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The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED 1812 • ISSN 0028-4793 • WWW.NEJM.ORG

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SOCIETY Volume 346(3), 17 January 2002, pp 175-179

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Chronic Urticaria and Angioedema

[Clinical Practice]

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

A 35-year-old woman presents with a three-month history of daily generalized hives. The hives are pruritic, red wheals that range from 1.5 to 8.0 cm (0.5 to 3 in.) in diameter. She has frequent episodes of lip swelling and has also had three episodes of tongue swelling, one of which was associated with tightness of the throat. How should she be evaluated and treated?

The Clinical Problem

The case vignette describes a typical patient with chronic urticaria ([Figure 1](#)) and angioedema. The disorder is diagnosed when hives occur on a regular basis for more than six weeks. This interval is sufficient to rule out most identifiable causes of acute

urticaria, such as drug reactions and food or contact allergies. Angioedema accompanies urticaria in approximately 40 percent of patients and, when present, typically affects the lips, face (particularly the periorbital area), hands, feet, penis, or scrotum. Occasionally there may be swelling of the tongue or pharynx, but the larynx is virtually never involved. Another 40 percent of patients have hives alone, and about 20 percent of patients have angioedema but not urticaria.



Figure 1. Typical Urticarial Lesions in a Patient with Chronic Urticaria. The lesions are erythematous, roughly circular, and sometimes confluent, with areas of central clearing.

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Strategies and Evidence

Diagnosis

The most common alternative diagnosis is hives due to dermatographism ([Figure 2](#)); in severe cases, patients will have hives every day for months or years. They are commonly linear, but they can be any shape. In dermatographism, individual hives last 30 minutes to 2 hours, as they do in most other types of physically induced hives (e. g., cold urticaria, cholinergic urticaria, and solar urticaria). In contrast, the hives associated with chronic urticaria last 4 to 36 hours. [\[1\]](#) Patients with chronic urticaria may also have mild dermatographism, but the hives associated with primary dermatographism are much more severe.



Figure 2. Evidence of Dermatographism. Scratching the skin leads to a linear wheal within two minutes in a patient with dermatographism.

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The patient's history and findings on physical examination may suggest an underlying cause of urticaria. Occasionally, chronic urticaria and angioedema are manifestations of an underlying connective-tissue disorder or a systemic vasculitis in which the findings on histologic examination of the underlying skin may be consistent with a leukocytoclastic angiitis rather than the nonnecrotizing vasculopathy typical of chronic urticaria. However, cutaneous vasculitis accounts for less than 1 percent of all cases of chronic hives.

Hashimoto's disease is the only systemic disorder with a clear and common association with chronic urticaria and angioedema. [2,3] Less common is an association with Graves' disease. The percentage of patients with chronic urticaria who have antithyroglobulin antibody, antimicrosomal antibody, or both is 27 percent, and 19 percent have abnormal thyroid function. [3] There is no evidence to suggest that these antithyroid antibodies are pathogenic; the thyroid abnormality appears to be a parallel abnormality and may reflect the presence of an underlying autoimmune process.

Chronic urticaria appears to be an autoimmune disorder in a substantial fraction of patients. Approximately 35 to 40 percent of patients have a circulating IgG antibody

directed against the (alpha) subunit of the IgE receptor. [4-6] An additional 5 to 10 percent have antibodies against the (alpha) subunit of IgE. [7] These antibodies activate basophils and mast cells to release histamine, and complement fixation augments histamine release by formation of C5a anaphylatoxin. [8] The lesion is characterized by a perivascular infiltration of lymphocytes that are predominantly CD4-positive, an increased number of monocytes, and variable numbers of neutrophils and eosinophils, [9,10] similar to the findings in a late-phase allergic reaction.

Chronic urticaria was once considered to be a manifestation of an anxiety disorder or an allergic or idiosyncratic reaction to foods, food additives, or food dyes. There are no good data to support these suppositions. Adherence to a diet of rice, lamb, and water for five days has no effect on chronic urticaria or angioedema. [1] Data to support or refute an infectious cause of chronic urticaria, such as *Helicobacter pylori*, are still being debated, but an infectious cause is unlikely. [11] An autoimmune mechanism appears to be most likely, at least in a subpopulation of patients, but 60 percent of cases remain idiopathic.

