

CURRENT CONCEPTS**CHRONIC URTICARIA**

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THOUGH rarely life-threatening, widespread urticaria and its associated angioedema can be both debilitating and frightening. In some cases, lingual swelling requires treatment with epinephrine. Although accurate data on the prevalence of urticaria are unavailable, 15 to 23 percent of the U.S. population may have had this condition,^{1,2} which in many cases is prolonged and relapsing. On the basis of published data,³ a similar prevalence in the United Kingdom seems probable. Chronic urticaria is likely to be present at some time in about 25 percent of patients with urticaria. By chronic urticaria, I mean the occurrence of widespread wheals daily or almost daily for at least six weeks.

Since the cause of chronic urticaria cannot be determined in most cases, it is considered idiopathic. In physical urticarias, the application of a physical stimulus to the skin causes the formation of local wheals, itching, and in some cases, angioedema. The frequencies and salient features of the common forms of urticaria are shown in Table 1 and Figures 1 and 2. Chronic urticaria affects predominantly adults. It is approximately twice as common in women as in men.¹⁰ Up to 40 percent of patients who have chronic urticaria for more than 6 months still have urticarial wheals 10 years later.³

CLINICAL PRESENTATION

The wheals of chronic urticaria are smooth, edematous, pink or red, and surrounded by a bright-red flare. Usually they are intensely itchy, are found anywhere on hairless or hairy skin, and last less than 24 hours (usually about 12 hours). Clearing of the central area may result in an annular pattern. The larger swellings of angioedema originate subcutaneously or submucosally and may last longer than the wheals, depending on their size, and are usually less itchy. Urticaria and angioedema occur together in about half of affected patients.³ Both fade, leaving no trace, unless rubbing leads to bruising. Chronic urticaria frequently follows a remitting and relapsing course and is worse at night. Wheals that last more than 24 hours raise the possibility of other diagnoses, including urticarial vasculitis.^{11,12}

The coexistence of chronic urticaria and physical urticarias, including symptomatic dermatographism

and, in particular, delayed pressure urticaria, is a frequent source of diagnostic confusion.^{6,10,13} It is important to determine by appropriate challenge testing whether patients have a physical urticaria as the predominant cause of symptoms, since the investigation and treatment of such urticarias may be quite different (Table 1).¹⁴

The most important diagnostic pitfall, however, is that of overlooking urticarial vasculitis.^{15,16} Table 2 shows the clinical and histologic features that differentiate chronic urticaria from urticarial vasculitis.¹⁷ Systemic lupus erythematosus and Sjögren's syndrome may present with urticarial lesions, and in such cases the eruption usually turns out to be urticarial vasculitis.^{18,19} In all patients with this condition, evidence of autoimmune connective-tissue disease or systemic disease due to immune-complex deposition should be sought.

HISTOPATHOLOGICAL FEATURES

The characteristic microscopic picture in chronic urticaria,²⁰⁻²² unlike that in urticarial vasculitis (Table 2), shows no evidence of vascular damage, nuclear debris, or red-cell extravasation. The predominant cell types are lymphocytes of the T-helper phenotype that express HLA-DR antigen; these are arranged perivascularly. However, some patients with chronic urticaria that is otherwise characteristic have evidence on skin biopsy of neutrophils within capillary and post-capillary venular walls, but no structural damage. It is unclear whether this pattern is an intermediate one between "ordinary" chronic urticaria and urticarial vasculitis. The affected skin also contains an increased number of mast cells.²³ The kinetics of leukocyte recruitment have been studied with selected primary antibody markers of adhesion molecules.²⁴ In these studies, spontaneous wheals showed moderate expression of E-selectin and intracellular adhesion molecule 1 on vascular endothelial cells and of vascular-cell adhesion molecule 1 (VCAM-1) on perivascular cells.

