Common Allergic Diseases in Primary Care

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Objectives

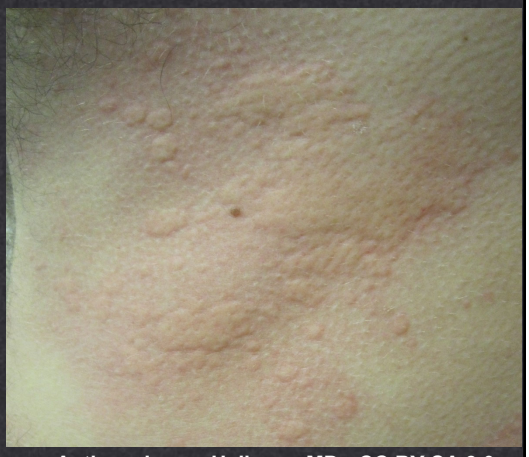
- Discuss allergic conditions that often present diagnostic or therapeutic uncertainty
- Outline initial approaches to evaluation and management
- Discuss first steps in treatment of these conditions
- Review criteria for referral to an allergist

Case #1

- 47 year old male
- History of hypothyroidism, hypertension
- Presents with 8 weeks of rash
- Diffuse, pruritic, erythematous
- Raised papules and confluent plaques
- Migratory, individual lesions last for 1-2 hours
- No new foods, topical products, medications

Case #1

- No relief with Benadryl
- Taking ibuprofen for joint pain associated with lesions
- Cell phone photo



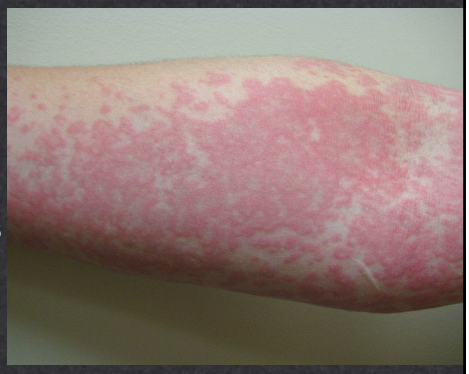
Urticaria

- Pruritic wheals
- Develop rapidly
- Central edema with surrounding erythema
- Generally last <24 hours
- Frequently associated with angioedema

Source: https://www.publicdomainpictures.net/en/view-image.php?image=213714&picture=stinging-nettle

Urticaria

- Acute (< 6 weeks)
  - Often with allergic trigger
  - Medication, food, environmental, illness
- Chronic (>6 weeks)
  - Majority symptomatic days
  - Chronic inducible (CindU)
  - Chronic spontaneous (CSU)



Author: James Heilman, MD - CC BY-SA 3.0

Chronic Inducible Urticaria

- Recurrent hives after specific stimuli
- Dermatographism
- Cold urticaria
- Cholinergic urticaria
- Delayed pressure urticaria
- Vibratory urticaria
- Lower rates of remission than spontaneous hives

Source: https://www.publicdomainpictures.net/en/view-image.php?image=293847&picture=treadmill-silhouette
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Chronic Spontaneous Urticaria (CSU)

- Hives independent of external stimuli
- Affecting 0.1-0.8% population
- Often presenting in 30s-50s
- High morbidity
- Majority self-limited
- Average duration of 2-5 years
- 30-50% with spontaneous remission at 1 year

