxis following appropriate epinephrine dosing and symptom-directed medical management (e.g. IV fluid bolus for hypotension).
 2. **The initial reaction must be treated with 3 or more appropriate doses of epinephrine (or initiation of an IV epinephrine infusion).**^c
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Biphasic anaphylaxis is highly likely when all of the following 4 criteria are fulfilled: ^d

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1. New/recurrent symptoms/exam findings must fulfill the 2006 NIAID/FAAN anaphylaxis criteria.¹
 2. Initial symptoms/exam findings must completely resolve prior to the onset of new/recurrent symptoms/exam findings.
 3. There cannot be allergen re-exposure prior to the onset of new/recurrent symptoms/exam findings.
 4. New/recurrent symptoms/exam findings must occur within 1 to 48 hours from complete resolution of initial symptoms/exam findings.
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^a The diagnosis of persistent anaphylaxis is independent of the management of the initial reaction. For reactions that do not fulfill persistent anaphylaxis criteria, please refer to Table III (clinical criteria for diagnosing persistent non-anaphylactic reactions).

^b Refractory anaphylaxis is not dependent on the duration of symptoms/exam findings.

^c Appropriate epinephrine dosing: 0.01 mg/kg IM epinephrine, maximum single dose 0.5 mg. Also includes manufacturer recommended dosing for epinephrine auto-injectors.

^d The diagnosis of biphasic anaphylaxis is independent of the management of the initial reaction. For reactions that do not fulfill biphasic anaphylaxis criteria, please refer to Table III (clinical criteria for diagnosing biphasic non-anaphylactic reactions).

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Table III: Clinical criteria for diagnosing persistent and biphasic non-anaphylactic reactions***Persistent allergic reactions are highly likely when the following criterion is fulfilled: ^a***

Presence of symptoms/exam findings that do not fulfill the 2006 NIAID/FAAN anaphylaxis criteria that persist for at least 4 hours.¹

Biphasic allergic reactions are highly likely when all of the following 4 criteria are fulfilled: ^b

1. New/recurrent symptoms/exam findings do not fulfill the 2006 NIAID/FAAN anaphylaxis criteria.¹
2. Initial symptoms/exam findings must completely resolve prior to the onset of new/recurrent symptoms/exam findings.
3. There cannot be allergen re-exposure prior to the onset of new/recurrent symptoms/exam findings.
4. New/recurrent symptoms/exam findings must occur within 1 to 48 hours from complete resolution of initial symptoms/exam findings.

^aThe diagnosis of persistent allergic reaction is independent of the management of the initial reaction.

^bThe diagnosis of biphasic allergic reaction is independent of the management of the initial reaction

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Figure legend**Figure 1: Algorithm for applying the anaphylaxis outcome definitions in clinical care and research**

Anaphylaxis not otherwise specified is defined as anaphylactic reactions that do NOT fulfill the following clinical outcomes: fatal anaphylaxis, persistent anaphylaxis, biphasic anaphylaxis, persistent non-anaphylactic reactions, or biphasic non-anaphylactic reactions.

a. There cannot be allergen re-exposure prior to the onset of new/recurrent symptoms/exam findings.

b. Appropriate epinephrine dosing: 0.01 mg/kg IM epinephrine, maximum single dose 0.5 mg or manufacturer recommended dosing for epinephrine auto-injectors.

c. Symptom-directed medical management such as an IV fluid bolus for hypotension or albuterol for wheezing.

d. Outcome definitions are not mutually exclusive (e.g. a patient who has refractory anaphylaxis may also have/develop persistent or biphasic anaphylaxis).

