Urticaria, Angioedema, and Anaphylaxis

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Practice Gaps

1. Recognize that chronic urticaria is not likely to be food related. Food testing is not indicated.
2. Understand the possible causes of urticaria.
3. Know the appropriate treatment of allergic and anaphylactic reactions.

Abstract

Urticaria and, to a lesser extent, angioedema are common occurrences in the pediatric population. There are multiple causes of acute and chronic urticaria and angioedema. Most causes are benign, although they can be worrisome for patients and their parents. An allergist should evaluate acute urticaria and/or angioedema if there are concerns of an external cause, such as foods or medications. Chronic urticaria and angioedema can severely affect quality of life and should be managed aggressively with antihistamines and immunomodulators if poorly controlled. Chronic symptoms are unlikely to be due to an external cause. Anaphylaxis is a more serious allergic condition characterized by a systemic reaction involving at least 2 organ systems. Anaphylaxis should be initially managed with intramuscular epinephrine. Patients who experience anaphylaxis should be evaluated by an allergist for possible causes; if found, avoidance of the inciting antigen is the best management. All patients should also be given an epinephrine autoinjector and an action plan. Foods are a common cause of anaphylaxis in the pediatric population. New evidence suggests that the introduction of highly allergic foods is safe in infancy and should not be delayed. In addition, the early introduction of foods such as peanuts may help prevent the development of food allergies.

Objectives

After completing this article, readers should be able to:

1. Identify the causes of urticaria, angioedema, and anaphylaxis.
2. Understand how to treat acute and chronic urticaria.

AUTHOR DISCLOSURE Drs Pier and Bingemann have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device in that there is no Food and Drug Administration (FDA) approval for cyclosporine in chronic urticaria. Also, antihistamines are recommended for use in non–FDA-approved doses in accordance with the literature for chronic urticaria and angioedema. Off-label use of agents for hereditary angioedema prophylaxis is also discussed.

ABBREVIATIONS

AAP	American Academy of Pediatrics
EIA	exercise-induced anaphylaxis
FDA	Food and Drug Administration
FDEIA	food-dependent exercise-induced anaphylaxis
Ig	immunoglobulin

3. Understand when and how epinephrine should be administered in the treatment of allergic reactions.

URTICARIA

Urticaria presents as raised, erythematous, and generally intensely pruritic wheals. Individual lesions usually last less than 24 hours but can migrate throughout the body and do not leave skin changes after resolution. Acute urticaria, which is most common in the pediatric population, occurs for less than 6 weeks, whereas chronic urticaria occurs most days of the week for more than 6 weeks. Chronic urticaria can be further delineated as spontaneous or inducible.

Urticaria is caused by the activation of dermal mast cells. Mast cells have the high-affinity receptor for immunoglobulin (Ig) E on the surface, which can be activated by cross-linking with IgE. Mast cells can also be activated through the interaction of IgG with the IgE receptor. This activation results in intracellular signaling and eventual downstream effects. Degranulation of the mast cell results in the release of histamine, serotonin, proteases, and tumor necrosis factor α. (1) Activated mast cells also release cytokines, such as interleukin-1, which results in continued inflammation. (1) Together, these substances result in the development of inflammation and, eventually, hives.

Acute Urticaria

Approximately 10% to 20% of the population will experience acute urticaria at some time in their life. (2) Acute urticaria has many causes, with the most common being viral infections, which has been attributed to approximately 40% of acute urticaria cases in both adults and children, with close to 60% in pediatric cases alone. (3)(4) Note that urticaria can occur both during and after an illness. Other potential causes of acute urticaria include medications (6.3%), insects (2.5%), and foods (1.3%) (Table 1). (5) As these percentages show, a specific cause of urticaria cannot always be identified. An allergy evaluation, including percutaneous skin prick testing and serum specific IgE levels, is warranted in the appropriate clinical setting, such as urticaria associated with food ingestion or medications. Of note, most IgE-mediated reactions, such as acute urticaria, occur within 2 hours of exposure. Two studies looking at food reactions showed that 100% of milk-allergic patients developed symptoms within 60 minutes of exposure, 79% of egg-allergic patients developed symptoms within 90 minutes of exposure, and 95% of peanut/tree nut–allergic patients developed symptoms within 20 minutes of exposure. (6)(7) This can help determine the potential trigger. Acute urticaria is treated with long-acting, nonsedating antihistamines, such as cetirizine or fexofenadine, until there is resolution. If a triggering antigen is found, avoidance is the definitive treatment (Table 2).

