Urticaria

Goal: Provide PCPs with initial workup algorithm for urticaria, including when to refer.

Inclusion Criteria

- Raised, red, itchy, pruritic, fleeting plaques

All urticaria is caused by release of histamine, but histamine release is not always IgE-mediated (type I allergic reaction).

* Consider the following categories of potential culprits of IgE-mediated allergic reactions:
  - Medications
  - Foods & food additives
  - Insect bites and stings
  - Latex
  - Blood products

Consider the following categories of potential culprits of direct mast cell activation (non-IgE mediated):
  - Narcotics (including codeine and dextromethorphan)
  - Anesthetic muscle relaxants
  - Vancomycin
  - Radiocontrast medium
  - Foods (tomatoes and strawberries especially)
  - Stinging nettle plant

NSAIDS (e.g. aspirin, naproxen, ibuprofen) can cause urticaria due to IgE-mediated allergic reactions or due to non-allergic mechanism (due to underlying abnormalities in arachidonic acid metabolism).

Diagnostic Workup

- Does the patient truly have urticaria? This includes 3 components:
  1) Area of central swelling, usually with surrounding erythema
  2) Itchiness
  3) Fleeting/migrating individual wheals (usually lasting 30 mins-24 hrs)

- Signs/symptoms concerning for anaphylaxis (involvement of at least 2 organ systems)?

- Urticaria preceded by exposure to potential identifiable trigger* within 2 hours of onset?

- Symptoms of acute viral or bacterial infection? (e.g. respiratory illness, UTI, otitis media)

- Travel to endemic area for parasitic infections, or found to have peripheral blood eosinophilia?

Consider these alternative conditions that may be mistaken for urticaria.

Non pruritic:
  - Auriculotemporal syndrome
  - Sweet syndrome

Pruritic:
  - Eczema
  - Contact dermatitis
  - Drug eruptions
  - Insect bites
  - Bullous pemphigoid
  - Erythema multiforme minor
  - Plant-induced reactions (e.g. poison ivy, poison oak)
  - Viral exanthem

Administer epinephrine, send to ER. Use ASAP score to guide decision making if diagnosis of anaphylaxis is unclear. After ER visit, refer to allergist.

Refer to allergist for workup of IgE-mediated allergic reaction or non-IgE mediated mechanism (through direct mast cell activation).

Diagnostic workup for infections targeted to current symptoms, treat accordingly.

  - Infections are associated with over 60% of pediatric acute urticaria cases. Mechanism is through autoimmune response to the infection, in which IgG develops against mast cells and triggers degranulation. Do not label the patient with an allergy to the drug! When child is well, either administer an observed dose in the office and watch for 1 hour, or refer to allergist for definitive allergy testing.

Order stool O&P.
  - Infections with *Ancylostoma*, *Strongyloides*, *Filaria*, *Echinococcus*, *Trichinella*, *Toxocara*, *Fasciola*, *Schistosoma mansoni*, and *Blastocystis hominis* have all been associated with urticaria.

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Acute urticaria: present <6 weeks.
Chronic urticaria: present most days of the week for >6 weeks.

In many patients, no specific etiology for urticaria can be identified. Acute urticaria is more likely to have an identifiable etiology than chronic urticaria.
Diagnostic Workup Cont. (Less Common Causes)

Urticaria associated with physical stimuli (e.g., cold exposure, sudden changes in body temperature, pressure or vibration against the skin, exercise, exposure to sunlight)?

Yes

Physical (inducible) forms of urticaria probably result from heightened sensitivity by the mast cell to environmental conditions, although the exact pathogenesis is unknown.

No

Diagnostic testing (challenge procedure) is not required, but can be helpful for confirming the trigger. Refer to allergy or dermatology if considering confirmatory diagnostic testing or if symptoms are refractory to exposure avoidance and antihistamines. (See "Physical urticarias" page for table of diagnostic tests and treatment suggestions for refractory symptoms.)

