Anaphylaxis in the Clinic

Pediatric Grand Rounds
Justin Jones, DO
Resident ETSU Pediatrics
PL-3

Case

- Chief Complaint:
  - 12-year-old boy is brought to the clinic after being stung by a bee.

- History of Present Illness:
  - He had been well until he was stung on his right forearm, while playing in the yard. He initially complained of localized pain and swelling. Fifteen minutes later, he began to complain of shortness of breath. His parents observed him to be wheezing. He also said that he felt very weak and dizzy. His parents brought him immediately to the clinic.

Case Continued

- Exam
  - VS: T 37.1, P 120, R 39, BP 69/45.
  - General: Mild respiratory distress. Drowsy and pale, but awakens to voice.
  - Skin: Generalized urticaria. Face moderately pale.
  - HEENT: No conjunctival edema. Lips and tongue are not swollen. Voice sounds normal.
  - Heart: Tachycardic without murmurs.
  - Lung: Mild wheezing and fair aeration with minimal retractions.
  - Abdomen: Soft and non-tender.
  - Extremities: The bee sting site on his right forearm is unremarkable with no foreign body seen.
Case Continued

- **Assessment:**
  - Early anaphylactic shock

- **Plan:**
  - Assess ABC’s
  - Oxygen
  - IM epinephrine
  - Activate 911 for transfer to nearest ER facility
  - Albuterol
  - IV is started with fluid bolus of normal saline
  - Diphenhydramine IV, Cimetidine IV, Methylprednisolone IV

Anaphylaxis

- **Definition**
  - Acute onset life threatening reaction that affects at least two body systems and often the whole body.

Emergent Recognition in the Clinic

- **Anaphylaxis is highly likely when any one of the following are present:**
  - Acute onset of an illness within minutes to several hours.
  - Skin, mucosal tissue, or both are involved. (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
  - Respiratory compromise
    - Can include dyspnea, wheeze—bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia
  - Persistent gastrointestinal symptoms
    - Crampy abdominal pain, vomiting
  - Reduced blood pressure (BP) or associated symptoms of end organ dysfunction
    - Hypotonia [collapse], syncope, incontinence
  - **Reduced BP after exposure to known allergen for that patient**
  - Infants and children: low systolic BP (age-specific) or greater than 30% decrease in systolic BP
Pathophysiology

- Increased secretion from mucous membranes
- Increased bronchial smooth muscle tone
- Decreased vascular smooth muscle tone
- Increased capillary permeability occur after exposure to an inciting substance.
  - These effects are produced by the release of mediators, which include histamine, leukotriene C4, prostaglandin D2, and tryptase.

- Classic form
  - Mediator release occurs when the antigen binds to antigen-specific immunoglobulin E attached to previously sensitized basophils and mast cells.
  - The mediators are released almost immediately when the antigen binds.

- Anaphylactoid reaction
  - Exposure to an inciting substance causes direct release of mediators, a process that is not mediated by IgE.
  - Increased mucous secretion and increased bronchial smooth muscle tone, as well as airway edema, contribute to the respiratory symptoms observed in anaphylaxis.
  - Cardiovascular effects result from decreased vascular tone and capillary leakage.
  - Histamine release in skin causes urticarial skin lesions

Epidemiology

- True incidence is unknown.
- Fatal anaphylaxis is relatively rare; milder forms occur much more frequently.
- Up to 500-1,000 fatal cases of anaphylaxis per year are estimated to occur in the United States.
- Lifetime prevalence of anaphylaxis is estimated at 1-2% of the population as a whole, no racial differences are known.
- Cultural and socioeconomic differences may influence exposure rates.
- Overall, women have a higher incidence of anaphylaxis than men, but, in some series of children, males predominate.
- Children most commonly affected by peanut allergy.

Morbidity/Mortality

- Approximately 1 in 5000 exposures to a parenteral dose of a penicillin or cephalosporin antibiotic causes anaphylaxis.
  - More than 100 deaths per year are reported in the United States.
- Fewer than 100 fatal reactions to Hymenoptera stings are reported each year in the United States.
- One to 2% of people receiving IV radiocontrast experience some sort of reaction.
  - The majority of these reactions are minor, and fatalities are rare.
  - Low molecular weight contrast causes fewer and less severe reactions.
Risk Factors
- Atopy
  - Prevalence of atopy is approximately 37-53% in patients with anaphylaxis
- Asthma
- Food Allergy
- Early Childhood

History
- Almost always involve the skin or mucous membranes.
  - More than 90% of patients have some combination of urticaria, erythema, pruritus, or angioedema.
  - The upper respiratory tract commonly is involved, with complaints of nasal congestion, sneezing, or coryza.
  - Cough, hoarseness, or a sensation of tightness in the throat may indicate significant airway obstruction.

