Anaphylaxis, Urticaria, and Angioedema

Emily W. Langley, MD,*
Joseph Gigante, MD†

Author Disclosure
Drs Langley and Gigante have disclosed no financial relationships relevant to this article. This commentary does not contain discussion of unapproved/investigative use of a commercial product/device.

Educational Gaps

1. Anaphylaxis can cause death; thus, clinicians must be aware of the characteristics of anaphylaxis and of proper therapy, including immediate administration of epinephrine. All patients at risk should carry self-administration epinephrine pens, with 2 epinephrine pens (twin pack) now recommended in case a second dose is needed for persistent symptoms. Given the 20% incidence of biphasic latent reactions, patients always should self-administer epinephrine and seek immediate emergency medical treatment.
2. Angioedema also can be life-threatening in association with urticaria or in the absence of hives or pruritus. Clinicians must be aware of the following: appropriate management, including investigation of various triggers, such as food, medications, and the possibility of a rare disorder of C1 inhibitor deficiency; appropriate treatment; and potentially life-saving prophylactic preventive measures.

Objectives

After completing this article, readers should be able to:

1. List the etiologic agents that commonly cause urticaria, angioedema, and anaphylaxis.
2. Recognize the signs and symptoms of anaphylaxis and be able to deliver rapid, effective treatment for anaphylaxis.
3. Distinguish between acute and chronic urticaria, and recognize the differences in their evaluation and treatment.
4. List the causes of papular urticaria.
5. Discuss the acute management of stinging insect anaphylaxis.

Anaphylaxis

Anaphylaxis is an acute, life-threatening systemic reaction that results from the sudden release of mediators from mast cells and basophils. Prompt recognition of the signs and symptoms of anaphylaxis is critical to providing rapid and effective treatment. Epinephrine is the most important medication for treating anaphylaxis, and earlier administration portends better prognosis.

Causes

The potential causes of anaphylaxis are numerous and include foods, medications, stinging insects, vaccinations, latex, and less common causes, such as exercise and immunotherapy (Table 1). The prevalence of life-threatening anaphylaxis is estimated to be 10 per 100,000 persons, but this number may be an underestimate because of poor recognition of signs and symptoms.

Food

The most common cause of anaphylaxis in the outpatient setting is food. Current estimates suggest that the prevalence of food allergy in North America is 6% of young children. Food allergens account for 30% of fatal cases of anaphylaxis, with approximately 200 deaths in the United States per year. The foods most commonly implicated in food-induced anaphylaxis

*Clinical Fellow, Allergy/Immunology, Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, TN.
†Associate Professor of Pediatrics, Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, TN.

Table 1. **Causes of Anaphylaxis**

Cause	Examples
Food	Peanut, tree nuts, fish, shellfish, cow milk, soy, egg
Medication	Antibiotics, nonsteroidal anti-inflammatory drugs, chemotherapy
Stinging insects	Honey bee, wasp, hornet, yellow jacket, fire ant
Natural rubber latex	Balloons, gloves, medical equipment
Vaccinations	Gelatin, egg, yeast, neomycin
Exercise-induced	Food-exercise, medication-exercise

are peanuts, tree nuts, fish, shellfish, cow milk, soy, and egg. In addition, sesame seeds have become increasingly important as a cause of anaphylaxis. Reactions can occur after the first known exposure or with any subsequent exposure. Prior tolerance to a food does not exclude the development of allergy. Children who have an allergy to peanuts or tree nuts, who have a history of food allergy or asthma, or who experience a delay in administration of epinephrine when symptoms warrant use of that drug are at the highest risk for severe food-induced anaphylaxis.

It is important to counsel families that food allergy in children can have varying prognoses. Food allergies to milk, egg, soy, and wheat usually are outgrown during the first decade of life. Food allergies to peanut, tree nuts, fish, and shellfish most commonly are life-long. Still, peanut allergy can be outgrown in 20% of children, so yearly evaluation by an allergist is important to identify these children, who may be candidates for oral food challenge and consequent reintroduction of an item into the diet.

Medications

Medications are the second most common cause of anaphylaxis in children. The 2 most frequent culprits are antibiotics, particularly β-lactam antibiotics, and nonsteroidal anti-inflammatory drugs (NSAIDs). Anaphylaxis also can be caused by chemotherapy drugs, especially cisplatinum and carboplatinum, and biologic agents and monoclonal antibodies, such as omalizumab, which is used for refractory asthma.

Radiographic Contrast

Anaphylactoid reactions associated with radiographic contrast material occur in approximately 1% of patients. The reactions are considered anaphylactoid because they present identically to immediate hypersensitivity reactions with urticaria, angioedema, severe vomiting, and respiratory symptoms, but they do not appear to be mediated by IgE or other immunologic mechanisms. Pretreatment with oral corticosteroids and antihistamines can reduce the risk of anaphylactoid reactions from radiographic contrast material.

Stinging Insects

Hymenoptera stings by bees, vespids (yellow jacket, hornet, and wasps), and stinging fire ants can cause anaphylaxis. Approximately 0.4% to 0.8% of children report systemic allergic reactions to insect stings. At least 50 cases of fatal anaphylaxis to insect stings occur annually in the United States.

Cutaneous symptoms alone occur in 60% of children with stinging insect hypersensitivity, and these cases do not warrant venom testing or consideration of venom immunotherapy for children younger than 16 years. Cutaneous symptoms can be treated symptomatically with cold compresses, oral antihistamines, and oral analgesics.

