

Approach to Urticaria, Angioedema, and Drug Allergy in Primary Care

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Disclosures

- Financial disclosures
 - Nothing to disclose
- Off label medication use
 - High dose antihistamines for chronic urticaria

Learning objectives

- Understand the relative contribution of allergies to urticaria/angioedema syndromes
- Differentiate the clinical presentations and disease spectrum of uncomplicated vs. complex urticaria/angioedema
- Adopt a practical approach to evaluation and attribution of allergies to common medications

Case

- 46 yo woman, h.o HTN, DMII (diet controlled), hypothyroidism
 - CC: 4 weeks of hives
 - Arms, outer thighs, belly, lower neck
 - Last 24 hours, new lesions appear, no bruises
 - Very pruritic, worse at night
 - Claritin, Zantac, Benadryl (latter→drowsiness) with partial relief of itching, not hives; <5 hive-free days in last month
 - Occasional sensation of lip swelling

Case

- Self-limited similar 4-week episode 10 years ago
- Denies dyspnea, throat tightness, wheeze
- ? Association with lobster
- ROS:
 - No change in bowel habits, heat/cold intolerance, arthralgias, new cleaning products (personal or household)

Case

- PMHx
 - HTN on lisinopril
 - Hypothyroidism – enlarged thyroid noted on PE in 1984 → inc. TSH → synthroid (recently 0.1)
 - DMII – diet and exercise controlled
- NKDA, NKFA
- Not on NSAIDs

Case

- PE
 - 99.1 124/78 68
 - Appears well
 - Visible wheals on lower arms and lower neck, itching legs
 - o/w unremarkable



Urticaria and angioedema

- Urticaria: Erythematous, blanchable, circumscribed, edematous papules involving the superficial portion of the dermis
 - Pruritic as a rule (histamine effect)
- Angioedema: Similar to urticaria, but less well circumscribed, involves deeper portion of dermis and/or subcutaneous tissues.
 - Typically more tender than pruritic – dull discomfort

Urticaria



Angioedema



Prevalence of overlap

- 50% have only urticaria
- 40% of patients have both urticaria and angioedema
- 10% have only angioedema
 - Angioedema without urticaria implies different diagnostic possibilities and risk

Saini, JACI IP, 2018

Sibbald, Int J Dermatol, 1991

Angioedema

- With urticaria – mast cell (histamine) mediated
 - Allergic reaction
 - » Foods
 - » Drugs (includes contrast media)
 - » Latex
 - Idiopathic/autoimmune
- Without urticaria – could be complement/bradykinin mediated
 - (Allergic reaction)
 - ACEI-induced, *usually* in first six months
 - Consider hereditary/acquired angioedema
 - Defect in C1 esterase inhibitor – quantitative & qualitative
 - Workup: C2, C4, C1est inhib quant/functional, (CH₅₀ OK; C3 no use)

Acute Urticaria/Angioedema

- Self-limited, with any given lesion resolving within hours. Acute episodes usually recur/persist for less than 6 weeks.
- Biopsy: dilation of cutaneous blood and lymphatic vessels, minimal or absent inflammatory cellular perivascular infiltrate.
- Mast cell activation and degranulation important in pathogenesis.
- 15-20% of individuals will have U/A at some point in their lives.

Khan, Allergy Asthma Proc, 2008

Acute U/A assessment: Hx

- Time course, activities, medications, infection, food ingestion, stinging insects
- Ask specifically about recent viral illness, NSAIDs, ACE inhibitors, herbal remedies, food supplements, shellfish, fish, strawberries, nuts
- Pruritis vs. tenderness, systemic symptoms
- Past history of hives, anaphylaxis, asthma, beta-blocker
- Family history, occupational history (latex)
- *Environmental allergies atypical as trigger of U/A*

U/A assessment: PE

- Vital signs
- Skin vs. mucosal involvement
- Urticaria and/or angioedema?
- Angioedema limited to face/oropharynx
- Stridor/wheezing

Laboratory evaluation

- Minimal for acute urticaria/angioedema
- Except:
 - Allergen-specific IgE for suspected food culprit (ImmunoCAP, others)
 - Skin testing for venom if *generalized* urticaria or anaphylaxis
 - (Large local reaction – low risk)
 - More severe cases
 - CBC and diff
 - LFTs
 - C4