Urticaria began 2-3 weeks after exposure to a new medication?

Yes

Consider serum sickness if patient has fever. Another potential clue: individual urticarial lesions are typically longer lasting (days to weeks) in serum sickness than in other etiologies of urticaria.

No

Urticaria onset correlates with starting a progesterone-based medication, or occurs cyclically during latter half of menstrual cycle?

Yes

There are rare reports of progesterone-associated urticaria. Consider switch to a different contraceptive (if applicable), or treat symptomatically.

No

Urticaria associated with systemic disorders is usually recurrent, persistent, and relatively difficult to treat.

Are individual lesions painful, long-lasting (longer than 24 to 36 hours), appear purpuric or ecchymotic, or leave residual ecchymosis or hyperpigmentation upon resolution (in the absence of trauma from scratching)?

Yes

Positive Darier's sign (development of localized urticaria and erythema within ~5 mins following rubbing, scratching, or stroking skin) by patient history? (Do not attempt to reproduce this in clinic.)

Yes

Order diagnostic labs for systemic condition of concern. Consider calling SCH provider line (206-987-7777) to discuss case with rheumatologist or dermatologist on call prior to ordering labs.

No

Urticaria associated with systemic disorders such as lupus, rheumatoid arthritis, celiac disease, thyroid disease, or other autoimmune disease?

Yes

If urticaria present <6 wks, treat symptomatically (see Treatment page). Two-thirds of cases of acute urticaria will resolve. If persistent or recurrent over >6 wks, continue to next page.

No

Call dermatology through SCH provider line to discuss potential biopsy; this could be urticarial vasculitis.

- Urticarial vasculitis can be may be a cutaneous or systemic disease, and it may occur in the setting of another rheumatologic disorder or rarely, a malignancy. It always requires biopsy for diagnosis (looking for leukocytoclastic vasculitis).

* Urticarial vasculitis is extremely rare in children

Facial swelling and lymph node enlargement may also be seen. This is a type III hypersensitivity and occurs after exposure to foreign proteins such as antivenoms, anti-toxins, anti-thymocyte globulin and chimeric monoclonal antibodies. Consult allergy and nephrology for further evaluation.

No

Order diagnostic labs for systemic condition of concern, such as lupus, rheumatoid arthritis, celiac disease, or other autoimmune disease. Consider calling SCH provider line (206-987-7777) to discuss case with rheumatologist or dermatologist on call prior to ordering labs.
Urticaria present or recurrent over a period of >6 weeks?

Yes

Routine lab tests are unlikely to be revealing when the clinical history does not suggest an underlying allergic etiology or the presence of systemic disease. Guidelines suggest initially obtaining a limited set of laboratories to screen for the systemic disorders that may involve urticaria:

1. CBC with diff
   - Eosinophilia should prompt evaluation for an atopic disorder or parasitic infection.
2. ESR or CRP
   - Significant elevations in ESR or CRP should prompt further investigation for systemic diseases, such as autoimmune, rheumatologic, infectious, or neoplastic diseases. Such an evaluation may include measurement of antinuclear antibodies, cryoglobulins, hepatitis B and C serologies, total hemolytic complement, and a serum protein electrophoresis. If high ESR or CRP, refer to rheumatology or dermatology rather than ordering these subsequent labs in the primary care setting.
3. Consider TSH +/- antithyroglobulin and antimicrosomal antibodies
   - Autoimmune thyroid disease is uncommon in children with chronic urticaria, and thyroid testing is not recommended by international guidelines as part of workup. However, urticaria can rarely be associated with autoimmune thyroid disease, so some clinicians choose to check these labs as part of the workup.

