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Anaphylaxis and Allergies: State of the Art

The emergency physician needs a firm grasp of the pathophysiology and presentation of allergy and anaphylaxis. The current treatment of anaphylaxis, urticaria, angioedema, and Stevens-Johnson syndrome will be presented. This course will include an in-depth discussion of state-of-the-art supportive and pharmacologic intervention in the emergency department. Prophylaxis and desensitization are discussed. An update on latex allergy will be presented.

- Describe the syndromes of acute urticaria, pruritus, angioedema, and anaphylaxis.
- Explain treatment options for each.
- Outline a “reasonable” evaluation of a symptomatic patient, recognizing cost-effectiveness issues.

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FACULTY

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Anaphylaxis and Allergies: State of the Art

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Allergy = Hypersensitivity

- Developed hypersensitivity of an organism to an antigen
- Antigen can be a protein or a hapten (an incomplete antigen incapable alone of causing antibody production, but capable of binding to a protein to become antigenic)
- Allows induction of various protective cellular reactions
- Allergy is IgE mediated. Antigen-specific IgE can be demonstrated to be the cause of allergic reactions via the Prausnitz-Kustner reaction. (Serum from allergic patient is injected into non-allergic individual. When exposed to the antigen, typical allergic reaction occurs. If IgE removed from serum prior to transfer, no allergic reaction occurs)
- Often represents a protective mechanism gone bad

Epidemiology of Allergy

- 20% of U.S. population is allergic to something
  - Inhaled proteins
  - Foods
  - Stinging insects
  - Medications
- Responsible for 400-800 deaths in U.S. annually (underestimate?)
- Respiratory and dermatologic manifestations most common

Allergy: Historical Perspectives

3300 BC	Pharoah Menses death	Hornet sting (first recorded allergic reaction?)
55 AD	Brittanicus	Horse allergy kept him from becoming emperor
1482	King Richard III	Strawberry allergy well recorded
1656	Borel	First skin test (egg)
1903	Richet	Described anaphylaxis (dog: sea anemone)
1911	Noon	Immunotherapy first practiced
1921	Prausnitz and Kustner	Serum allergy mediator demonstrated
1953	Riley and West	Mast cells, histamine described
1966	Ishizaka	Discovered IgE

Classification of Immunologic Reactions (Gell and Coombs*)

- Type I - immediate hypersensitivity reactions (IgE or rarely IgG_4 mediated)
- Type II - cytotoxic reactions (binding of circulating IgG or IgM antibody to a cell-bound antigen)
- Type III - immune complex reactions (circulating soluble antigen-antibody complexes escape from the circulation and result in immune complex deposition in the perivascular interstitial space)
- Type IV - cell-mediated immunity (T-cell mediated)

*This classification system is an immunologic oversimplification

Immediate Hypersensitivity Requires Three Conditions:

1. An antigen-induced stimulation of the immune system with specific IgE produced
2. A latent period after the initial antigenic exposure for sensitization of mast cells and basophils to occur (antigen binding to cell membranes)
3. Subsequent reexposure to that specific antigen

In humans there is a strong familial tendency to atopic disorders which one report has linked to a histocompatability locus on chromosome eleven. With the correct genetic predisposition, some allergens are recognized by antigen processing cells (macrophages and others) which through cytokine release and other mechanisms activate B cells to become plasma cells. These activated plasma cells produce antigen-specific antibody

B lymphocyte function and plasma cell antibody production are influenced by feedback pathways controlled by activated T helper and T suppressor cells

The IgE antibody binds via its Fc portion to the cell membranes of IgE receptor cells, mainly high affinity mast cells and basophils (as well as lower affinity macrophages, eosinophils, and others) and awaits antigen exposure

The allergy mechanism can be activated through both IgE mediated and non-IgE mediated pathways:

- IgE-Mediated (Atopic; Immune): Antigen-Antibody Complex
- Non-IgE-Mediated (Nonatopic; Non-Immune; Anaphylactoid):
  - Chemical Factors: Complement (C3a and C5a), drugs, anesthetics, salicylates, etc.
  - Physical Factors: Temperature, pressure, irritants, humidity, etc.
  - Infections (especially viral)
  - Neurogenic Factors: Psychogenic, vagal, exercise, etc.