Chronic Urticaria

The prevalence of chronic urticaria is estimated to be 0.5% to 5% in all ages, with the prevalence in children estimated to be 0.1% to 0.3%. (8)(9) The mean age at presentation is 6.7 years. (10) Spontaneous chronic urticaria, which is the most common type in children, has no known underlying cause or triggers. Inducible chronic urticaria is associated with a physical stimulus. These can include pressure, cold, sun, and vibration. The most common cause is dermatographic urticaria, which is estimated to account for 38% of cases. (10) Cholinergic urticaria is another subset of physical urticaria that results from an increase in body temperature, such as when sweating, exercising, or taking a hot shower. (8) Cholinergic urticaria wheals are usually small and pinpoint. (8) Chronic urticaria has also been associated with infections, such as *Helicobacter pylori,* Epstein-Barr virus, hepatitis B, and hepatitis C. (10) If the history is suggestive of chronic urticaria, no specific diagnostic evaluation is indicated. If symptoms are suggestive of urticarial vasculitis (lesions that last longer than 24 hours, skin changes such as discoloration or bruising, or lesions that are palpable/nonblanching), the patient should have a skin biopsy.

Chronic urticaria is more common in patients, including children, with autoimmune disease. Both hypothyroidism and hyperthyroidism are more common in patients with chronic urticaria. In addition, patients with chronic urticaria are more likely to have thyroid autoantibodies even with normal thyroid function. Other autoimmune diseases found in patients with chronic urticaria include celiac disease, Sjögren disease, systemic lupus erythematosus, rheumatoid arthritis, type 1 diabetes mellitus, and cryoglobulinemia. (11)

Although chronic urticaria is not life-threatening, it greatly affects quality of life. The Chronic Urticaria Quality of Life Questionnaire is a validated set of questions to help assess

TABLE 1. **Causes of Acute and Chronic Urticaria**

ACUTE URTICARIA	CHRONIC URTICARIA
Illness	Spontaneous
Viral	Physical
Bacterial	Cold
Parasitic	Solar
Medications	Aquagenic
Antibiotics	Pressure
Nonsteroidal anti-inflammatory drugs	Vibratory
Narcotics	Cholinergic
Radiocontrast media	Autoimmune
Insects Wasps Hornets Bees Yellow jackets Fire ants	
Foods	
Aeroallergens	

the effect of chronic urticaria (https://www.itchingforanswers.ca/docs/CU-Q2OL-Questionnaire.pdf). Compared with healthy individuals, patients with chronic urticaria had reduced physical and psychological scores. (12) In addition, scores were similar to patients with acne and worse than patients with psoriasis. (12) Other studies have also found higher levels of anxiety and depression in these patients. (12)

First-line therapy for chronic urticaria is second-generation, nonsedating antihistamines (Table 2). Cetirizine, levocetirizine, loratadine, and fexofenadine are safe and effective in the pediatric population. For chronic urticaria in pediatric patients (age 1–17 years), doses may need to be increased to 4 times the standard dose to be effective. (10) This dosing is not approved by the Food and Drug Administration (FDA), and risks (mild increase in the incidence of somnolence and greater risk of adverse effects such as dry mouth and constipation) and benefits (improved control of urticaria) should be reviewed with patients/caregivers. For patients unresponsive to this therapy, sedating antihistamines, such

TABLE 2. **Treatment of Urticaria and Angioedema**

CONDITION	TREATMENT
Acute urticaria	Long-acting, nonsedating antihistamines Avoidance of trigger if identified
Chronic urticaria/angioedema	Long-acting, nonsedating antihistamines at standard dosing Increase dose of long-acting, nonsedating antihistamine up to 4 times standard dosing Sedating antihistamines Omalizumab Cyclosporine
Hereditary angioedema	Prophylaxis: Berinert, Cinryze, and Haegarda Treatment: Berinert, ecallantide, conestat alfa, and icatibant

