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Anaphylaxis

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Dr Waibel has disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

Objectives After completing this article, readers should be able to:

1. Delineate the diagnostic criteria for anaphylaxis.
2. List the most common causes of anaphylaxis.
3. Describe the different types of insect sting reactions.
4. Discuss the differences between acute and chronic urticaria.
5. List the appropriate laboratory tests for chronic urticaria.

Anaphylaxis

A 4-year-old boy is attending a friend's summer backyard party in south Texas. His mother finds him crying after two "ant bites." Within minutes, the boy becomes diffusely flushed and has multiple raised erythematous lesions, facial edema, and audible wheezing.

Anaphylaxis is an immediate and potentially life-threatening reaction to an allergen. Although this review provides the practicing pediatrician a general overview of anaphylaxis, both the American Academy of Allergy, Asthma, and Immunology and the European Academy of Allergology and Clinical Immunology have published excellent practice parameters and position papers that address diagnosing, managing, and treating anaphylaxis. (1)(2)

Epidemiology

The term anaphylaxis, derived from the Greek "a" (contrary) and "phylaxis" (protection), was coined in 1902 by Portier and Richet. Their original experiments with sea anemone and dogs demonstrated that reintroduction of toxic venom in dogs who tolerated an initial dose resulted in unexpectedly severe symptoms, including itching, vomiting, diarrhea, and death. Over the past 100 years, multiple causative agents have been identified in children, the most common being foods, drugs, and insects. During the past 20 years, reported anaphylaxis cases and prescriptions for adrenaline have increased significantly. The prevalence of life-threatening anaphylaxis is estimated to be 5 to 15 per 100,000 persons, but most experts agree that anaphylaxis is both underrecognized and undertreated.

Abbreviations

AAE:	acquired angioedema
ACAAI:	American College of Allergy, Asthma, and Immunology
ASST:	autologous serum skin test
C1INH:	C1 esterase inhibitor
CU:	chronic urticaria
EIA:	exercise-induced anaphylaxis
FcεR1:	high-affinity IgE receptor located on mast cells, basophils, macrophages, and dendritic cells
FDEIA:	food-dependent exercise-induced anaphylaxis
HAE:	hereditary angioedema
Ig:	immunoglobulin
OAS:	oral allergy syndrome
SCIT:	subcutaneous immunotherapy
SLIT:	sublingual immunotherapy

Pathogenesis and Clinical Criteria

Any child who presents with a suspected or known anaphylactic episode requires a complete evaluation to ascertain possible triggers. Although there are case reports of delayed reactions starting 2 or more hours after exposure, symptoms typically occur within minutes to an hour or two. The most common symptoms are cutaneous (pruritus, flushing, urticaria, or angioedema), which occur in 80% to 90% of children. Although no definition for anaphylaxis is universally accepted, consensus criteria for anaphylaxis were published in 2006 (Table 1). The two most recognized mechanisms for anaphylaxis involve: 1) cross-linking of high-affinity immunoglobulin (Ig) E receptors (FcεR1) of the surfaces of mast cells and basophils after binding IgE and 2) nonIgE-mediated

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Table 1. Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) involving the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips–tongue–uvula)
AND AT LEAST ONE OF THE FOLLOWING:
 - a. Respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
 - b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
 - a. Involvement of the skin–mucosal tissue (eg, generalized hives, itch–flush, swollen lips–tongue–uvula)
 - b. Respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced PEF, hypoxemia)
 - c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
 - d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
 - a. Infants and children: low systolic BP (age-specific) or greater than 30% decrease in systolic BP*
 - b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2×age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years. Reprinted with permission from Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second Symposium on the Definition and Management of Anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol*. 2006; 117:391–397.

ated direct activation of mast cells (eg, opiates, radiocontrast media, vancomycin).

If anaphylaxis is suspected, establishing the diagnosis is paramount, as is consideration of a referral to an allergist-immunologist who has specialized training and expertise regarding laboratory interpretation, allergen identification and testing, avoidance counseling, and discussion of the risks and benefits of therapeutic options.

