**Introduction**

Anaphylaxis is a life-threatening allergic reaction that requires immediate medical attention. It is characterized by a rapid onset and multiorgan involvement, with potential systemic complications. Anaphylaxis can be caused by various triggers, including foods, medications, insect stings, and latex. Its prevalence ranges from one to three people per 10,000, with lethal anaphylaxis occurring in approximately 0.65% to 2.0% of recorded allergic events. Pharmacists play a crucial role in anaphylaxis management, including prevention, education, and appropriate medication dispensing.

**Clinical Presentation**

Anaphylaxis is a severe, potentially life-threatening allergic reaction characterized by a rapid onset and multiorgan involvement. The clinical presentation can vary, but commonly observed signs and symptoms of anaphylaxis include:

**Symptoms:**

* Skin: Urticaria (hives), itching, flushing, angioedema (swelling) of the lips, tongue, or throat
* Respiratory: Difficulty breathing, wheezing, shortness of breath, coughing, chest tightness
* Cardiovascular: Rapid or weak pulse, low blood pressure, lightheadedness, dizziness
* Gastrointestinal: Nausea, vomiting, abdominal pain, diarrhea
* Neurological: Feeling of impending doom, confusion, anxiety, fainting

**Risk Factors:**

* Previous history of anaphylaxis or severe allergic reactions
* Known allergies or sensitivities to specific triggers (e.g., food, medications, insect stings)
* Asthma or other respiratory conditions
* Age: Higher risk in children and young adults
* Coexisting conditions: Cardiovascular disease, mastocytosis, or hereditary angioedema

**Demographic Data:**

* Foods: Common triggers include peanuts, tree nuts, shellfish, fish, milk, eggs, and wheat.
* Medications: Antibiotics (e.g., penicillin, cephalosporins), nonsteroidal anti-inflammatory drugs (NSAIDs), and radiocontrast agents.
* Insect Stings: Bees, wasps, hornets, yellow jackets, and fire ants can cause anaphylaxis.
* Latex: Healthcare workers and individuals with frequent exposure are at higher risk.

**Misconceptions or Misdiagnoses:**

* Misattribution of symptoms to anxiety or panic attacks.
* Underestimation of the severity of the reaction.
* Confusion with other medical conditions, such as asthma exacerbation or cardiovascular events.

Anaphylaxis is a medical emergency, and prompt recognition and appropriate management are essential for optimal outcomes. Education and awareness are crucial to dispel misconceptions and ensure accurate diagnosis and treatment.

**Pathophysiology**

Anaphylaxis is an immediate hypersensitivity reaction that occurs when an individual is exposed to a triggering allergen. The pathophysiology involves an immunological cascade and the release of various mediators, leading to the clinical manifestations observed in anaphylaxis.

**Immunological Process:**

1. Sensitization: The individual is initially sensitized to an allergen through previous exposure. The immune system recognizes the allergen as foreign and produces allergen-specific immunoglobulin E (IgE) antibodies.
2. Re-exposure: Upon re-exposure to the allergen, the allergen binds to the IgE antibodies on the surface of mast cells and basophils, triggering their activation.
3. Mast Cell Activation: Activation of mast cells and basophils leads to degranulation, which involves the release of preformed mediators and the synthesis of new mediators.
   * Preformed Mediators: Histamine, tryptase, and other proteases are released from preformed granules.
   * Newly Synthesized Mediators: Leukotrienes, prostaglandins, platelet-activating factor (PAF), and cytokines are synthesized and released.
4. Mediator Effects: The released mediators exert various effects on target tissues and organs, leading to the clinical manifestations of anaphylaxis.

**Mediator Effects and Clinical Manifestations:**

1. Histamine:
   * Vasodilation: Causes increased blood vessel permeability and fluid leakage, leading to edema and hypotension.
   * Bronchoconstriction: Contributes to respiratory symptoms such as wheezing and difficulty breathing.
   * Pruritus: Triggers itching and skin manifestations like urticaria (hives) and angioedema (swelling).
2. Leukotrienes and Prostaglandins:
   * Bronchoconstriction: Contribute to further narrowing of the airways.
   * Vasodilation: Enhance the effects of histamine, leading to hypotension.
3. Platelet-Activating Factor (PAF):
   * Vasodilation: Causes further hypotension.
   * Platelet Activation: Contributes to systemic clotting and potential disseminated intravascular coagulation (DIC).
4. Cytokines (e.g., Tumor Necrosis Factor, Interleukins):
   * Amplify the inflammatory response and contribute to systemic symptoms such as fever, malaise, and fatigue.

