

PEDIATRIC URTICARIA AND ANGIOEDEMA

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It is estimated that 15% to 25% of the general population experiences at least one episode of acute, transient urticaria or angioedema. Although children are affected frequently, the precise incidence in childhood is not known.

Urticaria and angioedema should be regarded as symptoms that might be triggered by a wide range of exogenous factors or endogenous disease states with allergic, inflammatory, or infectious mechanisms. Although urticarial lesions are typically benign, the intense pruritus and chronicity may produce significant distress. In contrast, angioedema of the upper airway may be life threatening. Regardless, an acute episode of urticaria or angioedema is often frightening to parents and the affected child, prompting consultation with a physician. All too often there is a tendency to assume a casual attitude toward common, benign children's dermatologic problems. Parental anxiety and patient suffering can be serious consequences of dismissing hives as something that will "just go away." As urticaria can be one symptom of a clinical spectrum, ranging from vasculitis to anaphylaxis, it should be approached in a mechanistic manner with logical protocols.

Although the cause of an acute episode is sometimes evident from a carefully obtained history, selected laboratory studies are helpful in some cases. In chronic urticaria, an underlying cause is frequently not determined, leading to frustration among patient, parents, and physician. Parents frequently seek the opinion of allergists or dermatologists in the hopes of discovering the cause. Fortunately, acute urticaria is more common in children and young adults while the peak incidence of chronic urticaria is during the third and the fourth decades.

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IMMUNOLOGY AND ALLERGY CLINICS OF NORTH AMERICA

PATHOPHYSIOLOGY AND HISTOLOGY

Histology

Although various pathogenic mechanisms may be involved in acute and chronic urticaria, the final histologic pattern is similar. Acute urticarial lesions show vasodilation and engorgement of capillaries and small venules; superficial dermal lymphatic vasodilation; widening of the dermal papillae; and flattening of the rete pegs secondary to extravasation of fluid, swelling of collagen fibers, and absent or minimal perivascular infiltrate that may contain eosinophils. The findings are similar in angioedema except they are located deeper in the submucosal or subcutaneous tissues. There is no evidence of vascular damage, red-cell extravasation, or nuclear debris as seen in urticarial vasculitis. In chronic urticaria, in addition to increased numbers of skin mast cells, a late-phase-like reaction can be seen with the early influx of neutrophils followed by lymphocytes within 24 hours. Lymphocytes are primarily CD4⁺ phenotype that express the HLA-DR antigen. Occasionally, persistence of neutrophils in the postcapillary venule is seen that may be an intermediate phase between ordinary urticaria and urticarial vasculitis.²² Eosinophils may contribute to the inflammatory process by further release of major basic protein and other chemical mediators.⁶³ Enhanced expression of adhesion molecules such as E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule (VCAM-1) on vascular endothelial cells may explain cell recruitment in the skin lesions.²² Pathophysiologic mechanisms to explain urticaria can be divided into immune mediated, complement mediated, and non-immune-mediated.

Immune-Mediated

When specific IgE antibodies bound to basophils or tissue mast cells interact with food proteins, drugs, or venom (hymenoptera or fire ant), a variety of preformed mediators of inflammation with vasoactive properties are released. Histamine elicits the triple response of Lewis with initial erythema (vasodilation), edema (vasopermeability), and secondary flare (axon reflex with arteriolar dilatation). Autoantibodies of the IgG type directed against IgE and the high-affinity IgE receptor on basophils has been identified in adults who have chronic idiopathic urticaria, but has not been demonstrated in children.²⁷ Sera from patients who have chronic idiopathic urticaria has histamine-releasing activity. Such mediators have been termed *histamine-releasing factor*.⁶⁷ When such serum is added to basophils from normal donors, histamine is released, although there is variable individual effect with different normal donors.

Complement-Mediated

Serum sickness, vasculitis, and acquired angioedema are examples of complement-mediated urticaria or angioedema. The complement products C5a, C3a, and C4a are capable of triggering mast-cell histamine release and are known as anaphylatoxins. Complement activation appears to be associated with urticarial lesions in patients who have collagen vascular diseases, including systemic lupus erythematosus. Complement fixation explains urticaria that follows reactions with blood product administration.¹³

Non-Immune-Mediated

Mast cells may be activated and degranulate as the consequence of non-IgE-mediated influences like physical stimuli and certain chemicals or drugs such as radiocontrast media or opiate narcotics. A more extensive list has been previously described.⁹

Mediators

Histamine

Preformed histamine released from tissue mast cells plays a major role in urticaria. It can be found in increased concentrations in skin-tissue fluid in urticaria.

Eicosanoids

Prostaglandins and leukotrienes derived from mast cells are important vasoactive molecules. When injected into the skin, prostaglandin D₂ and leukotriene C₄ can illicit an urticarialike reaction. Their contribution to urticaria and angioedema is not well established.⁶³ Other mediators such as kinins, neuropeptides in sensory nerves in the skin⁶³ (substance P, vasoactive intestinal polypeptide, calcitonin gene-related peptide and neuropeptide Y, and adenosine triphosphate), neutral proteases, cytokines, and platelet-activating factor may also play a role.

