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Anaphylaxis: Current Insights into Diagnosis and Management for Emergency Clinicians

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Abstract

Background: Anaphylaxis is a severe, life-threatening allergic reaction that can occur rapidly after allergen exposure, presenting significant challenges in emergency medicine due to its unpredictable nature.

Objective: This review aims to evaluate the diagnosis and management of anaphylaxis, focusing on recent advancements and evidence-based practices for emergency clinicians.

Methods: The review synthesizes current literature on diagnostic criteria, emerging etiologies, treatment protocols, and the incidence of biphasic reactions, highlighting key findings from the Second NIAID/FAAN Symposium and the World Allergy Organization (WAO).

Results: The review emphasizes the importance of rapid recognition and treatment of anaphylaxis, with epinephrine as the first-line therapy. It discusses limitations of current diagnostic criteria and introduces new proposed criteria by the WAO. Additionally, it addresses the significance of alpha-gal anaphylaxis as an emerging trigger and the need for careful monitoring for biphasic reactions.

Conclusions: Staying updated on advancements in anaphylaxis management is crucial for emergency clinicians to ensure optimal patient care. Education on allergen avoidance and proper use of epinephrine autoinjectors is essential for at-risk patients. The review underscores the need for ongoing research to refine treatment strategies and improve outcomes for individuals experiencing anaphylaxis.

Categories: Pharmacology, Neurosurgery, Anesthesiology
Keywords: Anaphylaxis, epinephrine, WAO, biphasic reactions, Emergency Clinicians

Background and Introduction

Anaphylaxis is a severe, potentially life-threatening allergic reaction that occurs rapidly after exposure to an allergen, affecting multiple organ systems, including the skin, respiratory tract, gastrointestinal system, and cardiovascular system (1). It is primarily triggered by immunoglobulin E (IgE) antibodies, leading to the release of mediators from mast cells and basophils. Common triggers include foods (e.g., peanuts, tree nuts, shellfish), medications (e.g., antibiotics, non-steroidal anti-inflammatory drugs), insect stings, and latex. The incidence of anaphylaxis is rising globally, affecting approximately 0.05% to 2% of the population in the United States and up to 3% in Europe. Data from Asia is limited, but emerging studies suggest lower rates than in Western countries (2). This increasing prevalence highlights the need for healthcare professionals, especially in emergency medicine, to be well-informed about the diagnosis and management of anaphylaxis. Anaphylaxis is a critical medical emergency requiring prompt recognition and intervention. Symptoms can arise within minutes of allergen exposure, necessitating a high index of suspicion among healthcare providers (3). Clinical manifestations vary widely, from mild urticaria to severe respiratory distress and cardiovascular collapse. Timely diagnosis and treatment are essential to prevent serious complications and fatalities. The Second NIAID/FAAN Symposium established widely accepted diagnostic criteria for anaphylaxis, which have guided clinical practice (4). However, limitations in these criteria have led the World Allergy Organization (WAO) to propose updated guidelines that encompass a broader range of presentations. Emerging etiologies, such as alpha-gal anaphylaxis, present new challenges in diagnosis and management, particularly in areas where tick bites are common. This review aims to provide an updated evaluation of the diagnosis and management of anaphylaxis, focusing on recent advancements and evidence-based practices for emergency clinicians. Key areas of focus include diagnostic criteria, emerging etiologies, severity grading, and the latest treatment protocols. By synthesizing current literature and guidelines, this review seeks to enhance understanding of anaphylaxis and improve patient outcomes in emergency settings (5).

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3. Overview of Anaphylaxis as a Medical Emergency

Anaphylaxis Overview

Anaphylaxis is a life-threatening allergic reaction that can occur swiftly after allergen exposure. It affects multiple organ systems and requires immediate medical attention. Healthcare providers must understand its clinical features, epidemiology, and the importance of emergency preparedness, especially in emergency settings.

Clinical Manifestations

Anaphylaxis presents various symptoms that can occur together or in sequence, including:

1. **Cutaneous Symptoms:** Urticaria (hives), pruritus (itching), flushing (skin redness), and angioedema (swelling affecting lips, tongue, and throat).
2. **Respiratory Symptoms:** Wheezing, stridor (inhalation sound), dyspnea (shortness of breath), and persistent coughing(6).
3. **Cardiovascular Symptoms:** Hypotension (low blood pressure), tachycardia (increased heart rate), and dizziness or syncope (fainting).
4. **Gastrointestinal Symptoms:** Nausea, vomiting, abdominal pain, and diarrhea.

