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Clinical Reviews

CUSTOMIZING ANAPHYLAXIS GUIDELINES FOR EMERGENCY MEDICINE

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Abstract—Background: Most episodes of anaphylaxis are managed in emergency medical settings, where the cardinal signs and symptoms often differ from those observed in the allergy clinic. Data suggest that low recognition of anaphylaxis in the emergency setting may relate to inaccurate coding and lack of a standard, practical definition. **Objective:** Develop a simple, consistent definition of anaphylaxis for emergency medicine providers, supported by clinically relevant consensus statements. **Discussion:** Definitions of anaphylaxis and criteria for diagnosis from current anaphylaxis guidelines were reviewed with regard to their utilization in emergency medical settings. The agreed-upon working definition is: *Anaphylaxis is a serious reaction causing a combination of characteristic findings, and which is rapid in onset and may cause death. It is usually due to an allergic reaction but can be non-allergic.* The definition is supported by Consensus Statements, each with referenced discussion. For a positive outcome, quick diagnosis and treatment of anaphylaxis are critical. However, even in the emergency setting, the patient may not present with life-threatening symptoms. Because mild initial symptoms can quickly progress to a severe, even fatal, reaction, the first-line treatment for any anaphylaxis episode—regardless of severity—is intramuscular injection of epinephrine into

the anterolateral thigh; delaying its administration increases the potential for morbidity and mortality. When a reaction appears as “possible anaphylaxis,” it is generally better to err on the side of caution and administer epinephrine. **Conclusion:** We believe that this working definition and the supporting Consensus Statements are a first step to better management of anaphylaxis in the emergency medical setting. © 2013 Elsevier Inc.

Keywords—anaphylaxis; guidelines; epinephrine (adrenaline); allergic reaction; life-threatening reaction

INTRODUCTION

Despite the recent release of a number of guidelines and updated emergency medicine (EM) practice parameters on the management of anaphylaxis, there remain significant knowledge and practice gaps in the United States (US) (1–3). This was the conclusion of a multidisciplinary group of experts attending a July 2011 Roundtable meeting, *Anaphylaxis in Emergency Medicine* (Chicago, IL), who were given the directive of reviewing the current guidelines and how they are

applied in different emergency medical settings in the US (e.g., prehospital, community hospital, rural health care, academic medical center). The ensuing discussion identified gaps in knowledge and practice as well as barriers to care in each setting.

The group agreed that the root cause for many of the identified gaps in the treatment of anaphylaxis was the lack of a practical definition of anaphylaxis as it relates to EM. Although recent guidelines and practice parameters have published consensus definitions of anaphylaxis, there is a concern that emergency health professionals may not be fully utilizing them (1–6). The poor concordance may reflect the lack of consensus among the various guidelines, as well as differences in the likelihood of several of the cardinal signs and symptoms of anaphylaxis actually being due to anaphylaxis in the Emergency Department (ED) as opposed to findings in the allergist's office. The current body of evidence from retrospective data reviews and surveys of ED and Emergency Medical Services (EMS) providers confirms that a variety of definitions of anaphylaxis are being utilized that vary across regions and health care systems (7–9). The “definitions” can be complex and confusing for clinical providers and can lead to inconsistency of care provided.

The lack of a standardized practical definition of anaphylaxis likely contributes to under-diagnosis, under-reporting, under-treatment, and subsequently, life-threatening complications that could potentially be avoided. The Roundtable faculty agreed that a simple and consistent definition might encourage ED and EMS providers to consider the diagnosis more frequently. It was also recognized that the definition had to have face validity with everyday EM practitioners, with both sensitivity and specificity for anaphylaxis, to become a part of common practice. It was not the intent to create a new definition, but to build upon those suggested by other groups to provide a more clinically relevant definition for emergency providers. Thus, as a starting point, the working definition is taken from current guidelines, with some minor modifications as follows: *Anaphylaxis is a serious reaction causing a combination of characteristic findings, and which is rapid in onset and may cause death. It is usually due to an allergic reaction, but can be non-allergic.* The characteristic findings are described in the listing of the clinical criteria for identification (Table 1).