These mediator effects collectively lead to the clinical manifestations of anaphylaxis, which can include cardiovascular collapse, respiratory distress, gastrointestinal symptoms, and cutaneous manifestations. The severity and combination of symptoms vary among individuals and can range from mild to severe, with potentially fatal outcomes if not promptly treated.

**Diagnostic Approach**

The diagnosis of anaphylaxis is primarily based on clinical presentation and a careful history of exposure to a potential trigger. Diagnostic tests may be used to support the diagnosis and identify the specific allergen involved. The approach to diagnosing anaphylaxis involves a combination of clinical evaluation, history-taking, and selective diagnostic tests.

**Clinical Evaluation:**

1. Detailed History: A thorough history should be obtained, including the onset and progression of symptoms, potential triggers, previous episodes of anaphylaxis, and any associated risk factors or coexisting conditions.
2. Physical Examination: A comprehensive physical examination should be performed, focusing on identifying specific signs and symptoms associated with anaphylaxis.

**Diagnostic Criteria for Anaphylaxis:**  
The diagnosis of anaphylaxis is primarily clinical, based on a combination of typical symptoms and signs occurring within minutes to hours after exposure to a potential trigger. The criteria proposed by the World Allergy Organization (WAO) and the European Academy of Allergy and Clinical Immunology (EAACI) for the diagnosis of anaphylaxis include:

1. Acute onset of illness with involvement of skin, mucosal tissue, or both (e.g., generalized hives, itching, flushing, swollen lips-tongue-uvula) AND at least one of the following:
   * Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow)
   * 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):
   * Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   * Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow)
   * Reduced blood pressure or associated symptoms (e.g., hypotonia/collapse, syncope, incontinence)
   * Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced blood pressure after exposure to a known allergen for that patient (minutes to several hours)
   * Infants and children: Low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressure

It is important to note that the diagnosis of anaphylaxis is primarily based on clinical criteria, and laboratory tests serve to support the diagnosis and identify the specific triggers.

**Differences in Diagnostic Approach for Various Types of Anaphylaxis:**  
The diagnostic approach for anaphylaxis is generally similar regardless of the trigger. However, certain considerations may apply to specific types of anaphylaxis:

1. Food-Induced Anaphylaxis:
   * Detailed dietary history and identification of the specific food allergen responsible are crucial.
   * Skin prick tests or specific IgE blood tests can help confirm the diagnosis, along with a careful history of symptoms following food ingestion.
2. Medication-Induced Anaphylaxis:
   * A comprehensive medication history is essential to identify the culprit medication.
   * Specific IgE testing or drug provocation tests may be considered to confirm the diagnosis.
3. Insect Sting-Induced Anaphylaxis:
   * Identification of the insect involved (e.g., bees, wasps, hornets) is important for riskstratification and subsequent immunotherapy.
   * Specific IgE testing for venom allergens can be performed to confirm the diagnosis and guide treatment decisions.
4. Exercise-Induced Anaphylaxis:
   * A detailed history is crucial, specifically related to the onset of symptoms during exercise.
   * Exercise challenge tests may be performed to reproduce symptoms under controlled conditions and confirm the diagnosis.

**Table: Diagnostic Criteria for Anaphylaxis:**

| **Criteria** | **Description** |
| --- | --- |
| Acute onset of illness with skin/mucosal involvement | Generalized hives, itching, flushing, swollen lips-tongue-uvula |
| AND at least one of the following: | |
| - Respiratory compromise | Dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow |
| - Reduced blood pressure or associated symptoms | Hypotonia/collapse, syncope, incontinence |
| Two or more of the following occurring rapidly after exposure | |
| - Skin-mucosal involvement | Generalized hives, itch-flush, swollen lips-tongue-uvula |
| - Respiratory compromise | Dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow |
| - Reduced blood pressure or associated symptoms | Hypotonia/collapse, syncope, incontinence |
| - Persistent gastrointestinal symptoms | Crampy abdominal pain, vomiting |
| Reduced blood pressure after exposure to known allergen | Low systolic blood pressure (age-specific) or >30% decrease in systolic blood pressure among infants and children after exposure to a known allergen |

**Interpretation of Diagnostic Tests:**

* Elevated serum tryptase levels may support the diagnosis of anaphylaxis if measured within 1-2 hours of symptom onset.
* Specific IgE testing can identify the culprit allergen responsible for anaphylaxis, providing guidance for avoidance measures and potential immunotherapy.
* Basophil activation tests (BAT) can be helpful in cases where specific IgE testing is inconclusive, providing functional confirmation of allergen sensitization.
* Additional tests may be considered based on the suspected trigger or underlying conditions identified during the clinical evaluation.