Epidemiology and Incidence Trends

The incidence of anaphylaxis is increasing worldwide, affecting about 0.05% to 2% of the U.S. population and up to 3% in Europe. In Asia, prevalence data is limited, but studies indicate lower rates than in Western countries (7-8). Contributing factors include:

- **Increased Awareness:** More recognition has led to more reported cases.
- **Changes in Allergen Exposure:** Dietary shifts and greater exposure to allergens (e.g., peanuts, tree nuts) may be driving the rise.
- **Genetic and Environmental Factors:** Genetic predisposition combined with environmental triggers may influence allergy and anaphylaxis development.

Importance of Emergency Preparedness

Due to the rapid onset and potential severity of anaphylaxis, emergency preparedness is essential. Healthcare providers, particularly in emergency medicine, must be ready to recognize and manage anaphylaxis effectively. Key components include:

- **Training and Education:** Continuous education for healthcare providers on symptom recognition and epinephrine autoinjector use (9).
- **Emergency Protocols:** Established protocols for managing anaphylaxis in emergency departments, ensuring quick access to epinephrine and patient monitoring.
- **Patient Education:** Instructing at-risk patients on allergen avoidance, recognizing early symptoms, and the importance of carrying an epinephrine autoinjector.
- **Public Awareness Campaigns:** Initiatives to increase community awareness about anaphylaxis, enabling by standers to respond effectively in emergencies.

4. Defining Diagnostic Criteria for Anaphylaxis

Accurate diagnosis of anaphylaxis is essential for timely intervention and effective management. The diagnostic criteria have evolved, with significant contributions from organizations like NIAID/FAAN and the World Allergy Organization (WAO). This section outlines key aspects of diagnosing anaphylaxis, including symptom onset timelines, established definitions, current diagnostic criteria, limitations, and proposed updates (10).

4.1 Rapid Onset of Symptoms

Anaphylaxis is marked by rapid symptom onset, typically within minutes to hours after allergen exposure. The timeline varies by exposure route:

- **Immediate Reactions:** Symptoms may start within seconds to minutes, especially with intravenous or intramuscular allergens.
- **Delayed Reactions:** Symptoms can appear several hours later, particularly with oral allergens (e.g., certain foods).
- Recognizing rapid symptom onset is crucial for healthcare providers to initiate prompt treatment.

4.2 Established Definitions from the Second NIAID/FAAN Symposium

The Second NIAID/FAAN Symposium established key definitions for diagnosing anaphylaxis:

- **Anaphylaxis:** A serious allergic reaction that is rapid in onset and may be life-threatening, involving multiple organ systems.
- **Allergic Reaction:** An immune response to a specific allergen, ranging from mild to severe. These definitions highlight the need for clinicians to maintain a high index of suspicion when evaluating potential anaphylaxis, especially in emergency settings.

4.3 Diagnostic Criteria (Table 1)

Table 1: Diagnostic Criteria for Anaphylaxis (NIAID/FAAN)

Criteria	Description
Acute Onset	Symptoms occur within minutes to hours after exposure to a likely allergen.
Skin/Mucosal Involvement	Involvement of the skin or mucous membranes (e.g., urticaria, pruritus, flushing, swelling of the lips, tongue, or uvula).
Respiratory Compromise	Symptoms such as wheezing, dyspnea, stridor, or hypoxemia.
Reduced Blood Pressure	Systolic BP less than 90 mmHg or a decrease of more than 30% from baseline.
Gastrointestinal Symptoms	Symptoms such as abdominal pain, nausea, vomiting, or diarrhea.
Two or More Symptoms	The presence of two or more of the following after exposure to a likely allergen: skin/mucosal involvement, respiratory compromise, reduced BP, gastrointestinal symptoms.

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These criteria serve as a guideline for clinicians to identify anaphylaxis and initiate appropriate treatment.

4.4 Limitations and Challenges in Diagnosing Anaphylaxis

Despite established criteria, several limitations and challenges persist:

- Variability in Clinical Presentations: Anaphylaxis can manifest with a wide range of symptoms, and not all patients will show classic signs. Atypical presentations can complicate diagnosis(11).
- Potential for Underdiagnosis or Misdiagnosis: The variability in symptoms and overlap with other conditions (e.g., panic attacks, asthma exacerbations) increases the risk of underdiagnosing or misdiagnosing anaphylaxis, leading to treatment delays and increased morbidity(12).
- These challenges underscore the need for ongoing education and awareness among healthcare providers regarding the recognition of anaphylaxis.

4.5 WAO Proposed Criteria (Table 2)

In response to the limitations of existing criteria, the World Allergy Organization (WAO) has proposed updated diagnostic criteria for anaphylaxis. These criteria aim to provide a more comprehensive framework for diagnosis.