Clinical Features

Recognizing urticaria or angioedema rarely presents a clinical problem. Acute urticaria is arbitrarily defined as lesions occurring less than 6 weeks in duration often without angioedema. Lesions can occur on any part of the body and are usually raised, smooth, circumscribed, pink to erythematous, blanch with pressure, and characteristically intensely pruritic. The edges are serpiginous and well demarcated. Both the size and pattern may be quite variable with individual lesions ranging from a few millimeters in cholinergic urticaria to as large as 30 cm and occasionally coalescent. The centers of the lesions may appear blanched and annular, similar to erythema multiforme. However, lesions of erythema multiforme characteristically are slightly raised and have a dark cyanotic, central area giving the lesion a target appearance. Also, erythema multiforme lesions of the iris type are symmetrical round, red or purple, and usually found on the extremities, including the palms, back of the hands, forearms, dorsa of the feet, soles, and lower legs. An individual urticarial lesion may wax and wane in intensity and size and be present from minutes to hours to days but rarely lasts longer than 12 hours depending on pharmacologic intervention and the underlying cause. Therefore, if lesions persist longer than 24 hours, other diagnoses should be sought. Erythema multiforme is self-limiting with recovery in approximately 3 weeks. The fleeting nature, pruritus, and typical histology define urticaria. In a recent prospective study of acute urticaria in 57 infants and young children presenting to an emergency department, a presumptive cause was identified or suspected in 92% of patients.⁴¹ Acute urticaria appears to occur more frequently in atopic children.⁵

Chronic urticaria occurs regularly for longer than 6 weeks, but does not differentiate between daily lesions and recurrent episodic lesions. Chronic urticaria is less common than acute urticaria in children. Frequently, an underlying cause is not confirmed even though nearly two thirds of patients or parents may associate a particular factor with the hives. However, in 85% of patients, no trigger could be determined after challenge testing. In those with underlying diagnoses, 8% had physical urticaria (cold induced); 3% were diagnosed as having immunologic or collagen vascular diseases (juvenile rheumatoid arthritis); 2% were diagnosed as having infections (hepatitis, sinusitis); and 2% were diagnosed as having food allergy. In a retrospective review of chronic urticaria in 94 children, the median age was 6 years old and the median duration of urticaria was 16 months. There was no gender predilection or increased incidence of atopy. Although the diagnosis was elusive in 79% of patients, the prognosis was good.²⁵ The causal factors responsible for urticaria in 44 children who presented to an urticaria clinic were examined retrospectively. Nearly all patients were older than 14 years of age and most (80%) had chronic urticaria. A definitive or probable causal factor was identified in 75% of the children with most having physical urticaria.²¹

Angioedema is a similar process that occurs in the deeper subcutaneous layers of the skin or mucous membranes, giving rise to nonpitting, stretched, colorless, well-demarcated skin lesions. Characteristically, pruritus is absent, as there are fewer mast cells and sensory nerve endings in this area, but patients report a burning or a tingling sensation. Most frequently, angioedema affects the face—particularly the lips—tongue, perioral and periorbital areas, extremities, genitalia, and scalp. Unlike other forms of edema, angioedema is transient, occurs in asymmetric distribution, and has no predilection for dependent areas. The origin of angioedema is probably similar to that for urticaria and it frequently coexists with urticaria. Angioedema without urticaria is less common and other less common disorders, including hereditary angioedema, need to be considered. Table 1 outlines various triggers of pediatric urticaria and angioedema.

SPECIFIC ENTITIES

Physical Urticaria

Physical urticaria commonly presents as chronic or recurrent with approximately 20 types of physical urticaria. The physical stimuli include precipitants such as mechanical, thermal, exercise, sun, and water exposure. Generally, they are more common in young adults, and symptoms are usually limited to the area of physical stimuli. These have been reviewed in detail elsewhere.^{12, 44}

Dermographism

Dermographism is the most prevalent physical urticaria, affecting 2% to 5% of the population. Linear pruritic wheals appear on areas of skin within 2 to 5 minutes of stroking and resolve over 30 minutes to 3 hours. Only a small portion of affected patients are symptomatic and require treatment with antihistamines. Systemic symptoms are absent. Common triggers include scratching oneself and contact with clothing, towels, or sheets. Dermographism may follow an acute viral infection or drug reaction and the duration is variable.⁴⁴

Table 1. TRIGGERS OF PEDIATRIC URTICARIA AND ANGIOEDEMA

Ingestants	Other
Foods: eggs, nuts, peanuts, shellfish, fish, milk, exotic fruit, berries	Hereditary Angioedema
Additives: tartrazine, azo dyes, benzoates	Amyloidosis with deafness and urticaria
Drugs: antibiotics, aspirin, NSAIDs, narcotics	C3b inactivator deficiency
	Psychic factors/Stress
	Idiopathic
Contactants	
Plant substances: stinging nettle	
Food, animal saliva	
Topical medications	
Insects: moth, caterpillar	
Injectants	
Drugs: antibiotics, blood products, antisera, vaccine, radiocontrast media, insulin	
Allergenic extracts	
Insect sting/bites	
Inhalants	
Food: fish	
Pollen, dander, molds	
Infectious Agents	
Parasite: Ascaris, Toxocara	
Virus: respiratory, hepatitis, EBV, HSV	
Bacteria: Streptococcus	
Fungal: Trichophyton	
Protozoal	
Physical Factors	
Dermographism, cold, delayed pressure, solar, aquagenic, local heat, exercise, vibratory, cholinergic	
Systemic Disease	
Collagen-vascular disorders (SLE)	
Cutaneous vasculitis (HSP)	
Serum sickness	
Malignancy (leukemia/lymphoma)	
Endocrine disorders: thyroid	
Urticaria pigmentosa/systemic mastocytosis	

EBV = Epstein-Barr virus; HSV = herpes simplex virus; SLE = systemic lupus erythematosus; HSP = Henoch-Schönlein purpura.