The additional presence of any respiratory or gastrointestinal symptoms or signs or symptoms of hypotension, including dizziness or syncope, should prompt immediate administration of epinephrine and immediate evaluation in a local emergency department. After stabilization of the patient, referral to an allergist should be made for venom skin testing and consideration of immunotherapy.

For venom allergic children, the risk of a systemic reaction to an insect sting, even into adulthood, is approximately 30%. Venom immunotherapy has been shown to be effective. The risk of a subsequent systemic reaction after a completed course of venom immunotherapy, typically administered over 3 to 5 years, is reduced to less than 5%, and if a reaction occurs, it is usually mild.

Latex

Natural rubber latex is an emerging cause of anaphylaxis, especially in the health-care setting and in certain patient populations. Latex allergy is caused by sensitization to any of the antigens from the *Hevea brasiliensis* tree. In certain patient subsets, such as children born with spina bifida, those with bladder extrophy, and those requiring frequent bladder catheterizations, the prevalence of latex allergy is as high as 75%. In these specific patients, latex avoidance from birth has helped to decrease the risk of sensitization. Latex-induced anaphylaxis is also a common cause of intraoperative anaphylaxis and is responsible for up to 17% of cases of intraoperative anaphylaxis.

The most common mode of sensitization is direct contact with latex products, including medical gloves, catheters, and dental instruments; however, patients also can develop severe symptoms on inhalation of the latex

antigen aerosolized by cornstarch powder that occurs when donning gloves. Patients with latex allergy should be educated to avoid any possible latex-containing product. A comprehensive list of these products, with additional valuable patient information on latex allergy, can be found at American Latex Allergy Association website (http://www.latexallergyresources.org/).

Vaccination

Anaphylaxis to vaccines is an exceedingly rare but important cause of a life-threatening allergic reaction. The rate of anaphylaxis to vaccines is estimated to be 0.65 per 1 million doses. Immediate hypersensitivity reactions are usually caused by components of the vaccine rather than the immunizing agent itself. Examples of vaccine components that are known to cause anaphylaxis are gelatin, egg, chicken, yeast, and neomycin. In suspected cases of anaphylaxis to a vaccine, patients can undergo skin testing to the components of the vaccine, such as gelatin, and to the vaccine itself. This information can then be used to determine the safety of future vaccinations with the same agent.

Exercise

Exercise and physical exertion can lead to systemic mast cell mediator release, resulting in anaphylaxis. The symptoms usually start within a few minutes of exercise and consist of flushing, pruritus, diffuse warmth, urticaria, and fatigue. These early symptoms may progress to angioedema, laryngeal edema, gastrointestinal symptoms, hypotension, or collapse if exercise is continued. Typically, high levels of exertion, such as jogging or doing aerobics, are most risky for these patients; however, some patients can have symptoms with low-impact exercise, such as walking.

In many cases, there must be a cotrigger or cofactor before any symptoms occur. Examples of cotriggers are ingestion of specific foods, use of NSAIDs, drinking alcoholic beverages, menstruation, or high pollen exposure. The most commonly implicated foods are wheat, grains, nuts, and seafood. In situations that involve food cotriggers, having eaten the specific food 4 to 6 hours before exercise is common. When the ingestion of NSAIDs is a factor, taking the medication may have preceded exercise by up to 24 hours. This type of anaphylaxis is termed *food-exercise–induced anaphylaxis* or *medication-exercise–induced anaphylaxis.*

Immunotherapy

Subcutaneous allergen immunotherapy (allergy shots) is another potential cause of anaphylaxis. The rate of systemic reactions to immunotherapy is estimated to be less than 1%. Fatal reactions are estimated to occur in 1 in 2.5 million injections, making this outcome exceedingly rare. However, in children with poorly controlled asthma, the risk of a systemic reaction is increased. Therefore, it is critical that asthma control be optimized before starting immunotherapy and that immunotherapy be held during asthma exacerbations. Furthermore, immunotherapy should be given only in a health-care setting in which clinicians are trained in the recognition and treatment of anaphylaxis. In addition, it is imperative that patients wait the recommended 30 minutes after an injection because most systemic reactions related to immunotherapy occur within the first 30 minutes.

Idiopathic

When a causative allergen or inciting physical factor is not found, the diagnosis of idiopathic anaphylaxis is made. This is a poorly understood disease and should be considered only after a thorough detailed history has been completed, appropriate allergy testing has been performed, and other mimickers of anaphylaxis have been excluded. Idiopathic anaphylaxis is considerably rare in adults and adolescents and even less frequent in children. If the cause is truly idiopathic, it is important to screen for underlying systemic mastocytosis by obtaining a baseline serum tryptase level.

Diagnosis

The diagnosis of anaphylaxis is based on prompt recognition of its signs and symptoms, which may include but are not limited to flushing, urticaria, pruritus, angioedema, cough, wheezing, stridor, dyspnea, abdominal cramping, vomiting, diarrhea, dizziness, and syncope. The absence of cutaneous symptoms argues against anaphylaxis but cannot completely rule it out. Other conditions that should be considered in the differential diagnosis are vasovagal or neurogenic syncope, vocal cord dysfunction, asthma exacerbation, panic attack, isolated angioedema, food poisoning, and other causes of shock, such as sepsis or cardiogenic shock.