### Identifiable causes of urticaria

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<td>Abdominal</td>
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<table>
<thead>
<tr>
<th>IgE-mediated allergic cases</th>
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<tbody>
<tr>
<td>Medications</td>
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<tr>
<td>Insects</td>
</tr>
<tr>
<td>- Stinging (insect stings, bees, wasps, hornets, fire ants)</td>
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<tr>
<td>- Biting (mosquito, leeches, lice)</td>
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<tr>
<td>Foods</td>
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<tr>
<td>- Blood products (artificial transfusion reactions)</td>
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<tr>
<td>- Latex (contact or inhaled)</td>
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<tr>
<td>- Contact allergens (animal saliva, raw foods)</td>
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<tr>
<td>- Aerosolized (inhalation)</td>
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<td>- Food additives</td>
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<tr>
<th>Direct mast cell activation</th>
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<tr>
<td>Nociceptors</td>
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<tr>
<td>- Muscle relaxants (e.g., succinylcholine)</td>
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<td>- Radiographic agents</td>
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<tr>
<td>- Nerve conduction</td>
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<table>
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<tr>
<th>Physical stimuli</th>
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<tr>
<td>Dermatographism</td>
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<tr>
<td>Delayed pressure</td>
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<tr>
<td>Cold</td>
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<tr>
<td>Cholinergic</td>
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<tr>
<td>Vibratory</td>
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<tr>
<td>Aquagenic</td>
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<tr>
<td>Solar</td>
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<td>Exercise/tension</td>
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<tr>
<th>Miscellaneous mechanisms</th>
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<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
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<tr>
<td>Serum sickness</td>
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<tr>
<td>Transfusion reactions (distinct from IgE-mediated reactions)</td>
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<tr>
<td>Herxheimer associated (prosthetics)</td>
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<tr>
<td>Shivering, malaise</td>
</tr>
</tbody>
</table>

IgE: immunoglobulin E.
Symptomatic Treatment

Start here:
1) Avoidance of trigger, if identified.
2) Long-acting, non-sedating H1 antihistamine (cetirizine, levocetirizine, loratidine, or fexofenadine are all appropriate choices).

Symptoms improved?

Yes

Dosing of non-sedating H1 antihistamine can be escalated to BID, TID, or even QID. Some pediatric patients with chronic urticaria may need doses up to 4 times the standard effective dose to be effective. This dosing is not approved by the FDA and risks (mild increase in incidence of somnolence and greater risk of adverse effects such as dry mouth and constipation) and benefits (improved control of urticaria) should be reviewed with caregivers.4

No

Symptoms improved?

Yes

Trial one or more of the following interventions (no head-to-head studies exist comparing these)9 while continuing the H1 antihistamine:
- Prednisone burst (1 mg/kg/day) for 3-5 days. No taper needed.5
- H2 antihistamine (weak evidence)
- Leukotriene modifiers (e.g. montelukast; weak evidence, be aware of black box warning for suicidality)

No

Symptoms improved?

Yes

Referral to allergist or dermatologist for consideration of Omalizumab, a monoclonal antibody that targets IgE, approved for age 12 years+ for chronic urticaria. Dosing is 150-300mg Q 4 wks.4

No

Continue treatment for the duration of time that symptoms had been present prior to achieving improvement.
(E.g. if urticaria had been present for 3 days, continue current effective treatment x3 days before trialing off. If urticaria had been present 1 month or longer, wait 1 month before trialing off. The exception is prednisone, which should only be given for 3-5 days regardless of preceding symptom duration.)
If urticaria resumes upon trial off of antihistamines and/or leukotriene modifiers, resume these medications and wait the same amount of time before trialing off again.

Patients with history of anaphylaxis should be prescribed an EpiPen. Patients with urticaria without an identifiable trigger and without anaphylaxis should not be prescribed an EpiPen.
The algorithm below is copied from Seattle Children’s Anaphylaxis clinical standard work pathway: 

1. If the patient is clearly in anaphylaxis:
   GIVE EPINEPHRINE FIRST
   DO NOT WAIT TO SCORE THE PATIENT

2. Use the score:
   a) To aid in the diagnosis of anaphylaxis and need for epinephrine, for patients where the diagnosis is unclear.
   b) To obtain a symptom score, sometimes after treatment is initiated, in order to track symptom severity over time.

