When to see an allergist?

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Ways we can help

- Single or limited consultation
- Co-management between Primary Care Providers and Allergist/Immunologist
- Ongoing Allergy/Immunology specialty care

Disclosures

I have no relevant financial relationships.

Reasons for referral

- ★ Asthma
- Cough
- ★ Rhinoconjunctivitis
- Dermatitis
- Sinusitis
- ★ Urticaria and Angioedema
- ★ Anaphylaxis
- Drug allergy
- Food allergy
- Stinging insect allergy
- Immunodeficiency

Learning Objectives

- At the completion of the session attendees will be able to:
  - Describe situations for which referral to an allergist is recommended
  - Describe the specialized role of allergists in the evaluation and management of a patient presenting with symptoms of an allergic disease
  - Discuss evidence supporting the role of allergists in facilitating diagnosis of allergic problems
  - Discuss evidence that intervention by an allergist can improve outcomes

Allergists' Specialized Training

- Allergy testing (skin test and in-vitro)
- Correlation of history with allergy testing
- Broncho provocation testing (e.g., exercise, methacholine)
- Environmental control instructions
- Inhalant immunotherapy
- Immunomodulator therapy (anti-IgE, anti-IL5 etc)
- Venom immunotherapy
- Food and drug challenges
- Drug desensitization
- Evaluation of immune competence
- Education (disease, medications, monitoring)
- Management of chronic or recurrent conditions where allergy is not always identified
  - Rhinosinusitis, conjunctivitis, asthma, cough, urticaria/angioedema, eczema, anaphylaxis

Why does it matter?

- Allergic diseases affect more than 56,000,000 Americans
- Allergies are the 6th leading cause of chronic illness in the U.S.
- Allergic conditions are the most common health issues affecting children in the U.S.
  - In 2015, 8.2 percent of adults and 8.4 percent of children were diagnosed with hay fever
- Allergies are increasing. They affect as many as 30% of adults and 40% of children in the United States.
- Annual cost of allergies exceeds $18 billion.
- Allergist-immunologist care improves outcomes, and optimal use of their services should improve the public health

Case 1

- 15 year old female with difficulty breathing with exercise.
  - She is a soccer player.
  - She complains of: feeling like she "can't get enough air in", chest tightness, slight cough, and "wheezing".
  - Symptoms typically start 5-10 minutes into the half and improve within a few minutes of rest
  - Past Medical History: seasonal allergic rhinoconjunctivitis, mild intermittent asthma
  - Symptoms thus far not responding to albuterol 2puffs prior to soccer

Focus areas for today

- Asthma
- Urticaria & angioedema
- Anaphylaxis
- Allergic Rhinoconjunctivitis

Case 1

- Additional historical information
  - "Wheezing" is inspiratory (not expiratory)
  - No history of syncope, palpitations, denies Fhx cardiac issues
  - She just made her H.S. varsity team for the first time
  - She is a very good student
  - As an aside: patient's mother wants this "fixed" as it is impacting her play … (no pressure)

Case 1

"Problems breathing when I play soccer"

Case 1

- Vital signs and physical exam: completely normal
- Spirometry: completely normal

How the Allergist/Immunologist Can Help: Consultation and Referral Guidelines Citing the Evidence Asthma Diagnosis

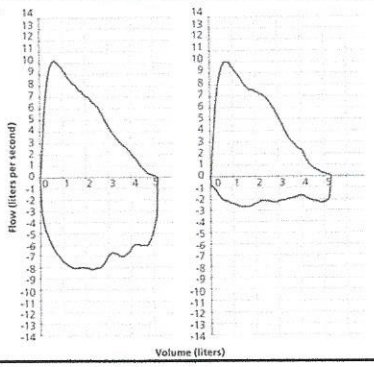
Who to refer to an allergist/immunologist:

- Patients with respiratory symptoms suggestive of asthma but with normal PFT and no significant reversibility.
- Exercise-induced symptoms that are atypical or do not respond well to pre-treatment with albuterol.