After agreeing upon the working definition, the faculty developed consensus statements to summarize why the definition is needed and to encourage its practical application. This article presents those consensus statements, each with a brief discussion. It is not the intent to provide a comprehensive review of how to diagnose and manage anaphylaxis in the emergency medical setting. For that,

the reader is directed to the current guidelines and other recent reviews (1–3,10,11). We wish to point out, however, that the consensus statements presented here expand the discussion and can be considered as a “call to action” for emergency health professionals.

The Roundtable meeting was chaired by the first author, Richard Nowak, and the expert faculty included all of the listed authors. All of the faculty met criteria for authorship and approved the Consensus Statements.

DISCUSSION

Consensus Statements

1. “The traditional mechanistic definition of anaphylaxis is not useful at the bedside.” When asked to define anaphylaxis, even some allergists have admitted that, “Anaphylaxis is hard to define, but I know it when I see it.” However, other clinicians might not recognize anaphylaxis on instinct alone (5).

Discussion: There is a “disconnect” in how anaphylaxis has historically been defined and how the term is used clinically. Traditionally, allergy textbooks and guidelines have defined anaphylaxis mechanistically—based on immunoglobulin E levels, mast cells, basophils, cytokines, and inflammatory mediators (12,13). However, that approach is not helpful at the bedside; and the issue is further compounded by existing clinical definitions that are, themselves, variable. Anaphylaxis has been defined clinically as reactions that range from mild—such as simple urticaria—to life-threatening—such as those involving hypotensive shock (5).

The definition of anaphylaxis affects all aspects of clinical practice—from when to consider it as a diagnosis to how to manage the patient, from how to code a serious allergic reaction to how to design an appropriate clinical trial (7,14). It is our consensus that the traditional mechanistic definition of anaphylaxis is not useful for non-allergists, and acknowledging this is the starting point to improving care of the anaphylaxis patient in the prehospital and ED settings.

Whether or not an enhanced definition will improve care is not known. Will better recognition and standard protocols yield fewer deaths from anaphylaxis or decreased risks of hospitalization or recurrence? Data are needed. What is known, however, is that almost all studies of anaphylaxis care in the ED identify the lack of, or inconsistency in, definition and criteria as a significant contributing factor to poor patient outcomes (4,5,7–9,14–17).

2. Most acute episodes of anaphylaxis are managed by ED clinicians and not by allergists. The diagnosis and management of anaphylaxis in the ED differs from that in the allergy clinic.

Table 1. Full Definition of Anaphylaxis for Emergency Health Professionals (1–3)

Part 1. Working Definition: Anaphylaxis is a serious reaction that is rapid in onset and may cause death. It is usually due to an allergic reaction but can also be non-allergic.

Part 2. Clinical criteria to diagnose an acute anaphylactic episode: Anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:

1. Acute onset (minutes to several hours) of an illness involving the skin, mucosal tissue, or both (e.g., 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 PEF, hypoxemia)
 - b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia, syncope)

OR

2. Two or more of the following that occur rapidly (minutes to several hours) after exposure to a likely allergen for the patient:
 - 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 PEF, hypoxemia)
 - c. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia, syncope)
 - d. Persistent gastrointestinal symptoms (e.g., crampy, abdominal pain, vomiting)

OR

3. Reduced BP occurring rapidly (minutes to several hours) after exposure to known allergen for the patient
 - a. Infants and children: low systolic BP (age specific) or > 30% decrease in systolic BP
 - b. Adults: systolic BP < 90 mm Hg or > 30% decrease from baseline

PEF = peak expiratory flow.

