Etiology, Classification, and Treatment of Urticaria

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GOAL

To understand urticaria to better manage patients with the condition

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Discuss the clinical classification of urticaria.
2. Recognize how to diagnose urticaria.
3. Identify treatment options.

CME Test on page 50.

This article has been peer reviewed and approved by Michael Fisher, MD, Professor of Medicine, Albert Einstein College of Medicine. Review date: December 2006.

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Drs. Guldbakke and Khachemoune report no conflict of interest. The authors discuss off-label use of colchicine, cyclophosphamide, cyclosporine, dapsone, intravenous immunoglobulin, methotrexate, montelukast sodium, nifedipine, plasmapheresis, rofecoxib, sulfasalazine, tacrolimus, thyroxine, and zafirlukast. Dr. Fisher reports no conflict of interest.

Urticaria is among the most common skin diseases. It can be acute, chronic, mediated by a physical stimulus, or related to contact with an urticant. Some cases result from an underlying small vessel vasculitis. Our understanding of this condition is continuously expanding, and autoimmune mechanisms are now recognized as a cause of chronic urticaria. A search of the PubMed database (US National Library of Medicine) for "urticaria" yields more than 12,000 results. Our goal is to discuss the current understanding of the etiology, classification, and treatment alternatives. As the topic is comprehensive, our discussion will be limited to a concise review.

Cutis. 2007;79:41-49.

Accepted for publication June 8, 2006.

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Urticaria has been recognized since the days of Hippocrates. The name of the condition dates back to the 18th century, when the burning and edema of the skin was likened to that caused by contact with nettles (*Urtica dioica*). Urticaria affects

10% to 25% of the population worldwide at some point in their lives.[1] The condition is characterized by short-lived edema of the skin, mouth, and genitalia related to a transient leakage of plasma from small blood vessels into the surrounding connective tissues. Urticaria may present with superficial edema of the dermis (wheals) or deeper edema of the dermal, subcutaneous, or submucosal tissues (angioedema).[2] Wheals typically are itchy with a pale center, maturing into pink superficial plaques. Areas of angioedema tend to be pale and painful; last longer than wheals; and may involve the mouth and rarely the bowel.

