ALLERGY & IMMUNOLOGY
GENERAL SESSION

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Disclosures

• I have no relevant financial relationships with the manufacturers(s) of any commercial products(s) and/or provider of commercial services discussed in this CME activity.

• I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.
Objectives

• Conduct and interpret allergy testing in the appropriate context
• Determine which patients may benefit from allergy testing
• Prescribe appropriate treatment based upon symptoms and diagnosis
• Recognize causes of urticaria and angioedema
**ABP Specifications**

- Specific recommendations from the ABP regarding Allergy & Immunology content will be denoted throughout this presentation by use of “**”
Hygiene Hypothesis

- Notable increase in atopy over last decade(s)
- Theory that early life exposures help drive immune response**
  - Children who are raised on farms have less atopy
  - Exposure to infection and endotoxin shifts from Th2 $\rightarrow$ Th1 response
- As we become ‘cleaner’, our immune systems don’t have to fight infection and shift towards allergy
Atopy: Natural History

- Strong genetic component**
- Atopic march is common
  - Eczema in early infancy
  - +/- food allergy
  - Allergic rhinitis in early childhood
  - Asthma develops early/late
Definitions

- **Allergy**: An immunologic response to an allergen that results in reproducible symptoms that occur immediately (within a few hours) and with every exposure**
  - Hives
  - Swelling
  - Rhinorrhea
  - Congestion
  - Difficulty breathing
  - Difficulty swallowing

- Vomiting
- Hypotension (passing out)
- Anaphylaxis

**Type IV: Delayed, T-cell mediated hypersensitivity**
- Cow’s milk protein induced proctocolitis
- Atopic dermatitis
Definitions

• **Intolerance**: A non-immunologic response to a substance (food) that causes gastrointestinal symptoms with exposure
  • Not always reproducible
  • More subjective complaints
  • Not always immediate
    • Bloating
    • Gassiness
    • Heartburn
    • Vomiting
    • Constipation
    • Diarrhea

  • May mimic immunologic reactions to foods
  • Can often tolerate the suspected food protein as an ingredient in other foods
    • Person who suspects milk allergy but can eat yogurt
  • May represent a normal response to certain foods or meals that is misinterpreted as an adverse reaction
Sensitization ➔ Allergy

- Sensitization
  - The detection of specific IgE toward an allergen through skin prick, intradermal, or serum specific IgE testing

- IgE mediated hypersensitivity
  - Characteristic clinical symptoms upon exposure to an allergen AND…
  - The detection of specific IgE toward that allergen
Diagnostic Testing

• Skin prick testing
  • Detects presence of specific IgE bound to cutaneous mast cells
  • Introduce small amount of allergen percutaneously – wheal/flare in 15 minutes
    • High negative predictive value
    • Low positive predictive value ~50%*

• Serum testing (formerly RAST)
  • Detects levels/presence of specific IgE in serum
  • Very high false positive rate**
  • NOT a useful screening tool** – esp. with eczema
Skin Prick and Serum IgE Testing – Similarities**

- High negative predictive value
- Low positive predictive value
- Size of test confers likelihood of allergy being present
- Test results DOES NOT determine severity of reaction
- High correlation between these tests
  - Especially when negative
Diagnostic Testing & Medications**

- Skin prick tests
  - **Blocked by H1/H2 antihistamines**, possibly long term oral/topical steroids, tricyclic antidepressants
    - Stop antihistamines 5-7 days prior
  - **Not affected by**: antileukotrienes, nasal steroid sprays, inhaled steroids, albuterol

- Serum IgE testing
  - **Not affected by any medication**
Pearls of Wisdom

- Both skin and blood testing have high **FALSE POSITIVE** rates
  - Many people without allergy will have positive tests
  - The best test is what happens upon exposure
  - “Shotgun” testing, or testing of patients without symptoms is not recommended
Allergic & Nonallergic Rhinitis
Allergic Rhinitis: Presentation

• Typically doesn’t present until 10-12 months of age at the earliest**
  • Perennial aeroallergens

• Seasonal allergies typically do not appear before 3-4 years old**
  • Indoor:
    • Dust mites, cat, dog, cockroach, mold spores
  • Outdoor:
    • Tree pollen – early spring
    • Grass pollen – late spring, early summer
    • Weeds – summer, autumn
    • Ragweed – mid-August until frost
    • Mold spores – all seasons during damp, rainy weather
Allergic Rhinitis: Presentation**

- Ocular
  - Itching, swelling, lacrimation
  - **Never unilateral!!!**
  - Photophobia and pain are uncommon
- Nasal
  - *Itching*, sneezing, rhinorrhea, congestion
  - ‘Shiners’ are nonspecific finding
- Unlikely to be directly due to aeroallergens:
  - Eczema, urticaria, angioedema, anaphylaxis
Allergic Rhinitis: Complications**