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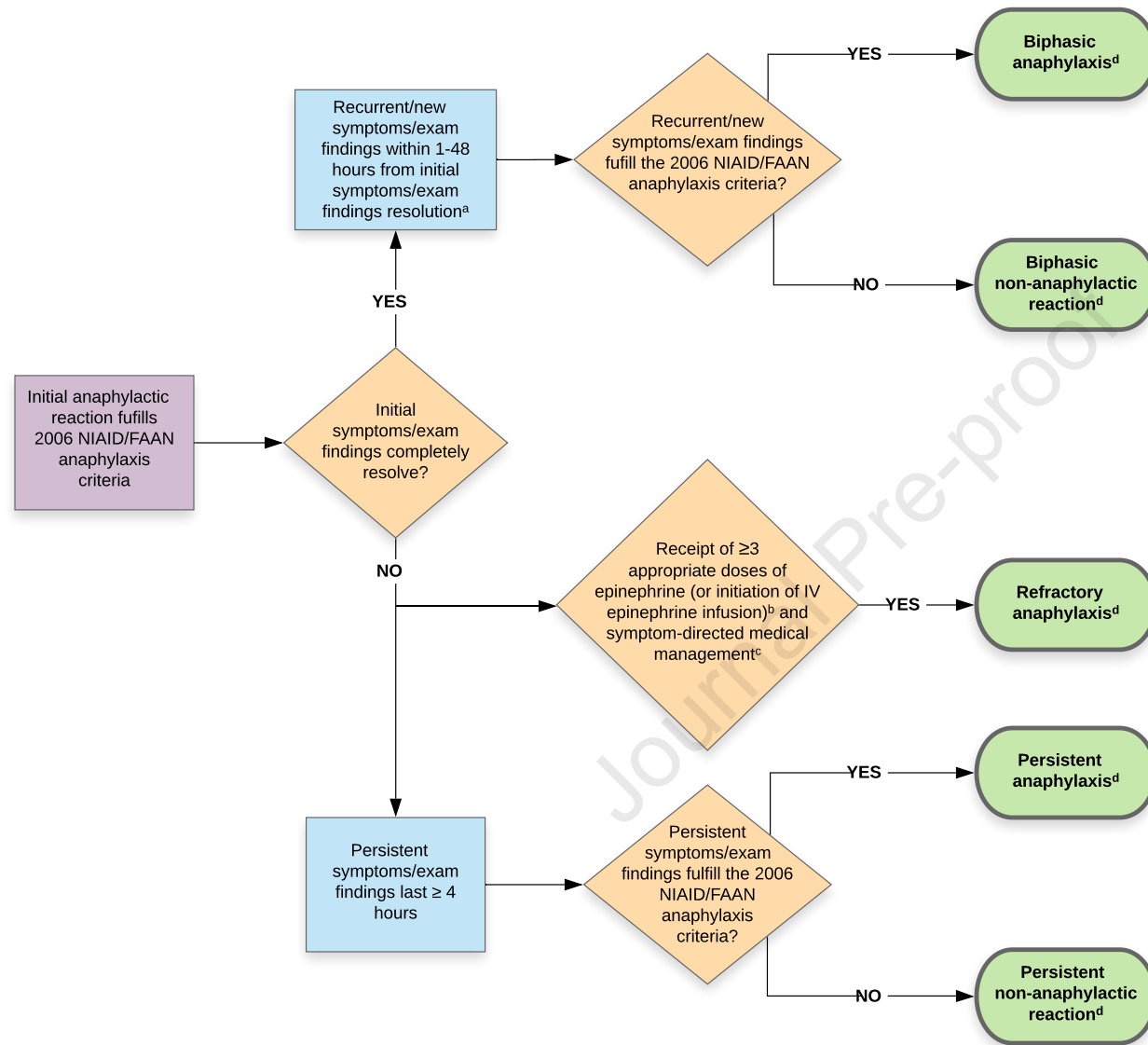
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Supplemental document E1: Outstanding questions to address with the Delphi process

Topic 1: Outcome definitions, patient population, care locations, allergens

Definitions

The first topic sought to assess what anaphylaxis outcome definitions the group should develop, and what anaphylaxis diagnostic criteria would be used during the Delphi process.

Definitions were intended to provide clear, concise descriptions and criteria of common clinical courses following anaphylactic reactions, specifically persistent and recurrent symptoms/exam

findings and the timing of such symptoms in relation to the initial reaction. Proposed definitions

included: 1) persistent symptoms/exam findings that fulfill anaphylaxis criteria following an

anaphylactic reaction; 2) refractory symptoms/exam findings that fulfill anaphylaxis criteria

following an anaphylactic reaction despite treatment with epinephrine; 3) persistent

symptoms/exam findings that do not fulfill anaphylaxis criteria following an anaphylactic

reaction; 4) biphasic symptoms/exam findings that fulfill anaphylaxis criteria following an

anaphylactic reaction; 5) biphasic symptoms/exam findings that do not fulfill anaphylaxis criteria

following an anaphylactic reaction.