**Actions based on Anaphylaxis Score:**

**SCORE 1 - 4 pt.** Acute anaphylaxis may still be developing. Routine use of epinephrine is not indicated, but may be appropriate if symptoms are recent and progressing rapidly, or if indicated per the patient’s anaphylaxis action plan. Place on monitors, observe closely in an environment with staff trained to monitor and treat for anaphylaxis, prepare to treat if needed.

**SCORE ≥ 5 pts.** Acute anaphylaxis is very likely. In the appropriate clinical context, epinephrine is indicated.

This score is only a guide. The decision to give epinephrine is a clinical decision that may vary by patient.

**ANAPHYLAXIS SCORE ASSISTING PROVIDERS (ASAP)**

* Score only current symptoms and signs, unless 1 hour time frame is noted (skin, abdominal) *

<table>
<thead>
<tr>
<th>ASPECT</th>
<th>0 Absent</th>
<th>1 Mild</th>
<th>2 Moderate</th>
<th>3 Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>SKIN &amp; MUCOSA</td>
<td>No signs or symptoms</td>
<td>Mild itching: 1-3 hives; flushing, erythema or hives that resolved in past hour after antihistamine</td>
<td>Severe itching: &gt;3 hives; flushing, erythema or raised rash (patchy or onset over &gt;1 hour); face or lip edema, angioedema, red eyes</td>
<td>Rapid <strong>WITHIN THE PAST 1 HOUR</strong> whole body flushing, erythema or hives; tongue or introral edema</td>
</tr>
<tr>
<td>RESPIRATORY</td>
<td>No signs or symptoms</td>
<td>Occasional sneeze or cough; mild nasal congestion or runny nose; throat tickle; hoarseness</td>
<td>Frequent sneezing or cough; severe nasal congestion or runny nose; subjective trouble swallowing or breathing; throat or chest tightness; chest pain; coarse breath sounds</td>
<td>Stridor, wheeze, drooling or not swallowing, snuff position, dysnea, diminished breath sounds, hypoxia</td>
</tr>
<tr>
<td>CARDIOVASCULAR</td>
<td>No signs or symptoms, normal pulse, no hypotension (MAP = 5th %ile)</td>
<td>Tired; lightheaded; mildly dizzy; unexplained tachycardia; delayed capillary refill</td>
<td>Very dizzy/near fainting; pallor; weak pulse; sweaty; somnolent. Infants: listless or lethargic</td>
<td>Hypotension (MAP &lt;5 %ile); cyanosis; confusion; fainting; loss of consciousness, bradycardia, arrest.</td>
</tr>
<tr>
<td>ABDOMINAL &amp; PELVIC</td>
<td>No signs or symptoms</td>
<td>Nausea without vomiting; mild abdominal cramps or pain; uterine cramps; urinary incontinence</td>
<td>Mod-severe pain; cr vomiting and/or diarrhea &gt;3 total <strong>WITHIN THE PAST 1 HOUR</strong> (or since epinephrine if it was given in the past hour)</td>
<td>Vomiting and/or diarrhea &gt;3 total <strong>WITHIN THE PAST 1 HOUR</strong> (or since epinephrine if it was given in past hour)</td>
</tr>
<tr>
<td>NEUROLOGICAL</td>
<td>No signs or symptoms</td>
<td>Anxious (without explanation); headache</td>
<td>Feeling of impending doom (like something terrible is about to happen)</td>
<td></td>
</tr>
<tr>
<td>RISK FACTORS</td>
<td>No suspected exposure, no history of allergies</td>
<td>Moderate Risk: Symptom onset 1-10 hours after possible exposure AND no allergy history; known allergies with no exposure</td>
<td>High Risk: Rapid onset, e.g., &lt; 1 hour post-exposure (food, drugs, contrast); OR known allergies with possible exposure</td>
<td></td>
</tr>
</tbody>
</table>

**TOTAL SCORE**
Physical Urticarias

This information is taken from the UpToDate article on "Physical (inducible) forms of urticaria".