as hydroxyzine, at standard dosing can be tried. When patients are unresponsive to high-dose antihistamines, omalizumab has been shown to be effective. Omalizumab is a monoclonal antibody that targets IgE and limits binding for IgE to high-affinity IgE receptors on mast cells and results in downregulation of the IgE receptor. Omalizumab is approved for patients 12 years and older for chronic urticaria. Dosing is 150 or 300 mg subcutaneously every 4 weeks and is not dependent on body weight or serum IgE level. (10) Cyclosporine has also been shown to improve hives and pruritus in patients with chronic urticaria; however, this is an off-label use and is reserved for refractory cases given potential adverse effects (kidney damage, hypertension, infection, headache). (1) The typical starting dose is 3 mg/kg divided into 2 daily doses. Blood pressure, kidney function, and fasting lipid levels should be monitored closely while patients are receiving cyclosporine. (13) Fortunately, chronic urticaria is self-limiting in many patients, especially children and those with no identifiable trigger; almost 50% are in remission after 1 year. (14) Approximately 30% of patients may continue to have symptoms beyond 5 years, and this group has not been well studied. (15)

Although the appearance of chronic urticaria is alarming, it is not life-threatening, and epinephrine autoinjector is not routinely indicated. The exception is cold-induced urticaria. Extensive cold contact, for example with water submersion, has the potential to result in anaphylaxis. (16) Therefore, patients with cold-induced urticaria should be prescribed an epinephrine autoinjector and educated on how to use it. (16) Cold avoidance as able is also recommended.

ANGIOEDEMA

Angioedema is nonpitting swelling of the submucosal or subcutaneous tissue. Typically this is asymmetrical, nondependent, and nonpruritic. It can occur in the extremities, abdomen, head/neck, and throat, which can be a medical emergency due to airway compromise. (17) Angioedema may be associated with urticaria (~40% of cases), usually due to histamine release, or without urticaria, typically kinin mediated. (18) Studies have suggested that 15% to 25% of the population experiences an episode of angioedema at some point in life. (15) Similar to urticaria, angioedema is classified as acute if it occurs for less than 6 weeks and as chronic if it occurs for more than 6 weeks.

Angioedema can be caused by mast cell degranulation, through similar mechanisms as described previously herein for urticaria, resulting in increased inflammation and vascular permeability. This type of angioedema is commonly accompanied by urticaria, suggesting that angioedema without urticaria is bradykinin mediated and not histamine mediated. Bradykinin results in vasodilation and increased vascular permeability. (19) Angioedema can result when too much bradykinin is being synthesized or when it is not being broken down. (19)

There are many causes of angioedema. Most cases are idiopathic, with no underlying cause identified. Angioedema can be associated with allergic triggers, such as foods, medications, insect stings, and aeroallergens. (20) These allergens cause angioedema through IgE-mediated mechanisms. Delayed angioedema has been described in the pediatric population after ingestion of mammalian meats, which is thought to be due to allergy to galactose-α-1,3-galactose. (21) Angioedema due to an allergy usually presents with urticaria, but it has been estimated that 10% to 15% of patients determined to have angioedema with an allergic trigger presented with angioedema alone. (17)

Infections, particularly viral infections, are a common cause of angioedema, especially in the pediatric population. Implicated infectious agents include herpes simplex, coxsackie A and B, hepatitis B, and Epstein-Barr virus; angioedema has been associated with otitis media, pharyngitis, sinusitis, and urinary tract infections. (17) Parasitic infection, such as with trichinosis, can cause angioedema. (13) Medications such as nonsteroidal anti-inflammatory drugs and angiotensin-converting enzyme inhibitors can also cause angioedema. Angiotensin-converting enzyme inhibitor angioedema can present at any time while taking the medication. Swelling occurs over hours and can last 1 to 3 days. (18)

Hereditary angioedema is an uncommon (1 in 10,000 to 1 in 150,000 affected worldwide), autosomal dominant condition that causes decreased levels or decreased function of C1-inhibitor protein, which leads to increased levels of bradykinin. C1-inhibitor dysfunction can be acquired, commonly due to underlying autoimmune disease or malignancy, which is rare in the pediatric population. (22) These forms of angioedema usually do not present with urticaria, which can be a helpful distinguishing factor. In patients with hereditary angioedema, symptoms initially present during late childhood and early adolescence. Approximately 50% of patients have their first attack before 10 years of age. (22) Symptoms typically worsen during puberty and continue throughout adulthood. The time between attacks is variable and can range from weeks to years. Most attacks occur without an identifiable trigger,

but some proposed triggers include cold, trauma, medications, infections, and stress. (22)