It can be difficult to distinguish food poisoning from anaphylaxis because both can present with nausea, vomiting, diarrhea, and abdominal cramping; however, there are several important differences to consider. Allergic reactions that are IgE mediated typically occur rapidly and usually within 1 hour of ingesting the food. Non–IgE-mediated reactions, such as food poisoning, occur more slowly and may be delayed by as much as 24 hours from ingestion. In addition, 80% to 90% of cases of

food-induced anaphylaxis present with cutaneous findings of hives, angioedema, or both, whereas cutaneous findings are uncommon in food poisoning.

A careful history from the patient, parent, caregiver, or other witnesses is helpful in determining a potential trigger. A serum tryptase level taken within 6 hours of a suspected anaphylactic reaction may help to confirm the diagnosis, but the tryptase level may not be elevated in some cases of food-induced anaphylaxis. The causative agent may be obvious in most cases; still, referral to an allergist is warranted so that skin tests, specific IgE in vitro testing, or challenge tests may be considered for more definitive diagnosis, especially in difficult cases.

Treatment

The mainstay of short-term treatment for anaphylaxis is epinephrine in the form of aqueous epinephrine in a 1:1000 dilution (0.01 mg/kg in children; maximum, 0.3 mg). Epinephrine should be administered intramuscularly in the outer aspect of the thigh every 5 minutes as needed to control symptoms. The child should be placed in the recumbent position to slow hemodynamic compromise. Second-line therapy includes diphenhydramine, 1 to 2 mg/kg every 6 hours as needed, ranitidine, 1 to 2 mg/kg every 12 hours as needed, or other histamine$_2$ (H_2)-receptor antagonists. In addition, inhaled β-agonists may be used to treat bronchospasm or wheezing. Glucocorticosteroids may not be helpful for short-term treatment but can be considered for prevention of recurrent or protracted anaphylaxis. Oxygen therapy and intravenous fluid replacement should be given if needed for severe signs, such as hypoxia or hypotension.

Long-term management involves identifying the causative agent if possible and providing education regarding avoidance of the offending agent. Patients with food-induced anaphylaxis and their families should be instructed on reading food labels and must learn to identify foods to avoid. They should be provided a Food Allergy Action Plan, which lists the patient's allergies and gives instructions for the administration of medications should there be an unintentional exposure or an allergic reaction. An example of such a plan can be found on the Food Allergy and Anaphylaxis Network website (http://www.foodallergy.org/).

The plan should be implemented at the patient's school or childcare center, and all caregivers should be educated on the correct technique for the administration of epinephrine. Parents, pediatricians, and allergists can work together as a team with the child's teachers and school administrators on prevention strategies, so that unintentional exposures of the allergenic food are minimized and a treatment plan is in place in the event of an allergic reaction.

The presence or absence of IgE-mediated medication-induced anaphylaxis must be determined carefully to educate appropriately patients about medications that may cross-react with the offending agent. For example, penicillin allergy is reported in up to 10% of children; however, studies report that only 0.3% to 3% of these patients who have a history of penicillin allergy have evidence of IgE-mediated type 1 hypersensitivity when skin testing or radioallergosorbent testing is performed. In most cases, the reaction is non–IgE-mediated, manifesting as vomiting, diarrhea, headache, or a nonurticarial, nonpruritic rash.

Each class of cephalosporins has a different rate of cross-reactivity with penicillin, which is based on the presence or absence of the 7-position side chain on the β-lactam ring. For example, the increase in attributable risk of an allergic reaction to first-generation cephalosporins in penicillin-allergic patients is 0.4%, whereas the increased risk is negligible for third-generation cephalosporins. Thus, it is recommended that first-generation cephalosporins be used with caution in patients who have a history of anaphylaxis or other IgE-mediated reactions to penicillin. Later-generation cephalosporins may be given with low risk.

Patients who have had non–IgE-mediated reactions to penicillin, such as a nonpruritic, maculopapular rash, may receive cephalosporins with no increased risk of allergy. However, extreme caution should be used for patients who have a history of Stevens-Johnson syndrome or toxic epidermal necrolysis associated with a particular medication. These patients should know that the same drug and structurally related drugs should be strictly avoided in the future.

Patients with venom hypersensitivity can take steps to prevent insect stings, which include maintaining a high level of vigilance, wearing shoes while outdoors, and exercising caution when drinking out of cans and bottles. Patients also can avoid wearing brightly colored clothing, scented lotions, soaps, or perfumes that might attract insects. They should use caution around areas where stinging insects are commonly present, such as near brightly colored flowers (honeybees), in the eaves of homes and buildings (wasps), and around uncovered food and trash (yellow jackets). These patients also may be candidates for venom immunotherapy.

Regardless of the cause of anaphylaxis, patients who have a history of anaphylaxis should carry a self-administration epinephrine pen with them at all times and be educated on the proper technique for its use. In fact,

new recommendations suggest having 2 epinephrine pens (twin pack) in case a second dose is needed for persistent symptoms after the first dose. Children should have self-administration epinephrine pens in all locations in which they spend time, including home, school, childcare facilities, or other caregivers' homes. In addition, patients should carry identification, preferably on a medical alert bracelet, identifying their risk for anaphylaxis.