Chronic Urticaria/Angioedema

- Daily or almost daily for more than 6 weeks
- Twice as common in women as in men
- 20% of those who have urticaria for more than 6 months still have urticaria 5 years later
 - But 80% won't...typical duration 2-5 years
- Urticaria and angioedema occur together in almost half of affected patients
- Wheals that last more than 24 hours raise possibility of urticarial vasculitis

Bernstein, J Allergy Clin Immunol, 2014

Saini, J Allergy Clin Immunol IP, 2018

Chronic urticaria – assessment: History

- How long have you had hives?
- Have you identified any food triggers of the hives? ASA? NSAIDS?
- Do individual hives last more than 24 hours? **More than 48 hours?**
- **Do you see bruises when the hives go away?**
- Do hives occur at pressure points, such as waist band, shoulder strap, shoes?
- Any joint pains, swelling or stiffness? Raynaud's?

Chronic urticaria: Classification

- Physical urticarias; 'Inducible'
- Chronic idiopathic urticaria (ca. 90% CU)
 - New terminology: Chronic *spontaneous* urticaria)
- Urticaria pigmentosa (mastocytosis)
- Urticarial vasculitis
 - Hypocomplementemic
 - Nonhypocomplementemic
- Ca. 5%: food, medication

Moolani, F1000 Research, 2016
Kaplan, NEJM, 2002

Physical/'Inducible' urticarias

- Dermatographia: wheal and flare induced by light stroking, can be symptomatic
- Cholinergic: associated with exercise or hot shower, smaller wheals, more prominent flare
- Cold: itchy pale or red swelling, "ice cube test"
- Pressure/'Delayed pressure urticaria': large painful or itchy swelling, onset may be delayed and may take >24 hours to resolve, steroids uniquely helpful
- Solar, aquagenic: (<5%)

Maurer, JACI IP, 2018

Dermatographia



Cholinergic urticaria



Cold urticaria – Ice cube test



Cold urticaria – Ice cube test



Urticaria occurs upon rewarming

Cold urticaria



The menu...



Dermatographia



Cold (ice cube test)



Cholinergic (chest)



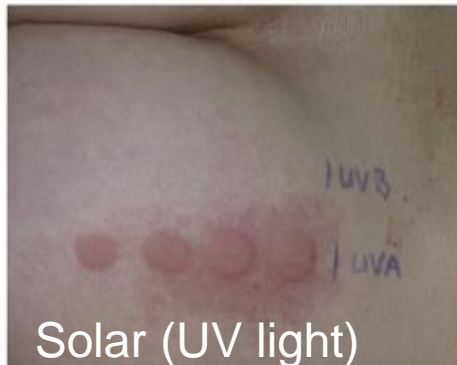
Delayed pressure



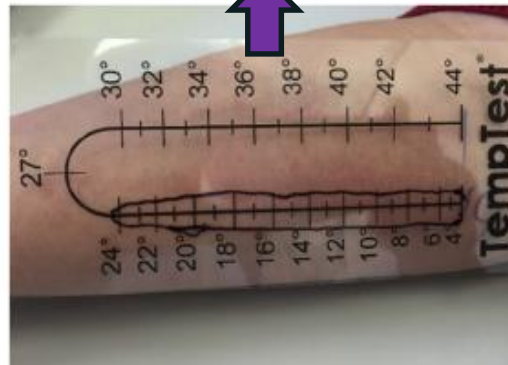
Cold (TempTest)



Cholinergic (arm)



Solar (UV light)



General advice: Physical urticaria

- Avoid heat
- Avoid ETOH
- Avoid ASA, NSAIDs (also applies to chronic spontaneous urticaria)
- Avoid nonspecific mast cell activators (tomato, citrus, strawberries, shellfish, chocolate)
- Use emollients

Chronic urticaria: Laboratory investigation

- Controversial as <5% of chronic urticaria is related to systemic disease
 - Urticarial vasculitis – different appearance/duration of lesions
- Health screen for reassurance; r/o eosinophilia
- TSH, antithyroid peroxidase Ab, antithyroglobulin Ab
- C3/C4, if suspicious of urticarial vasculitis
- ESR will be elevated in 1/3, not specific
- ANA only if clear reason to suspect SLE
- ?Hepatitis B and C screen, cryoglobulins