There are many conditions that mimic angioedema. Contact and irritant dermatitis can cause swelling and erythema. (13) Schnitzler syndrome typically presents with angioedema, nonpruritic rash, fever, and bone pain. (23) Swelling can also be a concern in a variety of connective tissue disorders, such as systemic lupus erythematosus, dermatomyositis, and Sjogren syndrome. Structural abnormalities, such as superior vena cava syndrome and other causes of obstruction to the venous outflow tract, can create swelling that mimics angioedema. (22)

Diagnosis of angioedema relies heavily on clinical history, including symptoms, associated physical findings, and possible triggers. If history is suggestive of an IgE-mediated mechanism, percutaneous skin testing and/or antigen specific IgE serum testing should be performed. If there is concern for hereditary or acquired angioedema (patients without accompanied urticaria), a C4 level is an appropriate initial screen, which would be low in these conditions. A C1-inhibitor level and function can be obtained if there is high clinical suspicion. If the results of this testing are normal, the diagnosis of idiopathic urticaria is made, and no further evaluation is typically warranted.

First-line management of angioedema is avoidance if a trigger has been identified. Similar to chronic urticaria, antihistamines titrated up to 4 times standard dosing have been used (Table 2). For refractory patients, sedating antihistamines (such as hydroxyzine) or immunomodulators (omalizumab or cyclosporine) have been added in the pediatric population. (17) For patients with hereditary angioedema, there are also numerous FDA-approved C1-inhibitor replacements for both acute attacks and prophylaxis. There are currently 3 plasma-derived C1-inhibitor concentrates—Berinert®, Cinryze®, and Haegarda®—available for prophylaxis in the United States. Cinryze (Takeda Pharmaceutical Co, Lexington, MA) is FDA approved for patients 6 years and older for prophylaxis; it is used off-label for acute treatment. Berinert (CSL Behring, King of Prussia, PA) is FDA approved for pediatric patients (age ≥6 years) as a treatment for hereditary angioedema and is also used off-label for prevention. Haegarda (CSL Behring) is approved for patients 12 years and older for prophylaxis. Other acute treatments include a kallikrein inhibitor, ecallantide (age ≥12 years); a recombinant C1-inhibitor preparation, conestat alfa (age ≥13 years); and a bradykinin B_2 receptor antagonist, icatibant (age ≥18 years). Berinert is the only FDA-approved treatment for acute flares in patients younger than 12 years. (18) Because hereditary angioedema is not histamine mediated it does not typically respond to corticosteroids, antihistamines, or epinephrine.

ANAPHYLAXIS

Anaphylaxis is defined as an acute, potentially life-threatening systemic reaction that may include respiratory distress, hypotension, urticaria, angioedema, and gastrointestinal symptoms (vomiting, diarrhea). (24) Although urticaria can be very concerning for parents, anaphylaxis occurs more rapidly and involves more than 1 body system. Anaphylaxis is caused by a similar mechanism as urticaria and angioedema, resulting in systemic vasodilation, increased vascular permeability, and bronchospasm. Anaphylaxis can present differently at different ages. Children younger than 6 years are more likely to experience vomiting and cough. Older children (approximately 12 years of age) are more likely to experience throat/chest tightness, dizziness, hypotension, and cardiovascular collapse. (25) It is estimated that the lifetime prevalence of anaphylaxis is 0.05% to 2.0%. (26) The incidence of anaphylaxis is 3 times higher in patients 0 to 4 years of age than in any other age group, and most episodes occur within the first 2 years of life. (26) Death from anaphylaxis is rare (0.12–1.06 deaths per million person-years). (27) Drugs are the most common cause of fatal anaphylaxis. (28) In pediatric patients, deaths are most common in adolescents, which has been attributed to an increase in risk-taking behaviors. (26) Risk factors for severe anaphylaxis include asthma and underlying respiratory/cardiac disease. (29)