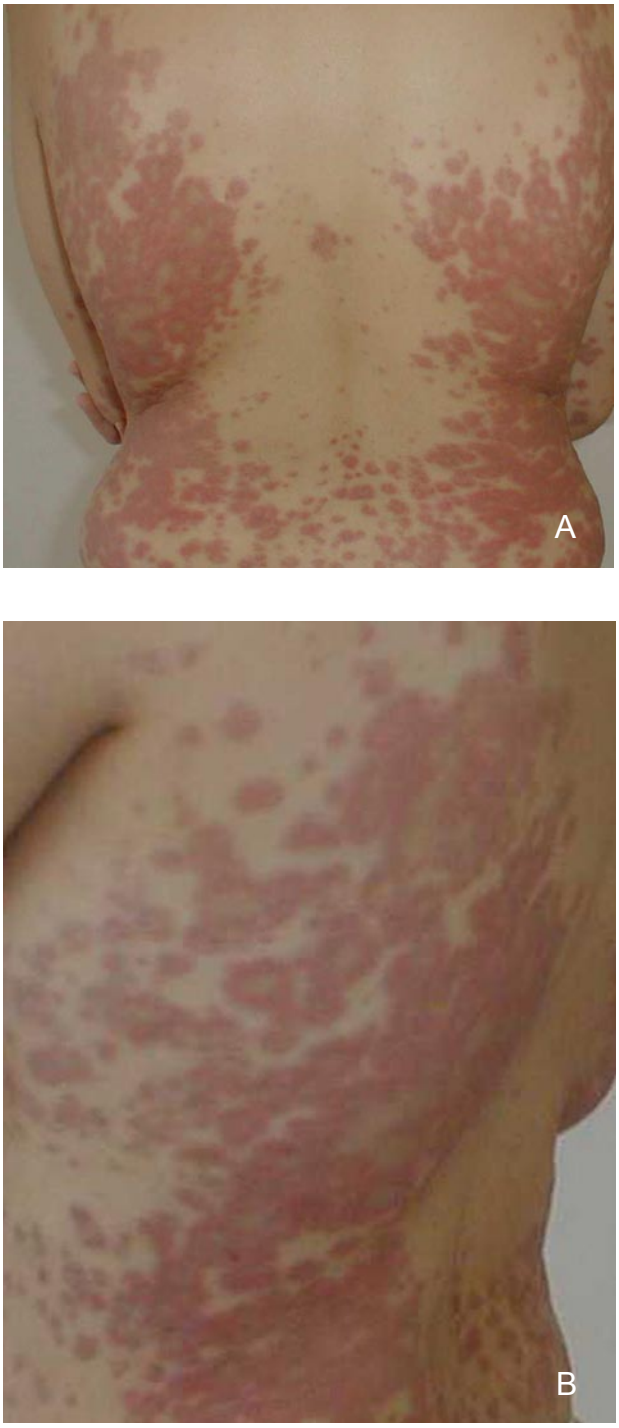
Case Report

A 40-year-old woman in otherwise good health presented with a 5-year history of recurrent pruritic light red lesions on her chest and back. She reported that individual lesions would last up to 24 hours in one area before disappearing, while other new crops of lesions would develop in other areas of her body. She had no associated facial edema or lip or throat involvement, and she denied taking any medications. Her history failed to reveal any potential triggers for the eruptions. On physical examination, multiple elevated superficial erythematous papules and plaques were noted, with shapes varying from annular to circinate, areas of central clearing, and targetlike lesions on the trunk and extremities. The lesions blanched with pressure (Figure). The woman had no mucosal involvement, scars, or change in pigmentation. Results from the remainder of the physical examination were unremarkable.

Because of the extent of involvement and the erythematous to violaceous aspect of certain lesions, a 3-mm punch biopsy was performed to rule out urticarial vasculitis. Histology results were consistent with urticaria with red blood extravasation but without vasculitis. Our patient initially was treated with topical clobetasol propionate ointment, 10 mg of cetirizine hydrochloride, and topical calamine lotion. At follow-up one week later, she mentioned that she had improved after 5 days of treatment but began developing new lesions 2 days prior to her second visit. Given the severity of pruritus and after a discussion of the role of corticosteroids for acute urticaria, a taper dose of prednisone was prescribed at 40 mg/d, in addition to 60 mg of fexofenadine hydrochloride twice daily. The patient was lesion- and symptom-free after 7 days of treatment, with no recurrence one month later.

Comment

Urticaria may be acute or chronic. Acute urticaria is idiopathic in more than 50% of patients but can occur as a type 1 hypersensitivity reaction to food or wasp or bee stings; an immunologic response to blood products, infection, or febrile illness; or an adverse effect of drug therapy by various mechanisms, such as penicillin or angiotensin-converting enzyme inhibitors.[3] As opposed to acute urticaria, chronic urticaria is defined by recurrent episodes occurring at least twice weekly for 6 weeks.[2] Urticaria occurring less frequently than this, over a long period, is more



Symmetric involvement of the back with wheals (A and B).

accurately termed *episodic* because it is more likely to have an identifiable environmental trigger. All chronic urticaria implicitly go through an acute stage (<6 weeks). Although many classification systems of chronic urticaria exist, a concise clinical classification is included in the Table.[2] Urticarial vasculitis is a small vessel vasculitis but is included in the classification because it is clinically indistinguishable from other urticarial lesions.

Urticarial lesions in chronic urticaria typically last 4 to 36 hours and can occur in individuals of any age (though it is most common in women), usually with few systemic symptoms.[4] Pruritus is nearly always severe, especially at night, and may prevent sleep. Fifty percent of cases resolve spontaneously by 6 months, but of those that do not, 40% still have symptoms of urticaria 10 years later.[4] The severe effect of chronic urticaria on quality of life often is underestimated.[5]

Ordinary Urticaria—Patients previously classified as having chronic idiopathic or "ordinary" urticaria are now divided into 2 groups: 50% to 60% of these patients have chronic idiopathic urticaria (CIU), and the remainder have chronic autoimmune urticaria (CAU).[6] Results from a study in children demonstrated that autoimmune urticaria occurs in children in as many as 30% of chronic cases.[7] CAU is caused by an immunoglobulin (Ig) G antibody to the α subunit of the IgE receptor (35%–40% of cases) or to IgE (5%–10% of cases).[6] The IgG subclasses that appear to be pathogenic are IgG1; IgG3; and, to a lesser degree, IgG4 (though not IgG2).[6] Complement activation augments histamine secretion by release of C5a.[8] CAU has been reported to be associated with antithyroid antibodies (27% of cases)[6,9]; autoimmune conditions such as vitiligo, rheumatoid arthritis, and pernicious anemia; and low vitamin B_{12} levels.[10] Patients with demonstrable histamine-releasing autoantibodies have a very strong association with HLA-DR4 and its associated allele HLA-DQ8.[11]