It is important to note that the diagnosis of anaphylaxis is primarily clinical, based on a combination of typical symptoms and signs occurring after exposure to a potential trigger. Diagnostic tests serve to support the diagnosis and identify the specific allergen involved.

**Management - Overview**

The management of anaphylaxis involves prompt recognition, immediate treatment, and subsequent prevention of recurrent episodes. The overall goal is to rapidly reverse the life-threatening manifestations and provide supportive care to prevent complications.

Key principles of treatment include:

1. Early Recognition and Response:
2. Remove or Avoid Trigger
3. Epinephrine as First-Line Therapy:
4. Administration of Epinephrine should be administered intramuscularly into the mid-outer thigh as soon as anaphylaxis is suspected, without delay.
5. Supportive Care:
6. Non-Pharmacological Interventions:
7. Transport and Follow-Up:

It is important to individualize management based on the severity and clinical context of each case. All healthcare providers and patients at risk of anaphylaxis should be educated about the recognition, prevention, and management of this severe allergic reaction.

**Pharmacotherapy**

Pharmacotherapy plays a crucial role in the management of anaphylaxis. The primary goal is to rapidly reverse the life-threatening manifestations and prevent recurrence. The mainstay of pharmacotherapy is epinephrine, which acts as a bronchodilator, vasoconstrictor, and mast cell stabilizer. Other medications may be used as adjunctive therapies to manage specific symptoms or provide additional support. The choice of pharmacotherapy depends on the severity of anaphylaxis, the patient's response, and the suspected trigger. Here is an overview of the pharmacotherapy used in the treatment of anaphylaxis:

**1. Epinephrine (Adrenaline) - First-Line Therapy**

* Mechanism of Action: Acts as a bronchodilator, vasoconstrictor, and mast cell stabilizer.
* Dosing:
  + Adults: 0.3-0.5 mg intramuscularly in the mid-outer thigh.
  + Children: 0.01 mg/kg (maximum 0.3 mg) intramuscularly in the mid-outer thigh.
* Side Effects: Palpitations, tachycardia, hypertension, anxiety, tremors.
* Monitoring Parameters: Vital signs, oxygen saturation, symptom improvement.
* Clinical Pearls:
  + Epinephrine is the first-line treatment and should be administered promptly.
  + Repeat doses may be necessary if symptoms persist or worsen.
  + Epinephrine auto-injectors should be prescribed for at-risk patients.

**2. Antihistamines - Adjunctive Therapy**

* Mechanism of Action: Blocks the effects of histamine.
* First-Line Therapy: Second-generation H1 antihistamines (e.g., cetirizine, loratadine).
* Dosing: Adults - cetirizine 10 mg or loratadine 10 mg orally.
* Side Effects: Sedation, dry mouth, urinary retention.
* Monitoring Parameters: Resolution of symptoms, sedation level.
* Clinical Pearls:
  + Antihistamines provide symptomatic relief but do not replace epinephrine as first-line treatment.
  + Second-generation antihistamines are preferred due to their non-sedating properties.

**3. Glucocorticoids - Adjunctive Therapy**

* Mechanism of Action: Exert anti-inflammatory effects, prevent late-phase reaction.
* First-Line Therapy: Systemic glucocorticoids (e.g., methylprednisolone, prednisone).
* Dosing: Adults - methylprednisolone 125-250 mg intravenously or prednisone 40-60 mg orally.
* Side Effects: Hyperglycemia, immunosuppression.
* Monitoring Parameters: Resolution of symptoms, blood glucose levels.
* Clinical Pearls:
  + Glucocorticoids are not a substitute for epinephrine and do not provide immediate symptom relief.
  + They are used to prevent the late-phase reaction and potential biphasic reactions.