There are many causes of anaphylaxis (Table 3). In infants and young children, the most common cause of anaphylaxis is food, with dairy, egg, and peanut being the most commonly identified culprits. (25) Tree nuts are also a cause of anaphylaxis in school-age children, with one studying finding the highest prevalence of cashew and hazelnut. (25) Galactose-α-1,3-galactose in mammalian meat can caused delayed angioedema, as mentioned earlier, and anaphylaxis several hours after exposure. (21) Food dye is not a common cause of food allergy. Drugs are also a cause of anaphylaxis (drug-induced anaphylaxis), and reactions typically appear in adolescence. Common culprits include antibiotics, analgesics, and radiocontrast media, which can cause anaphylaxis through IgE-mediated mechanisms and direct mast cell degranulation. (30) Shellfish allergy does not predispose to radiocontrast media allergy. (31) Latex is also a well-known cause of anaphylaxis. Current research suggests that in the general population the prevalence of latex allergy is approximately 4.3%. (32) However, the rates are higher in healthcare workers (9.7%) and susceptible patients (7.2%), such as

those with spina bifida and bladder exstrophy. (32) Anaphylaxis can occur after blood transfusion as well. This can occur in patients with IgA deficiency due to antibodies against donor IgA. (33)

Life-threatening systemic reactions to insect venom are rare. There are approximately 40 deaths per year due to insect venom. (34) The risk of a severe systemic reaction is approximately 0.4% to 0.8% in children and 3% in adults. (35)(36) Most reactions to insect venom are transient local swelling, erythema, or pain, which can be managed supportively. Large local reactions are characterized by swelling that is more than 10 cm in a continuous area. Patients with large local reactions have a less than 10% chance of anaphylaxis and, therefore, do not require insect venom immunotherapy. (37) Patients with systemic cutaneous reactions are also considered to be at low risk for anaphylaxis and do not require immunotherapy. However, lifestyle considerations (such as frequent time outdoors or hobbies with exposure to stinging insects), risk factors for future stings, and distance from health-care facilities need to be considered. Patients with a history of anaphylaxis to venom should be referred to an allergist for testing and likely initiation of venom immunotherapy because they have at least a 50% risk of anaphylaxis with subsequent stings. Venom immunotherapy is effective at decreasing the risk to less than 5%. (38) In addition to venom immunotherapy there is also fire ant immunotherapy. Unlike insect venom immunotherapy, the natural history is not as well established, and patients with limited systemic cutaneous reactions can be considered for immunotherapy. (38)

Immunotherapy is used for the treatment of allergic rhinoconjunctivitis and insect venom allergy. Subcutaneous immunotherapy is commonly given in pediatric offices for patient ease and preference. Immunotherapy can be given safely; however, providers should be aware of the potential risk of systemic reaction. Review of the literature suggests that systemic reaction to subcutaneous allergen immunotherapy is less than 1% but can increase up to 34% on rush protocols (where patients are given doses more frequently to reach maintenance dosing quicker). (39) The risk of systemic reaction increases during the height of pollen season and with dosing errors. (39) Patients should receive immunotherapy only when they are feeling well, and an assessment of lung function should be obtained before receiving immunotherapy for patients with asthma. Patients should be monitored for 30 minutes after injections because most reactions would occur during this time. Sublingual immunotherapy is available for grass (age 5–65 years), ragweed (age 18–65 years), and dust mites (age 18–65 years). Patients receive the first dose in a provider's office and take subsequent doses at home. The FDA requires that a script for self-injectable epinephrine be provided. The risk of systemic reaction is lower with sublingual therapy than with subcutaneous therapy and is estimated to be approximately 1 per 100 million. (40)

Exercise-induced anaphylaxis (EIA) and food-dependent EIA (FDEIA) are 2 rare but significant entities that clinicians should be aware of. In EIA, symptoms of anaphylaxis can be caused by a variety of activities, including yard work, walking, and running. (41) Symptoms can occur during or after physical activity, but it is usually difficult to predict attacks. In FDEIA, symptoms occur when there is an ingestion of the causative food minutes to several hours before exercise. Common causative foods include seafood, dairy, and wheat. Avoidance is the gold standard of treatment. Patients with FDEIA should avoid food ingestion 4 to 6 hours before exercise. (41)

