

# Urticaria and Angioedema

This guideline, developed by Robbie Pesek, MD and Allison Burbank, MD, in collaboration with the ANGELS team, on July 23, 2013, is a significantly revised version of the guideline originally developed by Jeremy Bufford, MD. Last reviewed by Robbie Pesek, MD September 14, 2016.

## Key Points

- Urticaria and angioedema are common problems and can be caused by both allergic and non-allergic mechanisms.
- Prompt diagnosis of hereditary angioedema (HAE) is important to prevent morbidity and mortality. Several new therapeutic options are now available.
- Patients with urticaria and/or angioedema should be referred to an allergist/immunologist for symptoms that are difficult to control, suspicion of HAE, or to rule out suspected allergic triggers.

## Definition, Assessment, and Diagnosis

### Definitions

- Urticaria is a superficial skin reaction consisting of erythematous, raised, blanching, well-circumscribed or confluent pruritic, edematous wheals, often with reflex erythema.<sup>1-3</sup> Urticarial lesions are typically pruritic, and wax/wane with resolution of individual lesions within 24 hours.
- Angioedema is localized swelling of deep dermal, subcutaneous, or submucosal tissue resulting from similar vascular changes that contribute to urticaria.<sup>1,2</sup> Angioedema may be pruritic and/or painful and can last for 2-3 days depending on etiology.<sup>3</sup>

- Urticaria alone occurs in 50% of patients and is associated with angioedema in 40% of patients. Isolated angioedema occurs in 10% of patients.<sup>1,2</sup>
- Hereditary angioedema (HAE) is a disorder involving defects in complement, coagulation, kinin, and fibrinolytic pathways that results in recurrent episodes of angioedema without urticaria, usually affecting the skin, upper airway, and gastrointestinal tract.<sup>4</sup>
- In children, acute urticaria is more common than chronic forms. Febrile illnesses, usually triggered by viruses, represent the most common cause of urticaria and angioedema. Other common triggers include acute allergic reactions to foods, medications, or insects. Physical urticarias, such as dermatographia, are also common.

## Acute Urticaria With or Without Angioedema

- Acute urticaria/angioedema represents a single episode or recurrent episodes lasting <6 weeks. Episodes may be self-limited, intermittent, or recurrent, and are often related to allergic reactions (food, drug, and stinging insect venom), infection, physical stimuli, or non-IgE-mediated mast cell degranulation.<sup>1</sup>
- Etiologies
  - Allergic (IgE-mediated): foods, drugs, stinging insect venom, environmental allergens, latex. Suspected triggers are often temporally associated and reproducible.<sup>1-3</sup>
  - Non-immunologically mediated mast cell degranulation: foods (strawberries, certain cheeses and tomatoes among others), drugs (NSAIDs, narcotics), alcohol, radiocontrast dyes.<sup>1-3</sup>
  - Infection: viral (EBV, hepatitis B/C, respiratory viruses including adenovirus, RSV, and parainfluenza), parasitic, bacterial (Streptococcus).<sup>1-3</sup>
  - Papular urticaria: associated with insect bites, typically on lower extremities

## Chronic Urticaria With or Without Angioedema

- Chronic urticaria/angioedema represents persistent or recurrent episodes lasting >6 weeks.
- Episodes may be intermittent, recurrent, or persistent.
- Potential etiologies for chronic urticaria/angioedema are extensive; however, a specific cause is often not identified.<sup>1</sup>
- Etiologies
  - Nearly 50% of patients with chronic urticaria/angioedema have no identifiable cause.<sup>2,3</sup>
  - Autoimmune etiologies occur in 30%-40% of patients.
    - IgG autoantibodies to IgE or IgE receptors may be present.
    - Antithyroid antibodies are associated with chronic urticaria/angioedema in up to 30% of patients and are often present in euthyroid patients.<sup>2,3</sup>
    - Infection: viral (EBV, hepatitis B/C), parasitic, bacterial (Streptococcus).<sup>1-3</sup>

## Physical Urticarias

- Physical stimuli may act as a trigger for recurring urticaria with/without angioedema

- Etiologies include dermatographism (mild trauma), cold, local heat, cholinergic (pinpoint wheals with large flare due to increased core body temperature), pressure (may be delayed), solar (sunlight/ultraviolet waves), aquagenic (water), exercise, vibratory<sup>2,3</sup>