Activation of the mast cell or basophil membrane receptor (usually by the allergen) causes several reactions:

- Adenyl cyclase inhibition, allowing depletion of cyclic AMP, which activates cAMP dependent protein kinases that phosphorylate cell proteins, leading to mediator production and release
- Opens calcium channels to activate phospholipases, which:
  - Generate lysophospholipids and diacylglycerol, both of which facilitate membrane-free granule fusion to the cell membrane, releasing preformed or primary mediators of anaphylaxis
  - Generate arachidonic acid, which is processed oxidatively to secondary mediators of the prostaglandin (through cyclooxygenase) or leukotriene (through lipoxygenase) class

Increased intracellular cAMP inhibits mediator production and release in hypersensitivity reactions while increased cGMP stimulates mediator production and release

There are many mediators of immediate hypersensitivity released by mast cells and basophils. They are of two types:

1. Preformed (stored in secretory granules)
2. Secondarily produced (or spontaneously generated) mediators

Preformed Mediators of Immediate Hypersensitivity:

- Histamine
  - Found in large quantities in secretory granules of mast cells and basophils
  - First identified mediator of allergic reactions
  - Two types of tissue histamine receptors exist (at least):
    1. H_1 receptor - Stimulation produces bronchial and smooth muscle contraction, increased vascular permeability, nasal mucus production and increased eosinophil and neutrophil chemokinesis and chemotaxis
    2. H_2 receptor - Stimulation increases airway mucus production, vascular permeability and gastric acid secretion, while causing bronchodilation and inhibition of basophil histamine release
- Eosinophilic Chemotactic Factor of Anaphylaxis (ECF-A)
  - Selectively attracts eosinophils to the site of target organ involvement in anaphylaxis
  - Eosinophils are major regulators of allergic reactions (Produce arylsulfatase, histaminase, and phospholipase, which degrade leukotrienes, histamine, and platelet activating factor, respectively)
- Neutrophil Chemotactic Factor of Anaphylaxis (NCF-A)
  - Primarily responsible for a second peak in anaphylactic activity occurring 4-12 hours after the primary response, and lasting up to 48 hours
- Kallikriens
  - Responsible for generation of kinins (including bradykinin) and activation of Hageman factor

- Many other, including enzymatic proteases (e.g. tryptase), acid hydrolases (e.g. beta-hexosaminadase, beta glucoronidase, arylsulfatase, superoxide dismutase, and peroxidase) and proteoglycans (e.g. heparin and chondroitin sulfates that bind histamine)

Spontaneously Generated Mediators of Immediate Hypersensitivity:

- Leukotrienes
  - Produced by lipooxygenase metabolism of arachidonic acid
  - LTB_4 is chemotactic
  - LTB_4, LTD_4, and LTE_4 comprise what was previously known as Slow Reacting Substance of Anaphylaxis (SRS-A). LTC_4 and LTD_4 are 1000 times more potent and LTE_4 ten times more potent in producing bronchoconstriction when compared on a molar basis to histamine
  - Also increase vascular permeability and amplify histamine effects
- Prostaglandins: Produced by cyclooxygenase metabolism of arachidonic acid
  - PGD_2 increases smooth muscle contraction, vascular permeability
  - PGE_1 and PGE_2 cause bronchodilation
  - PGF_2 and thromboxane B_2 are potent bronchoconstrictors

  Steroids block arachidonic acid generation, which inhibits both leukotriene and prostaglandin production. Aspirin and other nonsteroidal agents inhibit cyclooxygenase but not lipoygenase, thus reducing the ratio of prostaglandins, prostacyclin and thromboxane relative to leukotrienes, which in some sensitive patients may precipitate or exacerbate hypersensitivity reactions
- Platelet Activating Factor (PAF) is an unstored lipid which has many actions:
  - Aggregation and degranulation of platelets
  - Neutrophil aggregation
  - Neutropenia and basopenia
  - Thrombocytopenia
  - Smooth muscle constriction
- Various oxygen metabolites
- Others