Histologically, the 2 groups of urticaria are indistinguishable.[6] Advanced techniques show a perivascular nonnecrotizing infiltrate of $CD4^+$ lymphocytes consisting of a mixture of T_H1 and T_H2 subtypes, plus monocytes, neutrophils, eosinophils, and basophils. These cells are recruited because of interactions with C5a, cell priming cytokines, chemokines, and adhesion molecules.[6] A recent study also found inflammatory cells and mediator up-regulation in uninvolved CIU skin as a sign of prolonged and widespread "urticarial status."[12]

Physical Urticaria—Physical urticaria are classified and induced by a physical stimulus. Most physical urticaria occur within minutes of provocation and resolve within 2 hours, with the exception of delayed pressure urticaria, which may persist for 24 hours or longer.[13] Angioedema may occur in all physical urticaria except dermographism. Overlap between groups is common, and physical urticaria often occur as an added feature of chronic urticaria.

The most common type of physical urticaria is simple immediate dermographism, presenting with linear wheals at sites of scratching or friction. It occurs in about 1.4% to 5% of the population worldwide[14] and may be viewed as an exaggerated physiologic response. On average, dermographism runs a course of 2 to 3 years before usually resolving spontaneously.[15]

Delayed-pressure urticaria is a response to sustained pressure to the skin, presenting with deep erythematous edema after a delay of unknown cause lasting 30 minutes to 12 hours.[14,16] An increased level of interleukin 6 has been found in suction blister fluid over induced lesions.[2,15] The edema tends to be deeper, pruritic, and painful, and it may persist for days. Systemic features such as malaise, flulike symptoms, and arthralgia may occur. The prognosis is variable, but the mean duration is 6 to 9 years.[17] The response to antihistamines often is poor, and oral corticosteroids may be needed for disease control.[2]

Cholinergic urticaria usually presents with multiple, transient, pruritic, small, red macules or papules on the neck, trunk, forearms, wrists, and thighs in response to heat, often surrounded by an obvious flare. It mainly affects young adults, with an overall prevalence of 11% in this group.[18] Fifty percent of patients are atopic.[15] Angioedema and systemic manifestations such as headache, palpitations, abdominal pain, wheezing, and syncope may occur. The cholinergic sympathetic innervation of sweat glands is involved because the eruption can be blocked by topical anticholinergic drugs,[19] but how this leads to urticaria is unclear. The routine treatment is with low-sedation H_1-type antihistamines, with or without an anxiolytic such as oral propranolol. In severe cases, the anabolic steroid stanazolol has been used.[15]

Cold urticaria is a heterogeneous condition in which whealing occurs within minutes in response to cold exposure, most frequently in children and young adults. Wheals usually arise at the site of localized cooling but may be generalized following lowering of the body temperature.[16] Diagnosis may be confirmed by applying an ice cube for 5 to 15 minutes to the skin, allowing an interval for skin rewarming, and observing the development of whealing that occurs on skin rewarming. Systemic symptoms such as flushing, headache, abdominal pain, and syncope can occur if large areas

Clinical Classification of Urticaria*[2]

Condition	Group/Sex at Highest Risk	Aggravating Factors and Associations	Specialized Therapy
Ordinary Urticaria			
Chronic idiopathic urticaria	Women (2:1 ratio)	Aspirin, NSAIDs, ACE inhibitors, codeine	H_2-antagonists/doxepin hydrochloride
Chronic autoimmune urticaria		Dietary pseudoallergens	Low pseudoallergen diet
		Infections	Leukotriene antagonists/nifedipine, short-term corticosteroids/thyroxine, immunosuppressive therapy
Physical Urticaria			
Dermographism	Young adults/women	Skin stroking	Avoidance, PUVA/UVB
Delayed-pressure urticaria	Young adults/men	Vertical pressure	Avoidance of sharp edges and use of gel-filled soles, short-term corticosteroids, leukotriene antagonists/dapsone
Cholinergic urticaria	Young adults	Rise of body core temperature	Danazol/stanazolol
Cold urticaria	Children/ young adults	Skin cooling	Induction of physical tolerance
		Infections	3-wk trial with penicillin, leukotriene antagonists, short-term corticosteroids
Adrenergic urticaria		Stress	Propranolol
Aquagenic urticaria	Young adults/women	Water of any temperature	Avoidance
Exercise-induced anaphylaxis	Young adults	Physical exercise	Avoid food before exercise
		Diet and drugs	Food diary
Localized heat urticaria		Localized heat	Hardening through repeated heat exposure
Solar urticaria	Young adults/women	UV light±visible light	Photohardening, doxepin hydrochloride
Vibratory urticaria		Vibratory forces	Avoidance