PATHOPHYSIOLOGIC FEATURES

The clinical response of chronic urticaria to H₁ antihistamines and the finding of increased concentrations of histamine in skin-tissue fluid underscore the role of histamine, derived from mast cells in skin, as a major mediator of urticaria.²⁵ Among skin samples from 13 patients with this condition, those from 12 patients had higher concentrations of histamine in tissue with lesions than in tissue without lesions (mean value in lesional skin, 41 ng per milliliter; in normal skin, 19 ng per milliliter). Other mediators, including kinins,²⁶ eicosanoids,²⁷ and neuropeptides,²⁸ may also play a part in producing the lesions of chronic urticaria, but direct measurements of these mediators in the skin of affected patients have not been reported.

AUTOIMMUNE MAST-CELL DISEASE

I and others have recently identified a wheal-producing noncytokine mediator in the serum of some patients

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Table 1. Features of Common Types of Chronic Urticaria.

TYPE OF URTICARIA	AGE RANGE OF PATIENTS (YR)	PRINCIPAL CLINICAL FEATURES	ASSOCIATED ANGIOEDEMA	DIAGNOSTIC TEST
Chronic idiopathic	20–50	Profuse or sparse generalized, pink or pale edematous papules or wheals, often annular with itching	Yes	—
Symptomatic dermatographism	20–50	Itchy, linear wheals with a surrounding bright-red flare at sites of scratching or rubbing	No	Light stroking of skin causes an immediate wheal with itching. ⁴
Other physical urticarias				
Cold	10–40	Itchy pale or red swelling at sites of contact with cold surfaces or fluids	Yes	Ten-minute application of an ice pack causes a wheal within five minutes of the removal of ice. ⁵
Pressure*	20–50	Large painful or itchy red swelling at sites of pressure (soles, palms, or waist), lasting 24 hours or more	No	Application of pressure perpendicular to skin produces persistent red swelling after a latent period of 1 to 4 hours. ^{6,7}
Solar	20–50	Itchy pale or red swelling at site of exposure to ultraviolet or visible light	Yes	Irradiation by a 2.5-kW solar simulator (290–690 nm) for 30 to 120 seconds causes wheals in 30 minutes. ⁸
Cholinergic	10–50	Itchy, monomorphic pale or pink wheals on trunk, neck, and limbs	Yes	Exercise or a hot shower elicits an eruption. ⁹

*A 1993 study⁶ indicates that pressure-induced and spontaneous wheals appear concurrently in 37 percent of patients with chronic idiopathic urticaria.

with chronic urticaria. This mediator has a molecular weight of more than 100,000, is an IgG molecule, and releases histamine from both basophils in normal blood and mast cells in skin.^{29–32} With inhibition experiments using the human recombinant extracellular fragment of the high-affinity IgE receptor (FcεRI) alpha subunit, my colleagues and I identified IgG autoantibodies that interact with and cross-link alpha subunits of adjacent high-affinity IgE receptors.³⁰ These findings were subsequently confirmed independently by immunoblotting and immunoprecipitation.³²

Among 163 patients we studied who had chronic idiopathic urticaria, 98 had wheal formation in response to the intradermal injection of autologous serum.

Among the serum samples from these patients, 47 (48 percent) caused the release of histamine from basophil leukocytes of healthy donors, suggesting the presence of functional anti-FcεRIα autoantibodies, anti-IgE autoantibodies, or both.^{30,33} Other investigators have found slightly lower percentages^{31,32}; variation in the selection of patients may account for the differences. Clinically, patients with these autoantibodies are indistinguishable from those without them. Although an enzyme-linked immunoassay is being developed, we identify patients with antibodies by intradermal skin testing with autologous serum. The identification is confirmed by the ability of the serum samples to cause the release of histamine from basophil leukocytes of healthy donors with low serum IgG levels or atopic donors with high serum IgG levels.

Our data show a positive correlation between histamine-releasing activity and disease activity.³⁴ They indicate that autoantibodies are important in explaining why some people have severe, unremitting chronic urticaria. In preliminary studies, plasmapheresis,³⁴ intravenous immunoglobulin,³⁵ or cyclosporine^{36,37} was associated with remission in patients with autoantibodies and chronic urticaria. These measures are not established treatments, however, and should only be considered for patients with very severe disease who do not respond to other treatments, including oral corticosteroids.