Inciting factors and diagnostic tests for physical and other inducible urticarias

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Inciting trigger(s)</th>
<th>Diagnostic test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic dermographism (urticaria factitia)</td>
<td>Firm stroking, scratching, pressure</td>
<td>Moderate stroking of the skin with a blunt, smooth object (eg, closed ballpoint pen tip, wooden tongue depressor) or dermographometer.</td>
</tr>
<tr>
<td>Delayed-pressure urticaria/angioedema</td>
<td>Application of pressure 0.5 to 12 hours before onset of symptoms</td>
<td>Sling with weights placed over arm or shoulder for 15 minutes (7 kg weight on 3 cm wide shoulder strap). Patient reports symptoms over next 24 hours. Dermographometers are used in research (130 grams/mm² for 70 seconds).</td>
</tr>
<tr>
<td>Cholinergic urticaria</td>
<td>Elevation of body temperature (exercise, hot water, strong emotion, hot or spicy food)</td>
<td>Exercise using a machine (stationary bicycle or treadmill) to the point of sweating. Then, continue for 15 minutes. If this test is positive, then passive heating of one or both arms in 42°C warm water both to cause increase in body temperature of ≥1°C. Some patients may react to skin testing with own sweat.</td>
</tr>
<tr>
<td>Cold contact urticaria</td>
<td>Exposure of skin to cold air, cold liquids, or cold objects</td>
<td>Ice cube test - Melting ice cube in thin plastic bag for 5 minutes. TempTest where available to determine patient’s threshold.</td>
</tr>
<tr>
<td>Heat contact urticaria</td>
<td>Warm object in direct contact with affected skin</td>
<td>Application of test tube containing 45°C water or metal cylinder heated to 45°C to skin for 5 minutes.</td>
</tr>
<tr>
<td>Exercise-induced urticaria/neuropsy</td>
<td>Physical exertion</td>
<td>Treadmill testing.</td>
</tr>
<tr>
<td>Aquagenic urticaria</td>
<td>Skin contact with water of any temperature</td>
<td>Application of 35°C water in compress to upper body for 30 minutes.</td>
</tr>
<tr>
<td>Solar urticaria</td>
<td>Exposure of skin to sunlight (triggering wavelengths vary)</td>
<td>Exposure of normally covered skin to UVA (8.0 mJ/cm²), UVB (60 ml/cm²), and visible light (projector).</td>
</tr>
<tr>
<td>Vibratory urticaria/angioedema</td>
<td>Lawn mowing, riding a motorcycle, horseback riding, mountain biking, exposure to vibrating machinery, holding some steering wheels</td>
<td>Vortex mixer is held against skin for 10 minutes.</td>
</tr>
</tbody>
</table>

UV: ultraviolet A radiation therapy; UVB: ultraviolet B radiation therapy.


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**Diagnostic considerations**

It’s generally best to defer administration of these tests to allergists or dermatologists: “During these challenges, physical stimuli are applied to the skin for a specified amount of time (usually a few minutes) and then removed. Urticaria typically develops after removal of the stimulus. Leaving the stimulus in contact with the skin until urticaria or angioedema actually appear can result in excessive exposure and systemic symptoms. Similarly, exposure time may need to be reduced in patients who describe unusual levels of sensitivity.”

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**Treatment of refractory symptoms**

“Patients who fail to respond to avoidance of the triggering stimulus combined with safe and practical doses of a second-generation antihistamine should be considered candidates for chronic therapy with omalizumab. Other therapies for refractory disease, depending upon the specific disorder, include phototherapy, physical desensitization protocols, and immunomodulatory agents.”
References