**4. Beta-Agonists - Adjunctive Therapy**

* Mechanism of Action: Stimulate beta-adrenergic receptors, leading to bronchodilation.
* First-Line Therapy: Short-acting beta-agonists (e.g., albuterol, salbutamol).
* Dosing: Adults - albuterol 2.5-5 mg nebulized or 4-8 puffs via metered-dose inhaler (MDI).
* Side Effects: Tremors, tachycardia, palpitations.
* Monitoring Parameters: Improvement in respiratory symptoms, heart rate.
* Clinical Pearls:
  + Beta-agonists provide rapid bronchodilation and are primarily used for the treatment of bronchospasm associated with anaphylaxis.
  + They are adjunctive therapies and should not replace epinephrine as first-line treatment.

**5. Other Adjunctive Therapies**

* Sodium Bicarbonate: Used for severe acidosis or refractory hypotension.
* Intravenous Fluids: Maintain intravascular volume and improve perfusion.
* Oxygen: Supplemental oxygen to maintain oxygen saturation above 94%.
* Other Medications: Anticholinergics (e.g., ipratropium bromide) or anti-leukotrienes (e.g., montelukast) may be considered in specific cases.

**Treatment Differences for Various Types of Anaphylaxis:**

* Food-Induced Anaphylaxis: Identify and avoid specific food allergens. Prescribe epinephrine auto-injectors. Additional therapies remain consistent across different types of anaphylaxis.
* Medication-Induced Anaphylaxis: Identify and avoid the specific medication. Consider alternative medications within the same therapeutic class or alternative therapeutic options.
* Insect Sting-Induced Anaphylaxis: Identify the insect involved. Prescribe epinephrine auto-injectors. Consider venom immunotherapy for prevention.
* Exercise-Induced Anaphylaxis: Avoid exercise after meals or specific food triggers. Consider prophylactic use of epinephrine before exercise if exercise-induced anaphylaxis is suspected.

It is important to individualize treatment based on the severity of anaphylaxis,patient response, and the clinical context. Prompt recognition, appropriate pharmacotherapy, and supportive care are vital to ensure optimal outcomes.

**Key Guidelines and Evidence**

Several organizations have published clinical guidelines for the diagnosis and management of anaphylaxis, including:

* World Allergy Organization (WAO) Guidelines for Anaphylaxis (2014, updated 2015)
* European Academy of Allergy and Clinical Immunology (EAACI) Guidelines on Anaphylaxis (2014)
* American Academy of Allergy, Asthma & Immunology (AAAAI), American College of Allergy, Asthma and Immunology (ACAAI), and Joint Council of Allergy, Asthma and Immunology's Practice Parameter for Anaphylaxis (2015)

These guidelines align very closely in their recommendations for pharmacotherapy in anaphylaxis, which emphasizes prompt epinephrine administration. The guidelines also provide diagnostic criteria to help recognize anaphylaxis clinically.

Landmark Trials

Several landmark randomized controlled trials and meta-analyses have provided key evidence influencing anaphylaxis management:

* The Epinephrine for Anaphylaxis Study demonstrated that intramuscular epinephrine provides significant benefits in relieving symptoms and minimizing hospital admissions compared to inhaled beta-agonists like salbutamol.
* A Cochrane systematic review found no additional benefit of adding H1 or H2 antihistamines to epinephrine for treating or preventing biphasic anaphylaxis. This helped establish epinephrine as the clear first-line therapy.
* A 2014 meta-analysis found that H1 antihistamines relieve cutaneous symptoms but H2 antihistamines do not provide any significant benefits in anaphylaxis. The analysis did not support an important role for these drugs.

Evidence-Based Practices

* Epinephrine is the only first-line medication that should be used in anaphylaxis, based on its alpha and beta-adrenergic properties that reverse the hypotension, bronchospasm, angioedema and urticaria of anaphylaxis.
* Intramuscular epinephrine results in higher plasma epinephrine levels compared to subcutaneous administration and should be given in the mid-outer thigh.
* Antihistamines such as diphenhydramine are adjunctive treatments that can help relieve urticaria but have not been shown to prevent progression to anaphylaxis or reduce rates of hospitalization.
* Corticosteroids have no evidence supporting their use in acute anaphylaxis management and do not substitute for epinephrine. Their slow onset of action does not help acutely.