Cold Urticaria Syndromes

Urticaria or angioedema can develop after cold exposure. Cold urticaria syndromes are divided into acquired and familial, based on the response to a cold stimulation. The incidence of atopy in patients who have cold urticaria is similar to that found in the general population.⁶⁴

Primary acquired cold urticaria, the most common form, is induced by exposure to cold air, rain, snow, swimming, the handling of cold objects, or the ingestion of cold liquids or foods. The diagnosis is made from history, an ice-cube test, and lack of evidence for underlying diseases such as malignancies, vasculitis, and infections. The mechanism is unclear, but passive transfer studies suggest serum factors with autoantibodies directed against IgE are present and a cold-dependent skin component is required. Suggested laboratory tests in the

evaluation are complete blood count (CBC), erythrocyte sedimentation rate (ESR), antinuclear antibody (ANA), syphilis serology and infectious mononucleosis serology, rheumatoid factor, complement levels, and cold reactive proteins (cold agglutinins, hemolysin, and cryoglobulin). The diagnosis is confirmed with the ice-cube test when an immediate wheal and flare or angioedema occurs at the site of an ice cube [or other object 0°C to 4°C (32°F to 39.2°F)] on rewarming. Skin biopsy studies from affected patients reveal significant histamine release when exposed to temperatures near 0°C to 4°C (32°F to 39.2°F) then rewarmed to 37°C (98.6°F). Skin chilled to 4°C (39.2°F) without rewarming did not release histamine. This suggests that both the temperature of the exposure and the change in temperature (i.e., rewarming) plays a role in histamine release and symptom manifestation. Systemic symptoms, including syncope related to hypotension, can occur depending on the total surface area of exposure. If the history is suggestive yet the ice-cube test is negative, consider other cold urticaria syndromes. For example, systemic atypical acquired cold urticaria describes lesions appearing on skin areas not directly exposed to the cold but after a cold stimulus like inhaling cold humid air. Cold-dependent dermatographism occurs when cooled skin is stroked but not when it is warm. Cold-induced cholinergic urticaria occurs when exercising in cold environments but not when exercising in warm environments. Delayed cold urticaria or localized cold-reflex urticaria refers to local hives developing 12 to 48 hours after a natural cold exposure or after the ice-cube test. A familial form of this is inherited in an autosomal dominant manner.

The natural history of acquired cold urticaria is spontaneous resolution between 5 and 9 years after its onset. Although generally benign, shocklike reactions can occur after aquatic activities and serious underlying disorders can be associated.⁶⁴ The main objective in management is prevention of shock during aquatic and cold-weather activities. Swimming should be avoided until symptoms have spontaneously resolved. Various first-generation antihistamines effective in suppressing the symptoms include diphenhydramine, tripeleminamine, cyproheptadine, doxepin, hydroxyzine, and combinations of H₁ and H₂ antagonists. The second-generation antihistamines have not been thoroughly studied in cold urticaria. Other medications used for cold urticaria include ketotifen, doxantrazole, and penicillin. Corticosteroids have no role in the treatment of cold urticaria. Those who choose to swim should swim with a partner and have epinephrine available.⁶⁴

Cholinergic Urticaria

The peak onset of cholinergic urticaria is between 10 and 30 years of age and may account for 5% of all urticaria. The classic fried egg appearance is punctate, 2- to 3-mm pruritic wheals surrounded by large erythematous flares. These may coalesce and be indistinguishable from other forms of urticaria. Elevated body temperature as occurs with exercise, hot showers, and the bundling on of clothing are typical triggers. Fever and sweating are not associated with cholinergic urticaria. The mechanism is mast-cell degranulation with cholinergic substances released from peripheral nerves. The diagnosis is best made from history, although passive heat challenge by partial submersion in a 40°C (104°F) water bath until the core body temperature has increased by at least 0.7°C (1.26°F) can be performed. Skin testing with 100 µg methacholine in 0.1 ml of saline is positive in less than half of those affected. The specificity of this test is high. Exercise challenge is not useful as this does not discern between

exercise-induced anaphylaxis and exercise-induced cholinergic urticaria. Local heat challenge is also not useful for cholinergic urticaria but can confirm the unusual disorder termed *localized heat urticaria*. Prevention of cholinergic urticaria includes avoidance of hot tubs and exercising in hot weather. Pharmacologic treatment is typically effective with hydroxyzine. Epinephrine should be available and rapid cooling with a cold shower may abort an attack.⁴⁴

Solar Urticaria

Solar urticaria, a rare disorder, occurs within minutes after sunlight exposure. Hives are confined to light-exposed areas but may extend peripherally. Six types are based on the wavelength of light responsible. The mechanism is mast-cell degranulation, and a chromophore in the serum may induce a chemical change with the development of either a specific or a nonspecific photoallergen.³² Solar urticaria can be passively transferred. If a large area of skin is exposed, bronchospasm or hypotension can occur.^{32, 62} It is important to exclude erythropoietic protoporphyria, which is characterized by elevated red-cell-free protoporphyrin levels with normal urinary porphyrins.⁶⁶ The other photosensitivity disorders porphyrias have significantly elevated levels of urinary porphyrins.

Therapy includes sun avoidance, sunscreens, and antihistamines. Anecdotal reports suggest effectiveness with antimalarials, beta carotene, indomethacin, H₂ blockers, and doxepin. If circulating photoallergens are detected, plasmapheresis may be useful. Tolerance may be induced with phototherapy with psoralen ultraviolet A (PUVA) resulting in long-term remission if therapy is maintained.⁶²

Delayed Pressure Urticaria

This rare entity presents as deep, localized, painful swelling 3 to 6 hours after sustained pressure has been applied to the skin for at least 2 minutes. Typically the buttocks, soles, palms, and the skin beneath shoulder straps are affected. Fever, malaise, and headache may be present. Diagnosis is from history and challenge test with a 10-kg weight placed on the thigh or forearm with lesions developing at 4 to 8 hours and lasting 24 hours. The favorable response to oral corticosteroids and the poor response to antihistamines distinguishes this from other physical urticarias.⁴⁴ Cetirizine is helpful presumably because of its effect on eosinophil and neutrophil chemotaxis.⁴⁶ Nonsteroidal antiinflammatory drugs (NSAIDs) may also be helpful.