Condition	Group/Sex at Highest Risk	Aggravating Factors and Associations	Specialized Therapy
Urticarial Vasculitis	Middle-aged women/men	Trauma and pressure	NSAIDs
		Infection	Systemic corticosteroids
		Drugs (cimetidine, diltiazem hydrochloride)	Immunosuppressive therapy
Contact Urticaria		Direct contact	Avoidance, NSAIDs, antihistamines
Angioedema Without Wheals	Children and adolescents	C1 inhibitor deficiency	Purified C1 inhibitor concentrate
		Drugs (ACE inhibitors, NSAIDs)	Danazol/stanozolol, tranexamic acid

*NSAIDs indicates nonsteroidal anti-inflammatory drugs; ACE, angiotensin-converting enzymes; PUVA, psoralen plus UVA.

are affected. The cause is unknown, but a serum factor, possibly IgM or IgE, has been implicated.[20] A heterozygous deficiency of the protease inhibitor α1-antichymotrypsin has been demonstrated and may be etiologically important in some patients.[21] The prognosis is good, with spontaneous improvement in an average of 2 to 3 years.[15] Ninety-six percent of cases of cold urticaria are primary.[22] The diagnosis of secondary acquired cold urticaria depends on being able to demonstrate cryoglobulins, cold agglutinins, or possibly cryofibrinogens.[17] These findings should, in turn, lead to investigations for an underlying cause, such as hepatitis B or C infection, lymphoproliferative disease, or infectious mononucleosis.[15]

Other uncommon forms of physical urticaria include adrenergic urticaria, which develops during phases of stress and has been associated with an increase in the plasma concentrations of norepinephrine, epinephrine, and prolactin.[23] Aquagenic urticaria is precipitated by skin contact with water of any temperature.[3] Exercise-induced anaphylaxis involves urticaria, respiratory distress, or hypotension after exercise. In localized heat urticaria, wheals occur on skin in direct contact with warm objects. Solar urticaria is a rare condition that occurs within minutes of exposure to UV light waves ranging from 280 to 760 nm[14]; it usually disappears in less than one hour. Vibratory urticaria occurs after a vibratory stimulus and can be a hereditary autosomaldominant disorder or an acquired sporadic disease.[24]

Urticarial Vasculitis—Urticarial vasculitis describes a distinct entity in which the gross cutaneous lesions resemble urticaria and histologically show features of a vasculitis. The diagnosis is suggested clinically by wheals lasting more than 24 hours and residual bruising.[25] Although the clinical lesions may present as typical urticaria, pathophysiologically, it is a different disease caused by deposition of antigen-antibody complexes in vessel walls, a type 3 reaction causing vascular damage.[17] Lesions often occur at pressure points and may resolve with residual purpura. Extracutaneous manifestations include transient and migratory arthralgia (50%); gastrointestinal symptoms (20%); and pulmonary obstructive disease (20%), particularly in smokers and patients with renal disease (5%–10%).[17] Normocomplementemic urticarial vasculitis usually is idiopathic, but hypocomplementemic urticarial vasculitis may be associated with underlying systemic lupus erythematosus, Sjögren syndrome, or cryoglobulinemia.[2] Primary urticarial vasculitis can occasionally evolve into systemic lupus erythematosus.[26] Patients with urticarial vasculitis often improve on nonsteroidal anti-inflammatory drugs (NSAIDs), but some patients may need immunosuppressive therapy.

Contact Urticaria—Contact urticaria develops at the site(s) of contact of an urticant and can be divided into an allergic subgroup caused by an IgE-allergen interaction and a nonallergic subgroup that is IgE independent. The allergic form typically

is seen in children with atopic dermatitis sensitized to environmental allergens such as grass, animals, food, or latex, and it may be complicated by anaphylaxis. Natural rubber latex is one of the most important causes today.[27] This type appears within minutes, fades within 2 hours, and is partially inhibited by antihistamines. Nonallergic contact urticaria is caused by the direct effect of the urticant on blood vessels and includes irritants such as benzoic acid and cinnamic aldehyde in cosmetics. It may take 45 minutes for lesions to appear and urticaria is partially inhibited by NSAIDs.