The mainstay treatment of acute anaphylaxis is the administration of 1:1,000 epinephrine (0.01 mg/kg, maximum of 0.5 mg) intramuscularly in the anterolateral thigh, which can be repeated every 5 to 15 minutes as needed. (42) There are no absolute contraindications to the administration of epinephrine, and the delay in administration is associated with progression to severe anaphylaxis and potential death. (42) Airway protection and cardiovascular support with intravenous fluids should also be used in acute management. In addition to the previously mentioned therapies, β-adrenergic agonists, such as albuterol, can be used. (42) Antihistamines can be used for symptom control of urticaria and pruritus that may accompany anaphylaxis but should not be used as first-line therapy. In addition, there is limited evidence that corticosteroids should be used in anaphylaxis because they have not been shown to

TABLE 3. **Causes of Anaphylaxis**

Foods: peanuts, tree nuts, cow milk, eggs, shellfish, soy, wheat, fish
Medications: antibiotics (penicillins, cephalosporins), radiocontrast media, neuromuscular blocking agents, chemotherapy, nonsteroidal anti-inflammatory drugs, aspirin
Insects: wasps, hornets, bees, yellow jackets, fire ants
Allergy immunotherapy: subcutaneous, sublingual, oral immunotherapy
Latex
Exercise-induced, food-dependent exercise-induced
Idiopathic

decrease the risk of biphasic reactions. (43) In a biphasic reaction, patients will recover from their initial anaphylaxis but will have a recurrence of symptoms without being exposed to the triggering antigen. The second reaction typically occurs 8 to 10 hours after the initial reaction. (44) The reaction should be managed as any anaphylaxis. Patients should be monitored for 4 to 8 hours after experiencing anaphylaxis. Longer monitoring could be considered in patients with asthma, in those with a history of severe/biphasic anaphylaxis, and/or if they required multiple doses of epinephrine. (44)

Patients with a history of anaphylaxis should be prescribed an epinephrine autoinjector. An epinephrine autoinjector should also be prescribed to children with a history of food allergy, even if their initial reaction did not result in anaphylaxis. Previous allergic reactions do not predict future reactions, and anaphylaxis can occur with any allergen exposure. Children weighing 10 kg or less can receive a 0.1-mg dose (through Auvi-Q®; Kaléo, Richmond, VA), 10 to 30 kg can receive 0.15 mg, and greater than 30 kg can receive 0.3 mg. Auvi-Q is the only epinephrine autoinjector device approved for pediatric patients weighing less than 10 kg, and it has a shorter needle length. There are many devices for the other weight groups. Table 4 compares some of the available devices and their average costs, which will vary based on insurance plans. Epinephrine kits with vials or ampules of epinephrine are a low-cost alternative. However, these are not routinely recommended for home use given the high rate of error with dosing and timely administration. (46)

Parents and children, when age appropriate, should be educated on how to use the autoinjector, with correct use demonstrated during the visit. They should also be educated on the proper storage and the necessity to carry 2 autoinjectors at all times given that 30% of patients with anaphylaxis require a second dose of epinephrine. (42) Parents should also be educated that when using an epinephrine autoinjector it is important to immobilize the leg during administration to prevent lacerations and incomplete administration of the medication. If the needle comes out, it should not be inserted again. (47) There are websites that show patients how to use an epinephrine autoinjector, and these should be provided to patients when an autoinjector is prescribed (eg, www.epinephrineautoinject.com, www.epipen.ca, www.foodallergy.org, www.auvi-q.com).

Patients and their families should also be given an action plan, with instructions on what symptoms warrant the use of epinephrine. The American Academy of Pediatrics (AAP) Section on Allergy and Immunology has an allergy and anaphylaxis plan that can be found on the AAP website (https://healthychildren.org/SiteCollectionDocuments/AAP_Allergy_and_Anaphylaxis_Emergency_Plan.pdf). (48) Patients are commonly advised to use epinephrine for any respiratory symptoms and/or if more than 2 body systems are involved, such as hives (skin) with vomiting (gastrointestinal). Antihistamines can be used for mild allergic reactions, such as itching or a few hives, but are not first-line treatment for anaphylaxis. Food avoidance practices should be discussed, with potential referral to a dietitian who is familiar with pediatric food allergies. Any