Discussion: Although the majority of the anaphylaxis literature—including guidelines and practice parameters—is published in allergy journals, the ED is the most common clinical setting for treating anaphylaxis. A review of anaphylaxis in children and adolescents over a 6-year period reported that 71% of cases were treated in the ED or in an urgent care center (7). The number of annual ED visits for anaphylaxis in the US is estimated to be as high as 500,000 (4). However, multiple reviews and surveys of care provided in emergency settings have reported low concordance with guideline-recommended treatment, even in patients who were clearly diagnosed with anaphylaxis by medical record or by International Classification of Diseases, 9th Edition (ICD-9) code (4,9,15–18).

3. Anaphylaxis is under-diagnosed (and, hence, under-treated) in most prehospital care situations and EDs (4,19).

Discussion: The reported incidence of anaphylaxis in the EM literature is likely to be an underestimate of the true incidence, due to inconsistent use of consensus definitions and inaccurate ICD-9 coding (4,19). Anaphylaxis has a wide range of clinical presentations, and different diagnostic criteria (even different coding practices) may be applied among health care systems. By way of example, the number of diagnosed anaphylaxis cases was estimated to increase by 58% when a validated ICD-9-Clinical-Modification-based diagnostic algorithm that included anaphylactic signs and symptoms was applied to ED data from the Florida Agency for Health Care Administration (2005–2006) (14). Similarly, an earlier study evaluating the application of anaphylaxis coding to acute allergic reactions between 1993 and 2004 reported that 51% of 678 ICD-9-coded food-induced acute allergic reactions were actually anaphylaxis (19).

One identified problem is a limited ability of ICD codes to differentiate between various types and severities of allergic reactions in the ED. A 2012 review of pediatric records in a New York City ED reported that 213 patients met the Second Symposium criteria for anaphylaxis (see Table 1), but only 62 (29.1%) were actually coded as anaphylaxis (20). The majority (75%) were coded as “allergic reaction.” This type of under-diagnosis of anaphylaxis in the ED is not new. An earlier review of more than 19,000 ED visits identified 17 cases that met the criteria for anaphylaxis; but only four (23.5%) were diagnosed as such in the ED (18). That report, published in 1995, suggested the need for a standard definition and encouraged better clarity in the diagnostic criteria used to differentiate anaphylaxis from a diagnosis of “allergic reaction,” recommendations that were repeated in the 2012 survey (20).

4. It is important for prehospital and EM providers to recognize that a patient can have anaphylaxis without shock.

Discussion: Data suggest that the diagnosis of “allergic reaction” is often used by Emergency Physicians for patients who should have received a diagnosis of anaphylaxis (14–16,18–21). As noted previously, this may reflect a general lack of awareness of the spectrum of severity in anaphylaxis, the inaccuracies of current coding systems, or the absence of prospectively validated diagnostic criteria for anaphylaxis (4,6). There may also be a tendency by some health professionals to equate anaphylaxis with shock.

It is important to recognize that the patient may not present with life-threatening symptoms. The initial clinical presentation may be simply gastrointestinal complaints plus hives, or gastrointestinal distress with difficulty breathing. However, anaphylaxis occurs as

a continuum, so that even when the initial symptoms are mild, there is significant potential for rapid progression to a severe reaction, which may prove fatal. It often is impossible to predict the ultimate severity of an anaphylactic episode at the time of onset (22). Any delay in appropriate treatment increases the potential for morbidity and mortality (1–3,12,23,24).

5. Anaphylaxis causes significant morbidity and can be fatal.

Discussion: It has been estimated that approximately 1500 persons die annually in the US related to anaphylactic reactions to foods, drugs, latex, and insect stings (25). This translates to an annual mortality incidence rate between 0.002% and 1% (13,25). Although this is a low mortality rate, appropriate anaphylaxis management should be of great concern because many of these reactions have the potential to be fatal, and the patients who succumb are often young and otherwise in good health. Death usually occurs due to circulatory collapse or respiratory arrest, and may occur so rapidly that patients do not present with classic symptoms (26,27).