Why an allergist/immunologist:

- Allergist/immunologists perform methacholine challenges, which have a high sensitivity for current asthma.
- Further objective evaluation and confirmation with pulmonary function testing (including exercise challenge) in conjunction with appropriate allergist/immunologist evaluation will define diagnosis or differential diagnosis.

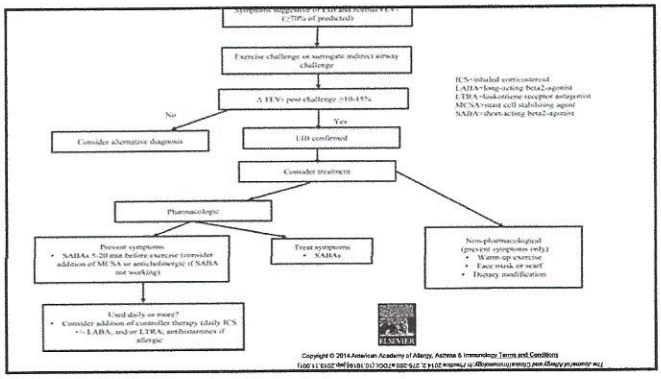
Case 1 - Spirometry Patterns



Case 1: Exercise Induced Dyspnea

Differential diagnosis

- Exercise induced bronchoconstriction
- Exercise induced laryngeal obstruction
- Exercise induced anaphylaxis
- Central airway obstruction
- Poor conditioning
- Cardiac issues



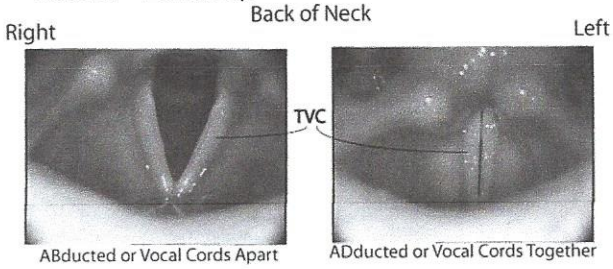
Case 1

	EIB	EILO	Exercise Anaphylaxis	Poor conditioning	Cardiac
Timing	During / after exercise 30-60 min	Abrupt onset/ end	Variable	Variable	Variable
Symptoms	Chest tightness, cough, wheeze	Throat tightness, inspiratory stridor	Hives, itching, cramping, angioedema	Heavy breathing	Syncope, Palpitations
Methacholine	Positive	Positive or Negative		Negative	Negative
Other					Family hx

Case 1 – Evaluation and Management

- Baseline spirometry with inspiratory loop
- Methacholine challenge
- Exercise challenge
- Aeroallergen skin testing
- Video of symptoms
- Adjustment of asthma therapy (if indicated)
- Breathing exercises
- Referral for airway evaluation

Case 1 – Followup



How the Allergist/Immunologist Can Help: Consultation and Referral Guidelines Citing the Evidence Urticaria/Angioedema

Who to refer to an allergist/immunologist:

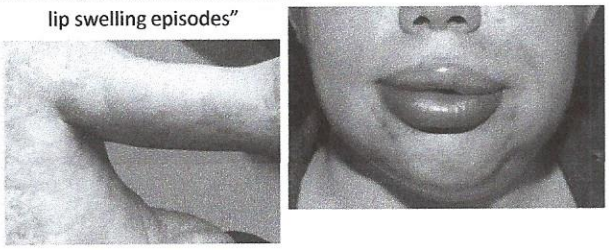
- Patients with chronic urticaria or angioedema, i.e. those with lesions recurring persistently over a period of six weeks or more.
- Patients who may have urticarial vasculitis or urticaria with systemic disease (vasculidities, connective tissue disease, rarely malignancies).

Why an allergist/immunologist:

- Allergist/immunologist training and expertise should allow appropriate differential diagnosis, determination of the need for biopsy, elimination of a specific inciting agent and optimal pharmacotherapy.