Self-administration epinephrine pens must be carried for all patients at risk for anaphylaxis. For children under 30 kg, the dose is 0.15 mg. For children greater than or equal to 30 kg, the dose is 0.3 mg. Given a 20% incidence of biphasic latent reactions, after self-administration of epinephrine for anaphylaxis, patients should always seek immediate emergency medical attention.

Urticaria

Urticaria is a rash that consists of pruritic, blanching, erythematous, circumscribed, or (often) coalescent wheals. Urticarial lesions are found commonly on the trunk and extremities but may involve any part of the body (Fig 1). The lesions typically migrate and do not persist in a given location for more than 24 hours. Acute urticaria is defined as an eruption that has been present for less than 6 weeks; in contrast, chronic urticaria refers to persistent or recurring lesions lasting 6 weeks or more. In children, acute urticaria is more common than chronic urticaria.

Acute Urticaria

Causes

From 15% to 25% of people will experience acute urticaria at some period in their lives. The causes of acute urticaria are numerous and overlap with many of the causes of anaphylaxis. Urticaria can be provoked by allergens, physical factors, and disease states. Common allergens include foods, medications, insects, pollens, and animal dander. Physical factors, such as cold, pressure, heat, and light, can trigger urticaria. Another common cause of urticaria in children is infectious illness, especially from viruses.

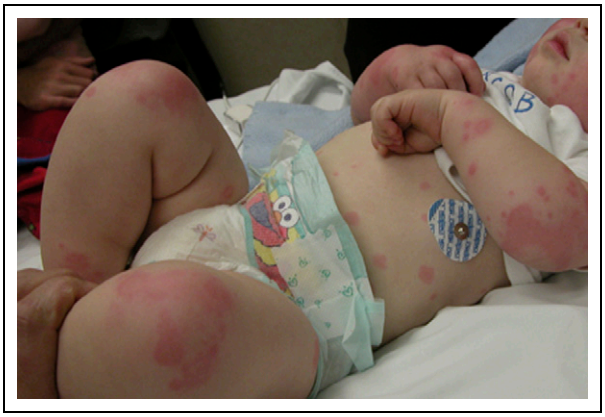

Figure 1. Coalescing urticarial wheals of different sizes on the trunk, extremities, and face of a young child with acute urticaria.

Diagnosis

The diagnosis of urticaria is based on clinical history and physical findings. It is important to distinguish urticaria from other similar dermatologic conditions. Erythema multiforme lesions may resemble urticaria and may be triggered by the same etiologic agents, such as infections and medications. Erythema multiforme is distinguished from urticaria by the targetoid appearance of the lesions. Patients who have erythema multiforme are at risk for development of mucosal and systemic involvement, as seen in Stevens-Johnson syndrome. Cutaneous manifestations of mast cell syndromes, such as urticaria pigmentosa or solitary mastocytomas, also can mimic urticaria. As with anaphylaxis, determining a causative agent may be straightforward or challenging. Patients with a history of a specific allergen exposure, such as a food or drug, should be evaluated with appropriate diagnostic testing, whether skin prick or in vitro specific IgE testing.

Papular urticaria is another common cause of papular, pruritic skin eruptions that should be considered in the differential for acute urticaria. These lesions also can be chronic or recurrent in some children and are caused primarily by insect bite–induced hypersensitivity. The lesions are typically papular or vesicular and usually are grouped in linear clusters on exposed areas of skin, sparing the genital, perianal, and axillary regions (Fig 2). The prevalence of papular urticaria peaks in children from the ages of 2 to 10 years. The eruption accounts for ~5% of office visits to the dermatologist and peaks in the spring and summer months. The most common causes of papular urticaria are cat and dog fleas, followed by mosquitoes and the common bedbug (*Cimex lectularius*), the prevalence of which is increasing.

The management of papular urticaria includes prevention by use of protective clothing, insect repellent, flea-control measures in the home, and frequent washing of pets and bed linens. Mid-potency topical corticosteroids and oral antihistamines often are effective for the associated pruritus. In children with chronic and recurrent lesions, the delayed-type hypersensitivity component may render antihistamines less effective. Intralesional corticosteroids may be considered in severe cases of papular urticaria.

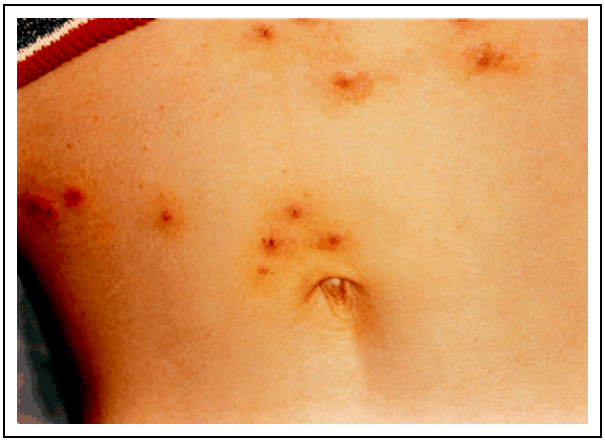

Figure 2. Grouped clusters of papular urticaria due to dog fleas on the trunk of a child.

Treatment

Treatment of acute urticaria is focused first on identifying the offending agent and avoiding it. Histamine blockers are the primary treatment for urticaria. Second-generation antihistamines (loratadine, cetirizine, and fexofenadine) are effective in controlling urticaria and generally cause fewer adverse effects, such as sedation and anticholinergic symptoms, compared with first-generation antihistamines. However, first-generation antihistamines may be used in conjunction with second-generation antihistamines if needed for additional histamine blockade. If maximal doses of an H_1-receptor antagonist do not achieve control of hives, an H_2-receptor antagonist, such as ranitidine or cimetidine, may be added.