Common Causes of Pediatric Anaphylaxis

FOOD. Although almost every food has been implicated, 90% of allergic reactions to food by children are caused by six allergens: milk, egg, soy, wheat, peanut, and fish. In the United States, peanuts and tree nuts account for most fatalities from cases of food anaphylaxis. IgE-mediated food reactions can range from atopic dermatitis to oral allergy syndrome (OAS) or anaphylaxis. Approximately 30% to 40% of moderate-to-severe cases of atopic dermatitis may be exacerbated by a food allergen. Physicians should consider skin or blood IgE testing for affected patients, but the specific selection of food tests and interpretation of the results should be undertaken carefully and often in concert with an allergist-immunologist. OAS frequently occurs in patients who have allergic rhinitis. Patients experience localized and generally self-limited reactions in the oropharynx to heat-labile food proteins. Common examples are raw fruits and vegetables such as apples, peaches, cantaloupe, celery, bananas, and potatoes.

DRUGS. Penicillin is the most common cause of drug-induced anaphylaxis. Because the likelihood of a true IgE-mediated penicillin allergy is less than 20%, based on history alone, patients often are referred to an allergist-immunologist for evaluation and skin testing. The negative predictive value of penicillin skin testing for immediate-type reactions is 97% to 99%, but standardized skin testing materials such as benzylpenicilloyl polylysine or minor determinants either no longer are available or are not approved by the United States Food and Drug Administration, respectively. Cephalosporins share the beta-lactam ring, but the low risk of cross-reactivity in penicillin-allergic patients prompted the 2001 American Academy of Pediatrics Subcommittee on Management of Sinusitis to recommend cephalosporins as long as the previous penicillin reaction was not “anaphylaxis.” For patients who have a history of penicillin anaphylaxis and require either penicillin or a cephalosporin, consultation with an allergist-immunologist should be considered, after which a detailed discussion usually ensues regarding avoidance, graded challenge, or drug desensitization. Nonbeta-lactam antibiotics, aspirin, nonsteroidal anti-inflammatory drugs, and chemotherapy agents account for the next most common drug causes. Skin testing procedures have been described for some drugs but are limited because they have not been studied in large pediatric cohorts.

INSECTS. The most common and well-validated causes of insect anaphylaxis occur from the order *Hymenoptera*. (3) The three *Hymenoptera* families of clinical importance are the vespids (yellow jackets, wasps, hornets), bees (bumbees and honeybees), and stinging ants (black and red fire ants). Transient and localized pain or itching, termed normal reactions, are the most common reactions and do not require allergy evaluation. The next type of stinging insect reaction is the large local reaction. Such reactions result in marked erythema and swelling that peak at 24 to 48 hours, often involve an entire extremity or cross a joint, and resolve without sequelae in 3 to 10 days. Large local reactions, which require only observation and symptomatic care, frequently are misdiagnosed as cellulitis. Large local reactions are important because they are IgE-mediated and increase the risk for future anaphylaxis with subsequent stings. However, most experts still regard this risk as low enough (~5% to 10%) not to warrant allergen immunotherapy or prescription of an epinephrine autoinjector.

When a systemic reaction occurs after an insect sting, obtaining the history is crucial. Children who experience cutaneous-only symptoms (ie, urticaria, angioedema, flushing) and who are younger than age 16 years at the time appear to be at significantly lower risk for future anaphylaxis (5% to 10%) compared with children who have respiratory, gastrointestinal, or cardiovascular symptoms (20% to 40%) or older adolescents (>16 years) who have cutaneous-only symptoms (10% to 20%). (4) For patients at higher risk for anaphylaxis, venom immunotherapy is available for the previously described insects and significantly reduces the reaction risk.

LATEX. Latex allergy is caused by sensitivity to antigens from the rubber tree *Hevea brasiliensis* and affects up to 75% of those who have spina bifida and 10% to 15% of health-care workers. The cause of latex allergy in patients who have spina bifida is unknown, but early and frequent exposure to latex-containing medical products is the suspected mechanism. Patients who have latex allergy often experience repeated reactions due to accidental exposure in other environments, such as during dental procedures or gynecologic examinations, after using latex condoms, when playing with balloons, and when using other products that contain latex. The American Latex Allergy Association can provide resources and detailed lists of alternate nonlatex-containing commercial products such as adhesive strips and swimming goggles (available at <http://www.latexallergyresources.org>).

VACCINES. Anaphylaxis after routine vaccination is rare, with the risk estimated at 0.65 cases per 1 million doses. Vaccine components that have been implicated include latex in vial stoppers, egg, gelatin, and neomycin. (5) For many vaccines, the decision to administer a subsequent dose to a patient who reports an immediate adverse reaction can be aided by skin or serum IgE testing to the implicated component (eg, gelatin) or skin testing to the vaccine itself.