Beyond these definitions, the group was also asked whether there was a need to develop separate anaphylaxis diagnostic criteria for infants, given the potential for the 2006

NIAID/FAAN anaphylaxis criteria to not have adequate sensitivity for diagnosing anaphylaxis in infants who may present with subtle symptoms (e.g. drowsiness, excessive crying, clinging to

caregivers, or cessation of play).^{E1} Lastly, given there have been recommendations to develop a

severity scoring system for acute allergic reactions,^{E2} the group was asked whether there was a

similar need to develop a severity grading system specific to anaphylaxis for application in clinical care and research.

Definition application

Given the intent of the study was to develop outcome definitions that could be easily and broadly applied in clinical practice and research, we wanted to assess whether participants agreed that definitions should be applicable to broad categories of patient ages, allergens, and care settings while recognizing that there may be unique clinical scenarios for which the definitions should not be used.

Patient ages and care settings

We sought to assess what patient ages (e.g. infants, children, adults) the outcome definitions should apply. Additionally, although anaphylaxis can occur in any setting (e.g. non-healthcare locations such as schools and homes, or hospital-based locations such as the ED or operating room), we sought to stipulate what care locations the definitions would apply.

Allergens and conditions

The group wanted to determine whether there are specific allergens or triggers (including conditions that may cause anaphylaxis such as mast cell activation disorders) for which the definitions should or should not apply. Inherent to this was the realization that allergists and ED providers may approach this question from two unique, but important perspectives. Specifically, allergists may be more inclined to think mechanistically (e.g. IgE mediated vs non-IgE mediated reactions) and incorporate pathophysiological explanation for reactions compared to ED providers who practice in an environment in which they are forced to make rapid diagnostic and management decisions based on pattern recognition, limited historical information, and without

laboratory diagnostics (e.g. allergen IgE levels, skin prick testing). Thus, when assessing what allergens to incorporate/exclude from the definitions, a critical question was whether this designation should be based on phenotypic characteristics (symptoms/exam findings), pathophysiologic mechanisms (e.g. IgE vs non-IgE mediated reactions), or a combination of the two.

Topic 2: Persistent anaphylaxis, refractory anaphylaxis, persistent allergic reactions

For the second topic, we sought to develop definitions for persistent symptoms/exam findings after an anaphylactic reaction. Inherent to this topic is the word “persistent,” which describes the duration of symptoms/exam findings and does not reflect the treatment of the initial reaction (e.g. receipt of epinephrine). However, there was recognition that there may also be value in developing a definition of symptoms/exam findings that persist despite treatment with epinephrine. Thus, the group sought to assess whether there was need to develop separate outcome definitions to describe three clinical courses of patients with persistent symptoms/exam findings after an anaphylactic reaction: 1) persistent symptoms/exam findings that fulfill NIAID/FAAN anaphylaxis criteria despite treatment with IM epinephrine^{E3}, 2) persistent symptoms/exam findings that fulfill NIAID/FAAN anaphylaxis criteria independent of the treatment of the initial reaction, 3) persistent symptoms/exam findings that do not fulfill NIAID/FAAN criteria.

Questions related to refractory anaphylaxis included: 1) To be categorized as refractory anaphylaxis, how many doses of epinephrine (1, 2, 3 or more) need to be administered without resolution of anaphylaxis (e.g. if patients do not respond to said dose(s) of epinephrine the reaction may be categorized as refractory)? 2) To be categorized as refractory anaphylaxis, in addition to treatment with appropriate epinephrine dosing, does the reaction need to be treated

with appropriate medical management of specific symptoms? Although epinephrine is the first line therapy to treat anaphylaxis and should be administered repeatedly or as a continuous intravenous infusion for refractory symptoms, patients may also require other resuscitative interventions such as an IV fluid bolus for hypotension, inhaled beta agonists for persistent wheezing or respiratory distress, or supplemental oxygen for hypoxia or shock. Additionally, there was question as to whether the definition of refractory anaphylaxis is based solely on the persistence of anaphylaxis following appropriate epinephrine dosing and medial management of specific symptoms/exam findings (e.g. IV fluid bolus for hypotension), or if it is also dependent on the duration of symptoms/exam findings.