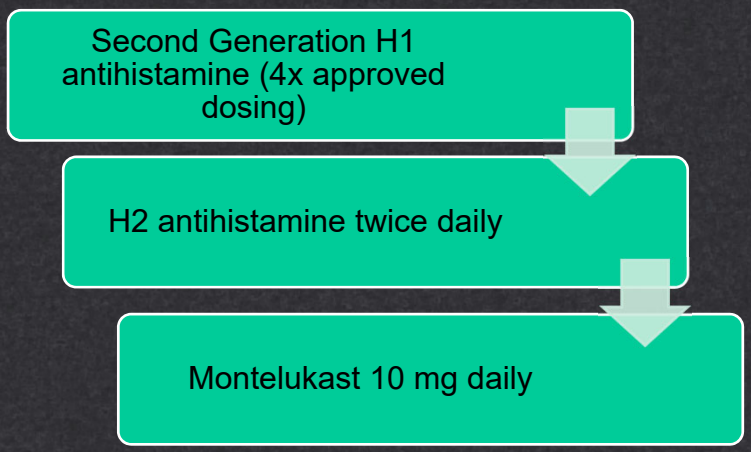
Chronic Spontaneous Urticaria

- Exacerbating factors
  - Physical - temperature, pressure, vibration
  - NSAIDs
  - Stress
  - Alcohol
  - Opiates
- Associated conditions
  - Autoimmunity – celiac, SLE, thyroid
  - Malignancy

Chronic Spontaneous Urticaria

- Evaluation
  - History and physical
  - Medications
  - Bruising, lesions lasting multiple days
  - CBC, CMP, CRP/ESR, TSH
  - G6PD function
  - Skin biopsy if vasculitic concern
- Testing low yield if no clear risk factors
- Skin testing for foods, aeroallergens not recommended

Treatment



- If not improving, consider cyclosporine, Xolair, dapsone

Our Patient

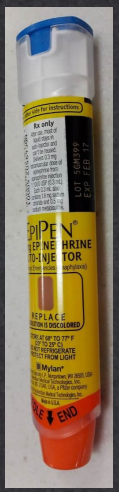
- Diagnosis of chronic spontaneous urticaria
- CBC, CMP, TSH, ESR/CRP unrevealing
- Cetirizine 20 mg BID, famotidine 20 g BID; ibuprofen held
- Modest improvement, montelukast added
- Improved, but still flaring twice weekly
- Starts Xolair 300 mg monthly with marked improvement
- At 12 months, no further significant flares
- Medications are held with no recurrence of symptoms

Chronic Urticaria Take Home Points

- Chronic urticaria require >6 weeks duration
- Generally without food or aeroallergen triggers
  - Food eliminations are unlikely to be beneficial
- Patients may have autoimmune background but often no clear trigger
- Generally require high dose antihistamines for adequate control
- Majority of patients with spontaneous resolution
- Referral to allergy if unresponsive to antihistamines, montelukast

Case #2

- 35 year old healthy female
- Recurrent abdominal pain, then hives and wheezing
- Has required treatment in ED, epinephrine injector provided
- Two episodes in the middle of the night
- No symptoms within 2 hours of meals
- No changes in diet, new medications



Case #2

- Food diary reviewed
  - Beef brisket, pork chops on evenings of episodes
- Anaphylaxis of unclear etiology
- Girl Scout troop leader
- Camping trip to Tennessee 4 months ago
- Had to remove tick from sock line

Source: https://www.publicdomainpictures.net/en/view-image.php?image=53766&picture=tent-by-the-lake

Another Medical Mystery

- 2005 – Severe anaphylaxis reported to cetuximab
- Monoclonal antibody for metastatic colorectal cancer
- Occurred with initial exposures
- Similar episodes reported throughout southeastern US
- Antibody analysis showed IgE toward oligosaccharide
- Galactose-alpha-1,3-galactose (alpha-gal)
- Severe allergic reactions generally attributed to proteins

Another Medical Mystery

- Concurrent reports of patients with repeated anaphylaxis
- Patients often spent large amount of time outdoors
- History of mammalian meat ingestion 3-5 hours prior
- Several reported tick bites in preceding months
- Similar geographic distribution to cetuximab patients

Source: https://www.publicdomainpictures.net/en/view-image.php?image=211453&picture=double-cheeseburger

Another Medical Mystery

- Alpha-gal IgE found in patients with delayed meat reactions
- Alpha-gal is found in non-primate mammalian meat
  - Symptoms with beef, pork, lamb, venison
  - No issues with fish, poultry
- Distribution of reactions similar to Lone Star tick
- Alpha-gal IgE titers increased post-tick bite