Angioedema Without Wheals—It is useful to classify angioedema occurring without wheals as a separate entity because its etiology may be associated with hereditary angioedema, which must be excluded. The condition usually is idiopathic or caused by a drug reaction to angiotensin-converting enzyme inhibitors, aspirin, or NSAIDs. Hereditary angioedema is a rare autosomal-dominant condition with a prevalence between 1:10,000 and 1:150,000 in the general population and is caused by a deficiency (type 1, 85%) or dysfunction (type 2, 15%) of C1 inhibitor.[28] A low level of C4 in the serum is a constant and diagnostic feature. A third type affecting primarily women and exacerbated by estrogens recently has been described.[28] Patients have lifelong episodic angioedema and may experience colicky abdominal pain. Laryngeal involvement can be life threatening. Treatment is difficult and involves fluid replacement and purified C1 inhibitor concentrate for acute attacks (not approved in the United States) and prophylactic treatment with anabolic androgens and antifibrinolytics.[28]

Diagnosis—The diagnosis of urticaria is primarily clinical; extensive laboratory tests are very rarely needed—only when indicated by the patient history.[3] Some authors argue that laboratory investigations are unnecessary for mild ordinary urticaria responding to antihistamines.[29] Taking a thorough patient history has been found to be almost as effective in identifying a cause as a complete diagnostic evaluation.[30] In acute urticaria, if the history indicates a type 1 hypersensitivity reaction, confirmation is possible by a prick test or laboratory radioallergosorbent tests.[3] Many physical and contact urticaria can be confirmed by a challenge of the offending agent. An initial baseline investigation with a complete blood count and erythrocyte sedimentation rate should be taken in more severe cases to identify any internal disease or raise the possibility of urticarial vasculitis.[17] Of note, a biopsy is more sensitive and specific for ruling out urticarial vasculitis than are a complete blood count and erythrocyte sedimentation rate.

A search for thyroid autoantibodies is appropriate for all chronic urticaria not responding to first-line therapies with antihistamines, especially when autoimmune urticaria is suspected.[2] Further investigations are guided by clinical suspicion, which may include a skin biopsy, autoimmune screening, urinalysis, serum cryoglobulins, and hepatitis B and C serology.[31] The only available test to screen for autoantibodies against the IgE receptor is the autologous serum skin test. This test should be performed with care because infections could be transmitted, particularly if, by mistake, patients were not injected with their own serum.[31] Measurement of C4 is indicated only in patients who present with angioedema alone and should be followed by a determination of the levels and function of C1 inhibitor, if C4 is below reference range.[29]

Management and Treatment—Management of urticaria depends on its cause. Aggravating factors should be identified from the history, and triggering stimuli for physical urticaria should be avoided. Simple cooling lotions such as menthol 1% or 2% in an aqueous cream often are useful.[32] Aspirin and NSAIDs should be avoided because they aggravate symptoms in 30% of patients.[33] Patients taking low-dose aspirin for its antithrombotic properties usually can continue regular treatment. Avoiding codeine and other opiates also is recommended because an enhanced skin test reaction may be found in chronic urticaria.[34] Avoiding dietary pseudoallergens, such as food coloring and natural salicylates, is controversial.[14,35] This generally has only a small role unless proven by a double-blinded placebo-controlled challenge.[2]

The mainstays for treatment of urticaria are oral antihistamines, as they reduce pruritus and wheal duration and numbers. Oral antihistamines have been reported to produce moderate or good response in 44% to 91% of patients with all types of urticaria.[36,37] Antihistamines can be grouped into first-generation (sedating), second generation (minimally sedating), third-generation (nonsedating), and H_2 antagonists.[17] The physiologic and pathologic actions of histamine are mediated through 4 histamine receptor subtypes: H_1, H_2, H_3, and H_4.[38] The erythema, wheal formation, and itching associated with urticaria are mainly due to activation of H_1 receptors and the less contributory role of H_2 receptors.[38] Histamine H_3 receptors are located presynaptically on postganglionic sympathetic norepinephric nerves, including sympathetics innervating the heart and blood vessels. The contribution of H_3 receptors to skin responses mediated by histamine has not been fully elucidated. However, in a recent experimental study, the authors reported that

the combination of H_1 and H_3 antagonists might be a novel approach for the treatment of urticaria.[38]