PERIOPERATIVE ANAPHYLAXIS. Perioperative and interoperative anaphylaxis are rare, occurring in 1 in 5,000 to 1 in 25,000 operations. Common causes of anaphylaxis during this period include muscle relaxants, latex, antibiotics, induction agents, opioids, colloids, and blood products.

EXERCISE. Exercise-induced anaphylaxis (EIA) and food-dependent exercise-induced anaphylaxis (FDEIA) occur typically in older adolescents and young adults. Both can be life-threatening, but the food-dependent type occurs only when the patient has eaten within 2 to 4 hours of exercise. Interestingly, patients who have FDEIA do not have problems either exercising without having eaten or eating without having exercised. Some common foods associated with FDEIA are shellfish, wheat, and celery. Patients who have EIA usually describe symptoms starting at a reproducible level of intensity and often can avoid symptoms by reducing the intensity level of exercise.

IMMUNOTHERAPY. Subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) involve the administration of an allergen in increasing doses until a maintenance dose is reached. SCIT is approved for allergic rhinitis, allergic asthma, and hymenoptera anaphylaxis; SLIT has been successful in patients who are monosensitized to an aeroallergen. Most patients generally tolerate immunotherapy well, but patients receiving SCIT can experience anaphylaxis from the allergy shot (estimated risk is 1 in 200 to 1 in 1,000 injections). Rare cases of fatal anaphylaxis (1 in 2.5 million injections) have been reported. Patients are advised to remain in the clinic for 30 minutes after the injection because most reactions occur within this period.

IDIOPATHIC. Idiopathic anaphylaxis is a diagnosis of exclusion, and a careful history is required. Conditions that can mimic anaphylaxis should be considered in an extensive differential diagnosis for anaphylaxis. Such disorders include systemic mastocytosis, vasovagal re-

sponses, pheochromocytoma, severe asthma, globus hystericus, drug overdose, scombroidosis, and carcinoid syndrome.

Treatment

The most important aspect of treatment is to recognize the signs and symptoms of anaphylaxis. Because most children (80% to 90%) experience cutaneous symptoms, parents and clinicians alike often administer an antihistamine and observe the patient. A recent Cochrane review was unable to make any recommendations regarding histamine₁ (H₁)-antihistamines for the treatment of anaphylaxis. (6) Drug absorption for antihistamines may be slow, so when clinical improvement is seen after administration of H₁-antihistamines during anaphylaxis, it is likely due either to spontaneous improvement or endogenous compensatory mechanisms. If the scenario is anaphylaxis, epinephrine should be the initial and immediately administered medication. There is no absolute contraindication to administration of epinephrine in a child.

Although epinephrine may be administered subcutaneously, intramuscularly, intravenously, or endotracheally, most clinical presentations at school, home, or in a clinic prompt intramuscular administration in the lateral thigh, the preferred route and location. The recommended dose is 0.01 mg/kg, with a maximum initial dose of 0.50 mg.

Because patients who have a diagnosis of anaphylaxis always should carry an epinephrine autoinjector, the clinician must decide whether to provide the 0.15-mg or the 0.30-mg dose. Although the decision may appear easy (ie, children weighing up to 30 kg receive the “junior” and children weighing 30 kg and more receive the “adult” autoinjector), children who weigh 10 kg or less actually are “overdosed” and those weighing 20 to 29 kg are “underdosed” with the junior. Providing parents with a vial and syringe to allow for a more exact dose, however, is highly discouraged. If epinephrine is administered, patients should seek the emergency department because adjunctive measures such as the administration of oxygen, intravenous fluids, or intravenous epinephrine may be required in severe cases. Most episodes of anaphylaxis resolve after the initial epinephrine dose, but 10% to 20% of children may require a second dose. Children often are given a corticosteroid to help prevent a late-phase or biphasic reaction, although results are conflicting on its efficacy. Families should be advised that up to 20% of patients may experience a later reaction, usually 4 to 24 hours after the initial reaction.

Another question frequently asked is, “How many autoinjectors should the child have?” Children should

have an autoinjector for each location (eg, school, child care, home). Scenarios that support providing two autoinjectors for each location include the possibility of a misfiring, remote location, parent comfort level, or concern for failure to respond to the first dose (eg, child weighs >45 kg or uses beta blockers).

