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# Urticaria

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## IMPORTANT POINTS

1. Fifty percent of children who have urticaria will have angioedema at some time during an episode of urticaria.
2. Papular urticaria lesions are grouped and have central punctae.
3. Papular urticaria represents ectoparasite hypersensitivity usually to dog or cat fleas or mites.
4. Papular urticaria typically involves only one family member.
5. Large annular urticarial lesions can be mistaken for erythema multiforme, but they have a clear central zone rather than crusted or bullous centers.

## Definition

Urticaria results from transient extravasation of plasma into the dermis that causes a wheal characterized by tense edema with or without redness. Wheals have an abrupt onset and move from site to site within hours. Angioedema is the subcutaneous extension of urticaria that results in deep swellings within subcutaneous sites. Special forms of urticaria in children include papular urticaria, which is characterized by 10- to 20-mm wheals surrounding a 2- to 4-mm red papule, and the physical urticarias, which are triggered by heat, cold, sun, or water. Physical urticarias have typical wheals except for the so-called "heat and exercise urticaria," which is characterized by 10- to 20-mm red, blotchy macules with a 0.1-mm wheal in the center.

## Epidemiology

Urticarial states are common in infancy and childhood, although the exact incidence is not known. Several large studies indicate that 3% of preschool children and about 2% of older children suffer from urticaria. This high prevalence undoubtedly includes children who have single episodes of short-lived urticaria rather than a persistent condition. Of all children who have

urticaria, fewer than 5% have what can be documented as immunoglobulin E (IgE)-mediated allergic urticaria. In contrast, approximately 15% of children who develop urticaria have the physical condition. Most children fall into an "idiopathic" group.

## Pathogenesis

Histamine is the primary chemical mediator of transient urticaria, and the mast cell is central in all forms of transient urticaria and angioedema. Histamine may be released directly from cutaneous mast cells in response to certain foods or opiate drugs. Specific IgE antibodies bound to mast cell surfaces that "recognize" certain antigens, such as penicillin and other drugs, foods, and venom of certain stinging insects, cause the release of histamine after combining with antigen.

Complement fragments, activated by immune complexes, may activate mast cells to release histamine or exert direct vasoactive effects on cutaneous blood vessels. The latter mechanism most often is associated with infection, but careful documentation of the mechanism of histamine release involved with each inciting substance is not available. Eicosanoids may induce mast cell mediator release, and other cytokines have been implicated in urticaria.

In hereditary angioedema, a deficiency of the C1 esterase inhibitor permits unregulated cleavage of complement proteins once the complement system is activated, with particular consumption of C4. A C2

kinin activates the clotting system via the Hageman factor in hereditary angioedema. Complement cleavage products may be responsible for the edema and erythema.

In papular urticaria, a basophil infiltrate can be found around superficial dermal blood vessels. It represents a delayed hypersensitivity reaction to biting or stinging insects.

Histamine is not the chemical mediator in the physical urticarias. Neuropeptides are suspected in dermographism and heat and exercise urticaria; complement products are suspected in cold urticaria.

## Clinical Aspects

Common transient urticaria in children often follows infection (Table 1), encounters with stinging or biting insects (Table 2), ingestion of medications (Table 3) and certain foods (Table 4), or is associated with inflammatory systemic disease such as collagen vascular disease or thyroiditis (Table 5). The eruption is sudden in onset, pruritic, and char-

**TABLE 1. Infectious Agents Associated With Transient Urticaria**

• <i>Streptococcus</i>
• Infectious mononucleosis (Epstein-Barr virus)
• Hepatitis A, B, and C
• Adenovirus
• Enterovirus
• Parasites

**TABLE 2. Bites and Stings Associated With Transient Common Urticaria**

• Bees
• Wasps
• Scorpions
• Spiders
• Jellyfish

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**TABLE 3. Drugs Associated With Transient Common Urticaria**

• Penicillin
• Cephalosporins
• Salicylates
• Morphine, codeine, and other opiates
• Nonsteroidal anti-inflammatory drugs
• Barbiturates
• Amphetamines
• Atropine
• Hydralazine
• Insulin
• Blood and blood products

acterized by red raised 2- to 15-mm flat-topped wheals scattered over the body (Fig. 1). The edema can be appreciated by stretching the skin slightly to demonstrate whitish centers. Occasionally, large annular urticarial lesions up to 30 cm in diameter that have polycyclic borders will appear (Fig. 2). Wheals commonly last from 20 minutes to 3 hours, disappear, then reappear in other skin areas. An entire episode of transient urticaria often lasts 24 to 48 hours; rarely, it lasts 3 weeks. As urticaria resolves, flat dusky areas may develop. Persistent urticarias, when examined within the first 4 weeks of illness, may be indistinguishable from transient common urticaria.