Source: CDC/ Michael L. Levin, Ph. D

Another Medical Mystery Solved

- Tick bite → alpha gal sensitivity → delayed mammalian meat reaction
- Increased deer populations may account for wider exposure
- Slow metabolism of alpha-gal may result in delayed symptoms
- Unclear sensitizing factor in tick bite
  - Saliva, contamination from prior blood meal?
- Reported internationally, variable tick species
- Alpha-gal IgE can drop if no repeat sensitization/bite

Alpha-gal allergy

- Has been reported outside of the southeastern US
- Can occur in adults and pediatric patients
- Consider diagnosis with recurrent unexplained hives or anaphylaxis
- Careful dietary history, particularly mammalian meat
- Reactions reported to organ meat, gelatin, milk
- Commercially available IgE for alpha-gal
- Patients should avoid mammalian meats, carry epinephrine
- Tick avoidance measures per CDC guidelines

Our Patient

- Alpha-gal allergy suspected given dietary history
- IgE to alpha-gal sent and found to be substantially elevated
- Recommended avoidance of all mammalian meats
- Instructed to carry epinephrine auto-injector at all times
- Significant reassurance in identifying trigger
- No recurrence of episodes

Alpha-gal Allergy Take Home Points

- Consider alpha-gal in patients with recurrent hives/anaphylaxis
- Atypical in causative trigger (carbohydrate) and timing
- Careful dietary history - mammalian meat several hours prior
- May not occur with each ingestion
- History of tick bite exposure
- Epinephrine auto-injector for all affected patients
- Identification of trigger and avoidance with significant quality of life benefit

Case #3

- 18 year old male, works in landscaping
- Digs into yellow jacket nest at work
- Stung multiple times on the hand, swells to elbow
- Also develops scattered hives, lip swelling
- No wheezing, vomiting, loss of consciousness

Case #3

- Co-workers call 911
- He is given epinephrine in the field
- Modest improvement in skin symptoms
- Does not require ED transport
- Treats with antihistamines at home
- Swelling resolves after 4-5 days
- Presents for recommendations on allergy testing

Stinging Insect Allergy

- At least 40 deaths attributed annually to sting reactions
  - Likely underestimate
- Potentially life threatening sting reactions
  - 3% of adults
  - 0.4-0.8% of children
- Identification of at-risk patients potentially life-saving

Source: Author: Jonathunder
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Stinging Insect Allergy

- Stinging insects belong to order Hymenoptera
  - Honeybee, yellow jacket, yellow hornet, white faced hornet, wasps, fire ants
- Most stings occur in defense of insects/nest
- Honeybee – barbed, single sting
- Wasps, hornets, yellow jackets – multiple stings

Author:- CC BY-SA 3.0

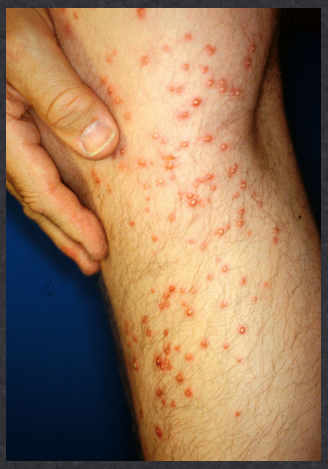
Source: https://en.wikipedia.org/wiki/Stinger#/media/File:Waspstinger1658-2.jpg

Stinging Insect Allergy

- Typical reaction – local swelling, pain
- Large local reactions (LLR)
  - Progressive gradual swelling contiguous with sting site
  - May last for up to 10 days
  - Often 10 cm or more, may cross joint lines
  - Can cause local compression, not typically dangerous
- Toxic reactions – may occur with multiple stings

Stinging Insect Allergy

- Fire ant stings
  - Sterile pustules can develop days after stings
  - Non-infectious
  - Self-limited



Source: USDA

Stinging Insect Allergy

- Cutaneous systemic reaction
  - Hives, angioedema, flushing, pruritus
  - Limited to skin (no tongue, throat involvement)
- Systemic reaction
  - Hives, angioedema
  - Wheezing
  - Nausea, vomiting, diarrhea
  - Hypotension, syncope