- Sinusitis
- Otitis media
- Poor asthma control/exacerbations
- Poor sleep quality
- Missed school
- Missed work
Nonallergic Rhinitis: Presentation**

- Ocular
  - Not a part of nonallergic rhinitis

- Nasal
  - *No significant itching*, +/- sneezing, rhinorrhea, congestion
  - ‘Shinners’ are nonspecific finding & very common
  - Mouth breathing
  - Snoring
Allergic Rhinitis: Treatment**

- **Antihistamines**
  - Fast acting, short lasting
  - Ideal for nasal itching, sneezing
  - Not very effective for congestion, postnasal drip – not effective for URI’s!
  - First generation – sedating, side effects → skip use if possible!
  - Second generation – less sedating, longer lasting

- **Ophthalmic drops**
  - Combination antihistamine/mast cell stabilizer most effective
  - Fast acting, short lasting
Allergic Rhinitis: Treatment*

• Intranasal steroid sprays
  • Not effective when used acutely or intermittently
  • Best medication for congestion, postnasal drip
  • Main side effect: epistaxis; little systemic absorption

• Leukotriene modifiers
  • Not very effective for rhinoconjunctivitis
  • Not indicated for use as monotherapy or first line therapy
  • Block part of late phase allergic response
    • No antihistamine properties
Allergic Rhinitis: Treatment

• **Topical and oral vasoconstrictors**
  • Avoid, avoid, avoid
  • Not effective at treating symptoms
  • Can lead to rebound phenomenon
    • Rhinitis/conjunctivitis medicamentosa

• **Immunotherapy**
  • Indicated for refractory symptoms despite optimal medical management/avoidance**
    • Not first line therapy
  • Weekly build up x 6-8 mos, then monthly injections x 3-5 years
  • *No benefit for at least 6-12 months***
    • Often need to continue all medications
Immunotherapy

- Pro**
  - Effective (80% with significant to dramatic improvement)
  - Only disease modifying treatment
  - May prevent sensitization to new allergens and progression of allergic rhinitis to asthma
Immunotherapy

• Con**
  • Painful (multiple shots)
  • Risk of reactions (anaphylaxis)
  • Inconvenient (watch 30 minutes post shot)
  • Slow onset of action (6-12 months)
  • Not all patients benefit
  • Must use correct allergens and concentrations
Allergic Rhinitis: Avoidance

- Outdoor aeroallergens
  - Keep bedroom windows closed at all times
  - Air conditioning effective at lowering indoor levels
  - Wash face/hair before bed each night

- Indoor aeroallergens
  - Dust mites: encasements for pillows/mattress, no stuffed animals, wash linens weekly in hot water, ideally no carpeting
  - Cat and dog dander: ubiquitous in any home with pets; keep out of bedroom 24/7, wash pets weekly
    - Removal from home – dander persists for 4-6 months
    - “Hypoallergenic pets” do not exist
Atopic Dermatitis
What is Eczema (Atopic Dermatitis)?

- Chronic, relapsing, remitting skin disorder hallmarked by dryness, pruritus, and inflammation

- Strong association with atopy, Th2 response**
  - 50% develop asthma
  - 75% develop allergic rhinitis
  - ~33% develop food allergies

But What Causes Eczema?**

- Strong genetic component leads to altered skin barrier/epidermis
  - Filaggrin loss of function mutations
  - SPINK5
- Leads to → increased transepidermal water loss → increased entry of allergens, irritants, chemicals → inflammation

Role of Allergens and Eczema**

- History is often unreliable in identifying potential food or environmental allergen triggers
  - Symptoms may not appear for hours to days after ingestion
- IgE testing is often unreliable in identifying potential food allergen
  - High rate of false positive testing
  - May be T cell mediated response (negative IgE testing)

Role of Allergens and Eczema

- A subset of infants (< 2-3 years of age) with refractory moderate-severe eczema may have food allergy contributing**
  - Only consider after thorough regimen of skin care
  - Egg, milk, peanut most commonly implicated
- Sensitization to aeroallergens can lead to chronic or seasonal flares of eczema lesions
  - Dust mite, pet dander, pollen
Role of Other Factors in Eczema

- Most children with eczema have non-allergen factors that exacerbate their chronic skin condition
  - Weather (humidity levels)
  - Irritants
    - Chemicals, topical products
    - Laundry detergent, soap
    - Manipulation/scratching of the skin
  - Psychosocial stressors
  - Illness
  - Infection
Role of Other Factors in Eczema