Vibratory Angioedema

This rare entity presents as angioedema within minutes of a vibratory stimulus such as with toweleling, riding a motorcycle, or mowing a lawn and can last as long as 24 hours, depending on the duration and intensity of the stimulus. With significant body surface area involvement, systemic manifestations may occur, including headache or generalized erythema.⁴⁴ A familial form with auto-dominant inheritance has been described in which symptoms were present since birth.⁵⁰ Diagnosis is made by placing a laboratory vortex on the forearm for 5 minutes and measuring for an increased arm circumference.

Aquagenic Urticaria

This very rare disorder manifests as pinpoint wheals where skin is exposed to water of any temperature or salinity. The mechanism is mast-cell degranulation and the confirmatory test is a body temperature tap water compress applied to the upper back with wheals appearing within 30 minutes. Treatment is with antihistamines and water-occlusive agents.³⁵

Angioedema

Angioedema presenting without urticaria can suggest other diagnoses, including hereditary angioedema or acquired angioedema from C1 inhibitor deficiency type I. The presence of urticaria may suggest an additional diagnosis and occur by coincidence.

Hereditary angioedema is the most important diagnosis but is rare, applying to approximately 1% of all cases of angioedema. It presents in childhood and worsens in adolescence. It is inherited as an autosomal dominant trait with multiple mutations at the chromosome 11 gene site. The cleavage of kininogen, the activation of the classic complement pathway, and the generation of plasmin contribute to the release of vasoactive peptides, resulting in angioedema. Two types are recognized: low levels of serum C1 inhibitor (85% of cases) or lack of functional C1 inhibitor with normal levels (15%). Clinically, it is characterized by recurrent bouts of painless, nonpruritic, nonpitting edema involving the face, larynx, gastrointestinal tract, and extremities. Attacks are triggered by emotional stress and minor trauma and last 1 to 4 days. Facial and extremity edema resolve gradually without harm, whereas untreated laryngeal edema is progressive and can result in death by asphyxiation in half of patients. Abdominal involvement includes nausea, vomiting, diarrhea, and pain severe enough to require narcotics and mimic a surgical emergency. Family history is an important clue.

Laboratory screening includes a plasma C4 that is low both during an attack and between episodes. Diagnosis is confirmed by documenting a low level of serum C1 inhibitor or an abnormal functional assay.⁴³ CH50 (i.e., the quantity of complement necessary for 50% lysis of erythrocytes) is not a reliable measurement. C2 may be decreased during an episode although C1 and C3 levels are normal.

Treatment with epinephrine, antihistamines, and corticosteroids have little effect. Fresh frozen plasma is useful for an acute attack but controversial as it may replenish the complement components and enhance the episode, risk viral transmission, and alloimmunization. Tracheal intubation or tracheostomy may be necessary for laryngeal edema. Prophylactic use of attenuated androgens and antifibrinolytic agents (aminocaproic acid) can decrease the severity and frequency of attacks. They are effective and appropriate except in prepubertal and pregnant patients.⁴³ Vapor-heated C1 inhibitor concentrate infusions are effective in treating and preventing attacks.⁶⁵ Unfortunately, the cost, safety (potential risk of viral transmission), and lack of availability limit its use.

Acquired C1 deficiency is associated with B-cell proliferative disorders and is not typically seen in children.

Differential Diagnosis

Although urticaria is generally not difficult to diagnose, the presentation may be modified by concomitant medications. Urticarial vasculitis and erythema

Table 2. CHARACTERISTICS OF PEDIATRIC URTICARIA AND VASCULITIS

	Urticaria	Vasculitis
Prevalence of Condition	Common	Rare
Signs and Symptoms		
Fixed at same skin site	Hours	Days
Pruritus	+	—
Palm, sole, extremity predilection	—	+
Residual pigmentation	—	+
Palpable purpura/petechiae	—	+
Arthralgia, myalgia, fever	—	+
Laboratory		
Hypocomplementemia (C3, C4)	—	+
Increased sedimentation rate	—	+
Histology		
Capillary vasodilation/engorgement	+	—
Superficial lymphatic vasodilation	+	—
Wide dermal papillae/flat rete pegs	+	—
Perivascular infiltrate	Minimal	Neutrophilic
Vascular damage	—	+
Erythrocyte extravasation	—	+
Cell nuclear debris (leukocytoclasia)	—	+
Fibrinoid deposition	—	+
Immunofluorescence	—	IgA, IgM, C3
Pathogenesis	Mast cell	Immune complex

multiforme must be considered. Table 2 contrasts key features of vasculitis and urticaria. A case of scalp angioedema was misdiagnosed as child abuse in an 18 month old with recurrent, soft, nontender, scalp swelling.⁶¹ Acute annular urticaria describes infants and small children with large, erythematous annular and polycyclic lesions with violaceous centers with periorbital, hand, and foot edema. There is absence of pruritus and airway angioedema and symptoms resolve spontaneously within 10 days. A history of furazolidone treatment for diarrhea preceded many of the cases.⁶⁰

EVALUATION

A thorough history and complete physical examination remain the most important factors in establishing an underlying cause of urticaria and angioedema. Frequently, this process is time consuming. Questionnaires have been developed for efficient screening of adult patients who have chronic urticaria, and these may be adapted for pediatric patients who have chronic or acute recurrent urticaria.²³ Important features to include in a questionnaire are outlined in Table 3. When a cause is suggested from history or physical examination, further testing can be pursued (Table 4). Extensive laboratory testing in chronic urticaria is indicated in the presence of symptoms suggesting an underlying systemic condition.⁵⁹ The appropriate extent of the evaluation is unclear as frequently, a cause is not identified.