Case 2

"I have itchy welts all over with some lip swelling episodes"



Urticaria

Inclusion Criteria	Exclusion Criteria
Pruritic	Fever
Blanching	Petechiae/purpura
Central swelling/ surrounding erythema	Blisters
Persists < 24 h	Severe joint pain

Case 2

- 42 year old woman with no significant allergic history presenting with 6 month history of itchy, red, raised, "welts"
  - Started abruptly, occur daily
  - Lesions are itchy and evanescent
  - No residual bruising or pigment change
  - No obvious triggers
  - Has had 5-6 episodes of lip and eyelid swelling throughout the past 6 months

Angioedema

- Swelling of the deep dermal & subcutaneous or submucosal tissues
- May co-exist with urticaria
  - 50% have both urticaria and angioedema
  - 40% have urticaria alone
  - 10% have angioedema alone
    - Bradykinin mediated (Hereditary angioedema, ACE inhibitor associated angioedema)
    - Idiopathic angioedema (histaminergic, non-histaminergic)

Clinical Assessment

- Appearance: urticaria/angioedema/other
- Associated features: itch, pain
- Extra-cutaneous features: abdomen, lung etc
- Triggers, timing of onset of symptoms, duration, response to treatment
- Concomitant medication, diseases, esp. atopic
- Stressors, pets, work, hobbies, holidays
- Quality of life

Common Causes of Chronic Urticaria

- Autoimmune
- Physical urticaria
  - Cold urticaria
  - Cholinergic urticaria
  - Dermatographia
  - Pressure

Bernstein et al. J Allergy Clin Immunol 2014;133:1270-7.

Urticaria: Acute vs Chronic

- Acute
  - Symptoms for <6 weeks
  - More common in children and atopics
- Chronic
  - Symptoms continuously or intermittently (daily or almost daily) for ≥ 6 weeks
  - More common in adults
  - Female/male = 2:1
  - No increased incidence in atopics

Effect of Urticaria on Quality of Life

- Urticaria can have a significant detrimental effect on quality of life (QOL) due to constant itch, effect on sleep and side-effects of medication
- Poor QOL / stress can be a trigger for urticaria
- Women tend to suffer more than men
- Ensure that QOL/life stressors/events are assessed/discussed in patients with urticaria as this can improve patient satisfaction/ outcome

O'Donnell BF. *Immunol Allergy Clin North Am*, 2014
Jauregui I et al. *J Investig Allergol Clin Immunol*, 2014

Causes of Acute Urticaria

- IgE mediated allergy (food, contact, medication, insect venom)
- Early contact dermatitis (eg, poison ivy, nickel)
- Exacerbation of Physical urticaria (eg, cold urticaria, cholinergic urticaria)
- Non-IgE medication (NSAIDs, opioid)
- Papular urticaria caused by insect sting (fleas, scabies, bed bugs)
- Infection (eg, parvovirus B19, EBV, other viral)
- Food toxin (eg, scromboid)

Bernstein et al. J Allergy Clin Immunol 2014;133:1270-7

Laboratory Work-up

- No diagnostic testing may be indicated
  - routine laboratory testing in patients whose history and physical examination lack atypical features rarely yields clinically significant findings
- Immediate hypersensitivity skin testing for inhalants or foods is not warranted
- Skin biopsy may be performed when vasculitis is suspected (bruising, persistence >48 h)

Bernstein et al. J Allergy Clin Immunol 2014;133:1270-7.