Moolani, F1000Research, 2016

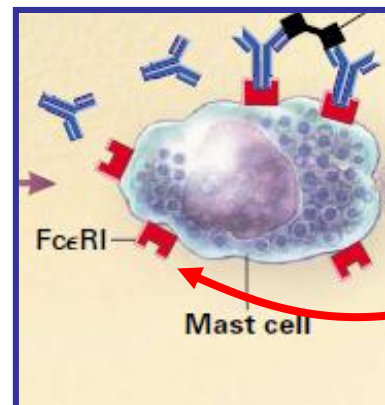
Khan, All Asth Proc, 2008

Case... continued

- Labs:
 - CBC with diff – mild anemia, 2% eos
 - LFTs normal
 - TFTs
 - T4, T3U, Free T4 index normal
 - TSH 11
 - Thyroglobulin Ab: 3.3 IU/ml (<1)
 - Thyroid peroxidase Ab 504 IU/ml (0-2)

Case

- Recurrent chronic urticaria related to autoimmune thyroid disease
 - Typically not related to clinical course of thyroid dysfunction nor treatment
 - Treatment similar to chronic spontaneous urticaria
 - May have more prominent symptoms that w/o autoAb
 - Some autoAbs likely have IgE receptor cross-reactivity



Sabroe, J All Clin Immunol, 2002

Chronic urticaria: Standard treatment

- Oral sedating antihistamines (act quickly)
 - diphenhydramine 25-50 mg, up to 4 times daily
 - hydroxyzine 25-50 mg, up to 4 times daily
- Oral nonsedating antihistamines (preferred)
 - cetirizine 10 mg, once or twice daily
 - loratadine 10 mg, once or twice daily
 - fexofenadine 60 mg, twice daily, or 180 mg/d
- Combinations of oral antihistamines may be helpful, e.g. cetirizine QD/BID with hydroxyzine qHS
- Oral steroids – brief course e.g. pred 40mg/d x 5d
 - Just to ‘get started’ if significant Sx – avoid repeated courses...
- If ineffective, contact or refer to Allergist/Immunologist

Angioedema

- With urticaria – mast cell (histamine) mediated
 - Allergic reaction
 - » Foods
 - » Drugs (includes contrast media)
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ACE Inhibitor-induced angioedema

- Complicates 0.2-0.7% patients taking ACEI
 - (Cough: 5-35%)
- Angiotensin converting enzyme inactivates bradykinin and substance P. Increased levels of these mediators thought to cause angioedema.
- Typical presentation: oral angioedema without urticaria, responds poorly to epinephrine and antihistamines, may occur intermittently.
- Usually resolves within a week of discontinuation, but recurrent angioedema can occur up to 1 month later

Bezalel, Am J Med, 2015

Hedner, BMJ, 1992

ACEI induced angioedema

Can you use another ACEI or ARB?

- Class effect, so no go with another ACEI
- ARBs?
 - There are reports of ARB reactions in patients with ACEI-induced angioedema
 - Some reports of ARB-induced angioedema ‘alone’
 - Still in minority, ‘risk/benefit’ decision based on underlying indication

Bezalel, Am J Med, 2015

Haymore, Ann All Asth Immunol, 2008

Nykamp, Ann Pharmac, 2007

Other non histamine-mediated angioedema

- Do NOT respond to Epi/anti-histamines (ref ACEI)
- Hereditary
 - Autosomal dominant (but about 15% new mutations)
 - Defects (quant. or qual.) in C1 esterase inhibitor cause unchecked bradykinin production and activation of classic complement pathway
 - Adolescent presentation, M=F, no racial predisp.
 - 'Crises': airway, skin, abdominal
- Acquired
 - Assoc. with rheumatologic dz, hematologic malignancy, or circulating anti-C1est inhibitor antibodies
- Refer...