Training and Education

A recent collaboration of the American College of Allergy, Asthma, and Immunology (ACAAI) and the American College of Emergency Physicians resulted in a panel consensus regarding the approach to anaphylaxis. The SAFE system incorporates (S) seeking support, (A) allergen identification and avoidance, (F) follow-up for specialty care, and (E) epinephrine for emergencies. (7) A pivotal article on fatal and near-fatal anaphylaxis from peanuts and tree nuts observed that most patients knew the food to which they were allergic, but accidentally ingested it. (8) Children and families must remain vigilant, particularly those who have food allergy, to avoid causative allergens. Referral to an allergist-immunologist can help in interpreting symptoms, determining appropriate skin or blood testing, and providing ongoing management. Patients who are prescribed epinephrine should be taught: 1) the reasons to administer epinephrine, 2) the method of administering the epinephrine (eg, must identify the correct end to inject, pull off the cap, inject into the lateral thigh, hold for 10 seconds), and 3) what to do after administering the epinephrine.

Practitioners should ensure that patients are comfortable administering epinephrine, which is readily achieved with a trainer device, and document the appropriate education and autoinjector training in the patient's chart. Finally, the fluid in these devices should remain at room temperature (ie, not in the car or refrigerator), and the devices need to be renewed when they expire (typically 1 to 2 years) or change color from clear to brown. One resource that is recognized worldwide is the Food Allergy and Anaphylaxis Network (available at www.foodallergy.org).

Summary and Prognosis

Anaphylaxis is a life-threatening condition, most commonly associated with foods, drugs, and insects. The SAFE acronym provides a framework for evaluation and management, stresses recognizing symptoms of a reaction, and recommends treating anaphylaxis with epinephrine. One distinct observation in a case series of near-fatal peanut and tree nut anaphylaxis was that the children who survived received epinephrine prior to or within 5 minutes of the onset of severe symptoms. (8)

Finally, the differential diagnosis of sudden and unexplained death in a child (eg, collapse on the playground) should include anaphylaxis. Measurement of postmortem tryptase and chymase may help identify anaphylaxis as the cause. (9)

Urticaria

A 12-year-old girl presents with a 4-month history of frequent welts that occur on her trunk and extremities. Although the lesions last less than 1 hour, the welts may occur multiple times in a day and respond poorly to diphenhydramine. During three episodes, the patient also experienced lip and face swelling. There is no family history of urticaria or angioedema. The parents are frustrated because they have no idea why these episodes are occurring.

As discussed previously, urticaria can be a symptom of anaphylaxis. However, urticaria affects up to 25% of people at some point in their lifetimes and typically is not associated with more severe systemic symptoms. Because many families agonize over the possible cause of their child's urticaria, the approach to understanding the causes, available diagnostic tests and their limitations, and therapeutic options is important.

Definition

The most recent guideline regarding urticaria, published by a European expert consensus panel, begins with the three most important questions to ask a patient (or parent) who has either urticaria or angioedema: (10)

1. Are the clinical symptoms consistent with urticaria? Lesions may be raised or flat, but almost always are raised, are pruritic or burning, and have surrounding erythema. Urticaria may recur multiple times a day, daily, or intermittently. Individual lesions should resolve completely within 24 hours. Lesions that last longer than 24 hours or leave residual bruising or hyperpigmentation should be referred for a possible biopsy to rule out urticarial vasculitis.
2. Is angioedema occurring? If so, does it occur with or without urticaria? Patients who experience angioedema alone without urticaria should be evaluated for hereditary and acquired angioedema. Approximately 50% of patients who have urticaria experience angioedema. The angioedema generally occurs less often than the urticaria but usually coincides with the urticaria. Onset frequently is sudden, with pronounced swelling of the dermis typically involving the face and mucous membranes (eg, lips, tongue, and throat). Angioedema usually resolves in 1 to 3 days.

Table 2. Classifications of Urticaria

Spontaneous Urticaria

- Acute urticaria
- Chronic idiopathic urticaria
- Chronic autoimmune urticaria

Physical Urticaria

- Dermatographism
- Heat- or cold-induced urticaria
- Delayed pressure urticaria
- Cholinergic urticaria
- Contact urticaria
- Solar urticaria

3. Have urticaria symptoms lasted for more than 6 weeks? Urticaria lasting longer than 6 weeks is termed "chronic" and dictates a completely different discussion from that for acute urticaria. Most cases of chronic urticaria (CU) are classified into three groups: idiopathic, autoimmune, and physical (Table 2).