Use of glucocorticosteroids should be reserved for children not responsive to H_1- and H_2-antihistamines or children afflicted with severe cases that involve significant angioedema. The prescribed course should be a short oral burst. For example, prednisolone may be given at a daily dose of 0.5 to 1 mg/kg (maximum dose, 60 mg), with tapering of the dose for 5 to 7 days, to prevent adverse effects associated with long-term steroid use. Although recurrence of symptoms may occur with discontinuation of steroid use, prolonged courses of corticosteroids should be avoided and alternative therapies considered.

Another alternative medication for treatment of acute urticaria is leukotriene modifiers, such as montelukast. This agent may be a reasonable addition to the regimen before considering corticosteroids in refractory cases. If there are any other signs or symptoms of anaphylaxis, such as laryngeal angioedema, respiratory, or gastrointestinal symptoms, a self-injectable epinephrine pen should be provided.

Chronic Urticaria

Causes

Chronic urticaria is defined by urticarial lesions persisting or recurring for more than 6 weeks. This condition affects 0.1% to 3% of children. In chronic urticaria, unlike acute urticaria, a specific exogenous cause typically is not found, and only 5% to 25% of patients with chronic urticaria are able to identify a cause for their symptoms. Despite this statistic, every effort should be taken to evaluate for possible causes, which include, medications, foods, physical factors, underlying infections, autoimmune conditions and external exposures, such as latex, hormonal shifts, and, in adults, underlying malignant tumors.

Physical factors are common triggers for chronic urticaria and can act alone or with urticaria of other causes. The main types of physical urticaria are dermatographic, cholinergic, cold, pressure, solar, vibratory, and exercise induced.

The differential diagnosis for chronic urticaria overlaps with that for acute urticaria and includes papular urticaria, urticaria pigmentosa, chronic pruritus without hives, contact dermatitis, and urticarial vasculitis. *Urticaria pigmentosa* is an important condition that must be differentiated from chronic urticaria. Urticaria pigmentosa is a form of cutaneous mastocytosis and, although usually benign, can be associated with systemic mast cell activation. Lesions of urticaria pigmentosa are reddish brown macules that wheal like a hive when stroked (positive Darier sign). Urticarial vasculitis is rare in children but typically presents with fever, arthralgia, and painful fixed urticarial and petechial lesions that last longer than 24 hours. Urticaria vasculitis is differentiated from typical chronic urticaria by the presence of nonpruritic, painful lesions with systemic symptoms.

Diagnosis

In the setting of chronic urticaria, pediatricians should conduct a complete review of systems to evaluate for possible underlying illnesses and a complete physical examination. In up to 35% of cases of chronic urticaria, infection may be the cause for the urticaria. Interestingly, positive serologic findings for *Chlamydia pneumonia* and *Helicobacter pylori* can be found for these illnesses even in asymptomatic patients.

Other reported infectious causes are viral infections, urinary tract infections, and parasitic infections. The association between chronic urticaria and malignant tumors is not well established in children; thus, extensive evaluation for occult malignant tumors is not recommended. Autoimmune diseases that have been associated with

chronic urticaria are thyroid disease, celiac disease, type 1 diabetes mellitus, inflammatory bowel disease, juvenile idiopathic arthritis, and systemic lupus erythematous.

The most common specific autoimmune association with chronic urticaria is autoimmune thyroid disease, which has been described in 15% to 24% of children who have chronic urticaria. If history, physical examination findings, or family history suggests possible thyroid dysregulation, thyroid function testing should be performed along with evaluation of the presence of autoantibodies, including anti-thyroid peroxidase and anti-thyroglobulin. The thyroid autoantibodies may not be pathogenic in all cases but might represent more of a reflection of autoimmune predisposition. However, in patients who have evidence of thyroid antibodies but have normal thyroid function, thyroid function should be evaluated periodically to assess for changes.

On the basis of the patient's history and physical examination findings and the recognition of associated disease states, further evaluation is initiated on a case-by-case basis. There are several proposed algorithms in the literature, but none are universally accepted. A reasonable approach is first-tier screening laboratory tests, consisting of complete blood cell count with differential, urinalysis, liver function tests, thyroid function tests, and erythrocyte sedimentation rate. If clinically relevant, additional testing for celiac disease, antinuclear antibody, complement assays, and serum cryoproteins, as well as further evaluation for infection, may be warranted.

If there is evidence of vasculitis, referral for skin biopsy may be indicated. If an allergic trigger is suspected, specific IgE or skin testing may be useful, keeping in mind that skin testing may be limited if a patient has dermatographism.

If no external triggers are identified and there is no evidence of an underlying disease state, one additional laboratory test can be helpful: the chronic urticaria index. The chronic urticaria index measures the presence of IgG autoantibodies directed against the IgE receptor α-subunit. This autoantibody is present in up to 30% of children with chronic urticaria and is one of several proposed causes of autoimmune urticaria.