History
- Eyes may itch and tearing may be noted. Conjunctival injection may occur.
- Dyspnea is present when patients have bronchospasm or upper airway edema.
  - Hypoxia and hypotension may cause weakness, dizziness, or syncope.
  - Chest pain may occur due to bronchospasm or myocardial ischemia (secondary to hypotension and hypoxia).

History
- GI symptoms of cramplike abdominal pain with nausea, vomiting, or diarrhea also occur but are less common, except in the case of food allergy.
- The clinician may not realize that, while reactions are usually rapid in onset, they also may be delayed.
- For reasons that are not well understood, a lack of dermal findings is more common in children than in adults.
Physical

- **General:** VS can be normal or abnormal with hypotension, tachypnea, tachycardia. May also have anxiety, tremor, or sensation of cold.
- **Skin:** Urticaria
  - Lesions are red and raised, and they sometimes have central blanching.
  - Cutaneous exposure (e.g., insect bite). The involved area is erythematous, edematous, and pruritic.
  - Angioedema usually is nonpruritic and associated lesions are nonpitting. Lesions most often appear on the lips, palms, soles, and genitalia.

Mechanisms

- **Drugs and foods** are the most common causes.
  - Peanuts, tree nuts, and shellfish are the most commonly implicated foods.
  - Antibiotics (especially penicillins) and nonsteroidal anti-inflammatory drugs are the most common drugs.
- **Foreign protein** is often the inciting agent.
  - On initial exposure, the antigen elicits generation of an IgE antibody.
  - The antibody residue binds to mast cells and basophils.
  - On reexposure, the antigen binds to the antibody, and the receptors are activated.
  - Clinical manifestations result from release of immune response mediators such as histamine, leukotrienes, tryptase, and prostaglandins.

Physical

- **Pulmonary:** Upper airway compromise may occur and stridor may be noted. Can have hoarseness, quiet voice, may lose speaking ability.
  - Complete airway obstruction is the most common cause of death in anaphylaxis.
  - Wheezing is common when patients have lower airway compromise due to bronchospasm or mucosal edema.
- **Cardiovascular:** Cardiovascular examination is normal in mild cases.
  - In more severe cases, compensatory tachycardia occurs due to loss of vascular tone.
  - Intravascular volume depletion may take place as a consequence of capillary leakage.
  - Relative bradycardia has been reported.

Mechanisms

- **Parenteral exposures** tend to result in faster and more severe reactions. Most severe reactions occur soon after exposure.
- The faster a reaction develops, the more severe it is likely to be.
- While most reactions occur within hours, symptoms may not occur for as long as 3-4 days after exposure.
**Drugs**

- Penicillin and cephalosporin antibiotics are the most commonly reported medical agents in anaphylaxis.
  - Because of their molecular and immunologic similarity, cross-sensitivity may exist.
  - Reports based on skin testing indicate that about 10% of patients allergic to a penicillin antibiotic are allergic to cephalosporins.
- Reactions to medications tend to be more severe and rapid in onset when the antibiotic is administered parenterally.
- A drug reaction may occur in a patient with no prior history of drug exposure.

**Hymenoptera Stings**

- Hymenoptera stings are a common cause of allergic reaction and anaphylaxis.
  - In the United States, Hymenoptera envenomations result in fewer than 100 reported deaths per year.
  - Local reaction and urticaria without other manifestations of anaphylaxis are much more common than full-blown anaphylaxis.
  - Generalized urticaria is a risk factor for subsequent anaphylaxis; but a local reaction, even if severe, is not a risk factor for anaphylaxis.
- Caution patients treated and released from the ED or clinic after an episode of anaphylaxis or generalized urticaria from Hymenoptera envenomation to avoid future exposure when possible.
  - Consider referral to an allergist for desensitization, particularly when further exposure is likely.
  - Consider prescribing a treatment kit with an epinephrine auto-injector and oral antihistamine. Both are effective measures in preventing or ameliorating future reactions.

**Food Allergy**

- Symptoms usually are mild and limited to the GI tract, but full-blown anaphylaxis can occur.
- Fatalities are rare compared to number of exposures; however, the number of exposures is so high that foods may be the most common cause of anaphylaxis.
- Anaphylaxis due to foods may be an under recognized cause of sudden death and an unappreciated cause of diagnosed anaphylaxis.
  - Commonly implicated foods include peanuts, tree nuts, legumes, fish and shellfish, milk, and eggs.
- Reports of severe allergic reactions to peanuts are increasing.