Table 2: WAO Proposed Criteria for Anaphylaxis

Criteria	Description
Systemic Involvement	Rapid onset of illness (within minutes to hours) with concurrent cutaneous and/or mucosal manifestations (e.g., widespread urticaria, pruritus, flushing, or angioedema).
Respiratory Compromise	Evidence of respiratory distress, such as dyspnea, wheezing, bronchospasm, stridor, or hypoxemia.
Hypotension	Signs of hypotension or impaired end-organ function (e.g., collapse, syncope, incontinence).
Severe Gastrointestinal Symptoms	Intense cramping abdominal pain or repeated vomiting, particularly following exposure to non-food allergens.
Isolated Trigger	Acute presentation of hypotension, bronchospasm, or laryngeal involvement within minutes to hours following exposure to a known allergen, even in the absence of typical cutaneous manifestations.

Implications for Clinical Practice

The WAO proposed criteria aim to address the limitations of previous definitions by encompassing a broader range of presentations. This is crucial in clinical practice, as it encourages healthcare providers to maintain a high level of suspicion for anaphylaxis, even in atypical cases. The updated criteria also stress the need for rapid intervention and the importance of recognizing the potential for severe reactions.

5. Emerging Etiologies

As our understanding of anaphylaxis evolves, new triggers have emerged that challenge traditional concepts of allergic reactions. A significant development is the recognition of alpha-gal anaphylaxis, notable for its unique characteristics and implications for diagnosis and management.

5.1 Introduction to Alpha-Gal Anaphylaxis

Definition and Significance of Alpha-Gal as a Trigger

Alpha-gal (galactose-alpha-1,3-galactose) is a carbohydrate found in non-primate mammals, such as cows, pigs, and sheep, but absent in humans and other primates. Alpha-gal anaphylaxis is a delayed allergic reaction occurring in sensitized individuals after ingesting mammalian meat or exposure to mammal-derived products. This condition is significant as it represents a unique sensitization mechanism that differs from traditional IgE-mediated food allergies.

The importance of alpha-gal as a trigger is linked to tick bites, particularly from the Lone Star tick (Amblyomma americanum), leading to increased cases of alpha-gal anaphylaxis in regions where these ticks are common.

5.2 Mechanism of IgE Response to Alpha-Gal

Immunological Mechanisms Involved

The mechanism underlying alpha-gal anaphylaxis involves the production of IgE antibodies specific to the alpha-gal carbohydrate. The process begins with a tick bite, introducing alpha-gal into the human body, which can lead to sensitization. The immune system recognizes alpha-gal as foreign and produces IgE antibodies against it.

Upon subsequent exposure to alpha-gal through mammalian meat or products containing alpha-gal, these IgE antibodies trigger the release of mediators from mast cells and basophils, resulting in anaphylactic symptoms (13). This mechanism is distinct from traditional food allergies, where allergenic proteins are ingested and elicit an immediate response.

5.3 Distinction Between Immediate-Onset and Delayed-Onset Anaphylaxis

Anaphylaxis can be categorized into two types based on the timing of symptom onset:

- **Immediate-Onset Anaphylaxis:** Occurs within minutes of allergen exposure, typically associated with classic food allergies (e.g., peanuts, tree nuts). Symptoms can include rapid respiratory distress and cardiovascular collapse.
- **Delayed-Onset Anaphylaxis:** Characterized by a delayed response, often occurring 3 to 6 hours after ingesting mammalian meat, as seen in alpha-gal anaphylaxis. Symptoms may include gastrointestinal distress (nausea, vomiting, abdominal pain), urticaria, and, in severe cases, respiratory compromise and hypotension. This delayed response complicates diagnosis, as patients may not connect their symptoms to prior allergen exposure.

5.4 Connection Between Tick Bites and Alpha-Gal Sensitization

Recent epidemiological studies have documented the connection between tick bites and alpha-gal sensitization. Individuals bitten by the Lone Star tick are at increased risk of developing alpha-gal anaphylaxis, as the tick's saliva may facilitate sensitization and IgE antibody production against alpha-gal.

Evidence shows a rising incidence of alpha-gal anaphylaxis in regions where the Lone Star tick is prevalent, particularly in the southeastern and midwestern United States. Many cases involve individuals experiencing anaphylaxis after consuming mammalian products, often following a history of tick bites. This emerging etiology emphasizes the need to consider alpha-gal as a potential trigger in patients with unexplained anaphylactic reactions, especially in endemic areas.