Questions related to persistent anaphylaxis included: 1) whether persistent symptoms/exam findings must fulfill NIAID/FAAN anaphylaxis criteria^{E3}, or, whether isolated symptoms (not including hypotension) could be classified as persistent anaphylaxis? 2) To be classified as persistent anaphylaxis, did initial reactions need to be treated with epinephrine, or is the diagnosis of persistent anaphylaxis independent of the management of the initial reaction? 3) After initial symptom onset, should there be a minimum duration of symptoms/exam findings to classify reactions as persistent?

Topic 3: Biphasec anaphylaxis and biphasec allergic reactions

For the third topic, we sought to develop a consensus definition of biphasec anaphylaxis and biphasec allergic reactions. Key questions related to this topic included: 1) Do biphasec anaphylactic reactions need to fulfill the 2006 NIAID/FAAN anaphylaxis criteria^{E3}, or can recurrent symptoms/exam findings be in isolation (e.g. urticaria or emesis) and not fulfill NIAID/FAAN criteria? 2) Do symptoms/exam findings from the initial anaphylactic reaction need to completely resolve prior to the onset of recurrent symptoms/exam findings? 3) Do initial

reactions need to be treated with IM epinephrine prior to the onset of recurrent symptoms/exam findings, or, is the definition of biphasic anaphylaxis independent of the management of the initial reaction? Although treatment with IM epinephrine is the first line therapy for anaphylaxis, there is the potential for symptoms/exam findings to resolve without receipt of epinephrine by the time patients are evaluated by healthcare providers, and, in this scenario patients may develop recurrent symptoms/exam findings following an asymptomatic period. 4) For reactions to be categorized as biphasic anaphylaxis, does the inciting allergen need to be known or suspected/likely? Although the inciting trigger may be unknown in 18% of biphasic reactions,^{E4} if the allergen is unknown there is potential that it may still be present (e.g. food in the gastrointestinal tract) and thus may elicit recurrent symptoms/exam findings. 5) Does there need to be a minimum time interval from resolution of initial symptoms to onset of recurrent symptoms/exam findings, and if so, what time interval should be used? 6) Should there be a maximum upper time threshold from resolution of initial symptoms to onset of recurrent symptoms/exam findings, and if so, what time interval should be used? For this question we wanted to determine whether there is a time threshold beyond which symptoms/exam findings would not be categorized as biphasic anaphylaxis, given extending this threshold may decrease the likelihood that recurrent symptoms are related to the initial reaction. Although 72 hours has been cited as an upper time threshold for categorizing biphasic anaphylaxis,^{E4-6} there is uncertainty as to whether symptoms that occur at or around 72 hours are truly related to the initial reaction or instead represent distinct reactions. Finally, given the potential for patients to have recurrent symptoms that do not fulfill biphasic anaphylaxis criteria, we felt it important to define these reactions. This is especially true given recurrent symptoms may influence clinical

decision making (e.g. length of clinic or ED observation, need for hospitalization) and are important to patients/families no matter whether they fulfill biphasic anaphylaxis criteria.

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Table E1: Literature search results, stratified by topic**Persistent**

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Table E2: Disagreement index (DI) calculation^{E7}

Lower Limit IPR = 33rd percentile of the series of ratings

Upper Limit IPR = 66th percentile of the series of ratings

 $IPR^a = (\text{Upper Limit IPR}) - (\text{Lower Limit IPR})$ $IPRCP^b$ (Central point of IPR) = Average of Upper Limit IPR and Lower Limit IPRAsymmetry Index = $(5) - (IPRCP)$ $IPRAS^c = 2.35 + (1.5 * \text{Asymmetry Index})$ Disagreement Index (DI) = $IPR/IPRAS$ 147 ^aIPR = Interpercentile Range148 ^bIPRCP = Interpercentile Range Central Point149 ^cIPRAS = Interpercentile Range Adjusted for Symmetry

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Table E3: Summary Delphi results, stratified by topic (Participants = 19)