The concept that at least some chronic urticaria is a manifestation of autoimmune mast-cell disease is also supported by the association of urticaria with autoimmune thyroid disease. Among 624 patients with chronic



A



B

Figure 1. Urticaria.

Panel A shows a 36-year-old man with chronic urticaria. Panel B shows a 42-year-old woman with urticarial vasculitis. The wheals in the patient with urticarial vasculitis have an indolent and pigmented appearance.



Figure 2. Physical Urticarias.

Panel A shows a 20-year-old man with dermatographism. Panel B shows a 41-year-old man with delayed pressure urticaria.

idiopathic urticaria, 90 (14 percent) had laboratory evidence of thyroid autoimmunity, as compared with an expected figure of less than 6 percent in the general population.³⁸ Forty-four of the 90 patients had clinical evidence of thyroid disease.³⁸

OTHER CAUSATIVE FACTORS

IgE-mediated reactions to foods are a well-recognized cause of isolated attacks of acute urticaria and angioedema. They have only occasionally been shown to be an important factor in chronic urticaria in adults. They may possibly be more important in children. In the 1970s, reactions to food preservatives and additives were reported in 39 of 52 patients with chronic urticaria and angioedema.³⁹ These additives included compounds of benzoic acid, such as 4-hydroxybenzoic acid and sodium benzoate, as well as several azo dyes, including tartrazine and sunset yellow. Working in a tertiary referral clinic, I have not seen such a high proportion of IgE-mediated reactions to food. In a placebo-controlled oral challenge study, no more than 10 percent of patients with chronic urticaria had confirmed reactions to food additives.⁴⁰ Nevertheless, because the prevalence of chronic urticaria evoked by food additives may be higher in other groups of patients,⁴¹ routine challenge testing of such patients is justified.

Aspirin exacerbates chronic urticaria in at least 30 percent of patients,⁴² but this response is dose-related and therefore probably does not have an immunologic basis. Other exacerbating factors include psychological stress⁴³ and intercurrent febrile illnesses.¹⁰ Focal infections (infections of the teeth, sinus, urinary tract, or gallbladder), candidiasis, and cancer are not important causes of chronic urticaria in adults.^{44,45} Parasitic infestations are also an uncommon cause in developed nations.

DIAGNOSIS

A practical approach to the diagnosis of chronic urticaria is shown in Figure 3. A careful history of medications taken, including aspirin and other nonsteroidal

antiinflammatory drugs, should be obtained. These medications can be exacerbating factors, if not causative ones. When urticarial vasculitis is suspected (as when the patient, after instruction in the expected duration of lesions, reports that individual wheals have persisted for more than 24 hours), a skin biopsy should be performed for histologic examination. The biopsy specimen should be taken at the edge of the wheal and should include both clinically normal and abnormal skin. Direct immunofluorescence examination of the bi-

Table 2. Features That Differentiate Chronic Urticaria from Urticarial Vasculitis.

FEATURE	CHRONIC URTICARIA	URTICARIAL VASCULITIS
Characteristics of wheals		
Duration (hr)	<24	>24
Purpura*	No	Yes
Pain	No	Yes
Itch	Yes	Maybe
Hyperpigmentation	No	Yes
Systemic signs		
Arthralgia	Maybe	Yes
Fever*	No	Yes
Abdominal pain	Maybe	Yes
Nephritis*	No	Yes
Obstructive airways disease	No	Yes
Laboratory findings		
Elevated erythrocyte sedimentation rate	Maybe	Yes
Increased acute-phase proteins	Maybe	Yes
Reduced serum C3*	No	Maybe
Serum immune complexes*	No	Maybe
Histologic features of skin		
Venular endothelial-cell swelling	Maybe	Yes
Leukocyte invasion of venular endothelium	Maybe	Yes
Extravasation of red cells*	No	Yes
Leukocytoclasia*†	No	Yes
Fibrin deposition	Maybe	Yes
Findings on direct immunofluorescence		
C3	No	Yes
Immunoglobulin	Maybe	Yes
Fibrin	Maybe	Yes
Response to treatment with antihistamines	Yes	Maybe

*This feature is a major diagnostic criterion of urticarial vasculitis.