## Urticarial Vasculitis and Autoinflammatory Diseases

- Urticarial vasculitis
  - Small vessel vasculitis involving the skin that may be associated with systemic vasculitis and other systemic symptoms (e.g., fever, joint pain, fatigue).
  - Lesions typically last more than 24 hours in one location and leave bruising, purple discoloration, or non-blanching petechiae in skin.<sup>1</sup>
- Muckle-Wells syndrome, Schnitzler's syndrome, Gleich's syndrome, Well's syndrome, familial cold autoinflammatory syndrome, neonatal-onset multisystem inflammatory disease are all autoinflammatory diseases that can lead to symptoms of urticaria and possibly angioedema. There are often other systemic symptoms, such as deafness, that can assist with diagnosis.<sup>3</sup>
- Malignancy/lymphoproliferative disorders<sup>2,3</sup>
- Cutaneous/systemic mastocytosis

## Angioedema Without Urticaria

- Drug-induced
  - Beta-lactam antibiotics, NSAIDs, and ACE inhibitors are common causes for angioedema, although many other drugs have also been implicated.<sup>5</sup> African Americans are at higher risk of ACE inhibitor-induced angioedema.
  - Other causes for angioedema including complement deficiencies, IgE-mediated allergy, mastocytosis, and other systemic diseases including malignancy should be ruled out.
- Hereditary angioedema (HAE)
  - HAE typically presents with episodic, peripheral edema of the hands and face but can also involve the genitalia, trunk, tongue, and larynx. Patients may also present with episodic swelling of the bowel wall leading to severe abdominal pain and vomiting.
  - Children with HAE usually become symptomatic between 5-11 years of age.<sup>4</sup>
    - Family history can be helpful as HAE is autosomal dominant.
    - Twenty-five percent (25%) of cases are spontaneous.<sup>6</sup>

## Other

- Acquired angioedema (AAE)
  - Type 1 is associated with B-cell lymphoproliferative disorders
  - Type 2 is associated with autoantibodies directed against C1 esterase; in addition to decreases in C1 esterase and C1 esterase function, patients will also have decreased C1q.
- Melkersson-Rosenthal syndrome (granulomatous cheilitis)
  - Chronic swelling of the lips due to granulomatous inflammation
  - May present with episodic swelling of one or both lips that becomes persistent over time

- Also associated with facial nerve palsy and fissured tongue
- Biopsy may reveal granulomas, but is frequently non-diagnostic, especially early in the disease.

## Diagnostic Evaluation

- An extensive laboratory evaluation is usually not indicated, but screening labs including complete blood count (CBC) with differential, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), liver function tests (LFTs), and urinalysis (UA) can be considered for persistent acute urticaria or chronic urticaria to evaluate for systemic disease.<sup>1,2</sup>
- Consider allergy evaluation/testing to confirm or exclude atopy or suspected allergic triggers based on history (foods, environmental allergens, stinging insect venom, drugs); IgE-mediated allergic sensitivity, especially to foods, is rarely the cause for chronic urticaria/angioedema.<sup>1</sup>
- Consider physical urticaria testing if suggested by history<sup>2,3</sup>
  - Linear skin scratch for dermatographism, ice cube test for cold urticaria
  - Warm water test tube for local heat urticaria, local pressure/weight bearing/compression for pressure urticaria
  - UV light for solar urticaria
  - Water/moist towel exposure for aquagenic urticaria
  - Exercise for cholinergic or exercise-induced urticaria
  - Vibrating tool exposure for vibratory urticaria
- Consider autoimmune evaluation if suggested by history or for persistent symptoms when initial screen is non-diagnostic.
  - Assess for autoimmune etiology with chronic urticaria index (CUI) and thyroid function testing with antithyroid antibodies.
  - Consider additional autoimmune evaluation as indicated.
- Skin punch biopsy if urticarial vasculitis (UV) is suspected or if symptoms are persistent and/or refractory to treatment;<sup>1</sup> if UV is confirmed on biopsy, evaluate for other systemic organ involvement and obtain complement levels (CH-50, C3, C4).<sup>1-3</sup>
- Consider serum tryptase with urine histamine and histamine metabolites to evaluate for possible anaphylaxis or mast cell disorders.<sup>1-3</sup>
- For patients with suspected autoinflammatory disorders, genetic testing should be performed.
- Suggest patient diaries to capture frequency, duration, intensity, triggers, and response to medication.<sup>2</sup>
- To evaluate for HAE, obtain C4 level along with quantitative and functional C1 esterase inhibitor studies.
  - Type I HAE is associated with abnormal C1 esterase inhibitor level with normal or low function.
  - Type II HAE is associated with normal or elevated C1 esterase inhibitor level, but low function.
  - C4 remains decreased between episodes.
  - Decreased factor XII levels are associated with Type III HAE, a form of HAE that is believed to be estrogen dependent.