Longhurst, Lancet, 2012
Nzeako, Arch Intern Med, 2001

Drug reactions

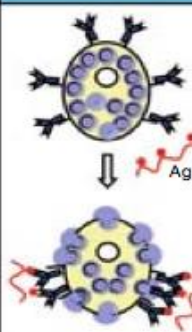
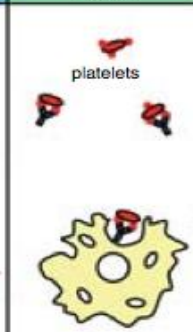
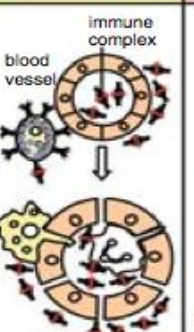
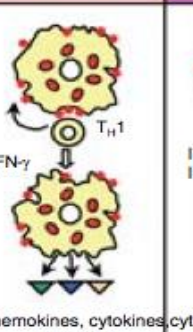
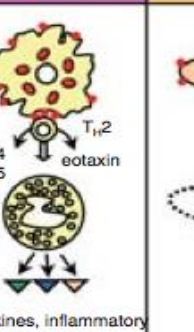
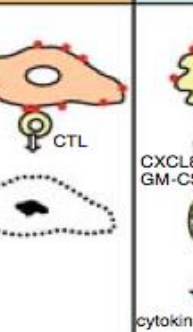
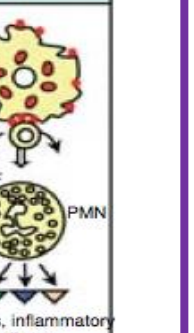
- Drug ‘Allergy’ vs. adverse reaction/ASE
 - Allergy vs. intolerance (can apply to foods or meds – e.g. lactose, NSAIDs → dyspepsia)
 - A drug allergy is a reaction/side effect that in most cases means the patient cannot safely take the medication regardless of dose.
 - Reproducible reaction, typically not ‘dose-related’
 - » Diphenhydramine causing somnolence
 - » ‘red man syndrome’ from vanco – dose *rate*-related
 - Not necessarily immune mediated – e.g. INH → liver injury
- A drug allergy is easy to enter, hard to remove!

Main classes of drug allergy

- Immediate-type
 - Ab (IgE) or direct activation of mast cells and basophils. (Abx (Ab), contrast (direct))
 - Anaphylaxis, urticaria, angioedema
- Delayed
 - Typically immune-mediated
 - Maculopapular rash
 - Severe, potentially fatal reactions a/w skin eruption
 - » DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms – liver>renal>pulmonary)
 - » Stevens-Johnson Syndrome
 - » TEN – Toxic Epidermal Necrolysis

Mucosal involvement

Antibody mediated hypersensitivity reactions (I-III) and delayed type cell/cytokine mediated hypersensitivity reactions (IV a-d)

	Type I	Type II	Type III	Type IV a	Type IV b	Type IV c	Type IV d
Immune reactant	IgE	IgG	IgG	IFN γ , TNF α (T _H 1 cells)	IL-5, IL-4/IL-13 (T _H 2 cells)	Perforin/ GranzymeB (CTL)	CXCL-8, GM-CSF (T-cells)
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Antigen presented by cells or direct T cell stimulation	Antigen presented by cells or direct T cell stimulation	Cell-associated antigen or direct T cell stimulation	Soluble antigen presented by cells or direct T cell stimulation
Effector	Mast-cell activation	FcR ⁺ cells (phagocytes, NK cells)	FcR ⁺ cells Complement	Macrophage activation	Eosinophils	T cells	Neutrophils
							
Examples	Allergic rhinitis, asthma, systemic anaphylaxis	Some drug allergies (e.g., penicillin)	Serum sickness, Arthus reaction	Tuberculin reaction, contact dermatitis (with IVc)	Chronic asthma, chronic allergic rhinitis, Maculopapular exanthema with eosinophilia	Contact dermatitis, Maculopapular and bullous exanthema, hepatitis	AGEP, Behcet disease

Pichler W.J. Delayed drug hypersensitivity reactions, Ann. Int. Med. 2003

Drug allergy – Evaluation/options

‘Highlights’

- Immediate

- Only 10-15% of patients who report PCN allergy have positive skin testing to PCN determinants (all comers...)
- If high risk, find an alternate class – if not available, these reactions are typically amenable to desensitization in ICU
 - Mechanism – unclear ?gradual mast cell ‘exhaustion’
- MUST continue medication to maintain desensitized state – antibiotics, ASA, chemo, etc.
- There are options for testing/treatment, especially in β -lactam antibiotics (e.g. possible reaction to amox, what about cefepime?)
 - 10% dose, observe, 90%. If no reaction: tolerant (not desensitization)
 - Does *not* necessarily require upgrade in level of care (Stepdown, MICU)

- Delayed

- Need to find alternate class – skin testing not applicable, nor is desensitization typically effective
 - » Exception – some protocols for sulfonamide Abx desensitization
 - » NEVER rechallenge/test to drug that has caused SJS/TEN

COVID-19 (mRNA) Vaccines

...a few bullet points

- Severe immediate-type reaction rates are low ($\sim 5/10^6$), slightly more common amongst individuals with prior severe allergic reactions to other meds
- Known PEG or polysorbate allergy (eg miralax, GoLyteLy, Pevnar) warrants caution but role of testing unclear as PEG quantities are low in vaccine
- Individuals with non-severe or delayed reactions can typically tolerate future doses
- *?Shift in approach – ‘treat through’ non life-threatening reactions rather than reflexively label as allergic*
 - Significant increase in shared decision-making with patients
- Practical approach – if unsure, a quick call to friendly allergist can resolve concerns efficiently.