TABLE 4. **Comparison of Epinephrine Autoinjectors (45)**

DEVICE	DETAILS	AVERAGE COST FOR A 2-DEVICE PACKAGE	ASSISTANCE PROGRAMS
EpiPen®, EpiPen Jr® (Mylan Inc, Canonsburg, PA)	Available in 0.15-mg and 0.3-mg prefilled syringes	$610	Savings card, patient assistance program, school programs
Adrenaclick® (Amedra Pharmaceuticals LLC, Horsham, PA)	Same as above	$395	Savings coupons
Generic autoinjector	Same as above	$300	
Auvi-Q®	Credit card sized with audio cues Available in 0.1-, 0.15-, and 0.3-mg dosing Smaller needle size	$4,900	Free for commercial insurance, patient assistance program
Symjepi™ (Sandoz Inc, Princeton, NJ)	Only available in 0.3-mg prefilled syringes currently	$250	
Epinephrine kits	Ampules or vials of epinephrine with needle and syringes	$20	

patient with anaphylaxis should be referred to an allergist for evaluation, who can perform testing when appropriate and reinforce teaching.

Food allergy is a significant concern among parents and pediatricians. A large population study in Australia used food challenges to verify food allergies in infants and estimated the prevalence of food allergies to be approximately 10% at 1 year of age. (49) A follow-up study at 4 years of age showed the prevalence of food allergies to be approximately 4%. (49) In recent years, significant studies have shown that early introduction of foods has the potential to decrease the risk of developing food allergies, leading to a change in recommendations of introducing highly allergic foods. The LEAP (Learning Early About Peanut Allergy) trial showed that early (5–11 months of age) introduction of peanuts into high-risk (severe eczema and/or known egg allergy) infants' diets greatly decreased the frequency of the development of peanut allergy in these high-risk patients. Based on the results of this study, it is now recommended that infants in these high-risk populations be referred to an allergist at approximately 4 to 6 months of age for skin testing, serum IgE testing, and likely oral challenge to peanut antigen when indicated. (50) This testing allows for further risk stratification of high-risk patients, with the hopes of capturing patients who have not yet developed peanut sensitization. These patients can then undergo oral challenge to peanut to confirm tolerance. For children with mild eczema, pediatricians should encourage the introduction of peanut antigen into the diet at 6 months of age. This can be accomplished through thinned peanut butter and/or peanut butter–flavored puffed maize (Bamba; Osem USA Inc, Englewood Cliffs, NJ). Infants and young children should not be given whole peanuts because they pose a choking hazard. Those without eczema can be introduced to peanut antigen per family preference.

There are currently no other recommendations on the early introduction of foods for the prevention of allergies. For example, the STEP (Starting Time of Egg Protein) trial showed that early introduction of egg protein into infants' diets did not significantly affect (although there was a trend toward significance) the development of egg allergy. (51) However, the early introduction of foods has been shown to be safe. In the EAT (Enquiring About Tolerance) trial, breastfed infants were given highly allergenic foods at 6 months of age, and there were no cases of anaphylaxis. (52) Currently it is not recommended to delay the introduction of foods, including highly allergenic foods. Infants should be introduced to these foods, as well as other non–highly allergic foods, when developmentally appropriate (usually 4–6 months of age). This has the potential to limit the development of food allergies with little risk of a systemic reaction. (53)

Summary

- Based on epidemiologic studies, acute urticaria is common in pediatric patients. (2) Although less common than acute urticaria, chronic urticaria also affects the pediatric population. Chronic urticaria is not life-threatening but can severely affect quality of life and warrants aggressive management. (8)(9)(12) Based on some research evidence as well as consensus data, chronic urticaria should initially be managed with high-dose antihistamines. Patients may require up to 4 times standard dosing for symptom control. (10)
- Based on some research evidence as well as consensus data, patients with chronic urticaria who do not respond to antihistamines may benefit from omalizumab. (10)
- Based on epidemiologic studies, angioedema is less frequent than urticaria but can occur in the pediatric population (with or without hives). Angioedema can be treated similarly to chronic urticaria. (15)
- Based on epidemiologic data, anaphylaxis in pediatric patients is most commonly due to foods, medications, and insects. (25)(29) First-line treatment for anaphylaxis is intramuscular epinephrine. (41) Corticosteroids, albuterol, and antihistamines can be used for symptomatic treatment of anaphylaxis. (43) Patients with a history of anaphylaxis should be prescribed an epinephrine autoinjector and an anaphylaxis action plan. (42)(48)
- Based on some research evidence, early introduction of peanut (approximately 4–6 months of age) may decrease the likelihood of the development of peanut allergies in high-risk infants. (50) Parents should not delay the introduction of other highly allergenic foods. (53)