In conclusion, recognizing alpha-gal anaphylaxis as an emerging etiology highlights the need for increased awareness among healthcare providers. Understanding sensitization mechanisms, the distinctions between immediate and delayed-onset reactions, and the connection to tick bites is essential for accurate diagnosis and effective management.

6. Grading Severity of Anaphylactic Reactions

Grading the severity of anaphylactic reactions is essential for guiding treatment decisions and predicting patient outcomes. Severity assessment is based on clinical presentation and the involvement of multiple organ systems.

6.1 Criteria for Assessing Severity

The criteria for assessing the severity of anaphylactic reactions typically include:

- Number of Organ Systems Involved: More affected organ systems indicate a more severe reaction.
- Degree of Respiratory Compromise: Symptoms like wheezing, stridor, or respiratory distress suggest a more severe reaction.
- Blood Pressure Changes: Significant hypotension or signs of shock are critical indicators of severity.
- Gastrointestinal Symptoms: Severe abdominal pain, vomiting, or diarrhea contribute to the overall severity assessment.

6.2 Symptoms and Signs of Severe Reactions

Symptoms indicating severe anaphylaxis may include:

- **Respiratory Symptoms:**
  - Wheezing or stridor
  - Severe dyspnea or difficulty breathing
  - Cyanosis (bluish discoloration of the skin)

- **Cardiovascular Symptoms:**
  - Hypotension (systolic blood pressure < 90 mmHg)
  - Tachycardia (heart rate > 100 beats per minute)
  - Dizziness or syncope (fainting)

- **Gastrointestinal Symptoms:**
  - Severe abdominal pain
  - Repeated vomiting
  - Diarrhea

- **Cutaneous Symptoms:**
  - Extensive urticaria or angioedema
  - Flushing or widespread rash

6.3 Definitions of Persistent and Refractory Anaphylaxis

- **Persistent Anaphylaxis:** Symptoms that continue for more than 4 hours despite appropriate treatment, requiring ongoing monitoring and additional interventions.
- **Refractory Anaphylaxis:** Symptoms that do not respond to standard doses of epinephrine and persist despite treatment, often requiring intravenous epinephrine and intensive monitoring.

6.4 Risk Factors Associated with Severe Reactions

Several risk factors can increase the likelihood of severe anaphylactic reactions, including:

- **History of Severe Reactions:** Previous severe anaphylaxis increases the risk of future severe reactions.
- **Asthma:** Poorly controlled asthma heightens the likelihood of severe anaphylaxis.
- **Age:** Very young children and elderly individuals may be at increased risk for severe reactions.
- **Comorbid Conditions:** Conditions like cardiovascular disease or respiratory disorders can exacerbate anaphylaxis severity.
- **Delayed Administration of Epinephrine:** Delays in administering epinephrine can lead to worse outcomes.

7. Treatment Protocols

Effective management of anaphylaxis is essential to prevent morbidity and mortality, with the prompt administration of epinephrine as the cornerstone of treatment.

7.1 Epinephrine: The Leading Drug Against Anaphylaxis

Epinephrine is the first-line treatment for anaphylaxis and should be administered immediately upon suspicion of the diagnosis to avoid severe complications or death. The recommended dosage is 0.3 to 0.5 mg (0.3 to 0.5 mL of a 1:1000 solution) via intramuscular (IM) injection for adults, and 0.01 mg/kg (up to 0.3 mg) for children. In severe cases, intravenous (IV) epinephrine may be necessary, starting at 0.1 to 0.5 mcg/kg/min. The preferred IM injection site is the anterolateral thigh, where peak plasma concentrations are reached within 5 to 10 minutes. If symptoms persist after 5 to 15 minutes, a repeat dose may be given, and IV epinephrine should be considered for unstable patients (9,7).

7.2 Antihistamines and Glucocorticoids: Adjunctive Therapies

While epinephrine is the primary treatment, antihistamines (e.g., diphenhydramine) and glucocorticoids (e.g., prednisone) can serve as adjunctive therapies to alleviate symptoms and prevent biphasic reactions (4-5). However, these medications do not provide immediate relief and should not replace epinephrine, as they primarily address cutaneous symptoms and do not effectively manage respiratory or cardiovascular compromise. Current evidence supports their use alongside epinephrine, but further research is needed to clarify their role in acute management.

8. Incidence of Biphasic Reactions

Biphasic anaphylaxis is a phenomenon where symptoms recur after an initial resolution, typically occurring within hours to days without further allergen exposure. Symptoms may improve after the first episode, but can reappear within 1 to 72 hours, most commonly between 8 to 12 hours. These symptoms can include respiratory distress, hypotension, urticaria, and gastrointestinal issues, and their severity can range from

mild to life-threatening (6).