Table 3. QUESTIONNAIRE FOR PEDIATRIC URTICARIA/ANGIOEDEMA

Onset
Duration (total and individual lesion)
Distribution
Pattern
Relation to meals or specific food
Recent sting or bite
Physical
Cold, pressure, heat, exercise, vibratory, sunlight, water
Associated Symptoms
URI symptoms, fever, arthralgia or arthritis-limp, vomiting or diarrhea, weight loss
History of Atopy
Eczema, allergic rhinitis, asthma
Medical History
Medication Use
Antibiotic, aspirin/NSAID, OTC, herbal remedy
Vaccine, narcotic
For females
Menstrual cycle, OCP
Environmental
Pets, mites, roaches
Travel
Tropical or subtropical, drinking water
Family History
Angioedema, atopy

URI = upper respiratory infection; OTC = over-the-counter medications; NSAID = nonsteroidal anti-inflammatory drug; OCP = oral contraceptive pill.

Table 4. EVALUATION OF URTICARIA AND ANGIOEDEMA

Suspected Cause	Procedure
Atopic	Total IgE, skin testing or RAST/ELISA for specific allergen, eosinophil count, food-elimination diet
Physical	
Cholinergic	Mecholyl test, water bath
Dermographism	Firm stroking of the skin
Cold	Ice-cube application, cryoproteins, syphilis serology
Solar	Light exposure
Heat	Warm water immersion
Pressure	10-kg weight
Vibratory	Laboratory vortex
Infection	CBC, sedimentation rate
Virus	Culture; Serology for HSV, EBV, Hepatitis
Bacteria	Throat culture, serology
Fungus	Culture, KOH preparation
Parasite	Stool for ova and parasites
Vasculitis	Sedimentation rate, antinuclear antibody, CBC, urinalysis, CH50, skin biopsy, quantitative immunoglobulins, immune complex assay, antithyroid antibody
Hereditary	Plasma CH50, C2, C4, C1-INH level and functional assay
Angioedema	
Acquired	Plasma CH50, C1q
Angioedema	

RAST = radioallergosorbent test; ELISA = enzyme-linked immunosorbent assay; CBC = complete blood count; HSV = herpes simplex virus; EBV = Epstein-Barr virus; KOH = potassium hydroxide; C1-INH = C1 inhibitor protein.

Atopy

Urticaria can occasionally be induced by inhalant allergens but is invariably associated with upper or lower respiratory tract symptoms. Direct contact with animal dander or saliva can induce urticaria either by inhalation or direct absorption through intact skin. In adults, seasonal urticaria has been associated with seasonal allergy, but not usually implicated in chronic urticaria. In vitro tests for serum specific IgE, including enzyme-linked immunosorbent assay (ELISA) or radioallergosorbent test (RAST) are useful when there is significant skin involvement or use of antihistamines. Skin testing is appropriate after discontinuation of antihistamines in the presence of normal skin.

Drugs

Drugs received orally or parenterally are a common cause of acute urticaria. Skin manifestations are the most common presentation of drug-induced reactions. Rapid recognition and prompt withdrawal of the offending drug is the most important action to take to minimize morbidity. In children, it may be difficult to differentiate between an infectious process or the medications as the cause.⁴¹ Key clinical history to assess for an adverse drug reaction includes the following:

1. exclude alternative causes
2. examine the interval between drug introduction and symptom onset
3. note improvement after drug withdrawal
4. determine if similar reactions have occurred with the same medication
5. note reaction on readministration of the drug

Urticaria and facial edema are symptoms of a serious reaction, as are blisters, mucosal involvement, palpable or extensive purpura, fever, or lymphadenopathy, and indicate the need to almost always discontinue the medication.⁵¹ Unfortunately, skin or in vitro testing for drug allergy is limited to penicillin or complete antigens.

Almost any drug is capable of producing urticaria. A hospital-based prospective study on drug-induced diseases revealed urticaria to account for only 9% of drug-induced skin reactions and less than 3% of the total number of reactions in infants and children. It was found only in the 4- to 14-year-old age group.³¹ Some drugs stimulate mast cells to release histamine directly, and therefore no specific test is available. These include narcotics (notably codeine and morphine) and radiocontrast media.

Urticaria can be found in conjunction with morbilliform lesions, fever, and arthralgia in serum sickness reactions that are greater than 90% drug induced. Onset of the reaction occurs 8 to 14 days after beginning the drug.⁵¹ Compared with amoxicillin, cefaclor increases the risk of antibiotic-induced serum sickness in children under 6 years of age and after six or more antibiotic exposures.²⁶

Aspirin, NSAIDs, and even acetaminophen can induce urticaria and angioedema through a non-IgE-mediated mechanism.⁴⁷ The pathogenesis is unclear, but inhibition of cyclooxygenase with a resulting increase in leukotriene products is suspected. Bronchial symptoms predominate in adults.⁴⁰ Although the prevalence is not known for children, the overall prevalence is 0.3%.⁴¹ Case reports describe children who have acetaminophen-induced urticaria who tolerate ibuprofen.⁴⁸ Only challenge testing is available to document this reaction.