The FcεRI is a high-affinity IgE receptor present on mast cells and basophils. When receptor-bound IgE on these cells is cross-linked by a multivalent antigen or allergen, a complex intracellular cascade is initiated, leading to degranulation and release of preformed mediators, such as histamine, tryptase, chymase, and proteoglycans. The release of these mediators manifests physically as the characteristic wheal appearance of urticaria and other allergic symptoms, including rhinitis, pruritus, angioedema, wheezing, and, the most severe form, anaphylaxis.

Treatment

The principles of chronic urticaria treatment are similar to the treatment of acute urticaria. If a specific offending agent is identified, it should be eliminated or avoided. Nonspecific agents that are known to exacerbate urticaria include aspirin, other NSAIDs, opiates, and alcohol; therefore, these should be eliminated. In addition, physical stimuli that exacerbate symptoms, such as cold, heat, pressure, exercise, and solar radiation, should be avoided. If any underlying infection or disease state is identified, it should be appropriately treated.

Symptomatic treatment should be initiated for patient comfort even while evaluation is ongoing. The mainstay of treatment for chronic urticaria is antihistamines. First- or second-generation H_1-receptor antagonists are effective for most patients. One common approach is to use a second-generation antihistamine, such as cetirizine, once to twice daily for chronic suppression and a first-generation antihistamine, such as diphenhydramine or hydroxyzine, to treat pruritus not completely relieved by the second-generation antihistamine or to add desired sedative effects, especially at night.

Many patients will respond to H_1-receptor antagonists alone, but others will need additional medications to control symptoms. As mentioned previously, H_2-receptor antagonists, such as ranitidine or cimetidine, may be added to the H_1-receptor antagonists for additional histamine blockade. In addition, leukotriene modifiers can be added as a third medication for refractory cases. Glucocorticosteroids are nearly universally effective but should be reserved only for those children with severe disease while pursuing consultation with an allergy/immunology specialist.

Specialists may use other therapies for children with chronic urticaria that has been refractory to standard therapies. Examples of these medications include hydroxychloroquine, sulfasalazine, dapsone, omalizumab, colchicine, mycophenolate mofetil, and cyclosporine. These medications all require close monitoring for adverse effects and should be used only by those specialists experienced in prescribing these immune-modulating medications. Table 2 compares the causes, evaluation, and treatment of acute and chronic urticaria.

Angioedema

Angioedema is the swelling of deep subcutaneous areas in the skin or mucous membranes. This disorder manifests as swelling of a finger, hand, lip, eyelid, or, in extreme cases, tongue or throat (Fig 3). Angioedema commonly occurs in association with acute or chronic urticaria. In rare cases, the edema can occur without urticaria.

Causes

The causes of angioedema with urticaria have been described previously, with foods and medications as the leading triggers. The most common medications implicated in angioedema are angiotensin-converting enzyme inhibitors and NSAIDs. Special attention should be given to the patient's medication list and over-the-counter preparations. If angioedema occurs alone without a history of hives or pruritus, a rare disorder of C1 inhibitor deficiency should be considered. Both hereditary and acquired forms of angioedema can be caused by C1 inhibitor deficiency; however, acquired forms of angioedema are exceedingly rare in children.

Hereditary angioedema (HAE) is disease that presents typically in childhood or adolescence with a mean age at onset between 8 and 12 years. There are 3 types of HAE. Type 1 is secondary to insufficient levels of C1 inhibitor. Type 2 is associated with normal levels but dysfunctional C1 inhibitor. Type 3 has normal functional levels of C1 inhibitor, although some patients may have mutations in the coagulation factor XII (Hageman factor). Type 3 HAE is nearly nonexistent in children and adolescents.

Patients born with HAE present with recurrent, episodic, nonpruritic swelling of skin and mucosal tissues. The most severe manifestations of HAE are laryngeal edema that may lead to death by asphyxiation and severe abdominal attacks manifested by intestinal edema. The swelling can occur anywhere on the body, however, including lips, eyelids, hands, feet, and genitals. The swelling usually develops over the course of 24 hours and then resolves spontaneously in the next 24 to 36 hours.

In many cases, the swelling begins spontaneously, but it can be triggered by minor injury, dental work, infection, stress, or menstruation. The frequency of the swelling is patient specific, occurring as frequently as once per week or as rarely as once per year. The disease is inherited commonly in an autosomal-dominant fashion; therefore, if a diagnosis of HAE is made, testing of first-degree relatives is recommended.

Diagnosis

Making the diagnosis of HAE can be difficult, and most HAE is not properly diagnosed for at least 10 years from onset of symptoms. The abdominal attacks may be mistaken for an acute abdominal condition, such as appendicitis or mechanical obstruction. The peripheral or facial edema may be mistaken for an allergic reaction or cellulitis. However, with proper suspicion, the diagnosis can be made promptly and confirmed by laboratory evaluation.

Some clinical features help to distinguish the angioedema of HAE from that of an allergic reaction. The angioedema of HAE occurs without pruritus or urticaria, develops more gradually over several hours, and is poorly responsive to antihistamines, corticosteroids, or epinephrine. Many patients describe a prodromal localized discomfort at the site of the swelling or fatigue up to 16 hours before the onset of swelling, which is in contrast to the acute onset of swelling that results from the more usual reactions to allergens.