Initially, a minimally sedating second- or third-generation antihistamine, such as loratadine,[39] fexofenadine hydrochloride,[40] and cetirizine hydrochloride,[41-44] should be given at a once-daily oral dosing. When one antihistamine is not helpful, it is usually worth trying a different one, and some physicians combine 2 or more antihistamines at the same time.[3] It is common practice to exceed the licensed dose in severely affected patients.[31] High doses of antihistamines have effects beyond the blockade of histamine receptors, and actions that are not due to antagonism of H_1 receptors may account for the efficacy of older antihistamines.[45] As a general rule, antihistamines are safe and have few substantial adverse effects; drug interactions are rare. If possible, it is best to avoid all antihistamines in pregnancy, though none have been proven teratogenic. If one is used, the consensus is that chlorpheniramine maleate is among the safest.[46]

Addition of a sedating first-generation antihistamine such as hydroxyzine at night can be helpful, especially if nocturnal pruritus prevents sleep. The use of a sedating antihistamine as monotherapy is less desirable because of impairment of cognitive function, including driving performance and concentration. The addition of a H_2 antagonist to conventional H_1 antihistamines may be helpful in some patients.[3,47] Doxepin hydrochloride at low doses (10–50 mg) is used for its potent H_1 and H_2 receptor antagonist properties. Doxepin hydrochloride is highly sedative and especially suitable for patients with associated depression.[48]

Oral corticosteroids given in short reducing courses may be needed for severe exacerbations not responding to full-dose antihistamines. Relatively high doses of up to 40 to 60 mg of prednisone may be needed for disease control. Alternate-day steroids may be used for patients with severe disease.[6] Long-term administration should be avoided.[1]

Many patients feel reassured by carrying an epinephrine pen for self-administration if they are prone to severe attacks. Leukotriene antagonists (zafirlukast and montelukast sodium) have been shown to be superior to placebo in the treatment of patients with chronic urticaria.[49,50] Nifedipine has a small effect in chronic urticaria and often is used for patients with concomitant hypertension. Thyroxine recently was reported to suppress CIU symptoms associated with antithyroid autoantibodies in some patients.[51]

Given the role of the immune system in a subset of patients, immunosuppressive therapy is considered for patients with a severe disabling course. Cyclosporine at 2.5 to 5 mg/kg per day is of proven value in autoantibody-positive chronic urticaria[52] but also is effective in most cases of severe autoantibody-negative disease.[15] Tacrolimus also has shown promise in a recent trial.[53] Other options include plasmapheresis[54] and intravenous immunoglobulin.[55,56] Optimal treatment protocols have yet to be confirmed. Treatments for CIU with only limited or anecdotal supportive evidence include sulfasalazine, methotrexate, rofecoxib, colchicine, dapsone, and cyclophosphamide.[3]

Future treatment may involve development of selective immunotherapy targeting the IgE receptor or vaccinations to down-regulate and induce tolerance to the IgE receptor. Other potential strategies include blocking formation of C5a and use of therapeutic antibodies such as anti-IgE, anti–tumor necrosis factor α, and anti–interleukin 5.[2]

Conclusion

There is no single way to manage urticaria and angioedema. Most patients are treated successfully with antihistamines. However, patients with severe antihistamine-resistant urticaria may be very disabled by their disease, and the treatment can pose a major challenge to the physician.

REFERENCES

1. Henderson RL Jr, Fleischer AB Jr, Feldman SR. Allergists and dermatologists have far more expertise in caring for patients with urticaria than other specialists. *J Am Acad Dermatol.* 2000;43:1084-1091.
2. Grattan CEH, Sabroe RA, Greaves MW. Chronic urticaria. *J Am Acad Dermatol.* 2002;46:645-657.
3. Kozel MM, Sabroe RA. Chronic urticaria: aetiology, management and current and future treatment options. *Drugs.* 2004;64:2515-2536.
4. Negro-Alvarez JM, Miralles-Lopez JC. Chronic idiopathic urticaria treatment. *Allergol Immunopathol (Madr).* 2001;29:129-132.
5. Grob JJ, Revuz J, Ortonne JP, et al. Comparative study of the impact of chronic urticaria, psoriasis and atopic dermatitis on the quality of life. *Br J Dermatol.* 2005;152:289-295.
6. Kaplan AP. Chronic urticaria: pathogenesis and treatment. *J Allergy Clin Immunol.* 2004;114:465-474.
7. Brunetti L, Francavilla R, Miniello VL, et al. High prevalence of autoimmune urticaria in children with chronic urticaria. *J Allergy Clin Immunol.* 2004;114:922-927.
8. Kikuchi Y, Kaplan AP. A role for C5a in augmenting IgG-dependent histamine release from basophils in chronic urticaria. *J Allergy Clin Immunol.* 2002;109:114-118.
9. Gruber BL, Baeza M, Marchese M, et al. Prevalence and functional role of anti-IgE antibodies in urticarial syndromes. *J Invest Dermatol.* 1988;90:213-217.