• # 1 cause of poorly controlled eczema:
  • Lack of understanding regarding:
    • Chronic nature of the underlying condition
    • Knowledge/avoidance of triggers
    • Control of pruritus
    • Need for frequent application of moisturizer
Non-IgE Mediated Food Allergy
Food Allergy: Non-IgE Mediated

• Milk protein induced proctocolitis
  • Painless, gross blood in stool
  • Presents in first 1-2 months of life
  • Resolves within ~72 hours of removal
    • Don’t play formula roulette
  • Can switch to soy formula; elemental not necessary
  • No role for skin prick or serum IgE testing** – T cell mediated
  • Resolves by 12 months of age
    • Reintroduce without any further testing
Food Protein Induced Enterocolitis Syndrome

- Non-IgE mediated immunologic reaction to foods
- Presents during infancy
- Delayed onset vomiting +/- diarrhea, dehydration that occurs 1-3 hours after eating a food
- Milk, soy, rice most common food triggers
- There are no tests currently available to diagnose**
  - Skin prick and serum IgE testing negative (non-IgE mediated condition)
- No role for any other type of testing – history +/- challenge guides diagnosis
Food Protein Induced Enterocolitis Syndrome

- Can result in profuse vomiting, diarrhea, lethargy, hypovolemic shock
- NOT associated with urticaria/angioedema/anaphylaxis
- Epinephrine, antihistamines are NOT effective
- Supportive care with IV fluids, anti-emetics
- Families should have letter to present to ED physician
- Natural history is to resolve by 3-? years of age
Urticaria and Angioedema
Urticaria=Hives=Welts=“Welps”
What is Urticaria?**

- Cutaneous lesions
- *Pruritic*
- Erythematous
- Raised
- Blanch with pressure
- Can occur anywhere on body
- Individual lesions last < 24 hours
- Can occur at any age
What does NOT Constitute Urticaria?

- Morbilliform rash
- Scarlatiniform rash
- Macular erythema
- Purpura
- Vesicular eruption
- Inflammatory plaques (eczema)
- Scabies
- Candidal dermatitis
- Rhus dermatitis
Pathophysiology

- Mast cells (tissue) and basophils (circulation) are main cells involved
- Variety of stimuli can cause activation and degranulation
- **Histamine** is immediately released from preformed granules
  - Erythema
  - Edema
  - Pruritis
Timing is Everything

• Can affect any age, race, gender
• ~50% experience both urticaria and angioedema, 40% with isolated urticaria, 10% with angioedema

• **Acute** urticaria/angioedema:
  • 6 weeks duration or less
  • ~20% of general population

• **Chronic** urticaria/angioedema:*
  • > 6 weeks
  • ~0.5% of general population
Common Causes of Acute Urticaria**

- Viral, bacterial, fungal, helminthic infections
- Drug reactions
- Foods
- Direct contact with allergens (pets)
- Transfusion reactions
- Insects (papular urticaria)
- Idiopathic
Common Causes of Chronic Urticaria**

- Majority are idiopathic
- ~45% have evidence of autoimmunity
  - IgG against IgE or Fc-epsilon receptor
- Physical urticarias
- Malignancy
- Collagen vascular disease
- Familial
- Mastocytosis
History Suggestive of IgE-mediated Hypersensitivity

- Identifiable trigger
  - Is it a common cause of allergy?
  - Typically requires ingestion

- Symptoms:
  - Onset within minutes or 1-2 hours of exposure
  - Reproducible with each exposure
  - Duration typically less than 12-24 hours
  - Improve with antihistamines/epinephrine
  - Does not recur without exposure to offending allergen
  - Involvement of other organ systems
History *NOT* Suggestive of IgE-mediated Hypersensitivity

- Long list of suspected triggers
- Suspected trigger is not recognized as a common or highly allergenic item
- No identifiable trigger
- Delayed symptom onset after exposure ( > 3 hrs)
- Symptoms not reproducible with each exposure
- Able to tolerate allergen in other forms
- Symptom duration >24 hours in acute urticaria
- *Chronic urticaria*
Urticaria: Treatment**

• 2nd generation antihistamines
  • Often twice daily in higher dosages
• Avoid corticosteroids as much as possible!
  • Rebound effect
• 1st generation antihistamines
  • May use in conjunction with 2nd gen but not 1st line therapy
• Realistic expectations for patient/family
• Avoid ‘shotgun’ testing
Physical Urticarias

- Dermatographism
- Cold induced
- Cholinergic
- Delayed pressure
- Vibratory
- Solar
- Aquagenic
What is Angioedema?