Table 2. Comparison of Acute and Chronic Urticaria

	Acute Urticaria	Chronic Urticaria
Causes	Viruses Foods Medications Insect bites or stings Physical factors Allergens (pollens, animal dander)	Idiopathic Autoimmune Physical factors Medications Chronic infections Foods (rarely)
Evaluation	Skin prick or specific IgE testing based on history	Skin prick or specific IgE testing based on history Complete review of systems to evaluate for possible underlying infection or illness Consider screening laboratory tests
Treatment	Avoidance of offending agent, if known First- and second-generation histamine$_1$-blockers Add histamine$_2$-blocker Leukotriene modifier Oral corticosteroids reserved for refractory cases	Avoidance of offending agent, if known Treatment of underlying illness, if applicable First- and second-generation histamine$_1$-blockers Add histamine$_2$-blocker Leukotriene modifier Oral corticosteroids reserved for refractory cases Immunomodulators

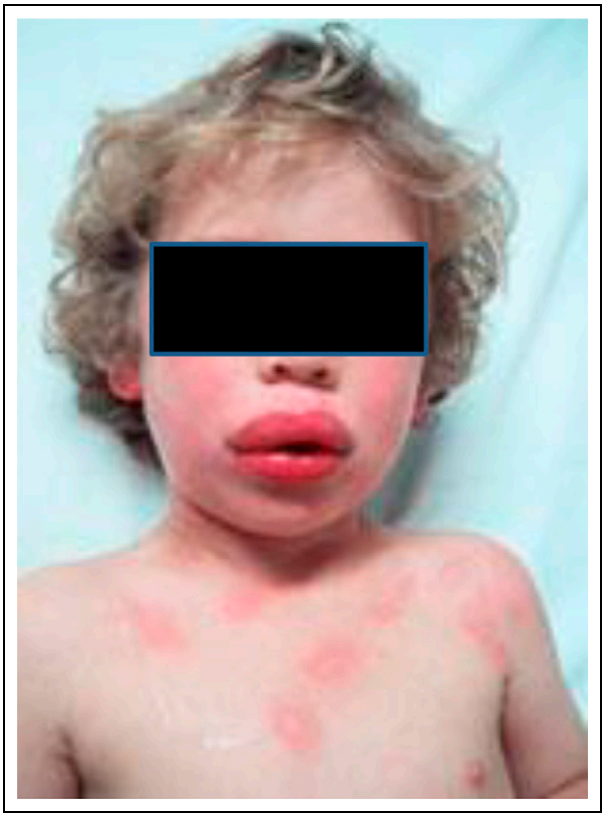

Figure 3. Significant lip angioedema with urticaria on the chest of a child.

The diagnosis of HAE is made by confirming a deficiency in the C1 inhibitor, either quantitatively or qualitatively. Measurement of complement levels is a valuable screening test. In HAE, the C4 level is low and the C3 level is normal, even in asymptomatic patients. Occasionally, C4 is normal even when the patient is asymptomatic; thus, definitive testing requires measurement of total and functional levels of C1 inhibitor. The level of C1 inhibitor must be less than 50% of normal on 2 separate occasions to make the diagnosis of type 1 HAE. For the diagnosis of type 2 HAE, the C1 inhibitor function must be less than 50% of normal on 2 separate occasions.

Treatment

The treatment of HAE begins with immediate management of the patient's airway, if compromised. Intubation may be necessary for protection of the airway if laryngeal edema is present. Supportive measures, including fluid administration, antinausea medication, and analgesics, may be appropriate for severe abdominal attacks. Once the patient is stabilized, the mainstay of treatment of HAE is replenishment of deficient C1 inhibitor. The most commonly used medication for treatment of an acute attack is human concentrate C1 inhibitor (Berinert®; CSL Behring, King of Prussia, PA). Fresh-frozen plasma also contains C1 inhibitor and other complement components and may be considered as a second-line therapy for acute attacks if C1 inhibitor concentrate is not available. Newer treatments are available, such as kallikrein inhibitor, ecallantide, and the bradykinin B_2-receptor antagonist, icatibant, but they have not been studied in children and should not be used.

In children with severe or frequent attacks occurring more than once per month, long-term prophylaxis should be considered. The 3 therapies used for short- or long-term prophylaxis are human C1 inhibitor (Cinryze®; ViroPharma, Inc, Exton, PA), attenuated androgens, such as danazol or oxandrolone, and antifibrinolytics, such as tranexamic acid.

Summary

- All patients at risk for anaphylaxis should carry the appropriately dosed epinephrine pen and be taught when and how to use the device.
- The causes of acute and chronic urticaria overlap, but often the specific cause is not found in cases of chronic urticaria. The mainstay of therapy for both acute and chronic urticaria is antihistamines.
- Food allergy is increasing in prevalence, especially in children. Food allergies to peanut, tree nuts, fish, and shellfish are usually life-long. Food allergies to milk, egg, soy, and wheat usually are outgrown by the first decade of life. It is important to identify the children who may be candidates for oral food challenges.