Acute Urticaria

Patients whose symptoms have lasted fewer than 6 weeks are considered to have "acute" conditions. A careful history often reveals recent nonspecific symptoms such as fever, sore throat, dysuria, or a sick contact. Almost 60% of cases of acute urticaria result from a proven or probable infection, usually viral. Reassurance and symptomatic treatment generally are all that is required.

Chronic Urticaria

The exact prevalence of CU in children is unknown, although it is considerably less than the estimated 1% prevalence for all ages. Invariably, one of the first requests of parents is to test for food allergies. Performing skin or serum IgE food testing in a child who has no substantiating clinical history is wrought with pitfalls. In addition, patients experience urticaria on days when their specific diet varies (ie, ate completely different foods) and on awakening hours after their last meal. Both scenarios are inconsistent with an IgE-mediated reaction. For these reasons, food or aeroallergen IgE testing is not recommended for children who have CU. Some studies have suggested that artificial flavors, colors, or additives (eg, tartrazine, monosodium glutamate, monosodium benzoate, sodium metabisulfate) are nonIgE-provoking "pseudoallergens" that cause 1% to 2% of CU cases. Most of these studies are in adults and demonstrate the lack of



Figure 1. Positive autologous serum skin test (ASST). Two intradermal skin tests are placed: human serum albumin control (-) and the patient's serum (S). The ASST (S) shows an 8-mm wheal compared with the 0-mm wheal of the negative control test (-).

symptom reproducibility in almost all patients during double-blind, placebo-controlled tests.

In recent years, from 30% to 50% of both pediatric and adult cases of CU have been identified as autoimmune. The mechanism involves a circulating autoantibody directed against the high-affinity IgE receptor (FcεR1) located on mast cells and basophils. Binding of this autoantibody leads to crosslinking of receptors, degranulation, and mediator release. One diagnostic test that may help identify such patients is the autologous serum skin test (ASST). A positive ASST is defined as the presence of a wheal 1.5 mm greater than the negative control with surrounding erythema, read at 20 to 30 minutes (Fig. 1).

Physical Urticaria

Dermatographism is the most frequent physical urticaria, affecting up to 5% of the population, and can coexist in patients who have CU. Patients who experience pruritus and a raised erythematous rash after scratching are classified as having “symptomatic” dermatographism (Fig. 2).

Other types of physical urticaria involve specific situations. Heat-induced urticaria is elicited after direct contact with hot objects. Heat-induced urticaria is different from cholinergic urticaria, which occurs during a brief increase in core body temperature such as during exercise, bathing, or sweating. Cold-induced urticaria occurs after exposure to cold air or cold water on the skin. Swimming in cold water has caused fatal reactions in

some patients who have cold-induced urticaria. Rarely, cold-induced urticaria is due to cryoglobulinemia, syphilis, or leukemia.

Delayed-pressure urticaria results in the development of typically painful and pruritic swelling 4 to 8 hours after significant pressure. Avoidance of causative factors (eg, heavy backpack, prolonged walking) can help, but most patients respond poorly to antihistamines. Contact urticaria usually is a localized IgE-mediated reaction to a specific agent such as food, aeroallergen (eg, rolling in the grass), animal, or cosmetic. Finally, solar urticaria is a rare disorder that is divided into six subtypes based on the suspected mechanism and causative wavelength.

Laboratory Testing

As discussed previously, the history and physical examination are the most important aspects of the evaluation. The ACAAI practice parameter on acute and chronic urticaria recommends considering a limited evaluation that includes complete blood count, erythrocyte sedimentation rate, liver function testing, and urinalysis. (11) However, if results of a complete history, review of symptoms, and physical examination do not suggest a specific cause, it is reasonable to delay testing until the symptoms are chronic.

Thyroid testing that includes measurement of thyroid-stimulating hormone and antiperoxidase antibody also should be considered in cases of CU. In one study of 187 consecutive children ages 4 months to 7 years who had CU, 8 (4.2%) had evidence of thyroid autoantibodies. (12) Interestingly, patients who have



Figure 2. An 18-year-old male who has dermatographism symptoms manifesting daily. Light scratching of the skin generates the typical raised wheal and surrounding erythema within 1 to 2 minutes.