Estimates suggest that 20% to 30% of patients experiencing anaphylaxis may have a biphasic reaction. Factors influencing this incidence include the severity of the initial reaction, with more severe cases posing a higher risk for biphasic episodes. Delays in administering epinephrine during the initial reaction can also increase the likelihood of recurrence, as can underlying conditions like asthma (9). Certain allergens, particularly foods, are associated with a higher incidence of biphasic reactions.

Given the potential for biphasic reactions, careful monitoring and observation post-anaphylaxis treatment are critical. Patients should be observed for at least 4 to 6 hours, especially if they experienced severe symptoms or required multiple doses of epinephrine. Continuous monitoring of vital signs and educating patients about biphasic symptoms are essential for ensuring safety and prompt intervention if symptoms reappear (13).

9. Recommendations for Management of Anaphylaxis (Table 3)

Effective management of anaphylaxis requires a comprehensive approach that includes immediate treatment, patient education, and ongoing monitoring. The following recommendations summarize key management strategies:

Table 3: Recommendations for Management of Anaphylaxis

Recommendation	Description
Immediate Epinephrine Administration	Administer epinephrine IM in the anterolateral thigh at a dose of 0.01 mg/kg, with a maximum of 0.5 mg in adults and 0.3 mg in children. Repeat every 5-15 minutes if symptoms persist.
Monitoring and Observation	Patients should be observed for at least 4-6 hours after anaphylaxis to monitor for potential biphasic reactions. Those with severe symptoms or requiring multiple doses of epinephrine should be admitted for further observation.
Patient Education	Educate patients on allergen avoidance, recognizing early symptoms of anaphylaxis, and the importance of carrying an epinephrine autoinjector. Ensure patients can demonstrate proper use before discharge.
Follow-Up Care	Schedule follow-up appointments to review the patient's allergy history, discuss potential triggers, and update emergency action plans.
Emergency Action Plans	Develop individualized emergency action plans for patients at risk for anaphylaxis, outlining steps to take in case of exposure and symptoms.
Community Awareness	Promote awareness of anaphylaxis in schools, workplaces, and community settings to ensure that bystanders can respond appropriately in an emergency.

These recommendations aim to enhance the management of anaphylaxis and improve patient outcomes through timely intervention and education.

9. Recommendations for Management of Anaphylaxis (Table 3)

Recent evidence updates have reinforced the importance of recognizing and managing anaphylaxis effectively. The following table summarizes key updates relevant to emergency clinicians:

Table 4: Summary of Evidence Updates on Anaphylaxis

Update	Description
Increased Incidence	Studies indicate a rising incidence of anaphylaxis, particularly related to food allergies and emerging triggers like alpha-gal.
Revised Diagnostic Criteria	The WAO proposed new diagnostic criteria to address limitations in existing definitions, emphasizing the need for a high index of suspicion.
Importance of Epinephrine	Epinephrine remains the first-line treatment, with evidence supporting rapid administration and the need for repeat doses in severe cases.
Role of Adjunctive Therapies	Antihistamines and glucocorticoids may be used as adjuncts but should not replace epinephrine in acute management.
Biphasic Reactions	Awareness of biphasic reactions is critical, with recommendations for extended observation after initial treatment.
Patient Education	Emphasis on the importance of patient education regarding allergen avoidance and the use of epinephrine autoinjectors.

These updates highlight the evolving understanding of anaphylaxis and the need for emergency clinicians to stay informed about best practices.

11. Conclusion

Conclusion

In conclusion, anaphylaxis is a serious medical emergency that requires immediate recognition and intervention (14-15). Key updates in management highlight the importance of rapid epinephrine administration, ongoing monitoring, and patient education to prevent future reactions (16).

Staying current with advancements in the field is essential for emergency clinicians to provide optimal care for patients at risk of anaphylaxis. The evolving landscape of allergens, including emerging triggers like alpha-gal, underscores the necessity for continuous education and awareness (17).

Call to Action: Emergency clinicians are encouraged to enhance patient care by implementing the recommendations outlined in this review, promoting awareness of anaphylaxis in their communities, and ensuring that patients are well-informed about their condition and management strategies (18-20). By doing so, we can improve outcomes for individuals experiencing anaphylaxis and reduce associated morbidity and mortality.

Authors' Contributions

- All authors contributed to the study conception and design.
- Material preparation was performed by Amjad Noor.
- Data collection was conducted by Zeeshan Khan
- Data analysis was performed by Gayathri Gururamalingam.
- The first draft of the manuscript was written by Nida Hassan.
- All authors commented on previous versions of the manuscript.
- All authors read and approved the final manuscript.

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