Autoimmune Associations of Chronic Spontaneous Urticaria

- Antibody to alpha subunit of the high affinity IgE receptor – 35-40%
- IgG antibody to IgE – 5-10%
- Anti-thyroid antibodies (anti thyroglobulin or anti peroxidase) – 25%
  - Low titer ANA with speckled pattern (with no evidence of SLE) – 30%
- Clinical associations: increased incidence of Hashimoto's

Kaplan. Allergy Asthma Immunol Res. 2017
Viswanathan et al. Ann Allergy Asthma Immunol 2012

Hereditary Angioedema C1 Inhibitor Deficiency

- 1/30,000 to 1/80,000
- Disease severity is highly variable
  - Between patients and within families
  - No correlation between disease severity and C1 INH concentration
  - 1/3 few symptoms, 1/3 intermittent, 1/3 severe

Nanda MK et al. JACI Pract, 2015
Zuraw BL et al, JACI Pract, 2013
Buillet & Gompel, Immunol Allergy Clin North Am, 2013

Management of Chronic Urticaria

Step 4 (inadequate response after 4-6 months) — Add or switch to Cyclosporine

Step 3 (inadequate response after 2-4 weeks) — Add Omalizumab

Step 2 (inadequate response after 2-4 weeks) — Antihistamine (up to 4x dose)

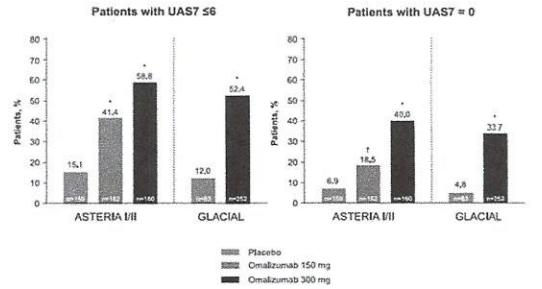
Step 1 — Non-sedating H1 Antihistamine

Modified from Zuberbier T et al. Allergy 2018

Clinical Features

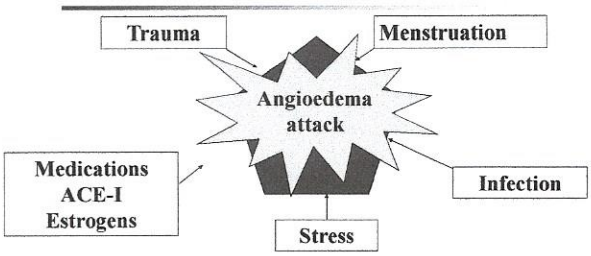
- Angioedema without urticaria (face, extremities, genitals, intestines or larynx)
- Angioedma is NOT warm, usually nonpruritic and nonpitting
- Angioedema of the gut wall may cause severe abdominal pain suggestive of acute abdomen
- Historic figures suggest that 1/3 of patients at risk of dying of upper airway obstruction without therapy

Omalizumab for Chronic Urticaria



Casale et al. J Allergy Clin Immunol Pract 2015;3:743-50

Known Triggers of HAE Attacks



- Only 39% of patients can identify the cause of an episode

Take Home Messages

- Urticaria and angioedema are common and can have a significant detrimental effect on patient's QOL
- Mast cell activation and degranulation lead to urticaria and angioedema, which usually respond to antihistamines and may be due to physical as well as allergic triggers
- Isolated angioedema: consider bradykinin induced disease – stop any ACE inhibitors and replace with alternatives, or consider HAE

Case 3

- 25 year old female without significant past medical history presenting post ED visit for "anaphylaxis"
- She reports the onset of diffuse itching starting while running on the treadmill at a fitness center. She continued to run for a few more minutes then stopped and went to the restroom due to the onset of abdominal cramping. She vomited on her way to the restroom, started to feel chest tightness and passed out. EMS was called – she was given epinephrine on arrival. She doesn't really remember much until she woke up in the ED.