References

1. Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol.* 2010;126(3):477–480

2. American College of Allergy, Asthma, & Immunology. Food allergy: a practice parameter. *Ann Allergy Asthma Immunol.* 2006; 96(3 suppl 2):S1–S68

3. Waserman S, Watson W. Food allergy. *Allergy Asthma Clin Immunol.* 2011;7(suppl 1):S7

4. Golden DB, Moffitt J, Nicklas RA, et al; Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma & Immunology (AAAAI); American College of Allergy, Asthma & Immunology (ACAAI); Joint Council of Allergy, Asthma and Immunology. Stinging insect hypersensitivity: a practice parameter update 2011. *J Allergy Clin Immunol.* 2011;127(4):852-854

5. Gawchik SM. Latex allergy. *Mt Sinai J Med.* 2011;78(5): 759–772

6. Kelso JM, Li JT, Nicklas RA, et al; Joint Task Force on Practice Parameters; Joint Task Force on Practice Parameters for Allergy &

Immunology. Adverse reactions to vaccines. *Ann Allergy Asthma Immunol*. 2009;103(4 suppl 2):S1–S14
7. Pichichero ME. A review of evidence supporting the American Academy of Pediatrics recommendation for prescribing cephalosporin antibiotics for penicillin-allergic patients. *Pediatrics*. 2005; 115(4):1048–1057
8. Joint Task Force on Practice Parameters. The diagnosis and management of urticaria: a practice parameter part I: acute urticaria/angioedema part II: chronic urticaria/angioedema. *Ann Allergy Asthma Immunol*. 2000;85(6 pt 2):521–544
9. Zitelli KB, Cordoro KM. Evidence-based evaluation and management of chronic urticaria in children. *Pediatr Dermatol*. 2011;28(6):629–639
10. Hernandez RG, Cohen BA. Insect bite-induced hypersensitivity and the SCRATCH principles: a new approach to papular urticaria. *Pediatrics*. 2006;118(1):e189–e196
11. Wahn V, Aberer W, Eberl W, et al. Hereditary angioedema (HAE) in children and adolescents—a consensus on therapeutic strategies. *Eur J Pediatr*. 2012;171(9):1339–1348
12. Longhurst H, Cicardi M. Hereditary angio-oedema. *Lancet*. 2012;379(9814):474–481

PIR Quiz

This quiz is available online at http://www.pedsinreview.aappublications.org. NOTE: Learners can take *Pediatrics in Review* quizzes and claim credit online *only*. No paper answer form will be printed in the journal.

New Minimum Performance Level Requirements

Per the 2010 revision of the American Medical Association (AMA) Physician's Recognition Award (PRA) and credit system, a minimum performance level must be established on enduring material and journal-based CME activities that are certified for *AMA PRA Category 1 Credit™*. In order to successfully complete 2013 *Pediatrics in Review* articles for *AMA PRA Category 1 Credit™*, learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity.

In *Pediatrics in Review*, *AMA PRA Category 1 Credit™* may be claimed only if 60% or more of the questions are answered correctly. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

1. A previously healthy 12-year-old female developed hives, shortness of breath, and dizziness during her fourth-period class following lunch. For lunch the girl ate a peanut butter and grape jelly sandwich, an apple, a chocolate chip cookie, and a container of milk. Which of the following food items is most likely to have caused this reaction?

   A. Apple.
   B. Chocolate.
   C. Cow Milk.
   D. Grape Jelly.
   E. Peanut Butter.

2. For the girl in the previous question, the school nurse administered a dose of epinephrine. Shortly afterwards the girl felt well. Twenty minutes later, she began to experience similar symptoms. Which of the following actions is most appropriate to initiate now?

   A. Diphenhydramine.
   B. Epinephrine.
   C. Glucocorticosteroid
   D. Placement into the recumbent position.
   E. Ranitidine.

3. A 6-year-old male presented in late spring with large (3 cm by 3 cm) circular vesicular lesions with pinpoint centers distributed in a linear fashion on both lower arms. This was the fourth incident of similar symptoms. He has had no systemic symptoms. Which of the following is the most appropriate treatment for this child's lesions?

   A. Diphenhydramine.
   B. Epinephrine.
   C. Leukotriene modifier.
   D. Mid-potency topical steroid.
   E. Ranititdine.

4. Over a 24-hour period a 10-year-old girl developed swelling of her face, including lips and eyelids plus both hands. She had no itching or visible rash. She had a history of two previous similar episodes. She was otherwise well except for a recent tooth extraction in concert with placement of dental braces. Which of the following is the most appropriate next step in management for this child?

   A. C3 and C4 testing.
   B. Diphenhydramine.
   C. Epinephrine.
   D. Third-generation cephalosporin.
   E. Penicillin skin testing.

5. A 9-year-old boy developed nausea, abdominal cramping, vomiting, and diarrhea three hours after eating supper. He had eaten fish sticks, potato salad, and milk. He had no rash, swelling or other cutaneous findings. Which of the following treatments was most appropriate for this boy?

   A. Epinephrine.
   B. Diphenhydramine.
   C. Fluids.
   D. Glucocorticosteriods.
   E. Oxygen.

Parent Resources From the AAP at HealthyChildren.org

The reader is likely to find material relevant to this article to share with parents by visiting these links:

- http://www.healthychildren.org/English/health-issues/injuries-emergencies/Pages/Anaphylaxis.aspx
- http://www.healthychildren.org/English/health-issues/conditions/skin/Pages/Hives.aspx
- http://www.healthychildren.org/English/health-issues/conditions/skin/Pages/Hives-Symptoms.aspx

Anaphylaxis, Urticaria, and Angioedema

Emily W. Langley and Joseph Gigante

Pediatrics in Review 2013;34;247
DOI: 10.1542/pir.34-6-247

Anaphylaxis, Urticaria, and Angioedema

Emily W. Langley and Joseph Gigante

Pediatrics in Review 2013;34;247
DOI: 10.1542/pir.34-6-247