Allergy is an inflammatory disease:

- Immunologically regulated:
  - Heredity
  - Autoimmune diseases
- Interface between several components:
  - Protein recognition (acquired allergy)
  - Inflammatory baseline
  - Neurologic component (substance P)
- Allergy = Neuroimmunoallergic Inflammation

As further evidence of the complex immunochemistry of allergic reactions, we now know that cytokines modulate mediator secretory response to allergic stimuli:

- Increased by:
  - Interleukin 3,4
  - Connective tissue-activating peptide III
  - Others
- Decreased by:
  - Interleukin 8
  - Others

Time Course of Allergic Reactions

"Classic" Allergic Reaction (Immediate Hypersensitivity) occurs in minutes:

- Vascular leakage
- Flushing
- Hypotension

- Smooth-muscle contraction
- Mucus secretion
- Pruritus

Late Phase Reaction occurs in hours to days:

- Infiltration with eosinophils and neutrophils
- Fibrin deposition
- Infiltration with mononuclears (macrophages, fibroblasts)
- Tissue destruction

Most allergic reactions will become evident within seconds to minutes after exposure to a triggering antigen, although a delay of several hours may occur in rare situations, especially with some oral ingestions. Other things being equal, the sooner a reaction occurs after antigen exposure the more likely it is to be severe. A second wave of allergic response occurs 4-12 hours after antigen exposure, may be severe and may last up to 48 hours. The clinical significance of this second wave of inflammatory response is probably minimal

Allergic reactions occur with varying degrees of severity, depending on:

- Degree of hypersensitivity (number of IgE molecules present on the mast cells and basophils and their affinity for the allergen, as well as number of mast cells and basophils)
- The quantity, route and rate of antigen exposure (Parenteral exposure gives higher risk of anaphylaxis than oral or topical)
- Pattern and quantity of mediator release
- Target organ sensitivity and responsiveness

Hypersensitivity reactions can be of variable severity:

- Mild: Urticaria only
- Moderate: Urticaria plus angioedema and bronchospasm
- Severe: Anaphylaxis (Airway angioedema also usually considered severe)

Types of Hypersensitivity Reactions:

Urticaria:

- Involves only the superficial portion of the dermis
- Presents as well-circumscribed wheals which may coalesce
- Always pruritic
- Occurs frequently (up to 1 in 5 have had)
- Acute - lasts less than 6 weeks; Chronic - greater than 6 weeks (Chronic urticaria may require diagnostic work-up for unusual causes)

Angioedema:

- Well demarcated localized edema involving the deeper layers of the skin including the subcutaneous tissue
- Skin, gastrointestinal tract, upper airway commonly involved
- Airway involvement may be fatal

Anaphylaxis:

- A clinical syndrome
- Characterized by a severe reaction of multiple organ systems to an antigen-induced, IgE driven mediator release in previously sensitized individuals
- Hypotension, bronchoconstriction and/or upper airway obstruction are common
- Portier and Richet first described anaphylaxis in 1902, when they described the increasing sensitivity in dogs to repeated injections of sea anemone toxin (“ana”=backward and “phylax”=protection)

- Anaphylaxis accounts for at least 400-800 deaths/year in the United States alone. Penicillin (100-500 deaths/year) and hymenoptera stings (40-100 deaths/year) are the two most common causes of fatalities resulting from anaphylaxis

Anaphylactoid reactions are "allergic type" reactions which prompt mediator release through a non-immunologic mechanism

Causes of Hypersensitivity Reactions:

- IgE Dependent Mechanisms
  - ♦ Antibiotics and other drugs
    - ★ Many low molecular weight drugs act as haptens and must bind to serum proteins to be antigenic
    - ★ True anaphylaxis with penicillin occurs once in about every 5000 patients and remains the leading cause of fatal anaphylaxis (one per 7,500,000 exposures). Cephalosporin cross-sensitivity to penicillin is 2-16%; only significant if severe angioedema or anaphylaxis occurred with penicillin
    - ★ Horse serum containing agents, such as snake antivenon and antilymphocyte serum, still cause frequent anaphylaxis today (Tetanus antisera is now human derived, and in one study no cases of allergic reaction occurred in 250 people given tetanus toxoid who had previously had anaphylactic reactions to equine tetanus antisera)
    - ★ Local anesthetics rarely cause allergic reactions (Two types: esters include procaine, cocaine, tetracaine and benzocaine; and amides, which include lidocaine, bupivicaine, and mupivicaine). Allergic reaction to lidocaine and other anesthetics if often due to methylparaben, a preservative not present in the IV injectable form of the drug
    - ★ Allergic reactions to insulin rarer with new human insulin
  - ♦ Foods
    - ★ Especially peanuts, tree nuts, shellfish, fish, eggs, some fresh fruits
    - ★ Some food reactions are secondary to added agents, such as antibiotics and sulfites
  - ♦ Pollens
  - ♦ Fungi and molds
  - ♦ Helminths
  - ♦ Hymenoptera venom (includes fire ant stings)
    - ★ Systemic reaction occurs in up to 1-3%
    - ★ Hymenoptera venom skin test gives a positive reaction in 15% of the general population
    - ★ Anaphylaxis recurrence rate is 35-60% if previous reaction from stinging insect
    - ★ Referral for immunotherapy **standard of care** for severe stinging insect reactions
  - ♦ Latex
    - ★ First described 1979 (urticaria - gloves)
    - ★ Frequency of sensitization:

General nursing	2.6%
Surgeons	9.0%
Spina bifida patients	29.0%

    - ★ Reactions: Local (2/3) to anaphylaxis
    - ★ Risk factors for latex hypersensitivity:
      - Atopic history
      - Repeat exposure (gloves, catheters)
  - ♦ Many others, including some viral and bacterial infections
- Nonimmunologic Causes (non-IgE mediated)
  - ♦ Direct mast cell-releasing agents
    - ★ Opiates
    - ★ Some antibiotics (Neomycin)
    - ★ Curare and D-tubocurare
    - ★ Radiocontrast media
      - Allergic reactions occur in 1-2%, with fatal results in about 1 in 50,000-100,000 studies

Risk factors:
- Previous allergic reaction to agent (35% recurrence rate)
- History of atopy (11% risk)
- Increased age
- Dehydration
- Renal or hepatic dysfunction
- Cardiac disease
- Dye factors (dose, osmolality, ionic content)

Pathogenesis unclear

Risk reduction:
- Alternate imaging technique
- Patient education (informed consent)
- Pretreatment (12-24^{o} prior to dye load) with diphenhydramine, steroids
  - Lowers recurrence rate to about 10%
- Nonionic, low osmolality contrast agents
  - Lowers recurrence rate to 4% w/o pretreatment
  - Lowers recurrence rate to 0.5% w/ pretreatment

- Agents which presumably alter arachidonic acid metabolism:
  - Aspirin and nonsteroidal anti-inflammatory agents
  - Azo dyes and benzoates
- Idiopathic causes
  - Cold
  - Light
  - Cholinergic
  - Vibratory
  - Exercise-related
  - Dermatographism

- Complement-Mediated Reactions Mimicking Type I Hypersensitivity
  - Hereditary angioedema
    - Secondary to C_1 esterase inhibitor deficiency
    - Autosomal dominant inheritance
    - Suggested by family history, lack of urticarial lesions or itching, prominence of recurrent self-limited attacks of circumscribed subepithelial edema of the skin (angioedema) and gastrointestinal tract (causing abdominal colic) as well as the upper respiratory tract (causing laryngeal edema)
    - Diagnosed by antigenic and functional assays of C_1 esterase inhibitor (5-25% of normal) with levels of C_4 also reduced
    - Treated with danazol, an anabolic agent
    - Fresh frozen plasma infusion can abolish acute attacks
    - Epinephrine, antihistamines, and corticosteroids ineffective in attack prevention or treatment
    - Airway management is critical
  - Acquired angioedema
    - May occur with lymphoproliferative disorders
  - Reactions to blood products (IgA deficient patients)
    - A population subclass exists who are IgA immunoglobulin deficient, and may have preformed antibodies of the IgG_4 subclass to IgA secondary to previous transfusions
  - Necrotizing vasculitis
  - Serum sickness
- Angiotensin Converting Enzyme Inhibitor Induced Angioedema