10. Mete N, Gulbahar O, Aydin A, et al. Low B12 levels in chronic idiopathic urticaria. *J Investig Allergol Clin Immunol*. 2004;14:292-299.
11. O'Donnell BF, O'Neill CM, Francis DM, et al. Human leucocyte antigen class II associations in chronic idiopathic urticaria. *Br J Dermatol*. 1999;140:853-858.
12. Caproni M, Giomi B, Volpi W, et al. Chronic idiopathic urticaria: infiltrating cells and related cytokines in autologous serum-induced wheals. *Clin Immunol*. 2005;114:284-292.
13. Black AK, Lawlor F, Greaves MW. Consensus meeting on the definition of physical urticarias and urticarial vasculitis. *Clin Exp Dermatol*. 1996;21:424-426.
14. Henz BM. Physical urticaria. In: Henz BM, Zuberbier T, Grabbe J, et al, eds. *Urticaria: Clinical, Diagnostic and Therapeutic Aspects*. Berlin, Germany: Springer Verlag; 1998:55-89.
15. Greaves M. Chronic urticaria. *J Allergy Clin Immunol*. 2000;105:664-672.
16. Kontou-Fili K, Borici-Mazi R, Kapp A, et al. Physical urticaria: classification and diagnostic guidelines: an EAACI position paper. *Allergy*. 1997;52:503-513.
17. Bolognia JL, Jorizzo JL, Rapini RP, eds. *Dermatology*. New York, NY: Mosby; 2003:287-311.
18. Zuberbier T, Althaus C, Chantraine-Hess S, et al. Prevalence of cholinergic urticaria in young adults. *J Am Acad Dermatol*. 1994;31:978-981.
19. Herxheimer A. The nervous pathway mediating cholinergic urticaria. *Clin Sci (Lond)*. 1956;15:195-204.
20. Wanderer AA, Maselli R, Ellis EF, et al. Immunological characterisation of serum factors responsible for cold urticaria. *J Allergy Clin Immunol*. 1971;48:13-22.
21. Lindmark B, Wallengren J. Heterozygous alpha 1-antichymotrypsin deficiency may be associated with cold urticaria. *Allergy*. 1992;47:456-458.
22. Neittaanmaki H. Cold urticaria: clinical findings in 220 patients. *J Am Acad Dermatol*. 1985;13:636-644.
23. Haustein UF. Adrenergic urticaria and adrenergic pruritus. *Acta Derm Venereol*. 1990;70:82-84.
24. Mathelier-Fusade P, Vermeulen C, Leynadier F. Vibratory angioedema. *Ann Dermatol Venereol*. 2001;128:750-752.
25. O'Donnell B, Black AK. Urticarial vasculitis. *Int Angiol*. 1995;14:166-174.
26. Bisaccia E, Adamo V, Rozan SW. Urticarial vasculitis progressing to systemic lupus erythematosus. *Arch Dermatol*. 1988;124:1088-1090.
27. Wakelin SH. Contact urticaria. *Clin Exp Dermatol*. 2001;26:132-136.
28. Zuraw BL. Current and future therapy for hereditary angioedema. *Clin Immunol*. 2005;114:10-16.
29. Grattan C, Powell S, Humphreys F. Management and diagnostic guidelines for urticaria and angio-oedema. *Br J Dermatol*. 2001;144:708-714.
30. Kozel MM, Mekkes JR, Bossuyt PM, et al. The effectiveness of a history-based diagnostic approach in chronic urticaria and angioedema. *Arch Dermatol*. 1998;134:1575-1580.
31. Zuberbier T, Greaves MW, Juhlin L, et al. Definition, classification, and routine diagnosis of urticaria: a consensus report. *J Investig Dermatol Symp Proc*. 2001;6:123-127.
32. Bromm B, Scharein E, Darsow U, et al. Effects of menthol and cold on histamine-induced itch and skin reactions in man. *Neurosci Lett*. 1995;187:157-160.
33. Doeglas HMG. Reactions to aspirin and food additives in patients with chronic urticaria, including the physical urticarias. *Br J Dermatol*. 1975;93:135-144.
34. Kaufman A, Rosenstreich DL. Mast cell heterogeneity in chronic idiopathic urticaria. *Ann Allergy*. 1990;65:367-373.
35. Ortolani C, Pastorello E, Ispano M, et al. Food allergy diagnosis protocol. *Allerg Immunol (Paris)*. 1988;20:48-50.
36. Humphreys F, Hunter JA. The characteristics of urticaria in 390 patients. *Br J Dermatol*. 1998;138:635-638.
37. Nettis E, Pannofino A, D'Aprile C, et al. Clinical and aetiological aspects in urticaria and angio-oedema. *Br J Dermatol*. 2003;148:501-506.
38. McLeod RL, Mingo GG, Kreutner W, et al. Effect of combined histamine H1 and H3 receptor blockade on cutaneous microvascular permeability elicited by compound 48/80. *Life Sci*. 2005;76:1787-1794.
39. Monroe EW. Loratadine in the treatment of urticaria. *Clin Ther*. 1997;19:232-242.
40. Nelson HS, Reynolds R, Mason J. Fexofenadine HCl is safe and effective for treatment of chronic idiopathic urticaria. *Ann Allergy Asthma Immunol*. 2000;84:517-522.
41. Breneman D, Bronsky EA, Bruce S, et al. Cetirizine and astemizole therapy for chronic idiopathic urticaria: a double-blind, placebo-controlled, comparative trial. *J Am Acad Dermatol*. 1995;33(2 pt 1):192-198.
42. Breneman DL. Cetirizine versus hydroxyzine and placebo in chronic idiopathic urticaria. *Ann Pharmacother*. 1996;30:1075-1079.
43. Kalivas J, Breneman D, Tharp M, et al. Urticaria: clinical efficacy of cetirizine in comparison with hydroxyzine and placebo. *J Allergy Clin Immunol*. 1990;86(6 pt 2):1014-1018.
44. Andri L, Senna GE, Betteli C, et al. A comparison of the efficacy of cetirizine and terfenadine: a double-blind, controlled study of chronic idiopathic urticaria. *Allergy*. 1993;48:358-365.
45. Kaplan AP. Clinical practice. chronic urticaria and angioedema. *N Engl J Med*. 2002;346:175-179.
46. Andrews AW, Fornwald JA, Lijinsky W. Nitrosation and mutagenicity of some anime drugs. *Toxicol Appl Pharmacol*. 1980;52:237-244.
47. Commens CA, Greaves MW. Cimetidine in chronic idiopathic urticaria: a randomised double-blind study. *Br J Dermatol*. 1978;99:675-679.