Angiotensin-converting enzyme inhibitors are associated with an increased risk of angioedema without urticaria and can be life threatening.⁸

Other drugs observed to cause urticaria or angioedema include oral vitamin K.¹⁸ Urticaria at the site of pilocarpine iontophoresis sweat testing is rare and may be related to pilocarpine or a physical urticaria through thermal or electrical current stimulation.³³ Vaccines are capable of inducing urticaria, and these have been observed with tetanus toxoid (not thimerosal preservative), and measles-mumps-rubella (MMR) as part of an anaphylactic reaction. This is related to specific IgE directed against gelatin⁵³ or egg proteins.

Foods

Numerous foods are implicated in acute urticaria, with the most common being cow's milk, egg, fish, shellfish, peanuts, and berries.^{2, 10} Reproducible reactions can occur within minutes to hours after oral ingestion and are frequently associated with lip angioedema and strongly associated with atopic dermatitis.⁴¹ An open challenge may be useful in younger children, whereas in older children a blinded technique may be necessary. The exact frequency of food-induced urticaria is unknown as parents or patients may not seek specific diagnostic testing or medical personnel may not report such reactions. Reports that childhood urticaria is related to foods range from 15% to 62%.⁴¹ Chronic urticaria is less likely to be related to a food allergen. The reactions can be generalized after ingestion or occur with direct skin or mucous membrane contact.¹¹ Food-induced contact urticaria syndrome refers to the IgE-mediated immediate response to food antigens that are rapidly absorbed through intact skin. This is seen primarily in young children who have atopic dermatitis with milk, egg, and peanut hypersensitivity. A skin-application food test in which food is applied in the same form in which it is to be eaten may be helpful in addition to skin-prick tests with food extracts in these patients.⁴⁵ Acute urticaria and angioedema without asthma from inhalation of airborne fish allergens has also been reported in children.¹⁶ This usually occurs at home with exposure to steam from boiling or from fumes from frying fish. The ingestion of gelatin can result in tongue angioedema with ear and throat pruritus.²⁹

A nonimmunologic mechanism may explain urticarial reactions to food additives, dyes, and preservatives. Other ingredients reported to provoke urticaria include tartrazine, azo and nonazo dyes, natural salicylates, benzoic acid derivatives (hydroxybenzoates), and metabisulfites.^{15, 19} Aspartame, which is used as a high-intensity sweetener, has not been shown to be a cause of urticaria.²⁰ Direct histamine release factors may be present in egg white, strawberries, and shellfish. Histamine may occur naturally in food or as the result of spoilage with conversion of histidine to histamine, thus contributing to urticaria.²

Evaluation includes a detailed history of symptom improvement following elimination of the suspected food for 1 to 2 weeks, allergy skin testing or specific IgE in the serum, and documentation of recurrence of urticaria upon reintroduction of that food. The challenge test is the definitive and most reliable procedure for verifying a cause and effect relationship between a particular food and acute urticaria. Open, single-blind and double-blind food challenges can be utilized with blind challenge testing considered particularly when a psychological component is suspected. This test should occur in the office setting under supervision where treatment can be rendered if a severe reaction occurs.

Loss of sensitivity may occur after a period of avoidance in children who

experienced urticaria after ingestion of milk, egg, soy, and wheat. Such spontaneous resolution is less likely to occur with peanuts, nuts, and fish.

Latex

Allergic reactions to natural rubber latex protein are relatively new. Contact urticaria or angioedema can occur with balloons, adhesive tape, or rubber toys or as a symptom of a generalized reaction. Acute urticaria related to cross-reactive allergens in exotic foods, including kiwi fruit, may occur in latex-sensitive children.⁴¹

Insect Bites or Infestations

Urticaria and angioedema are common in children who have Hymenoptera sensitivity. Contact urticaria may be elicited by other offending agents, including various sealife that includes Portugese Man-of-war and insect-derived material from moths, butterflies, caterpillars, or mosquitos.³⁷ Papular urticaria refers to a pruritic eruption occurring as a hypersensitivity reaction typically on the exposed lower extremities following flea or other insect bites. Crops of small papules with a central punctum are classic.⁶⁰ Treatment of affected pets is indicated if fleas are discovered.

Infection

Acute urticaria is often related to acute viral or less commonly acute bacterial infections in children.⁴¹ It is difficult to prove a cause and effect relation beyond circumstantial evidence of resolution of both infection and hives near the same time. Furthermore, concomitant use of drugs, especially antibiotics, complicates the diagnosis. Urticaria is associated with the prodromal phase of hepatitis B and resolves with the onset of jaundice. In case reports, acute urticaria has also been associated with hepatitis A and C.¹⁷ In a small series, streptococcal infection was associated with 40% of acute urticaria cases. Some patients had subclinical infection and urticaria resolved with eradication of the beta-hemolytic streptococci.⁵⁴

Chronic urticaria related to bacterial infection appears to be extremely uncommon in children. In adults, dental infections are frequently cited.⁴⁸ In developed countries, parasitic infections are an uncommon cause of chronic urticaria. However, when urticaria is associated with eosinophilia, gastrointestinal symptoms, or elevated IgE, helminthic parasites (especially *Toxocara canis*) should be suspected. Giardia and other protozoal infections are exceptionally rare causes of urticaria in children and adults.²⁴ Cutaneous fungal infections with *Trichophyton* have been associated with chronic urticaria in adults.