Contributing to the challenge, there is no single test to diagnose anaphylaxis or predict its outcome. For this reason, it is critical that all emergency professionals not only appreciate the potential morbidity and life-threatening nature of anaphylaxis, but also recognize the multiple factors (and cofactors) that can increase the likelihood of an acute episode as well as its severity and risk of fatality (Table 2) (1).

Prompt recognition and aggressive treatment—particularly the early administration of intramuscular (i.m.) epinephrine—will, in most cases, reduce the severity and associated morbidity of the acute episode (1–3,12,23,24,28). Withholding epinephrine in favor of antihistamine, steroid administration, and “watchful waiting,” or even establishing intravenous access in patients with a reasonable suspicion of anaphylaxis is risky—even in the presence of mild presenting symptoms.

6. Epinephrine should be the first-line treatment for all prehospital and ED patients with anaphylaxis. Early administration is critical. All current guidelines recommend that when a patient experiences a reaction that a health care provider considers as *possible* anaphylaxis, it is generally better to err on the side of caution and administer epinephrine (1–3).

Discussion: The first-line use of epinephrine is the standard of care for anaphylaxis and is a clear directive in all guidance documents published in the past two decades (1–3,12,23,24,28). However, concordance varies widely. In surveys of EM practice, the proportion of patients with severe allergic reactions or anaphylaxis who received epinephrine ranged from as low as 12%

to almost 80% (9,15,16,19,20). This probably reflects the fact that epinephrine is often not given to patients who do not have life-threatening cardiovascular (e.g., “shock”) or respiratory symptoms, as these patients, by many health system definitions and coding, are not considered to have anaphylaxis (8,9). The question of who should be treated with epinephrine has been further complicated by controversy in older guidelines that questioned the use of epinephrine for milder reactions (e.g., single organ involvement, cutaneous symptoms only) (28).

The current body of evidence supports the use of i.m. epinephrine as first-line treatment for anaphylaxis for all patients rather than alternative routes such as subcutaneous or intravenous (i.v.) (1–3,29,30). Delaying administration of epinephrine has been associated with increased reaction severity, increased morbidity, a greater likelihood of biphasic reactions, and an increased risk of fatality even in some cases in which the initial symptoms were mild (10,11,22,26,31,32).

The use of additional medications depends on the severity of the reaction and the initial response to epinephrine. Oral antihistamines are second-line supportive therapy with a slow (1 h or longer) onset of action. They may be useful to control cutaneous manifestations of an anaphylactic reaction (2,10,11). An inhaled beta-agonist can be used as adjunctive therapy for patients with pre-existing asthma who present with respiratory symptoms (1,2,10–12,22). Corticosteroids have not been shown to be effective for the acute treatment of anaphylaxis, but are sometimes used to reduce the likelihood of protracted anaphylaxis or recurrent reactions. There are no data to support these uses of corticosteroids, and further studies are warranted (2,10,11).

7. There are no absolute contraindications to the use of epinephrine for anaphylaxis. Serious adverse effects are very rare when epinephrine is administered at the appropriate intramuscular doses for anaphylaxis.

Discussion: Epinephrine is a direct-acting sympathomimetic agent that targets multiple organs by interacting with alpha- and beta-adrenergic receptors. Its clinical effects include vasoconstriction, decreased mucosal edema, increased inotropy, chronotropy, and bronchodilation. Epinephrine also down-regulates the continued release of mediators of anaphylaxis from mast cells and circulating basophils. The common transient side effects include pallor, tremor, anxiety, headache, and palpitations (10,11,22,26,31,32).