**Drugs**

- Aspirin and NSAIDs commonly are implicated in anaphylaxis. Bronchospasm is common in patients with reactive airway disease and nasal polyps. Cross-reactivity often occurs between the various NSAIDs.
- ACE inhibitors, widely used in the treatment of hypertension, are associated with angioedema in 0.5-1.0% of patients who take them. Systemic anaphylaxis is rarely associated with these agents.

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Environment Allergies

- Latex allergy is an increasingly recognized problem in medical settings, where use of gloves and other latex products is ubiquitous.
- Most reactions are cutaneous or involve the mucous membranes.
- Anaphylactic reactions occur and have been reported with seemingly benign procedures. For example:
  - Foley catheter insertion, intraperitoneal exposure to gloves during surgery.

Intravenous Radiocontrast Media

- IV administered radiocontrast media causes an anaphylactoid reaction that is clinically similar to true anaphylaxis and is treated in the same way. The reaction is not related to prior exposure.
- Shellfish or “iodine allergy” is not a contraindication to use of IV contrast and does not mandate a pretreatment regimen.
- The term iodine allergy is a misnomer. Iodine is an essential trace element present throughout the body. No one is allergic to iodine. Approximately 1.3% of patients who receive hyperosmolar IV contrast experience a reaction.
- Use of LMW contrast decreases incidence of reactions to approximately 0.5%.
- Reactions to radiocontrast usually are mild most commonly urticarial
- A history of prior reaction is not a contraindication to GI or GU use of these agents.
- Risk of a fatal reaction has been estimated at 0.9 cases per 100,000 exposures. Use of LMW contrast does not mandate a pretreatment regimen.
- Patients who receive hyperosmolar IV contrast experience a reaction.
- The term “iodine allergy” is not a contraindication to use of IV contrast and does not mandate a pretreatment regimen.

Exercise Induced

- Exercise-induced syndrome
  - Prior food ingestion followed by vigorous exercise
  - Aspirin/NSAID use prior to exertion
  - Premonitory fatigue, pruritis, flushing, diffuse warmth, erythema, urticaria
  - Urticaria: 1-2 cms in size unlike cholinergic urticaria
  - Progression to angioedema, GI colic, laryngeal edema

Catamenial

- Rare disorder
- Reaction to progesterone in the luteal phase of the menstrual cycle resulting in anaphylaxis
- Pathogenesis is still poorly understood
- Can be life threatening
- Progesterone challenge is diagnostic
- Treatment consists of H₂, H₁ receptor blockers, glucocorticoids and LHRH agonists
- Definitive therapy is hysterectomy with bilateral oophorectomy
Differential Diagnosis

- Angioedema
- Myocardial Infarction
- Anxiety
- Pulmonary Embolism
- Asthma
- Toxicity, Scombroid
- Conversion Disorder
- Urticaria
- Epiglottitis
- Tracheal Foreign Bodies
- Hereditary angioedema
- Monosodium glutamate poisoning

Masqueraders

- Scombroid fish poisoning
  - Tryptase normal
  - Mastocytosis
  - α-tryptase elevated
  - Vasovagal syndrome
  - Bradycardia, tryptase normal
- Cs esterase deficiency and angiodema
- Hypocomplementemia
- Low Cs esterase inhibitor
- Flush syndromes
  - Carcinoid syndrome
  - Non-organic syndromes
  - Munchausen syndrome
  - Vocal cord dysfunction
  - Globus hystericus

Dangers of anaphylaxis

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<th>% Adults</th>
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<tr>
<td>Gastrointestinal</td>
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<td>24</td>
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Workup

- When typical symptoms are noted in association with a likely exposure, diagnosis is virtually certain.
- The only potentially useful test is measurement of serum mast cell tryptase.
- Tryptase levels may aid in later diagnosis and treatment.
- Histamine: Peaks 5-30 minutes.
- Cardiac monitoring in patients with severe reactions and in those with underlying cardiovascular disease is important particularly when adrenergic agents are used in treatment.
- Pulse oximetry also is useful.
Sensitivity Testing

- Testing for sensitivity to penicillin antibiotics may be useful when a penicillin or cephalosporin antibiotic is the drug of choice for a serious infection in a patient who has a history of severe allergic reaction.
  - Obtain informed consent, and ensure that resuscitative equipment is immediately available.
  - Protocols for acute testing for allergy to penicillin or cephalosporin antibiotics involve administration of increasing IV doses of the chosen antibiotic, while observing the patient for pruritus, flushing, urticaria, dyspnea, hypotension, or other manifestations of anaphylaxis.
  - If no manifestations are observed, a full dose of the antibiotic may be administered safely.
- A suggested protocol for IV testing begins with 0.001 mg of the chosen drug. At 10-min intervals, incrementally increase the dose while observing the patient.
- Many other protocols exist. In most circumstances, perform desensitization on an inpatient basis. If the necessary resources are available, perform desensitization in the ED.