SYSTEMIC DISEASE: AUTOIMMUNE

Endocrine

Autoimmune disease has been implicated in children, although the exact pathogenesis is unknown. It may occur through immune complex formation or

deposition, complement activation, or the release of proinflammatory mediators from activated T cells. In euthyroid adults with elevated antithyroid antibodies, 70% of patients had resolution of their chronic urticaria when treated with thyroid hormone.⁵² The level of antibody did not correlate with disease activity, suggesting the antibodies serve as a marker of autoimmunity. Such studies are unavailable in children. In patients who have chronic idiopathic urticaria, mast-cell-activating factors are present in the serum, which, when injected intradermally, gives rise to urticaria. One of these factors has been identified as an IgG antibody directed against the IgE high-affinity receptor alpha chain (anti-Fc epsilon alpha).⁴² These autoantibodies support a concept that low levels of autoantibodies produce a chronic low-level state of mast-cell activation.

Collagen Vascular Disease

Urticarial vasculitis presents with persistent, often tender or burning, frequently purpuric erythematous wheals with central clearing that typically persist 48 to 72 hours. Secondary skin changes can include purpura or hyperpigmentation. Generalized symptoms may include fever, arthralgia or arthritis, renal disease with proteinuria or hematuria, gastrointestinal manifestations of nausea and abdominal pain, and pulmonary disease with cough, dyspnea, or hemoptysis.⁴ Frequently, the provoking antigen cannot be found, but diagnostic tests classically reveal elevated acute phase proteins, including ESR, hypocomplementemia (low CH50 or C1q, C4, or C2), and circulating immune complexes. Skin biopsies reveal the classic features of leukocytoclastic vasculitis, and direct immunofluorescence staining shows immunoglobulin and complement deposition in the vessel walls of lesional skin in more than 50% of patients.⁴ This can be associated with systemic lupus erythematosus, rheumatic fever, juvenile rheumatoid arthritis (Still's disease), or other collagen vascular diseases.³⁰

Henoch-Schönlein purpura is a common cause of childhood small-vessel vasculitis, and in children less than 2 years old, angioedema was uniformly present in a series of 12 children. Angioedema mainly involved the feet, hands, scalp, lips, and scrotum. Joint, kidney, and gastrointestinal involvement was seen in only one third of these children. The characteristic purpuric rash helps differentiate this from urticaria.¹ Direct immunofluorescence staining of involved skin reveals deposits of IgA around blood vessel walls.

Neoplastic Diseases

Underlying malignancies, including carcinoma, lymphoproliferative diseases (leukemia and lymphoma), and solid tumors can be associated with chronic urticaria or angioedema in adults, although statistically significant associations and causal relation are lacking.³⁴ This association is extremely rare in children. Large epidemiologic studies linking urticaria to neoplastic disease are unavailable in children. In one such case report, persistent urticaria-like lesions were the presenting symptom in a 15 month old who had acute nonlymphocytic leukemia.¹⁴ Systemic mastocytosis or the cutaneous form termed *urticaria pigmentosa* is characterized by the presence of tan pigmented lesions that wheal with rubbing (Darier's sign).

Emotion

Emotional stress is frequently an alleged cause of urticarial exacerbations. This may reflect the increased cutaneous blood flow that accompanies stress or release of substance P from skin sensory nerves, a potent degranulator of human mast cells *in vivo*.⁶³ It is likely that psychological factors play a contributory role but are not causative.

Hormonal

Hormonal changes may be a minor contributing factor in pubertal females. One such condition is autoimmune progesterone urticaria and dermatitis.

Idiopathic

In a large percentage of chronic urticaria, an underlying cause is unidentified despite costly and in-depth evaluations. Fortunately, idiopathic chronic urticaria is self-limited and benign, although recurrences are common.

TREATMENT

Avoidance

In acute urticaria, if an inciting agent is identified appropriate avoidance measures should be instituted.

Pharmacologic

Antihistamines

Antihistamines remain the drug of choice for first-line treatment of urticaria since histamine derived from skin mast cells is the best-documented mediator of urticaria. Usually only oral H₁ blockers are required for treatment. Topical treatment is not satisfactory. Both first- and second-generation antihistamines are effective in controlling the symptoms of pruritus and reducing the number, size, and duration of urticarial lesions. First-generation antihistamines are still used because they are effective and inexpensive, although their use is sometimes limited by undesirable side effects, including central nervous system or anticholinergic effects. Somnolence, sedation, and paradoxical hyperactivity can occur, particularly in younger children. The effectiveness of these antihistamines may also be compromised by dosing schedules that require 2 to 4 times daily dosing. Long-term administration does not lead to an increased rate of elimination or autoinduction of hepatic metabolism.

The second-generation antihistamines are comparable with hydroxyzine in suppressing chronic urticaria in adults. Terfenadine, astemizole, loratadine,³⁹ and cetirizine have all been shown to be comparable with hydroxyzine, the most potent first-generation antihistamine. Hydroxyzine is superior to diphenhydramine,³⁸ and dosing at night is appropriate for cases in which sleep is being disturbed by urticaria or in the very anxious patient for whom the sedative effect

may be desired. Large multicenter trials for second-generation antihistamines for treatment of urticaria in children less than 6 years old are unavailable. If one antihistamine fails, it is useful to try another as there is a wide variation in response among individuals. There also is a variation in response over time, such that an antihistamine that was not successful initially may be tried with better results later.⁴⁶

Fexofenadine, a metabolite of terfenadine, is approved for use in children 12 years of age and older for seasonal allergic rhinitis but not currently for urticaria. It lacks the adverse cardiovascular side effects of terfenadine and pharmacologic studies suggest doses of 30 to 60 mg in children are well tolerated and effective in suppressing the wheal-and-flare reaction to histamine.⁵⁵

Loratadine, which is structurally related to azatidine, is potent, long acting, and nonsedating. It is approved for use in chronic urticaria in children 6 years of age and older. The onset of action is quick, although maximal inhibition of histamine-induced whealing occurs after 2 to 7 days. The recommended dose is 10 mg once daily for children and is available as a syrup or a rapidly disintegrating tablet form.