FIGURE 1. Urticarial wheals of different sizes in a child.

**TABLE 4. Foods Associated With Transient Common Urticaria**

• Nuts
• Eggs
• Shellfish
• Strawberries
• Tomatoes

Subcutaneous extension of lesions, termed angioedema, may occur. These appear as large swellings that have indistinct borders around the eyelids and lips. They also may appear on the face, trunk, genitalia, and extremities. The face, hands, and feet are involved in 85% of patients; other areas are involved in 15%. Up to 50% of children who have urticaria exhibit angioedema, with swelling of the hands and feet occurring commonly.

Hereditary angioedema accounts for only 0.4% of cases of urticaria, but its specific diagnostic tests and associated high mortality deserve special mention. This autosomal dominant condition is associated with repeated attacks of swelling of the extremities, face, and throat accompanied by abdominal pain. The onset usually follows trauma such as surgery, dental manipulation, or accidents. It presents as a diffuse, brawny

**TABLE 5. Systemic Diseases Associated With Transient Common Urticaria**

<b>Collagen Vascular Disease</b>
• Lupus erythematosus
• Juvenile rheumatoid arthritis
• Polyarteritis nodosa
• Dermatomyositis
• Neonatal lupus syndrome
• Sjögren syndrome
• Rheumatic fever
<b>Inflammatory Bowel Disease</b>
• Crohn disease
• Ulcerative colitis
<b>Miscellaneous</b>
• Aphthous stomatitis
• Behçet disease
• Thyroiditis

swelling of the extremities in 75% of patients, abdominal pain in 52%, and swelling of the face and throat in 30%. Its onset usually occurs in adolescence, with the more severe symptoms associated with menses. Abdominal pain eventually becomes a major complaint in 93% of patients. These patients do not have typical urticarial wheals, but rather exhibit target-like lesions.



FIGURE 2. Annular urticarial lesions on an infant. Note the normal skin in the center in contrast to erythema multiforme in Figure 6.



*FIGURE 3. Grouped papules with central puncta in papular urticaria due to dog fleas.*



*FIGURE 4. Papular urticaria lesion with prominent central puncta.*

Severe airway edema accounts for the almost 30% mortality in untreated patients.

Only 25% of patients give a positive family history. The diagnosis should be suspected if the serum C4 level is persistently low. It is confirmed by functional assay of the C1 esterase inhibitor. In some children, hereditary angioedema is associated with lupus erythematosus or other collagen vascular diseases.

Papular urticaria lesions are grouped on exposed areas, often lasting for 10 to 14 days (Figs. 3 and 4). The central papule may be bullous. Papular urticaria is usually the result of an encounter with animal fleas or mites and is observed most often in toddlers. It is difficult to convince parents of the etiology when only one family member is reacting, even though all might be exposed.

Physical urticarias have some unique clinical features. In heat and exercise urticaria, increasing the skin surface temperature by 0.5°C is sufficient to induce an attack of blotchy lesions (Fig 5). Application of ice to the skin will induce a large wheal in cold urticaria. In dermatographism, light stroking of the skin will induce a wheal and flare reaction.

### Differential Diagnosis

The conditions to be considered in the differential diagnosis of urticaria are listed in Table 6. Urticaria, especially giant urticaria, frequently is confused with erythema multiforme (EM) (Fig 6).

Urticaria can be differentiated from mastocytosis by a skin biopsy because increased numbers of mast cells are seen in mastocytosis. Flushing states are flat rather than elevated. In juvenile rheumatoid arthritis, faint erythematous macules that have a clear center are present and associated with a spiking fever. Vasculitis lesions have purpuric centers; psoriasis and pityriasis rosea demonstrate scaling overlying the erythematous papules.