- Complement studies are usually normal in Type III HAE.
- Screen asymptomatic family members of HAE patients with complement studies (C4 level; C1 esterase inhibitor level and function); screening can be performed as early as 6 months of age.
- There is no clinical utility in monitoring levels of C4, C1 esterase, functional C1 esterase, or factor XII once the diagnosis of HAE is made.

## Management of Urticaria and Angioedema (excluding HAE)

- Attempt to identify underlying cause or trigger, but do not delay treatment for sake of work-up or lack of underlying etiology; avoid common urticaria triggers such as NSAIDs, alcohol, and narcotics.<sup>1</sup>
- Avoid confirmed, identified, or suspected triggers, including physical triggers; treat underlying cause (systemic or infectious), if identified.<sup>7</sup>
- Most of the treatment recommendations for urticaria/angioedema are extrapolated from adult data; there are few randomized studies in children.
- Second generation H1-antihistamines (cetirizine, fexofenadine, loratadine, levocetirizine, desloratadine) are the gold standards for treatment and are preferred over 1<sup>st</sup> generation sedating H1-antihistamines due to decreased sedation and anti-cholinergic effects.<sup>2,7</sup>
- Management of urticaria/angioedema often requires off-label use of medications in relation to dose, age, and indication.
- Pharmaceutical management steps for urticaria/angioedema<sup>1,2,7</sup>
  - Non-sedating H1-antihistamine daily at standard, age/weight-appropriate recommended dose with or without 1<sup>st</sup> generation sedating antihistamine as needed for breakthrough.
  - For poor control after 2 weeks, double the dose of non-sedating H1-antihistamine through twice-a-day dosing. Some patients may require up to 4 times the recommended dose (max dose cetirizine/loratadine: 40 mg/day, fexofenadine: 320 mg/day).
  - For poor control after 1-4 weeks, consider adding a scheduled 1<sup>st</sup> generation, sedating H1-antihistamine (hydroxyzine or diphenhydramine 1-2 mg/kg per day) at bedtime or every 6 hours as needed for breakthrough. Alternatively, consider adding an H2-antihistamine (e.g., ranitidine 4-6 mg/kg/day divided twice a day) prior to initiating sedating antihistamine.
  - Caution patients about potential sedation effect of 1<sup>st</sup> generation H1-antihistamines or doses of 2<sup>nd</sup> generation H1-antihistamines that exceed FDA dosing recommendations; this sedation effect may contribute to impaired learning and academic performance in children.
  - For poor control after 1-4 weeks, consider adding or substituting with a leukotriene receptor antagonist (e.g., montelukast) or a trial of doxepin (tricyclic antidepressant with potent H1- and H2- antagonist effects) titrated to effect.
  - Consider short courses of oral systemic corticosteroids for severe episodes that are poorly responsive to various stages of escalation of care, debilitating, or cause impairment in quality of life.
    - Long-term corticosteroid use is discouraged due to potential for side effects.
    - Consider involvement of allergist/immunologist prior to initiation of systemic steroids.
  - For continued poor control after 1-4 weeks, consider other second and third line agents in consultation with subspecialist (allergy/immunology) including, but not limited to, cyclosporine, tacrolimus, colchicine, hydroxychloroquine, sulfasalazine, dapsone, methotrexate, intravenous immunoglobulin, or omalizumab.
  - Omalizumab, an IgE monoclonal antibody that targets IgE and affects mast cell and

basophil function, is effective in controlling urticaria in patients  $\geq 12$  years who fail management with H1-antihistamines; patients should be monitored for development of anaphylaxis following injections.<sup>8</sup>