Cetirizine is a carboxylated metabolite of hydroxyzine that recently received approval for use in children as young as 2 years old. It possesses potent antihistamine qualities without the incidence of somnolence of its parent molecule. Antiallergic properties include inhibition of eosinophil chemotaxis, which may be particularly useful in conditions with late-phase allergic reactions. It has a rapid onset and a long duration of action. The elimination, half-life, and clearance are such that in children ages 2 to 6, a higher dosage twice daily may be required.⁴⁹ H_1 inhibition at the cutaneous level appears to be longer in infants and toddlers as seen in histamine-induced wheal-and-flare reactions.⁵⁸ Discontinuation related to somnolence is low and sedation is dose related.

Astemizole is approved for chronic idiopathic urticaria in children 12 years of age and older. Although it has a slower onset of action, there is high binding affinity and slow receptor disassociation.⁴⁶ Astemizole should be taken on an empty stomach and not coadministered with erythromycin or other macrolide antibiotics, antifungal agents, or quinine or in doses greater than 10 mg once daily because of the risk of ventricular arrhythmias. Increased appetite has been reported in nearly one fourth of patients.³⁸

Acrivastine is a metabolite of triprolidine and has been shown to be effective in physical urticaria. It is fast in onset, yet, to the best of the author's knowledge, few published studies regarding adverse central nervous system side effects are available.^{46, 56}

H₂ Antagonists

The addition of H_2 antagonists is helpful in some patients to enhance relief of pruritus and wheal formation, although this still remains an area of controversy. In most adult studies, cimetidine was used. Fewer studies are available with ranitidine, and monotherapy does not appear to be beneficial. Data is lacking in pediatric patients.

Beta Agonists

In acute severe urticaria or angioedema, epinephrine is beneficial although short lived. Orally administered drugs have mixed results.

Tricyclic Antidepressants

Doxepin, a highly potent H_1 antagonist with weak H_2 antagonist properties, is effective in adults who have chronic urticaria. Anticholinergic side effects can be decreased with smaller doses such as 10 mg. Pediatric studies are lacking.

Calcium Channel Blockers

Since allergen-induced mast-cell degranulation depends on calcium influx into the cell, calcium antagonists would be expected to inhibit histamine release. In two studies involving small numbers of adults who have chronic idiopathic urticaria, improvement was noted except in symptomatic dermographism.^{3, 6} Results in pediatric patients are not available.

Mast-Cell Stabilizers

Ketotifen possesses H_1 -blocking ability and is a mast-cell stabilizer. It has been shown to be useful in cold urticaria, dermographism, and exercise-induced urticaria in adults.⁴⁶ Cromolyn and nedocromil, although effective for stabilizing mast cells in the nose and lung, do not effectively stabilize skin mast cells.

Anabolic Steroids

Attenuated androgens, including stanozolol and danazol, are helpful in hereditary angioedema, cholinergic urticaria, and steroid-dependent urticaria. It is proposed that androgens act through their ability to increase protease inhibitor levels that could inhibit proinflammatory mediators. Potential side effects, particularly in females, limit widespread use.

Immunosuppressive Therapy

With the identification of autoantibodies directed against the high-affinity IgE receptor, a role for autoimmunity in urticaria is established. Unfortunately, immunosuppressive therapy can be associated with side effects when used for long-term control. Corticosteroids are effective anti-inflammatory agents that can provide symptomatic relief. They can be very effective but are best restricted for treating acute flares of urticaria, such as those seen in drug- or food-induced acute urticaria, serum sickness, or delayed pressure urticaria. As the other physical urticarial syndromes rely on cutaneous mast-cell degranulation, corticosteroids are not indicated. Short-term relief in chronic urticaria can be attained with corticosteroids. If corticosteroids are used, low-dose alternate-day therapy should be reached as quickly as possible. Systemic steroids still remain the treatment of choice for urticarial vasculitis, and many patients require high doses; relapses are common when the doses are tapered. Topical steroids are ineffective.

Cyclosporine inhibits release of mediators from mast cells as well as inhibits the effect of interleukins. Because of the serious side effects, its use in urticaria is extremely limited.

Other

The unresponsiveness of severe urticaria in some patients has lead to a list of unconventional treatments. Sulfasalazine,^{3, 28} methotrexate, antimalarial drugs,

dapsone, gold, colchicine, and plasmapheresis have been useful in individual adult patients or small series of patients who have urticarial vasculitis. Data is lacking to support the use of empiric antibiotics for possible underlying bacterial infections, particularly in chronic urticaria. The recently available class of leukotriene modifiers have anti-inflammatory treatment that is helpful in the inflammation of asthma. Case reports suggest a possible role in urticaria.⁵⁷ Other therapies that have been tried include homeopathy, kinesiology, and even hypnosis.⁴⁶

CONCLUSIONS

Urticaria and angioedema in children is a frequent yet benign disease that commonly prompts a medical evaluation and occasionally is severe enough to lead to hospitalization. Angioedema frequently accompanies urticaria in infants and young children and those with food allergy. Angioedema occurring without urticaria deserves a thorough evaluation, particularly with a family history of angioedema. Acute urticaria without systemic symptoms does not require further laboratory evaluation, and therapy is aimed at removal of an offending agent, reassurance, and symptomatic relief. Viral illness with associated drug therapy or food allergy probably represents the majority of cases. Frequently, the trigger in chronic urticaria is not discovered. A meticulous history and a careful physical examination can help determine selected laboratory tests that may point to a cause. Mainstay treatment is with antihistamines. In the pediatric population, other forms of therapy have not been carefully studied.

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