Question	Median ^a	DI ^b	Rounds
Definition application			
The definitions are designed to apply to the broadest categories of patient ages, allergens, and care settings while recognizing there will be specific clinical scenarios for which the definitions may not be applicable.	9	0.34	1
Anaphylaxis is a clinical diagnosis, thus the definitions can apply to all cases of anaphylaxis that fulfill NIAID/FAAN criteria no matter the allergen, pathophysiologic response (e.g. IgE mediated vs. non-IgE mediated), underlying conditions, or comorbidities.	8	0.34	1
The diagnosis of anaphylaxis we will utilize is the 2006 NIAID/FAAN anaphylaxis diagnostic criteria. ^{E3}	8	0.31	1
Need for definitions			
Anaphylaxis severity grading system	9	0.00	1
Infant anaphylaxis diagnostic criteria	8	0.03	3
Persistent anaphylaxis	9	0.34	1
Refractory anaphylaxis	9	0.34	1
Biphasic anaphylaxis	9	0.00	1
Persistent non-anaphylactic reactions	8	0.98	1
Biphasic non-anaphylactic reactions	9	0.37	1
Ages			
Patients less than 18 years of age will be categorized as children and those 18 years and older will be categorized as adults.	8	0.34	1
The definitions will apply to adults.	9	0.34	1
There should be an upper age threshold for which the anaphylaxis definitions do not apply.	1.5	0.13	1
The definitions will apply to pre-pubertal children.	9	0.00	1

The definitions will apply to post-pubertal children.	9	0.00	1
The definitions will apply to children including infants.	8	0.1	3
Care locations			
<i>The definitions will apply to the following care settings or individuals:</i>			
Out of hospital, non-healthcare setting (e.g. home or school)	9	0.02	1
Outpatient healthcare setting (primary or sub-specialty clinic)	9	0.00	1
Emergency department	9	0.00	1
Urgent care	9	0.00	1
Inpatient including stepdown and intensive care units	9	0.00	1
Perioperative	8	0.91	1
Operating room	9	0.34	1
Prehospital/emergency medical services personnel	9	0.00	1
Persistent anaphylaxis			
To be categorized as persistent anaphylaxis, symptoms/exam findings must fulfill the 2006 NIAID/FAAN anaphylaxis criteria.	9	0.34	1
The definition of persistent anaphylaxis is independent on the management of the initial reaction.	9	0.34	2
There should be a minimum duration of symptoms/exam findings for an anaphylactic reaction to be categorized as persistent anaphylaxis.	8	0.34	1
To be categorized as persistent anaphylaxis, symptoms/exam findings must last $\geq$ X hour(s).			
≥ 1 hour	1	0.00	1
≥ 2 hours	1	0.00	1
≥ 4 hours	9	0.15	2
≥ 6 hours	1	0.00	1
≥ 12 hours	1	0.00	1
≥ 24 hours	1	0.00	1
Refractory anaphylaxis			
The definition of refractory anaphylaxis is	9	0.00	1

characterized by the persistence of anaphylaxis following appropriate epinephrine dosing and medical management of specific symptoms/exam findings (e.g. IV fluid bolus for hypotension) and is not dependent on the duration of symptoms/exam findings.			
To be categorized as refractory anaphylaxis, the initial reaction must be treated with a minimum of 2 appropriate doses of epinephrine (e.g. if the patient does not respond to 1 dose of epinephrine and requires a 2nd dose, the reaction may be categorized as refractory).	1	0.00	3
To be categorized as refractory anaphylaxis, the initial reaction must be treated with a minimum of 3 appropriate doses of epinephrine (e.g. if the patient does not respond to 2 doses of epinephrine and requires a 3rd dose, the reaction may be categorized as refractory).	9	0.00	3
To be categorized as refractory anaphylaxis, the initial reaction must be treated with 3 or more appropriate doses of epinephrine (or initiation of an intravenous [IV] epinephrine infusion) in addition to symptom-directed medical management, such as an IV fluid bolus for hypotension.	9	0.02	1
To be categorized as refractory anaphylaxis, in addition to treatment with appropriate epinephrine dosing, patients must also receive appropriate medical management of specific symptoms/exam findings (e.g. IV fluid bolus for hypotension).	9	0.34	1
<i>Biphasic anaphylaxis</i>			
The anaphylaxis severity grading system that will be developed by this group can also be used to grade the severity of biphasic anaphylactic reactions.	9	0.34	1
To be categorized as biphasic anaphylaxis, recurrent symptoms/exam findings must fulfill the 2006 NIAID/FAAN anaphylaxis criteria.	8	0.71	1
To be categorized as biphasic anaphylaxis, the allergen(s) must be known or likely/suspected.	2	0.13	2