Angioedema (deep hives) (Table 7) should be differentiated from cellulitis and erysipelas, which are tender, warm red lesions. Chronic thickening of tissues occurs in lymphedema, in contrast to the acute stretching of tissue seen in angioedema. The angioedema of the hands and feet that accompanies urticaria may be confused with EM. A skin biopsy will make the distinction because urticaria shows dermal edema without epidermal injury and EM shows dermal perivascular mononuclear cell infiltrate and areas of epidermal necrosis. Persistent angioedema of the face or lip suggests lupus erythematosus or other collagen vascular diseases.

Considerable deep edema can develop in acute contact dermatitis, but vesiculation of the overlying epidermis and epidermal papules will help distinguish it from angioedema. Idiopathic scrotal edema of children and the Melkersson-Rosenthal syndrome are rare and can be distinguished from angioedema by the furrowed tongue and cranial nerve palsies of Melkersson-Rosenthal syndrome and the local-



*FIGURE 5. Tiny central wheal with large surrounding red "flare" in an adolescent who has heat and exercise (cholinergic) urticaria.*

ization of angioedema to the scrotum in idiopathic scrotal edema.

Papular urticaria can be mistaken for early varicella, Gianotti-Crosti syndrome, acute parapsoriasis, or lymphomatoid papulosis. A biopsy will distinguish these conditions.

### Management

Oral antihistamines are valuable in symptomatic control of urticaria. Hydroxyzine hydrochloride (2 to 4 mg/kg per day in two divided doses) and diphenhydramine hydrochloride (5 mg/kg per day in four divided doses) are the most helpful.

**TABLE 6. Differential Diagnosis of Urticaria**

- Erythema multiforme
- Mastocytosis
- Flushing
- Reactive erythemas
- Juvenile rheumatoid arthritis
- Vasculitis
- Guttate psoriasis
- Pityriasis rosea (early lesions)

If nocturnal urticaria is a problem, administration of hydroxyzine 1 hour before bedtime may be a sufficient single daily treatment. Nonsedating antihistamines are less effective in controlling urticaria.

Prediction of whether an antihistamine will be useful in specific circumstances of urticaria is difficult because individual responses vary significantly. Combinations of antihistamines occasionally may be required. In angioedema not controlled by antihistamines, pseudoephedrine (4 mg/kg per day in four divided doses) may be added. The same drugs may be used to treat chronic angioedema. In acute angioedema of the airway, epinephrine 1:1,000 (0.01 mL/kg per dose to a maximum dose of 0.5 mL) may be used. There is no evidence to support the use of systemic glucocorticosteroids in urticaria or angioedema. It is unclear whether the addition of histamine-2 (H<sub>2</sub>) block-

**TABLE 7. Differential Diagnosis of Angioedema**

- Cellulitis and erysipelas
- Lymphedema
- Acute contact dermatitis
- Idiopathic scrotal edema of children
- Melkersson-Rosenthal syndrome

ing drugs to H<sub>1</sub> antihistamines is of any additional benefit. Cromolyn sodium preparations, which may be efficacious in treatment of airway or bowel reactions, have not been particularly useful in skin reactions. Ketotifen may be useful in urticarias that persist for more than 6 weeks.

### Prevention

Allergen avoidance is an important strategy if the allergen can be identified. Virtually any drug may produce urticaria, but certain ones are implicated more frequently. Because drugs such as penicillin and aspirin account for most drug-induced urticaria in children, their use should be specifically reviewed in the patient's history. Cephalosporins produce an urticarial serum sickness-like reaction. Certain classes of drugs may release histamine directly from mast cells without any allergic interactions (Table 8). Foods suspected of causing urticaria should be avoided if this does not compromise nutrition.

Restriction diets are of little value if a suspected food factor has not been identified.

Acute attacks of hereditary angioedema are managed by intravenous fluid replacement and airway maintenance. Administration of danazol or stanozolol, synthetic attenuated testosterone, increases C1q esterase inhibitor levels and prevents the angioedema. Fresh frozen plasma or epsilon-amino

**TABLE 8. Drugs Producing Histamine Release in Mastocytosis**

- Opiates (codeine, meperidine, morphine)
- Polymyxin B
- Acetylsalicylic acid

caproic acid may be useful before surgical procedures. Patients who have angioedema should have an adrenergic agent available for airway attacks, and those who have hereditary angioedema should be advised of the high mortality and the need to continue taking prophylactic drugs.