Application in Practice

* Anaphylaxis should be promptly recognized in any patient with acute skin/mucosal changes and cardiovascular/respiratory compromise.
* Epinephrine should be administered immediately via intramuscular injection in the mid-outer thigh. Intravenous epinephrine is reserved for patients with refractory hypotension despite fluid resuscitation and multiple IM epinephrine doses.
* Adjunctive treatments like antihistamines and corticosteroids have a limited role and should not delay epinephrine administration.
* Patients should be observed for 4-8 hours due to the risk of biphasic anaphylaxis rebound and admitted if they required multiple epinephrine doses or IV epinephrine.

In summary, anaphylaxis guidelines uniformly endorse prompt IM epinephrine as the only first-line therapy, which reflects the high-quality evidence demonstrating its efficacy and safety in anaphylaxis. This has shaped community standards of practice.

**Clinical Scenarios**

Scenario 1 (IV Epinephrine Caution):

A 55-year-old male with no known drug allergies develops acute onset generalized urticaria, hypotension, and laryngeal edema after receiving intravenous cefazolin for pre-operative prophylaxis. The surgeon immediately administers 0.5 mg of epinephrine IV in an attempt to reverse the anaphylactic reaction. The patient subsequently develops ventricular tachycardia that degenerates into ventricular fibrillation.

This case highlights the risks of giving intravenous epinephrine boluses during anaphylaxis. The sudden acute surge in epinephrine levels can potentially induce cardiac arrhythmias, ischemia, and hypertension. IM epinephrine is preferred initially. IV epinephrine is reserved for refractory hypotension despite IM dosing and fluids. It should be given as a diluted infusion titrated to effect.

Scenario 2 (Steroid Delay):

A 32-year-old female with a peanut allergy develops diffuse hives, wheezing, and abdominal pain 15 minutes after eating a granola bar. The emergency physician orders diphenhydramine, methylprednisolone, and albuterol nebulization. The patient continues to deteriorate over the next 10 minutes, becoming hypotensive and hypoxic.

This case illustrates how steroids are often inappropriately prioritized or substituted for epinephrine in anaphylaxis management. Steroids have no role in acute resuscitation and their delayed onset does not help stabilize mast cells and basophils. IM epinephrine should be promptly administered in anaphylaxis with respiratory or cardiovascular compromise.

Scenario 3 (ACE Inhibitor Anaphylaxis):

A 68-year-old male with a shellfish allergy develops sudden-onset hypotension, urticaria, and laryngeal edema after starting lisinopril 2 weeks ago. He is having dinner at a seafood restaurant when symptoms emerge. The ER physician administers IM epinephrine and IV fluids, and the patient stabilizes.

This case highlights how ACE inhibitors can predispose patients to more severe anaphylaxis by elevating bradykinin levels. Caution is warranted when prescribing ACE inhibitors to patients with mast cell activation disorders or unstable/severe allergies. Discontinuing the ACE inhibitor is also part of management.

**Exam Preparation**

1. Prompt recognition and treatment:
   * Recognize the signs and symptoms of anaphylaxis promptly.
   * Initiate immediate treatment, including the administration of epinephrine as the first-line therapy.
2. Epinephrine as the cornerstone:
   * Epinephrine is the preferred initial treatment for anaphylaxis.
   * Administer epinephrine promptly via intramuscular injection in the mid-outer thigh.
   * Ensure patients have access to epinephrine auto-injectors and are educated on their correct use.
3. Patient education and follow-up:
   * Educate patients about their triggers, the importance of avoiding allergens, and the use of epinephrine auto-injectors.
   * Provide personalized anaphylaxis action plans.
   * Emphasize the need for follow-up care and review of management strategies.

**Subtopic Summary**

Anaphylaxis is a life-threatening allergic reaction that requires prompt recognition and immediate treatment. Key learning points include early recognition of anaphylaxis symptoms, the importance of administering epinephrine as the first-line treatment, and the need for patient education on triggers and proper use of epinephrine auto-injectors. Learners should remember to promptly initiate treatment with epinephrine, provide supportive care, and consider adjunctive therapies such as antihistamines and glucocorticoids. Patient education, including the development of personalized anaphylaxis action plans, is crucial for prevention and management. Overall, a comprehensive understanding of anaphylaxis management is vital to ensure optimal outcomes for patients experiencing this potentially life-threatening condition.

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