Stinging Insect Allergy

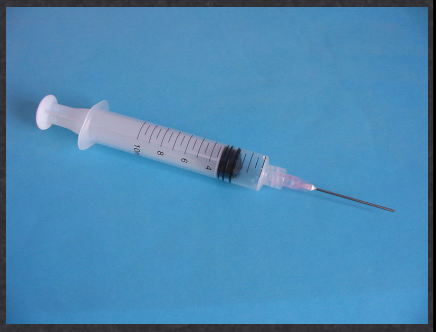
- Risk stratification
- Systemic reactors – up to 75% chance of future systemic
- Immunotherapy can drop risk to 5%
- Baseline tryptase level
- Referral for allergy testing
  - Percutaneous skin testing, intradermals, IgE testing
- Carriage of epinephrine injector x2 at all times
- Avoidance of ACEi, beta-blockers if possible

Stinging Insect Allergy

- Large local reactors – 4-10% chance of systemic
  - Generally not severe
- Cutaneous systemic reactors – low chance severe reaction
- Can be false positive tests, especially after sting
- Do not require epinephrine injectors
- No need for allergy testing, immunotherapy
- May be risk factors that prompt testing

Stinging Insect Allergy

- Testing and treatment for all available venoms
- 3-5 years unless high risk
  - Reaction to a shot/sting on treatment
  - Honeybee allergy
  - Severe initial reaction
  - Elevated tryptase
  - Frequent exposure
- Cluster and rush protocols available, safe



Our Patient

- Classified as cutaneous systemic reaction
- Discussion of low risk of severe systemic reaction
- Skin testing, IgE testing deferred
  - Risk of false positives, limited protective benefit of shots
- Epinephrine autoinjector not strictly indicated
  - He prefers to have this given his exposure

Our Patient

- Stinging insect avoidance measures
  - Avoiding eating outside
  - No straws/cans/open bottles outside
  - Avoid flowering plants
  - Cover trash cans
  - Avoid walking barefoot outside
  - Remove fallen fruit, pet feces
  - Monitor for nests in ground/bushes during yard work

Stinging Insect Allergy Take Home Points

- Careful history is crucial in risk stratification
  - Standard reaction
  - Large local reaction
  - Cutaneous systemic reaction
  - Systemic reaction
- Patients with systemic reactions or large local/cutaneous systemic reactions with risk factors warrant referral for testing
- Risk of false positive tests – only those considered for shots generally tested
- Allergy shots can be life-saving
- Prevention measures key, epinephrine for appropriate patients

Case #4

- 55 year old female with history of recurrent sinusitis
- History of penicillin allergy in childhood
- Developed a rash several days into treatment
- May have had some throat tightness
- Did not require ED visit
- No desquamation, mucosal ulceration, ocular involvement
- No re-exposure

Source: https://www.publicdomainpictures.net/en/view-image.php?image=24312&picture=medical-pills

Penicillin Allergy

- Approximately 10% of US population carries label
- More than 90% are not found to be allergic on evaluation
  - If reaction >10 years ago, risk severe allergic reaction 1-2%
- Inappropriate labeling associated with increased costs, risk
  - Side effects/cost of alternative treatments
  - Drug resistant organisms
  - Increased cost/length of hospital stays
  - Decreased cure rates
- IDSA, CDC advocate for de-labeling allergy

Penicillin Allergy

- Non-allergic
  - Family history, side effects
- Immediate hypersensitivity
  - Anaphylaxis
  - Histaminergic symptoms (hives, pruritus, swelling)
  - Rapid onset
- Delayed reactions
  - Morbilliform rash, delayed hives/angioedema
  - DIHS/DRESS, SJS/TEN, AGEP
  - Interstitial nephritis, hemolytic anemia, hepatitis

Penicillin Allergy

- If non-allergic, can re-challenge or de-label
- If strict contraindication, no testing available
  - SJS/TEN, hepatotoxicity, etc
- Reaction unclear or immediate allergy, referral
  - Skin testing
  - Graded dose challenge
  - Desensitization

Penicillin Allergy

- Skin testing
- Assessing for immediate IgE mediated allergy
- Performed with Pre-Pen (penicilloyl-polylysine)
  - Major allergenic determinant
- PCN G (10,000 units/ml)
  - Minor allergenic determinant
- Percutaneous testing
- Intradermal Testing