Diagnosis of Hypersensitivity Reactions:
- Depends largely on an appropriate history, and/or physical exam exhibiting evidence of urticaria, angioedema, bronchospasm, and/or vascular collapse
- Usually straightforward unless bronchospasm or vascular collapse occurs in isolation

- Always ask about ingestion of nonsteroidal anti-inflammatory agents and get a careful recent food and drug history
- Frequently confused with vasovagal episodes secondary to injection, sting or other antigen exposure

History:
- Precipitating event:
  - Medications, including OTC's
  - Foods
  - Environmental exposures
  - Physical agents/events
- Previous episodes:
  - Frequency
  - Duration
  - Effects of treatment

Don't forget to ask about allergies!
"Three cases of fatal anaphylaxis to antibiotics in patients with prior histories of allergy to the drug."
Hoffman DR: Ann Allergy 1989;62:91

Clinical Manifestations of Anaphylaxis and Related Pathophysiology:
- Vital Signs
- Skin
  - Uricaria
  - Angioedema
- Upper Respiratory Tract
  - Rhinitis
  - Laryngeal edema
- Lower Respiratory Tract
  - Bronchospasm
  - Increased secretions
- Cardiovascular System
  - Circulatory collapse (hypotension with tachycardia, rarely bradycardia)
  - Dysrhythmias
  - Cardiac arrest
- Gastrointestinal Tract
  - Abdominal colic
    - ★ Nausea, vomiting
    - ★ Diarrhea
- Eyes
  - Conjunctivitis
- Central Nervous System
  - Confusion
  - Coma
- Hematologic
  - Disseminated intravascular coagulation

Laboratory in Hypersensitivity Reactions
- Rarely useful in the Emergency Department
- Screening labs used to eliminate other causes

Treatment of Allergic Reactions:
- Eliminate antigen, or delay its absorption.
  - If oral ingestion, activated charcoal given early may reduce antigen load

    - If the antigenic material was injected into an extremity, loosely apply a tourniquet, inject epinephrine locally, and if stinger, remove without compression. Ice may also delay antigen delivery centrally
- The most useful drugs in the treatment of anaphylaxis are oxygen, epinephrine, and fluids
- The main cause of death from hypersensitivity reactions is respiratory failure. Circulatory failure is the other frequent cause of death

Oxygen:
- Be liberal
- Do ABG's or pulse oximetry to ensure tissue oxygenation if severe hypersensitivity reaction
- Early intubation with 100% O_2 may be very appropriate if no rapid response to therapeutic interventions (Orotracheal intubation usually best because of severe mucosal edema)

Epinephrine:
- Has both alpha and beta agonist activity
- Relatively contraindicated in older age groups, especially if known coronary artery disease or hypertension
- There are no contraindications in a true anaphylactic emergency
- Dose and route important considerations:
    - If mild/moderate reaction give SC or IM at 0.01 mg/kg up to 0.3 to 0.5 mg
    - If severe reaction, give 1-5 ml of 1:10,000 solution IV or IT over 2-3 minutes and titrate symptoms and signs with epinephrine drip (1 mg in 250 cc D_5W)
- Cardiac monitoring always indicated in this setting
- Inhalational epinephrine useful in severe laryngeal edema

Volume Expanders:
- Leaky capillaries and venules are a prominent problem in hypersensitivity reactions
- Crystalloid preferred over colloid: It may require several liters of isotonic saline or lactated Ringers to replete intravascular volume in severe hypersensitivity reactions
- Avoid hypo-osmolar and dextrose containing solutions
- Invasive hemodynamic and urine production monitoring are important in the severe reaction