- Similar pathophysiology as urticaria
- Deeper in dermis and subcutaneous tissues
- Unilateral or asymmetric swelling
- Skin retains color or has mild erythema
- May not be pruritic
- Most commonly affects face, tongue, extremities, and genitalia
Angioedema**

- Allergic
- Idiopathic
- ACE-inhibitor induced
- Hereditary

- Can think about as either histamine or bradykinin mediated
  - Histamine (allergic, most idiopathic)
  - Bradykinin (HAE, Factor XII, ACE-inhibitor, rare idiopathic)
Hereditary Angioedema

- Can present at any age, but usually later childhood/adolescence
- Gradual swelling for 24-36 hours, with plateau and resolution within 3-5 days
- NOT associated with urticaria
- C4 is screening test – always low, esp during acute attack
- Epinephrine, antihistamines, steroids NOT beneficial
- Now have several treatment options (all $$$$):
  - C1 esterase inhibitor replacement
  - Kallikrein inhibitor
  - Bradykinin receptor antagonist
## Hereditary Angioedema

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<th>C1 inhibitor level</th>
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<td>II</td>
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<tr>
<td>III</td>
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Drug Hypersensitivity
Let’s Get Technical for a Second…

- True ‘allergic’ reactions to antibiotics are uncommon in the general population, esp. children
- Adverse reactions after or while taking antibiotics are very common
  - Immunologic
    - Type I, II, III, IV
    - Not always predictable
    - Occurs in reproducible manner
  - Non-immunologic (idiosyncratic)
    - Unpredictable
    - Does not occur with every exposure
    - GI symptoms, cutaneous eruptions
What’s the Difference?

- Immunologic reactions to an antibiotic should preclude the re-administration of that particular antibiotic**
  - IgE mediated immediate onset reactions could lead to anaphylaxis
  - Type III – serum sickness, erythema multiforme
  - Type IV – almost always delayed onset cutaneous rashes

- Allergy testing is only commercially available for IgE mediated reactions to penicillin and no other antibiotics**

- Non-immunologic reactions should not be labeled as ‘allergy’ as they do not indicate a contraindication to re-administration
What’s the Big Deal?

• Penicillin allergy grossly overestimated in general population
• Less than 10% of children and adults reported to have penicillin allergy have positive skin test or symptoms upon challenge
• Misdiagnosis of drug allergy can lead to unnecessary avoidance
• Use of antibiotic alternatives
  • Inferior microbial sensitivity
  • Increased side effects/toxicity
  • Increased cost

How Can You Determine Allergy vs Side Effect?

• History
  • Timing of onset
  • Character of symptoms
  • Duration of symptoms
  • Have they received the drug again and if so, did they tolerate?

• Can perform skin testing for penicillin
  • Pre-pen
  • Penicillin G
  • Negative skin prick and intradermal testing associated with 97-99% negative predictive value
Penicillin Cross Reactivity

- Beta lactam antibiotics all share common beta lactam ring
  - This causes the minority of type I allergic reactions
  - Cross reactivity comes from similarity in side chains
Rates of Cross Reactivity

- Penicillin + 1st gen Cephalosporins = 4%
- Penicillin + 2nd, 3rd, 4th gen Cephalosporins = 0%
- Penicillin + Carbapenems = 8-50%
- Penicillin + Aztreonam = 0%

Venom Hypersensitivity
Venom Hypersensitivity

- Large local reactions are very common
  - Non-IgE mediated – no role for allergy testing, epinephrine, or immunotherapy
  - Not cellulitis when seen acutely!!!

- Diffuse cutaneous reactions < 16 years old:
  - Does not increase risk of anaphylaxis with future stings
  - No role for allergy testing, epinephrine, or immunotherapy

- Risk of anaphylaxis:
  - General population, never been stung = 10%
  - Large local reactions with stings = 10%
  - Diffuse cutaneous reactions < 16 yo = 10%
  - Prior history of anaphylaxis = 70%
Venom Anaphylaxis

- Anaphylaxis at any age:
  - Absolute indication for allergy referral and skin testing to venom
  - Carry self injectable epinephrine at all times
  - Risk of anaphylaxis with future stings ~70%
  - Risk of anaphylaxis after 5 years of immunotherapy ~5%

- Pearls:
  - Cannot perform venom allergy testing for at least 4-6 weeks after sting due to false negatives
  - Cannot rely on history to determine what caused sting
    - Must test for all: honey bee, yellow jacket, yellow hornet, white faced hornet, wasp
Changes You May Wish to Make in Practice

- Discontinue use of any serum IgE ‘panels’ to avoid unnecessary testing and misinterpretation
- Choose appropriate medications for treatment of allergic rhinitis based upon symptoms
- Avoid using corticosteroids in the treatment of urticaria
- Refer patients with suspected penicillin allergy for diagnostic testing & evaluation
Thank You