CU and thyroid autoantibodies usually are clinically euthyroid and have normal thyroid-stimulating hormone values. Although antihistamines still are considered first-line therapy in these patients, some small case series have demonstrated success using low-dose thyroxine to resolve the CU.

Other suggested laboratory tests have included hepatitis B and C serology, *Helicobacter pylori* IgG, and *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* titers. In chronic urticaria, the ASST should be considered, although this testing generally is performed by the allergist-immunologist or dermatologist, who has access to intradermal testing materials. Finally, because of parental anxiety and fear of legal claims, practitioners often (and unnecessarily) perform extensive investigations to rule out a malignancy. In the absence of any pertinent signs or symptoms (eg, weight loss, lymphadenopathy, anemia, abdominal pain), the general practitioner should be reassured that extensive testing is neither warranted nor helpful in making the diagnosis. New in vitro assays assessing for the FcεR1 IgG antibody and basophil histamine release are gaining acceptability and are available commercially.

Treatment

The goal of treatment for urticaria is to block mast cell and basophil mediators (histamine and tryptase) and to modulate the inflammatory, cellular, and immunologic components of the urticarial process. The most common medication used for the treatment of urticaria is an antihistamine.

Determination of efficacy also depends on the patient's symptom frequency. For example, the clinical response should be evaluated within 7 to 14 days in a patient who has daily symptoms. On the other hand, patients who experience symptoms only a few times per month may require therapy for 2 to 3 months to ascertain effectiveness.

Second-generation H₁-antihistamines are considered first-line therapy. This drug class has the advantage of a low adverse effect profile with daily to twice-daily dosing. If the usual dose is ineffective, most experts recommend increasing the dose up to fourfold. Apart from terfenadine and astemizole, which have been withdrawn from the market in the United States, the safety profile of second-generation antihistamines at a fourfold increase remains excellent. Also, one second-generation antihistamine may be more effective than another, and failure of one does not necessarily represent a class failure.

In addition to a daily second-generation H₁-antihistamine, patients should be provided a "rescue"

first-generation sedating antihistamine (eg, diphenhydramine, hydroxyzine) for "breakthrough" symptoms. Daily use of a sedating antihistamine is less desired because of effects on school performance but may be required in severe cases. Other medications that do not have an approved indication for chronic urticaria but have been shown to be successful in clinical studies include H₂-antihistamines, leukotriene receptor antagonists, thyroxine, plasmapheresis, intravenous immunoglobulin, cyclosporine, colchicines, dapsone, sulfasalazine, omalizumab, and corticosteroids. Corticosteroids rarely are necessary for either acute or chronic urticaria. In addition, long-term use should be avoided because of adverse systemic effects.

Summary and Prognosis

Because most cases of urticaria are acute, spontaneous resolution should occur within days to weeks. Urticaria that becomes chronic has a poorer prognosis, with an average duration of 12 to 36 months. Patients who have more severe symptoms, coexisting angioedema, or the presence of autoantibodies to the FcεR1 receptor may have longer disease duration. Quality-of-life studies of patients who have CU demonstrate similar symptom scores compared with patients who have chronic depression. Education and counseling can help patients and families understand and accept CU. Decisions regarding the maximum dose of sedating and nonsedating antihistamines should balance potential benefits and sedation adverse effects. Although not recognized in any consensus documents or practice parameters, the International Chronic Urticaria Society provides much needed resources and links for patients who have chronic urticaria (available at <http://www.urticaria.thunderworksinc.com>).

Angioedema

A 19-year-old male presents with a dozen episodes of lip and facial swelling within the past 12 months. He denies any associated hives and is not taking any medications. He recalls that during high school football, his hands and elbows often swelled after getting tackled, although he attributed the swelling to trauma. Recently, he also has experienced episodes of abdominal pain.

Angioedema involves transient swelling of the dermis or subcutaneous tissue. As discussed, angioedema may be a symptom of anaphylaxis or occur during episodes of urticaria. However, the differential diagnosis for patients who experience angioedema alone should include hereditary (as described in the vignette) and acquired angio-

edema, idiopathic angioedema (most common), angioedema due to angiotensin converting enzyme inhibitors, and Gleich syndrome.