Intramuscular injection into the anterolateral thigh, the preferred route of administration for epinephrine to treat anaphylaxis, attains higher plasma levels more quickly than subcutaneous administration (1,2,12,33). The dose

Table 2. Factors and Cofactors That Can Increase the Severity of an Anaphylactic Episode and the Potential Risk of Fatality or Near-fatality*

Factors	Comments
Age-related factors	
Infants	Cannot verbalize problems
Adolescents	Increased risk-taking behaviors
Young adults	Increased risk-taking behaviors
Pregnancy	Risk from medications during labor and delivery; may need careful monitoring during pregnancy to avoid triggers
Elderly	Medication risks may be increased; subclinical conditions may increase risk
Concurrent medication/drug use	
Beta-adrenergic blockers	Beta-adrenergic blockade may increase incidence and severity of anaphylaxis
Angiotensin-converting enzyme (ACE) inhibitors	ACE inhibitors may increase the risk of a severe anaphylaxis episode
Ethanol	May alter self-recognition of signs/symptoms; may increase risk-taking behavior
Recreational drugs	May alter self-recognition of signs/symptoms; may increase risk-taking behavior
Anti-depressants	May alter self-recognition of signs/symptoms; may increase risk-taking behavior
Concomitant diseases	
Asthma, respiratory conditions	Respiratory symptoms of an anaphylaxis episode may be exacerbated by underlying respiratory condition
Cardiovascular disease	Cardiovascular symptoms of an anaphylaxis episode may be exacerbated by underlying cardiovascular disease
Mastocytosis, clonal mast cell disorders	Release of inflammatory mediators associated with mast cell disorders may exacerbate symptom severity
Severe atopic disease – especially allergic rhinitis, eczema	Release of inflammatory mediators associated with severe atopic disease may exacerbate symptom severity
Depression, psychiatric conditions	May alter self-recognition of signs/symptoms
Other	
Exercise	May trigger an anaphylactic episode through direct effects on mast cells; usually associated with reactions to other triggers, such as foods
Acute infections	Compromised immune system and circulating inflammatory mediators may exacerbate symptom severity
Stress	Emotional stress, disruption of normal routine may alter self-recognition of signs/symptoms, hormones may aggravate response
Premenstrual status	Hormones may aggravate response

* Adapted from Simons et al., 2011 (1).

is 0.01 mg/kg of a 1:1000 (1 mg/mL) solution to a maximum of 0.5 mg in adults or 0.3 mg in children. Depending on the severity of the episode and the response to the initial injection, this dose can be repeated every 5–15 min as needed; most patients respond to one or two doses (1–3).

Fear of serious adverse effects is a commonly cited concern with epinephrine and probably contributes to its under-usage for anaphylaxis. However, the reality is that epinephrine toxicity is much more likely to occur with i.v. administration, particularly at high doses or rapid infusion rates (26,31). The severe physiologic responses seen in i.v. epinephrine (e.g., ventricular dysrhythmias, hypertensive crisis, pulmonary edema) are rare when using the preferred i.m. route and recommended dose for anaphylaxis (1,2,10,11,22,26,31,32). Using an epinephrine auto-injector, which delivers a pre-filled therapeutic dose, may allay some of the concerns related to confusion between epinephrine i.v. dosing for cardio-pulmonary resuscitation (1:10,000 dilution) and i.m. dosing by syringe (1:1000 dilution) (1,2,10,11,31). However, although extremely rare, acute ST-elevation myocardial infarction can occur, even with therapeutic i.m. epineph-

rine, and in the ED setting, hemodynamic monitoring is important (34).

In-depth discussion of the pharmacology and adverse effects of epinephrine is beyond the scope of this article. The reader is referred to the current guidelines and practice parameters, as well as several excellent reviews for more information (1,2,12,22–24).

8. Anaphylaxis is a long-term diagnosis, and management does not end with discharge from the ED. Patients are at risk for more episodes, and most episodes occur in the community, not in the medical setting.

Discussion: Anaphylaxis is a condition that carries the persistent risk of acute and potentially life-threatening episodes. Treating the acute event in the ED can be a first step towards reducing the risk, though prospective data are needed. All current guidelines recommend that patients treated in the ED for anaphylaxis should be discharged with an epinephrine auto-injector (or a prescription for an auto-injector), personalized written instructions about anaphylaxis to help them recognize symptoms, avoid triggers, and understand how to inject epinephrine, and a referral (preferably, allergist) for follow-up and long-term care (1,2,10,11,22,31,34).