Summary

- Environmental allergies are an unusual cause of urticaria/angioedema.
- The concern/risk ratio in urticaria/angioedema favors the patient (and the clinician...).
- Unexplained isolated recurrent angioedema warrants further evaluation and referral.
- Patients with reported distant PCN allergy are likely tolerant and can typically be given 3rd and 4th generation cephalosporins with monitoring and/or as graded challenge.

Some helpful points when evaluating patients with suspected allergy

'Choosing Wisely...'

- With patients c/o 'allergies', resist urge to send broad panels of *in vitro* tests, as the risk of FP is high. Contact your local friendly allergist for guidance, or limit to specific class of allergens *with clear clinical SSx. of a reaction* (eg grass, shellfish)...
- Avoid interpretation of broad testing panels brought in by patient from alternative medicine providers, especially IgG/IgG₄ testing.
 - IgG generation is a normal part of tolerance (and *increases* with allergy shots).
 - Vague Sx can lead to 'putting the bullseye around the arrows'
- Don't go down rabbit hole of identifying allergen by history (or testing) in patients with unexplained spontaneous urticaria. 'Bullying' eg Abx for URTIs!
- Specific IgE testing is rarely useful in determining trigger in adult patients with atopic dermatitis that flares. Foods are more common triggers in children and sIgE not always helpful there either.
- Shellfish allergy is NOT a contraindication to receiving iodinated contrast formulations. No validated test for contrast allergy. Reactions CAN occur with MRIs.
- Do NOT withhold useful sulfonamide-containing medications in patient with sulfonamide antibiotic allergy. Sulfa moiety on these medications is different from those on antibiotics and there is minimal cross-reactivity.
 - Furosemide, HCTZ, sulfonyleureas, celecoxib, ARV (protease inhibitors) ...
 - Dapsone (a sulfone) *may* have cross reactivity and test-dosing is reasonable (** ✓ for G6PD def **)
 - If reaction was SJS or similar severe reaction, consult with pharmacists/allergist as there are concerns with medications in the same sulfonamide class
 - Non-Abx sulfonamide medications leading to reactions *can* have cross reactivity within class.

Questions/Discussion

Considerations in referring to an Allergist

<u>Condition/Symptom</u>	<u>Indication</u>	<u>Rationale</u>	<u>Testing pre-referral</u>	<u>Referral back to Primary Care</u>
Anaphylaxis	- Uncertain trigger, need for emergency treatment	- Risk factor identification - Define specific testing as indicated - Patient Education	Tryptase within 12 hours of reaction	Trigger ID'd No recurrent episodes
Recurrent infections	- Recurrent/unresponsive infection without known congenital or acquired immunodeficiency	- Differentiate potential contributor(s) to ?ID - Specific workup for suspected/likely causes	- CBC with diff - Serum immunoglobulins with IgG subclasses - CXR	- Workup complete - Suppressive regimen defined if indic.
Hives/angioedema	- Sx >4 weeks or unresponsive to antihistamines - Family history of angioedema	- Determine cause if applicable, refine workup - Optimum management	Rx: loratidine or cetirizine 10mg po twice daily	Variable Natural Hx of urticaria defined, if possible
Rhinitis/sinusitis	- Change in/progressive Sx pattern - Perennial Sx failing convent. Rx - Prolonged loss of taste/smell	- Determine indications for and nature of testing - Optimum management - Secondary referral prn	NO sinus CT unless chronic anosmia or Sx of congestion primarily unilateral	Variable
Dermatitis/Rash**	- Difficult/progressive atopic exzema - Suspected contact sensitivity - Occupational rash - ** New non urticarial rash without triggers - first refer to Dermatology**	- Trigger identification and control measures - Optimum management - Secondary referral prn - ** Majority of non-triggered rashes are primary dermatoses**	Rx: Defined trial of low-mid potency topical steroids	Variable