48. Furukawa T, McGuire H, Barbui C. Low dosage tricyclic antidepressants for depression. *Cochrane Database Syst Rev*. 2003;(3):CD003197.
49. Ellis MH. Successful treatment of chronic urticaria with leukotriene antagonists. *J Allergy Clin Immunol*. 1998;102:876-877.
50. Spector S, Tan RA. Antileukotrienes in chronic urticaria. *J Allergy Clin Immunol*. 1998;101(4 pt 1):572.
51. Aversano M, Caiazzo P, Iorio G, et al. Improvement of chronic idiopathic urticaria with L-thyroxine: a new TSH role in immune response? *Allergy*. 2005;60:489-493.
52. Grattan CE, O'Donnell BF, Francis DM, et al. Randomized double-blind study of cyclosporin in chronic "idiopathic" urticaria. *Br J Dermatol*. 2000;143:365-372.
53. Kessel A, Bamberger E, Toubi E. Tacrolimus in the treatment of severe chronic idiopathic urticaria: an open-label prospective study. *J Am Acad Dermatol*. 2005;52:145-148.
54. Grattan CEH, Francis DM, Slater NGP, et al. Plasmapheresis for severe unremitting chronic urticaria. *Lancet*. 1992;339:1078-1080.
55. O'Donnell BF, Barr RM, Blac AK, et al. Intravenous immunoglobulin in chronic autoimmune urticaria. *Br J Dermatol*. 1998;138:101-106.
56. Klote MM, Nelson MR, Engler RJ. Autoimmune urticaria response to high-dose intravenous immunoglobulin. *Ann Allergy Asthma Immunol*. 2005;94:307-308.