†Leukocytoclasia is fragmentation of nuclei of neutrophil polymorphonuclear leukocytes.

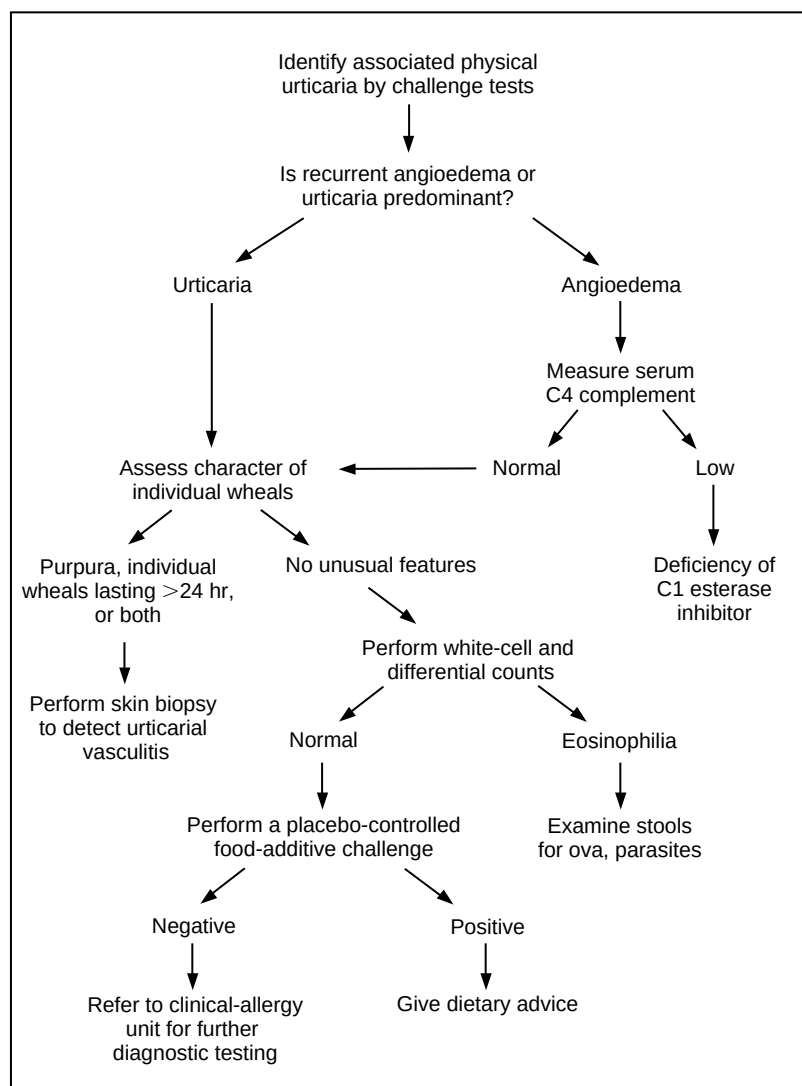


Figure 3. Algorithm for the Investigation and Diagnosis of Chronic Urticaria.

opsy specimen for perivascular deposition of immunoglobulins and complement is rarely of value.

When a physical urticaria is suspected, especially delayed pressure urticaria, dermatographism, or cholinergic urticaria, this possibility should be assessed by appropriate challenge testing (Table 1). If a coexisting physical urticaria is confirmed to be the predominant cause of the patient's symptoms, further investigations, such as those shown in Figure 3, are of little or no value.^{4,6,9} A prolonged history of repeated cutaneous or mucosal angioedema justifies screening for a hereditary deficiency of C1 esterase inhibitor, even in the absence of a family history, by measurement of the plasma concentration of complement C4. This concentration is rarely, if ever, normal, even between attacks.^{46,47}

If a total and differential white-cell count reveals eosinophilia, examination of the stool for ova and parasites is indicated. A screening thyroid-function test should be performed because of the diagnostic overlap between patients with chronic urticaria and patients

with clinical evidence of thyroid disease.³⁸ Otherwise, no other laboratory tests need be routinely performed.