- Intramuscular epinephrine auto-injector prescription and education should be provided to patients who have a history of laryngeal or oropharyngeal edema with or without other signs/symptoms of anaphylaxis.
  - Epinephrine is only indicated for use in acute allergic reactions and should not be used to treat chronic urticaria.
  - Epinephrine is ineffective in treating HAE.
- Anti-IL beta agents (canakinumab [Ilaris<sup>®</sup>], anakinra [Kineret<sup>®</sup>]) are available for treatment of patients with autoinflammatory disorders.
- Failure to respond to increasing doses of H1- and H2-antihistamines should prompt consideration for other diagnoses and a consultation with an allergy/immunology subspecialist.<sup>2</sup>
- Evaluate patients every 3-6 months to determine need for continued or alternative treatment options.
  - Anticipate and counsel patients on fluctuations in severity and the expectation of spontaneous remission, though symptoms may last several weeks, months, or even years.<sup>7</sup>
  - Once control of symptoms is achieved, therapeutic options should be withdrawn gradually while observing for recurrence.<sup>2</sup>

## Management of Hereditary Angioedema

### Referral & Management

Timely referral to and management of HAE by an experienced subspecialist (allergy/immunology) is crucial and includes patient education, treatment, follow-up, and evaluation of potential treatment-associated side effects.

- There is a 50% mortality rate in undiagnosed HAE. A medical alert bracelet or emergency management card is advised.<sup>6</sup>
- Common pediatric triggers include mechanical trauma, stress or excitement, respiratory infections, and menstruation.<sup>4</sup>
- Participation in contact sports, early daycare/preschool exposure, ACE inhibitors, angiotensin receptor blockers (ARBs), and estrogen-containing oral contraceptives, when appropriate, are discouraged.<sup>6</sup>

### Treatment

Treatment of HAE encompasses management of acute episodes, short-term prophylaxis, and long-term prophylaxis.

#### Acute Episodes

- HAE does not respond to antihistamines, epinephrine, and corticosteroids.
- C1 esterase inhibitor concentrate (Berinert<sup>®</sup>) is the most effective therapy for acute HAE attacks involving laryngeal edema, diffuse facial swelling, or severe abdominal attacks.

- Dose: 20 units/kg (Berinert<sup>®</sup> prescribing information) in children ≥12 years of age
- C1 esterase inhibitor concentrate should be made available for home use if possible.<sup>6</sup>  
(Berinert<sup>®</sup> is not covered for home use by Arkansas Medicaid.)
- Ecallantide (Kalbitor<sup>®</sup>) is a plasma kallikrein inhibitor approved for patients ≥16 years of age for acute HAE attacks
  - Thirty (30) mg administered subcutaneously in three 10 mg doses
  - Dose may be repeated once in 24-hour period for persistent symptoms (Kalbitor<sup>®</sup> prescribing information). Kalbitor<sup>®</sup> is not covered for home use by Arkansas Medicaid.
- Icatibant (Firazyr<sup>®</sup>) is a bradykinin B2 antagonist approved for patients ≥ 18 years of age for acute HAE attacks
  - Thirty (30) mg administered subcutaneously in abdomen
  - Approved for self-administration (Firazyr<sup>®</sup> is not covered for self-administration by Arkansas Medicaid.)
  - May use 3 doses at least 6 hours apart in a 24-hour period (Firazyr<sup>®</sup> prescribing information)
- Fresh frozen plasma (FFP), 1-2 units (10 mL/kg) if C1 esterase inhibitor concentrate not available; paradoxical worsening of symptoms has been reported.<sup>4,6</sup>
- Airway management is crucial; ICU monitoring should be considered for airway management, including preparation for intubation and tracheostomy.<sup>1,6</sup>
- Mild attacks not associated with facial or laryngeal edema usually respond spontaneously within 2 days and do not require acute treatment; however, long-term prophylactic doses, if applicable, can be doubled to prevent progression and speed resolution.<sup>4,6</sup>
- Acute attacks requiring treatment with Berinert<sup>®</sup>, Kalbitor<sup>®</sup>, or Firazyr<sup>®</sup> should be managed in a healthcare setting by healthcare providers trained in the treatment of hereditary angioedema. Patients may dose Berinert<sup>®</sup> (home infusion), Kalbitor<sup>®</sup> or Firazyr<sup>®</sup> at home, but should seek medical attention if the attack does not respond to treatment or involves facial/airway swelling. (These three drugs are not covered by Arkansas Medicaid for home use).
- The health care setting should be equipped with resuscitation equipment and other agents necessary to manage severe and/or progressing attacks.