Take Home Messages

- Angioedema due to ACE inhibitors or HAE will not respond to antihistamines or IM epinephrine
- In patients with chronic persistent urticaria, allergy tests are not indicated and patients are likely to have an immune cause
- In patients with associated bruising, scarring, systemic symptoms or intractable disease, refer to a specialist

Case 3

- ED records were obtained
- EMS reported vital signs on the scene – BP: 90/40; HR 140
  - 2nd dose epinephrine given in route to the ED
- In the ED vital signs: 118/60; HR 92
- Remarkable exam findings
  - Facial angioedema
  - Faint erythematous urticarial
  - good aeration, clear lungs

Case 3

"I was recently seen in the emergency department for anaphylaxis"

How the Allergist/Immunologist Can Help: Consultation and Referral Guidelines Citing the Evidence Anaphylaxis

Who to refer to an allergist/immunologist:

- Individuals with a severe allergic reaction (anaphylaxis) without an obvious or previously defined trigger.
- Persons with anaphylaxis attributed to food or drugs.

Why an allergist/immunologist:

- After a severe allergic reaction without a known cause, a trigger should be identified if at all possible. Suspected food and drug allergy should be confirmed if possible so that necessary avoidance can be instituted. An allergist/immunologist is the most appropriate medical professional to perform this evaluation, which may include
- skin testing, in vitro tests and challenges when indicated.

Anaphylaxis: Key Questions

- Suspected trigger and amount/dose
- Symptoms and timing – consistent with anaphylaxis?
- Treatment and response
- Associated factors
  - Exercise
  - Medications
  - Food
  - Infection
  - Alcohol
- Records of acute event (ER visit)
  - Can be very helpful to see vital signs, physical examination in cases where all symptoms subjective

Anaphylaxis: In Search of the Culprit!

- Direct testing (skin testing, serum specific IgE) based on patient history
  - Not in "screening" fashion
- Allergen specific IgE (positive skin test, detectable serum sIgE) indicates sensitization
  - Not always clinically significant
  - Must correlate history and testing

Differential Diagnosis

TABLE VI. Differential diagnosis of anaphylaxis

Common entities	Nonorganic disease
Acute generalized hives	Vocal cord dysfunction
Acute asthma	Munchausen syndrome‖
Syncope (faint, vasovagal episode)	
Panic attack	
Aspiration of a foreign body	Shock
Cardiovascular event (myocardial infarction, pulmonary embolus)	Hypovolemic Cardiogenic
Neurologic event (seizure, stroke)	Distributive (eg, spinal cord injury) Septic (might involve all of the above)
Postprandial syndromes	**Other**
Pollen-food syndrome*	Nonallergic angioedema
Scombroidosis†	Red Man syndrome (vancomycin)
Monosodium glutamate	Urticarial vasculitis
Sulfites	Hyper-IgE urticaria syndrome
	Progesterone anaphylaxis
	Pheochromocytoma
	Idiopathic systemic capillary leak syndrome
Excess endogenous histamine	
Mastocytosis/clonal mast cell disorders‡	
Basophilic leukemia	
Flush syndromes	
Perimenopause	
Carcinoid	
Autonomic epilepsy	
Medullary carcinoma thyroid	

JACI 2010;125(2):S161-181

Anaphylaxis: In Search of the Culprit!

- Refer to Allergist/Immunologist for evaluation/ management
- May evaluate for specific IgE (skin and/or blood testing) to allergens such as:
  - Foods
  - Insect venoms
  - Medications
  - Latex
- May consider challenge depending on history/test results
- Evaluation directed and based on history

Anaphylaxis: Lab Diagnosis

- Serum Tryptase
  - Mast cell mediator released early in a reaction
  - Measurable between 15 minutes and 3 hours after reaction
  - Often not detected in food-induced reactions
- Plasma histamine elevated initially, correlates with severity, but need to measure 5 to 15 minutes after reaction
- Urinary metabolites (N-methylhistamine, PGF2-alpha) longer lasting, can be measured in 24 hour urine sample
- Labs support diagnosis of anaphylaxis if positive, but do not rule out anaphylaxis if negative

Case 4

"My allergies are terrible"

Case 4

- 10 year old boy presenting with itchy, puffy, watery eyes, sneezing, rhinorrhea, congestion, cough, and chest tightness every April and May for the past 3 years. He is otherwise not symptomatic. He gave up playing baseball because he could not tolerate going outdoors.
- His parents have been treating him with long acting antihistamines, intranasal steroids, and over the counter eye drops with only partial improvement of symptoms