Removing the offending ectoparasite can prevent papular urticaria, but this may not be easy if the family pet is the source. Insect repellants can lessen the chances of being bitten. Individual lesions can be treated with topical steroid gels and oral antihistamines.

Recognition of the precipitating events for physical urticarias can allow avoidance strategies. Desensitization strategies are quite difficult to follow and are not recommended.

Photochemotherapy at qualified dermatologic centers may be considered in very symptomatic children.

### Prognosis

Cause-and-effect relationships often cannot be identified in transient urticaria and angioedema, but lesions can be expected to resolve by 1 month in most instances. Symptoms can be controlled with the use of antihistamines. An extensive and expensive allergy evaluation is not indicated for children who have had urticaria fewer than 6 weeks, and an evaluation of chronic urticaria should be guided by the history.

In papular urticaria, the hypersensitivity to ectoparasites declines after 6 to 12 months, and the child may no longer be sensitive, even while still exposed.

The physical urticarias are more persistent, lasting 2 to 4 years in most children, but well into adult life in some.



**FIGURE 6.** Target lesion of erythema multiforme with three zones of color change. Note necrosis with crust in the center of the lesion in contrast to the clear center in annular urticaria in Figure 2.

SUGGESTED READING

- Aoki T, Kojima M, Horiko T. Acute urticaria: history and natural course of 50 cases. *J Dermatol.* 1994;21:73-77
- Egan CA, Rallis TM. Treatment of chronic urticaria with ketotifen. *Arch Dermatol.* 1997;133:147-149
- Ghosh S, Kanwar AJ, Kaur S. Urticaria in children. *Pediatr Dermatol.* 1993;10:107-110
- Howard R, Frieden IJ. Papular urticaria in children. *Pediatr Dermatol.* 1996;13:246-249
- Legrain V, Taieb A, Sage T, Maleville J. Urticaria in infants: a study of forty patients. *Pediatr Dermatol.* 1990;7:101-107
- Sabroe RA, Greaves MW. The pathogenesis of chronic idiopathic urticaria. *Arch Dermatol.* 1997;133:1003-1008
- Tamayo-Sanchez L, Ruiz-Maldonado R, Laterza A. Acute annular erythema in infants and children. *Pediatr Dermatol.* 1997;14:231-234
- Tong LJ, Balakrishnan G, Kochan JP, Kinet JP, Kaplan AP. Assessment of autoimmunity in patients with chronic urticaria. *J Allergy Clin Immunol.* 1997;99:461-465
- Weston WL. What is erythema multiforme? *Pediatr Ann.* 1996;25:106-109

PIR QUIZ

11. A toddler receiving amoxicillin for an ear infection experiences the abrupt onset of rash while playing in a park. The eruption consists of 1- to 2-cm erythematous macules with pinpoint central wheals that resolve promptly with rest. The diagnosis that *best* fits the situation is:
- A. Dermographism.
  - B. Heat urticaria.
  - C. Hereditary angioedema.
  - D. Papular urticaria.
  - E. Penicillin allergy.
12. The swelling of hereditary angioedema reflects:
- A. A delayed hypersensitivity reaction.
  - B. Complement fragment-mediated histamine release.
  - C. IgE-mediated histamine release.
  - D. Neuropeptide release.
  - E. Vasoactive effects of complement cleavage products.
13. Hereditary angioedema is characterized by:
- A. A very low mortality risk.
  - B. Autosomal recessive inheritance.
  - C. Onset in infancy.
  - D. Recurrent abdominal pain.
  - E. Widespread wheals.
14. A 4-year-old girl develops a widespread nonpruritic rash over a 3-day period that consists of 1- to 2-cm oval, erythematous lesions that have concentric zones of color change surrounding crusted, necrotic centers. The *best* explanation is:
- A. Brown recluse spider envenomation.
  - B. Erythema multiforme.
  - C. Giant annular urticaria.
  - D. Papular urticaria.
  - E. Physical urticaria.
15. A 12-year-old child presents to your office with a widespread pruritic rash. No other family member is afflicted. The eruption consists of groups of papules with central puncta. You diagnose papular urticaria. As *preferred* oral therapy, you would select:
- A. Cromolyn sodium.
  - B. Hydroxyzine.
  - C. Loratadine.
  - D. Prednisolone.
  - E. Pseudoephedrine.

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