Hereditary angioedema (HAE) is rare, having a reported incidence of 1 in 10,000 to 1 in 50,000 individuals. Three types now are recognized, with type 1 accounting for 80% to 85% of cases. All three types can present with recurrent swelling episodes, recurrent attacks of abdominal pain, and episodes of airway obstruction. Up to 25% of patients describe a nonpruritic erythematous macular rash preceding the swelling episode. Types 1 and 2 generally are associated with a low C1 esterase inhibitor (C1INH) concentration and a non-functional C1INH, respectively. The loss of C1INH results in an inability to stop the complement cascade in affected patients, leading to depletion of C4, which is the appropriate screening laboratory test. Type 3 HAE occurs only in women and is associated with normal C1INH and C4 values.

Acquired angioedema (AAE) is less frequent than HAE in children. Type 1 AAE is associated with underlying lymphoproliferative disorders; type 2 AAE is associated with autoantibodies that inhibit C1INH function. Patients who have either type 1 and 2 AAE also have low C4 concentrations. Patients who have recurrent angioedema and eosinophilia without other organ involvement are considered to have Gleich syndrome, a disorder on the spectrum of hypereosinophilic syndrome.

Treatment

Untreated patients who have HAE or AAE are at significant risk for laryngeal edema and death. Specifically, surgical and dental procedures pose the highest risk because of laryngeal or palatal edema. Prophylaxis with an oral attenuated androgen is the preferred therapy in the postpubertal adolescent or young adult and can prevent most attacks. In Europe, purified C1 inhibitor concentrate is available as an intravenous infusion for either treatment of acute attacks or prophylaxis prior to surgery. Ongoing studies in the United States with C1INH concentrate have demonstrated equal promise. Previously believed to worsen possible angioedema episodes, fresh frozen plasma has been shown to be effective and safe both in preventing HAE exacerbations and for acute treatment. Although antihistamines, corticosteroids, and epinephrine are used for HAE attacks, none has been shown to alter the clinical course of the episodes.

Summary and Prognosis

With the addition of C1INH infusions and other developing therapies, patients may obtain excellent control of their symptoms. However, use of attenuated androgens generally is not recommended in prepubertal children, and C1INH substrate is awaiting approval in the United States. Referral to an allergist-immunologist can aid in identification and classification of the underlying cause. One resource for patients who have HAE or AAE is the United States Hereditary Angioedema Association (available at <http://www.hereditaryangioedema.com/>).

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Suggested Reading

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PIR Quiz

Quiz also available online at www.pedsinreview.org.

1. A previously healthy 5-year-old girl is brought to the emergency department soon after being stung by a "bee." You note several raised, white-red, intensely pruritic areas on her trunk; slight swelling of her lips and eyelids; and wheezing on auscultation of her chest. The *first* drug she should receive is:
 - A. Oral first-generation antihistamine.
 - B. Oral leukotriene receptor antagonist.
 - C. Oral second-generation antihistamine.
 - D. Parenteral epinephrine.
 - E. Parenteral glucocorticosteroid.
2. Among the following, life-threatening anaphylaxis in children occurs *most* often as a result of exposure to:
 - A. Exercise.
 - B. Foods.
 - C. Latex.
 - D. Perioperative drugs.
 - E. Vaccines.
3. A 12-year-old boy has a third episode of swelling of his lips associated with crampy abdominal pain. He has never had any hives or itching before and has none now. Your evaluation should begin with:
 - A. A complete blood count and differential count.
 - B. An autologous serum test.
 - C. Antiperoxidase antibody testing.
 - D. Complement 4 testing.
 - E. In vitro quantitative blood IgE testing.
4. A previously well 10-year-old boy has had hives for the past 2 days following a week of runny nose and cough during which no medications were administered. He has never had hives before. You suspect a viral origin. Findings on his physical examination, other than incessant scratching of obvious wheals, are unremarkable. Your *first* choice for treatment is:
 - A. Oral first-generation H₁-antihistamine.
 - B. Oral H₂-antihistamine.
 - C. Oral leukotriene receptor antagonist.
 - D. Oral second-generation H₁-antihistamine.
 - E. Parenteral epinephrine.
5. A previously well 13-year-old girl has had nearly daily hives for the past 6 months. The *most* likely explanation of her symptoms is:
 - A. Allergy to artificial flavoring.
 - B. An aeroallergen.
 - C. An occult food allergy.
 - D. Autoimmune urticaria.
 - E. Physical urticaria.

Anaphylaxis
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