9. Outcomes data are needed. A limited body of evidence exists demonstrating possible practice gaps in the management of anaphylaxis in the ED setting.

Discussion: Based on the current body of evidence, it can be inferred that how anaphylaxis is managed in the emergency setting frequently does not concur with guideline recommendations (8,9,14–17,19,26,27,32). The data are largely indirect—from case reports and retrospective reviews of medical databases—and do not answer key questions about patient outcomes, such as:

- What data show that not using epinephrine quickly results in more hospitalizations? Or increased morbidity, or recurrence?
- How do the outcomes for patients given antihistamines first for an anaphylaxis episode compare to patients treated immediately with epinephrine?
- Do patients who do not (re)fill epinephrine prescriptions do worse than patients who maintain their epinephrine and keep it with them?

Prospective studies are needed.

CONCLUSION

In conclusion, the current body of evidence indicates that most anaphylaxis cases are seen in an emergency medical setting, so proper diagnosis is critical. A critical factor contributing to failure of the emergency health professional to diagnose anaphylaxis may be the lack of a standard and practical definition applicable to the emergency medical setting. It is important to recognize that anaphylaxis may not appear life-threatening and that the patient may present without respiratory or cardiovascular symptoms. It is also important to recognize that an episode is usually unexpected and, although symptoms can be initially mild, variable, and non-specific, a reaction can quickly progress, becoming severe, and even fatal, in a short period of time.

At a time when anaphylaxis is increasing, particularly in young children, there is good reason to have a practical definition of anaphylaxis appropriate for emergency health professionals: “*Anaphylaxis is a serious reaction causing a combination of characteristic findings, and which is rapid in onset and may cause death. It is usually due to an allergic reaction but can be non-allergic*” (31). This working definition for ED and EMS providers, based on current guidelines and applied along with the supporting identifying criteria (Table 1), is a first step toward better recognition and treatment of anaphylaxis in the emergency medical setting (1–3).

Although this definition may not concur with all current coding systems, it should encourage all emergency health professionals to consider the diagnosis of anaphylaxis and not delay treatment. The corollary is that i.m.

epinephrine is the cornerstone of treatment for anaphylaxis and should be administered as soon as possible, even when anaphylaxis is only suspected. Based on the available evidence, the benefits of using appropriate doses of i.m. epinephrine for anaphylaxis far exceed the risk. Prompt injection is usually associated with positive outcomes, and anecdotal and clinical data have shown that delaying administration of epinephrine increases both morbidity and mortality (31).

Auto-injectors make administering epinephrine easy and quick—in the emergency setting as well as in the community. Patients treated for anaphylaxis in the ED should be prescribed self-injectable epinephrine on discharge. We also recommend they be provided with an anaphylaxis emergency action plan.

We recognize that ED operations and discharge procedures vary between regions, states, and health care systems. Nonetheless, we believe that the recommendations made in this article are a critical call to action for all ED and prehospital providers in the US.

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ARTICLE SUMMARY

1. Why is this topic important?

Knowledge and practice gaps affecting the management of acute anaphylactic episodes in the Emergency Department (ED) are well documented and, to some extent, reflect differences in practice between the emergency and allergy settings. Because the majority of episodes are seen in the ED, there is a need for a standard definition of anaphylaxis appropriate for emergency medicine health professionals.

2. What does this review attempt to show?

This review presents a working definition of anaphylaxis appropriate for all emergency health professionals, and develops recommendations for management in the emergency setting based on the application of that definition.

3. What are the key findings?

- A simple and consistent definition developed by emergency health professionals for emergency health professionals.
- Relevant, referenced consensus statements supporting application of the definition to patient care.

4. How is patient care impacted?

- Earlier identification of (possible) anaphylaxis in the emergency setting.
- Recognition that the patient may not initially present with life-threatening symptoms.
- Quicker resolution of most anaphylactic episodes by first-line treatment with intramuscular epinephrine, even for suspected cases.