Immunotherapy Prevents the Development of New Allergen Sensitizations

Group	No. of Patients	New Allergen Sensitization: None	Cat	Dog	Alternaria	Grass
Immunotherapy	22	10	6	4	2	1
Control group	22	0	12	8	6	6

A. Des Roches et al. JACI 1998;99:450-453

How the Allergist/Immunologist Can Help: Consultation and Referral Guidelines Citing the Evidence Allergic Rhinitis & Asthma Treatment: Immunotherapy

- Patient preference
- Unsatisfactory current therapy or adverse effects
- Unsatisfactory quality of life
- Concomitant asthma & allergic rhinitis
- Prevention of new sensitizations?

SLIT for Allergic Rhinoconjunctivitis Systematic Review

- Studies & participants
  - RCTs, + skin or blood test to aeroallergen
  - 63 studies, 5131 participants, age 4-74
- Findings
  - ↓ Symptoms & medication use by >40% in asthma & AR/ARC
  - ↓ Combined (symptom/med) score & ↑ QOL
- Conclusion
  - Moderate evidence for SLIT efficacy in asthma, AR & ARC

Lin SY, et al. JAMA 2013;309(12),1278-88.

Efficacy of Allergen Injection Immunotherapy for Seasonal Allergic Rhinitis

- Meta-analysis
  - 51 studies, 2871 participants (1645 active)
- Results
  - ↓ Symptoms: SMD -0.73 (95% CI -0.97 to -0.50, P < 0.00001)
  - ↓ Medications: SMD -0.57 (95% CI -0.82 to -0.33, p<0.00001)
- Conclusion
  - Significant reduction in symptom scores and medication use with no long term adverse effects

Calderon MA et al. Cochrane Database Syst. Rev. 2007; (1): CD001936.

SCIT is Cost-effective

- Retrospective analysis of Florida Medicaid claims data (1997-2004) of children
- 102,390 kids with newly diagnosed allergic rhinitis
  - 3048 (3.0%) received IT
  - Suboptimal treatment compliance (16% completed 3yrs)
  - Even so, significant reduction from pre-IT levels:
    - Pharmacy use (p< 0.0001)
    - Outpatient resource use (p<0.0001)
    - Inpatient resource use (p<0.02)
    - Costs (p<0.0001)

Henkin et al. JACI 2008;121(1):227-32.

Allergen Immunotherapy Mechanism of Action

- Regulatory T cells
  - Increase in T regulatory cells (CD4+CD25+)
  - Produce increased levels of IL-10 which suppresses T_H2 (allergic) immune response
  - Produce TGFβ which also decreases T_H2 response
  - Increase T_H1 cytokine production (IFN γ)
- Immunoglobulin class switch deviation
  - Increase in allergen specific IgA and IgG levels (esp. IgG4)
  - Early rise in specific IgE followed by a decline

Adapted from Cox L et al. Allergen immunotherapy: A practice parameter third update. J Allergy Clin Immunol. 2011;127(1 Suppl):S1-55.

Case 4

- He returned in late June feeling much better
- Antihistamines were held for skin testing
- He was remarkably sensitive for tree and grass pollens
- Given his history aeroallergen immunotherapy was recommended
- At follow-up the next spring his symptoms were improved and he was back to playing baseball
- By year #2 of immunotherapy he was off of all medications

Allergen Immunotherapy Indications

- Indicated for management of IgE mediated disorders:
  - Allergic rhinoconjunctivitis
  - Allergen-induced asthma
  - Atopic dermatitis
  - Hymenoptera and fire ant hypersensitivity

Case 4

- He was initially seen in May
- He had typical physical exam findings of severe AR/AC
- He also had a dry persistent cough
- Spirometry showed mild reversible obstruction
- Given a short course of prednisone for symptomatic relief and started on inhaled corticosteroid and prn short acting bronchodilator