### **Long-Term Prophylaxis**

Long-term prophylaxis is considered in patients with frequent, recurrent episodes (>1 episode per month) or history of life-threatening attack, including laryngeal edema, but is typically not necessary before the age of 6 years.<sup>6</sup>

- C1 esterase inhibitor, Cinryze<sup>®</sup>, is FDA-approved for HAE prophylaxis in adolescents and adults.
  - Standard dose is 1,000 units IV every 3-4 days
  - Usually dosed at home

- Antifibrinolytics, tranexamic acid (TXA) and epsilon-aminocaproic acid, are the preferred long-term prophylaxis agent in children and have a better safety profile than attenuated androgens. TXA (20 to 40 mg/kg daily divided twice a day to three times a day, maximum dose 3 grams/day) is better tolerated than epsilon-aminocaproic acid.<sup>4</sup>
- Attenuated androgens, which increase hepatic production of C1 esterase inhibitor, are recommended for antifibrinolytic treatment failures, contraindications, or severe side effects.
  - Danazol (Danocrine<sup>®</sup>) is the most commonly used androgen and is generally well tolerated.
  - Dose is titrated or tapered to lowest effective dose (starting dose 2.5 mg/kg per day; 50 mg/day initial dose; increased to maximum dose of 200 mg per day) and tapered to alternate day or twice weekly dosing if possible.
  - Oxandrolone has been also shown to be safe and effective in children.<sup>4,6</sup>

### Short-Term Prophylaxis

Short-term prophylaxis is indicated for surgery, dental, or other medical procedures involving the head and neck area, especially intubation.<sup>1,4</sup>

- Danazol 5 mg/kg/day (max 600 mg per day divided three times a day) or TXA 20-40 mg/kg divided twice a day to three times a day (max 3 gm per day) starting 5 days before the procedure and continued 2 days beyond.<sup>4</sup>
- Similar dosing regimens may also be used for a few days during acute infections, exposure to precipitating triggers or prodromal symptoms (erythema marginatum, joint pressure, itching, tingling, nausea, xerostomia, dyspepsia, diarrhea, anxiety, fatigue).<sup>4,6</sup>
- C1 esterase inhibitor concentrate 10-20 units/kg dosed 1 hour before the procedure; alternatively, FFP 10 mL/kg, can be used if C1 esterase inhibitor is not available.<sup>4</sup>

### Considerations in Pediatric Patients <12 Years of Age

- Children < 12 years of age typically have fewer attacks than adolescents or adults.
- Berinert, Cinryze, Kalbitor, and Firazyr are not currently approved by the FDA for treatment of HAE in this age group.
- Extreme caution should be used with attenuated androgens for long-term treatment in this age group due to the potential for masculinization, early onset puberty, and retarded growth.
- Fresh frozen plasma and antifibrinolytics can be used in the acute treatment of HAE attacks.

### Side Effect of Treatment Options

Routine monitoring for potential side effects of above treatment options is imperative.

- Fresh frozen plasma and C1 esterase inhibitor concentrate carry risk of blood-borne pathogens (recombinant C1 inhibitor product in development).
- Consider hepatitis A and B vaccination prior to use.
- Antifibrinolytics are associated with abdominal pain, muscle abnormalities, elevated creatine kinase, thrombosis, postural hypotension, and retinal changes.
- Attenuated androgens are associated with hirsutism, virilization, dyslipidemia, elevated liver



enzymes, irregular menses, and effects on growth and mental development.<sup>4,6</sup>

## When to Refer to Allergy/Immunology

- Chronic urticaria/angioedema or frequent or persistent acute urticaria/angioedema approaching chronic duration, especially with no identified cause or trigger<sup>1</sup>
- Confirmation or exclusion of suspected allergic or physical triggers through skin testing and/or serum specific-IgE testing with or without challenge procedure (oral food challenge or drug test dosing) or physical urticaria testing/provocation
- Acute urticaria/angioedema in patients
  - With no clear trigger
  - Who have difficulty avoiding triggers, or
  - Who are refractory to initial management<sup>1</sup>
- Evaluation and management of unusual causes of isolated angioedema, including HAE<sup>1</sup>
- Assistance in management of urticaria/angioedema with specific etiology, subtype or trigger, including, but not limited to, urticarial vasculitis, chronic idiopathic, autoimmune, physical, or thyroid autoimmunity<sup>1-4,6</sup>

*This guideline was developed to improve health care access in Arkansas and to aid health care providers in making decisions about appropriate patient care. The needs of the individual patient, resources available, and limitations unique to the institution or type of practice may warrant variations.*

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## References

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