PRACTICAL TIPS

- Chronic urticaria rarely has an external trigger. Laboratory evaluation and/or skin prick testing is not indicated in the absence of other systemic symptoms.
- Epinephrine is first-line therapy for anaphylaxis. Patients with a known allergy should be prescribed an epinephrine autoinjector and educated on how to use it.
- Early introduction of peanuts has been shown to decrease the risk of peanut allergy. Patients with severe eczema and/or egg allergy should be referred to an allergist for possible peanut introduction at 4 to 6 months of age.

References for this article are at http://pedsinreview.aappublications.org/content/41/6/283.

Pir Quiz

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1. A previously healthy 8-year-old boy is seen in the office with a complaint of itchy rash on and off for the past 7 weeks. His father reports that the itching occurs spontaneously with no identified trigger and can occur day or night. The family notes that the lesions are constantly fading away and new ones appearing. He has been active in his usual sports and school activities, and there is no change in the itching frequency with or without exercise. There has been no change in his breathing pattern or his appetite, and no associated fever. On physical examination of his skin there are numerous broad, raised areas of blanching erythema over his trunk and limbs. He has superficial excoriation marks but no open skin lesions. Which of the following is the most appropriate next step in the diagnostic evaluation at this time?
    A. Elimination diet.
    B. Hepatitis C immunoglobulin (Ig) G/IgM.
    C. No specific evaluation is indicated.
    D. Rheumatoid factor.
    E. Skin biopsy.
2. In approaching treatment for the patient in question 1, the clinician discusses with the family the most likely diagnosis and the recommended treatment plan. Which of the following is the most appropriate medication recommended for the treatment of this patient at this point in his course?
    A. Cyclosporine.
    B. Epinephrine.
    C. Fexofenadine.
    D. Hydroxyzine.
    E. Prednisolone.
3. A 16-year-old girl is brought to the emergency department for facial swelling. She was studying after eating dinner when she suddenly developed swelling of her face and lips. She is anxious and has some vague abdominal pain, but no vomiting, diarrhea, or respiratory distress. She is not itchy. Her physical examination is remarkable for nonpitting edema of the entire face such that her eyes are swollen shut and her speech is difficult due to extreme swelling of the lips. She does not have any rash. Which of the following is the most appropriate initial screening test in this patient?
    A. Anti-C1 level.
    B. Anti–galactose-α-1,3-galactose level.
    C. C4 level.
    D. Radioallergosorbent testing.
    E. Skin prick testing for allergic triggers.
4. An 11-year-old boy is referred to an allergist for grass allergies. He is scheduled to receive immunotherapy in the office. The allergist explains to the family how immunotherapy works and the risks associated with it. The parents are concerned about the child having a severe systemic reaction during immunotherapy. The allergist reassures the family that he and his staff will be prepared to provide emergency care in the unlikely event that a systemic reaction to immunotherapy occurs. Which of the following situations most elevates the risk of anaphylaxis during immunotherapy?
    A. Accelerated dosing schedule.
    B. Patient age.
    C. Sublingual route.
    D. Treatment during weeks with low pollen count.
    E. Upper respiratory infection.

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5. A 2-year-old child is brought to the urgent care center after developing a widespread rash consisting of red, raised wheals approximately 3 to 5 cm in diameter, oval in shape, and scattered over his entire body. He vomited twice in the car and is breathing rapidly, with a faint wheeze detectable from across the examination room. Which of the following is the most appropriate treatment to deliver at this time?

   A. Albuterol, 2.5 mg, nebulized inhalation.
   B. Diphenhydramine, 12.5 mg orally.
   C. Epinephrine, 0.15 mg intramuscularly.
   D. Epinephrine, 0.15 mg intravenously.
   E. Epinephrine, 0.15 mg subcutaneously.

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