Desensitization Regimens

- Desensitization regimens for penicillin and cephalosporin antibiotic allergy have been shown effective.
  - Because these regimens are lengthy (approximately 6 h), they have limited applicability to the clinic.
  - When patients wait for long periods in the ED or in an observation unit, consider desensitization regimens.
- A typical desensitization regimen involves administering the antibiotic of choice in an initial dose of 0.01 mg. While observing the patient, double the dose every 10-15 minutes until a full dose has been administered.
- Desensitization regimens do not protect against non-IgE-mediated reactions that may be severe or even life threatening like Stevens-Johnson syndrome.
- While theoretically attractive, premedication regimens have not been clinically shown to decrease incidence or severity of IgE-mediated allergic reactions to antibiotics.

Treatment

- First line is to assess Airway, Breathing, and Circulation
- Patient should be removed from stimulus as soon as possible
- Evaluation of skin, orientation, and weight of patient should be approximated
- Patient should be given oxygen especially if stridor or wheezing is present
- Epinephrine 0.01 mg/kg of 1:1000 solution with a maximum of 0.3 mls
  - Injection given intramuscularly in anterolateral thigh
- Epinephrine can be repeated if no clinical improvement in 5 minutes.
- Albuterol can be used in cases with respiratory distress and wheezing
- If hypotension a problem, administer IV fluids.
- Patient can also be placed in supine or Trendelenburg.
- When in the clinic call 911 for immediate transport to emergency department.

Treatment Cont.

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Further Care

- b2-agonist
  - Albuterol
- H1-antihistamine
  - Diphenhydramine/Benadryl
- H2-antihistamine
  - Cimetidine/Tagamet
- Steroids
- Methylprednisolone
- Glucagon
  - Inotropic, chronotropic, and vasoactive effects that are independent of beta-receptors.
  - Endogenous catecholamine release
- Vasopressors
- Possible intubation

Treatments success operationally may be defined as complete resolution of symptoms followed by a short period of observation. The purpose of observation is to monitor for recurrence of symptoms that can occur in biphasic anaphylaxis.

Hospital admission is required for patients who:
- (1) fail to respond fully
- (2) have a recurrent reaction or a secondary complication
- (3) experience a significant injury from syncope
- (4) need intubation

As with many other conditions, consider a lower admission threshold when patients are at age extremes or when they have significant comorbid illness.

Consider ICU admission for patients with persistent hypotension.

Inpatient management of airway compromise consists of continuation of parenteral and inhaled adrenergic agents and corticosteroids.

Cutaneous manifestations of anaphylaxis are treated with repeated doses of antihistamines.

Treatment outside clinic

- Patients who have been successfully treated for anaphylaxis usually should continue antihistamines for 2-5 days to prevent recurrence.
- When corticosteroids have been used as part of the initial treatment, common practice continues that treatment for a short period.
- Patients should be given Epi-Pen or Epi-Pen Jr. Auto-Injector: This product is an auto-injecting syringe containing 0.3 mL 1:1000 epinephrine solution, 0.3 mg (Epi-Pen) or 0.3 mL 1:2000 solution, 0.15 mg (Epi-Pen Jr).

Prevention

- Caution patients who are discharged after an episode of anaphylaxis to avoid exposure to an inciting agent.
  - When no inciting agent has been identified, consider referral to an allergist to identify the cause of anaphylaxis.
- Inform patients who react to Hymenoptera venom of the availability of desensitization therapy and consider a self-administered epinephrine prescription.
- On discharge, warn patients of the possibility of recurrent symptoms, and instruct them to seek further care if this occurs.
- Children are likely to outgrow most food allergies except shrimp and peanuts.

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Prevention

- Sting avoidance is important for hypersensitive persons. Patients must be educated concerning steps they can take to reduce the risk of insect stings.
  - Caution patients to avoid use of perfumes or hygiene products that include perfumes, particularly floral scents, as these attract flying Hymenoptera.
  - Brightly colored clothing attracts bees and other pollinating insects.
  - Avoid locations of known hives or nests, and avoid using equipment that disturbs the hive.
  - Persons who are sensitive to Hymenoptera and who must be outdoors should carry a sting kit.

References