Challenge testing for reactivity to food additives can be done on a placebo-controlled basis when the history suggests this possibility. Such testing should not be performed in patients with a history of severe angioedema, asthma, or episodes of anaphylaxis. Nor should it be done when the patient has a severe bout of urticaria. My practice is to administer 16 different food additives daily, along with an equal number of placebos that appear identical. The patient is instructed to keep a daily diary of wheal counts and to continue the regular daily dose of antihistamine, if such a medication has been prescribed. An additive that is potentially responsible for urticaria is identified by the exacerbation of urticaria within 24 hours of the ingestion of a numbered capsule. The potential culprit additive is then administered at least once more to confirm that the reaction can be reproduced. If all testing is negative and the patient's symptoms are still not well controlled, referral to a specialist may be indicated.

TREATMENT

Except for the few patients with chronic urticaria for whom an avoidable cause can be identified (such as a food additive), treatment is symptomatic. The mainstays are

antihistamines, with oral corticosteroids for patients with severe disease who do not respond to antihistamines.

All patients with chronic urticaria should be advised to avoid angiotensin-converting-enzyme inhibitors, aspirin, and other nonsteroidal antiinflammatory medications. A tepid shower temporarily alleviates pruritus. A 2 percent solution of ephedrine as a local spray is very useful for oropharyngeal edema. H₁ antihistamines⁴⁸ with a low potential for sedation are the most important first-line treatment, however.

The pharmacologic actions and use of H₁-receptor antagonists were recently reviewed in the *Journal*.⁴⁹ Terfenadine (60 mg orally twice daily) is adequate treatment for less severe cases. Paradoxically, urticaria is a recognized (although rare) side effect of this drug,⁵⁰ and cardiac arrhythmia may result from doses in excess of the recommended dose.⁵¹ Doses of antihistamines that can sedate the patient, including 25 mg of hydroxyzine, are useful at bedtime. Doxepin, a tricyclic

antidepressant drug with marked H_1 antihistaminic activity, is particularly valuable when severe urticaria is associated with anxiety and depression. This drug can be given at a dosage of 25 mg orally twice daily or as a single 25-mg dose at bedtime. Doxepin should not be given concurrently with monoamine oxidase inhibitors or terfenadine. Additional drugs that should be avoided when terfenadine is being taken include macrolide antibiotics, imidazole antifungal agents, and other medications that inhibit the hepatic mixed-function oxidase system.⁴⁹

The addition of H_2 antihistamines, such as cimetidine, to H_1 antihistamine therapy is of small but notable value in chronic urticaria.⁵² Delayed pressure urticaria, when present with chronic urticaria, generally responds poorly to H_1 or H_2 antihistamines.⁵³ Although no antihistamine is without risk in pregnancy, chlorpheniramine and tripeleminamine have good safety records in this context.^{54,55} Topical corticosteroids, topical antihistamines, and local anesthetics have no role in the management of chronic urticaria. Administration of the calcium-channel antagonist nifedipine or the β_2 -adrenergic agonist terbutaline together with an antihistamine has been proposed,⁵⁶⁻⁵⁸ but my experience with these drugs has not been encouraging.

When these measures do not adequately control chronic urticaria, a course of systemic corticosteroids is occasionally justified.⁵⁹ In adults, these medications are best administered daily as a single oral dose of 30 mg of prednisolone or prednisone early in the morning. The dose should be tapered when the urticaria subsides. The course should be completed within three weeks. Prolonged use of corticosteroids is almost invariably associated with reduced efficacy and toxic side effects.

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