Author: National Institute of Allergy and Infectious Diseases

Penicillin Allergy

- Histamine and saline controls
- Tests read at 15 minutes
- Positive test – wheal ≥ 3 mm negative control
- Approximately 50% PPV
- Approximately 97-99% NPV
  - If false negative, reaction generally mild

Penicillin Allergy

Graded Dose Challenge	Desensitization
Rules out immediate allergy	Induces temporary tolerance
Low risk patients	Higher risk patients
Performed in office	ICU/stepdown setting
2-3 doses (1%, 10%, 90%)	10 or more doses (1:100,000)
Monitoring for 30-60 minutes	15 minutes between doses
Avoid antihistamines, beta blockers	Avoid antihistamines, beta blockers

Our Patient

- Unclear nature of initial reaction
- Brought into allergy clinic for skin testing
- Negative SPT and intradermal testing for Pre-Pen and PCN G
- Challenged with 10% and 90% of treatment dose of amoxicillin
- Monitored for 2 hours without reactivity
- De-labeled as penicillin allergic
- Sinusitis 3 months later, treated with Augmentin without issue

Penicillin Allergy Take Home Points

- Penicillin allergy is much less common than reported
- Unnecessary allergy labeling increases risks, costs
- Careful history can help stratify risk
  - Side effect, possible immediate allergy, absolute contraindication
- Penicillin skin testing is available, high negative predictive value
  - Validated testing not available for other antibiotics
- Graded dose challenges can help rule out allergy
- Desensitization can be used for treatment, but tolerance transient

Conclusions

- Hives are common and often non-allergic
- Can aggressively treat with antihistamines, montelukast
- Consider referral >6 weeks for additional workup and treatment
- Keep alpha-gal allergy on differential for recurrent hives/anaphylaxis
- History is critical for risk stratification of venom allergy
- Refer for systemic reactions or severe large local/cutaneous systemic
- Penicillin allergy frequently reported but rare
- If unable to de-label, refer for skin testing, graded challenge

References

Viegas LP, Ferreira MB, Kaplan AP. The maddening itch: an approach to chronic urticaria. J Investig Allergol Clin Immunol 2014; 24(1):1-5.

Saini S. Chronic urticaria: Clinical manifestations, diagnosis, pathogenesis, and natural history. www.uptodate.com. Bochner BS, Callen J, Feldwig AM eds. Updated 10/25/18.

Maurer M, Fluhr JW, Khan DA. How to approach chronic inducible urticaria. *J Allergy Clin Immunol Pract*. 2018;6::1119-1130.

Saini SS, Kaplan AP. Chronic spontaneous urticarial: the devil's itch. *J Allergy Clin Immunol Pract.* 2018;6:1097-1106.

Khan DA. Chronic urticaria: Treatment of refractory symptoms. www.uptodate.com. Saini S, Callen J, Feldwig AM eds. Updated 5/10/19.

Khan DA. Chronic urticaria: Standard management and patient education. www.uptodate.com. Saini S, Callen J, Feldwig AM eds. Updated 2/19/19.

References

Steinke JW, Pltts-Mills TAE, Commins SP. The alpha-gal story: lessons learned from connecting the dots. *J Allergy Clin Immunol*. 2015;135:589-96.

Wilson JM, Schuyler AJ, Workman L, et al. Investigation into the α-gal syndrome: characteristics of 261 children and adults reporting red meat allergy. *J Allergy Clin Immunol Pract*. 2019;7:2348-58.

Golden DBK, Demain J, Freeman T, et al. Stinging insect hypersensitivity: A practice parameter update 2016. *Ann All Asthma Immunol*. 2017;118:28-54.

Macy E, Romano A, Khan D. Practical management of antibiotic hypersensitivity in 2017. *J Allergy Clin Immunol Pract*. 2017;5:577-86.

Solensky R. Penicillin skin testing. www.uptodate.com. Phillips EJ, Feldwig AM, eds. Updated 12/7/18.