To be categorized as biphasic anaphylaxis, initial symptoms/exam findings must completely resolve prior to the onset of recurrent symptoms/exam findings.	8	0.34	2
To be categorized as biphasic anaphylaxis, there cannot be allergen re-exposure prior to the onset of recurrent symptoms/exam findings.	9	0.34	1
The definition of biphasic anaphylaxis is independent of the management of the initial reaction.	9	0.34	1
There should be a minimum time threshold from resolution of initial symptoms/exam findings to the onset of new/recurrent symptoms/exam findings(e.g. Recurrent/new symptoms/exam findings must occur $\geq x$ minutes from resolution of initial symptoms/exam findings).	8	0.34	1
To be categorized as biphasic anaphylaxis new or recurrent symptoms/exam findings must occur X minutes from complete resolution of initial symptoms/exam findings.			
≥ 30 minutes	2	0.29	2
≥ 60 minutes	9	0.02	2
≥ 120 minutes	8	6.26	2
≥ 240 minutes	2	0.29	1
There should be a maximum time threshold from resolution of initial symptoms/exam findings to the onset of new/recurrent symptoms/exam findings.	8	0.21	1
To be categorized as biphasic anaphylaxis new or recurrent symptoms/exam findings must occur within X hours of complete resolution of initial symptoms/exam findings (e.g. if symptoms occur beyond 48 hours they cannot be categorized as biphasic reaction).			
24 hours	1	0.00	3
36 hours	2	0.52	1
48 hours	9	0.15	3
72 hours	1	0.00	1
<i>Persistent non-anaphylactic reactions</i>			
To be categorized as persistent allergic reaction, recurrent symptoms/exam findings do not fulfill the 2006 NIAID/FAAN anaphylaxis criteria.	9	0.00	1

The definition of persistent allergic reaction is independent of the management of the initial reaction.	9	0.34	2
There should be a minimum duration of symptoms/exam findings for a reaction to be categorized as a persistent allergic reaction (e.g. symptoms/exam findings must last ≥ 6 hours).	8	0.34	1
The minimum time thresholds developed for persistent anaphylaxis are applicable to the definition of persistent allergic reaction.	9	0.34	1
<i>Biphasic non-anaphylactic reactions</i>			
To be categorized as biphasic allergic reaction, recurrent symptoms/exam findings do not fulfill the 2006 NIAID/FAAN anaphylaxis criteria.	8	0.00	1
To be categorized as biphasic allergic reaction, the allergen(s) must be known or likely/suspected.	2	0.66	1
To be categorized as biphasic allergic reaction, initial symptoms/exam findings must completely resolve prior to the onset of recurrent symptoms/exam findings.	8	0.58	1
To be categorized as biphasic allergic reaction, there cannot be allergen re-exposure prior to the onset of recurrent symptoms/exam findings.	9	0.12	1
The definition of biphasic allergic reaction is independent of the management of the initial reaction.	8	0.34	1
There should be a minimum time threshold from resolution of initial symptoms/exam findings to the onset of new/recurrent symptoms/exam findings.	9	0.00	1
There should be a maximum time threshold from resolution of initial symptoms/exam findings to the onset of new/recurrent symptoms/exam findings.	8.5	0.34	1
The minimum and maximum time thresholds developed for biphasic anaphylaxis are applicable to the definition of biphasic allergic reaction.	9	0.34	1
<i>Anaphylaxis not otherwise specified</i>			
Anaphylaxis not otherwise specified is defined as anaphylactic reactions that do NOT fulfill	8	0.34	1

the following clinical outcomes: fatal anaphylaxis, persistent anaphylaxis, biphasic anaphylaxis, persistent non-anaphylactic reactions, or biphasic non-anaphylactic reactions.			
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^a A median appropriateness value for statements of 1.0 to 3.4 was considered “inappropriate;” 3.5 to 6.9, “uncertain;” and 7.0 to 9.0, “appropriate.”

^b Disagreement index^{E7}; $DI < 1.0$ = consensus reached; $DI \geq 1.0$ consensus not reached