Antihistamines:
H_1 Antagonist
- May be all that is required in mild allergic reactions
- By itself inadequate in severe anaphylaxis, as the dose required to reduce symptoms is itself toxic in this setting
- Diphenhydramine (PO, IM, IV) or hydroxyzine (only PO, IM) 1 mg/kg good starting dose
- Non-sedating agents may have increasing role
    - Cetirizine (Zyrtec®)
    - Loratadine (Claritin®)

H_2 Antagonist
- Cimetidine beneficial in 95% in one study
- May occasionally be effective when other agents are not
- Recommended dose 300 mg IV
- Limited sedation may be advantageous

Steroids:
- Not effective for 4-6 hours after dosing
- May attenuate late-onset hypersensitivity component (Not proven)
- Should be given in cases of severe laryngeal edema, bronchospasm, or hypotension, and probably even in mild allergic reactions
- Dose of 1 mg/kg prednisone for several days usually appropriate for most reactions

Others:
- Heliox
- Inhalational sympathomimetics (Ventolin, Alupent, etc.)
- Other parenteral sympathomimetics (Dopamine, Levophed, etc.)
- Aminophylline?
- Glucagon
  - Lowers intracellular cGMP levels and inhibits mediator release
  - May be particularly effective in patients on Beta-blockers
- Anticholinergics:
  - Both atropine and ipratroprium bromide (Atrovent®) also decrease intracellular cGMP and may be effective inhalationally for bronchospasm
  - May be particularly effective in patients on Beta-blockers

Prevention of Hypersensitivity Reactions:
- Avoid allergen exposure (well-timed vacation, air filtering devices, etc.)
- Pretreatment with antihistamines and steroids
- Recommend appropriate medic-alert bracelets
- Prescribe ANA-KIT or EPI-PEN (and make sure patient knows how to use it)
- Make allergist referral for severe reactions
  - Skin test when allergen suspected
  - Progressive desensitization if allergen not possible to avoid or eliminate

Immunotherapy = Hyposensitization
- Consists of repeated subcutaneous injections of gradually increasing concentrations of the allergens considered responsible for the symptom complex:
  - First introduced in 1911
  - Very effective if known antigen
  - Technique:
    - Define antigens by skin testing
    - SC injection of increasing antigen doses
    - Maintenance therapy
    - May induce acute allergic reaction
- Two types of response:
  1. Humoral
     - Increases specific IgG antibodies that act as blocking antibodies to prevent allergen exposure to IgE
     - Diminishes IgE production by stimulating the production of antigen-specific suppressor T cells
  2. Cellular
     - Decreases lymphocyte responsiveness to antigen
     - Decreases IgE production
     - Decreases basophil and mast cell sensitivity to allergen
- 95% effective in eliminating anaphylaxis on re-sting with venomous insects
- Occasionally effective elsewhere, but overused (Many positive "allergic reactions" on skin testing are clinically insignificant. Allergy shots do decrease symptoms of allergic rhinitis in 80% of patients whose symptoms are due to ragweed, grass, tree or mite allergy)

Disposition of Hypersensitivity Reaction Patients:
Clinical judgment required:
- When in doubt hospitalize:
  - All severe reactions not promptly resolved by therapy:
    - Airway angioedema, bronchospasm
    - Hypoperfusion or cardiac problem

- All patients on Beta-blocker therapy with significant reactions
- Anticipated severe late phase reaction
- Patients with inadequate support systems and significant allergic reaction

- Discharge plan:
  - Observe significant reactions at least 4-6 hours
  - H_1 and/or H_2 antagonist for at lease 24-48 hours (For most patients 5 mg/kg/day of diphenhydramine for 24-48 hours, or another antihistamine)
  - Consider steroids to modify the inflammatory reactions of allergy (should probably prescribe for most allergic reactions, 1 mg/kg/day for few days)
  - Consider Beta-agonist metered dose inhalers if significant wheezing
  - Education about antigen avoidance
  - Consider prescribing self-administered injectable epinephrine
  - Appropriate referral to private physician or allergist

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