Evaluation

There are few, if any, diagnostic tests for chronic urticaria and angioedema. The results of a complete blood count and urinalysis are typically normal, as are the values for blood chemical variables usually included in laboratory panels. If a connective-tissue disorder is suspected, measurement of the erythrocyte sedimentation rate, tests for antinuclear antibodies, and other serologic tests may be indicated, followed by a skin biopsy. Complement determinations are not indicated for patients who have hives alone (since the values are normal), nor need they be done when angioedema accompanies chronic urticaria, since patients with a hereditary or acquired deficiency of C1 inhibitor do not have hives. Only in patients who present with angioedema alone

is measurement of C4 indicated, followed by a determination of the levels and function of C1 inhibitor, if C4 levels are below normal. Thyroid-function tests, including tests for antithyroglobulin and antimicrosomal antibodies, may be helpful, given the association of chronic urticaria with thyroid disease, with an annual reassessment of function in euthyroid patients who have elevated antibody titers. Allergies (to food or food additives) are so rarely a cause of chronic urticaria that routine testing is not recommended unless particular clues are present. A skin biopsy may be helpful in patients who have fever, arthralgias, a prominently elevated sedimentation rate, lesions lasting 36 hours or more, or associated petechiae or purpura.

Therapy

Histamine H₁)-Receptor Antagonists

Nonsedating antihistamines such as loratadine, [12] fexofenadine, [13,14] and cetirizine [15-18] alleviate pruritus and decrease the incidence of hives in patients with mild chronic urticaria. Unfortunately, patients with more severe cases may not benefit from the usual recommended doses of these agents. A study of 439 patients revealed that fexofenadine, at a dose of 60, 120, or 240 mg per day, was significantly more efficacious than placebo, as assessed by the mean pruritus score, the mean number of wheals per day, the mean daily symptom score (the sum of the wheal and pruritus scores), and the degree of interference with sleep, activities of daily living, or both. [14] Increasing the dose from 120 to 240 mg per day increased the efficacy only slightly [13] and larger doses did not yield proportionate increases in efficacy.

A 10-mg dose of cetirizine, one of the active ingredients of hydroxyzine, is approximately equivalent to a 30-mg dose of hydroxyzine but is far less sedating. [17] In a placebo-controlled study of cetirizine and hydroxyzine, 180 patients were assessed with respect to the severity of pruritus, the number of lesions, the average

size and duration of lesions, and the number of episodes of hives. [18] Both agents produced similar improvements in every measured variable. [18] Only four patients given hydroxyzine and one patient given cetirizine withdrew from the study because of sedation. A potent new nonsedating antihistamine, mizolastine, which is available in Europe but not in the United States, appears to be efficacious for chronic urticaria.

High doses of antihistamines have effects beyond the blockade of histamine receptors, and actions that are not due to the antagonism of $H(1)$ receptors [19] may account for the efficacy of older antihistamines. In one study of 19 patients, treatment with a combination of $H(1)$ -receptor antagonists [20] (25 mg of hydroxyzine plus 4 mg of cyproheptadine, each given four times a day) led to an improvement in symptoms and inhibited the formation of histamine-induced wheals. When hydroxyzine (100 mg per day) was compared with terfenadine (the precursor of fexofenadine, now off the market), hydroxyzine was more effective. [21]

Combined $H(1)$ - and $H(2)$ -Receptor Antagonists

Approximately 85 percent of histamine receptors in the skin are of the $H(1)$ subtype, and the remaining 15 percent are $H(2)$ receptors. The addition of an $H(2)$ -receptor antagonist to an $H(1)$ -receptor antagonist augments the inhibition of a histamine-induced wheal-and-flare reaction once $H(1)$ -receptor blockade has been maximized. On the basis of this rationale, $H(2)$ -receptor antagonists have been combined with $H(1)$ -receptor antagonists in the treatment of chronic urticaria, with additional benefit, [20] although the increment is small. Doxepin, a tricyclic antidepressant, blocks both types of histamine receptors and is a much more potent inhibitor of $H(1)$ receptors than either diphenhydramine or hydroxyzine; however, sedation is an even greater problem and may limit the usefulness of this drug. [22]

Leukotriene Antagonists

Leukotriene antagonists (zafirlukast and montelukast) have been shown to be superior to placebo in the treatment of patients with chronic urticaria, [23,24] indicating that leukotrienes may also contribute to hives and swelling. There are no data to support the hypothesis that these agents have an additional effect once maximal H_1 - and H_2 -receptor blockade has been achieved.

Sympathomimetic Agents

Oral sympathomimetic agents such as terbutaline have been tried in patients with chronic urticaria and angioedema in an attempt to decrease erythema and swelling. However, since the side effects are substantial and include difficulty sleeping, a jittery feeling, and tachycardia - and since the efficacy of these agents is low - they are not generally recommended.

Corticosteroids

There are many patients with chronic urticaria and angioedema who have little response to even a combination of H_1 -receptor blockers, H_2 -receptor blockers, and leukotriene-receptor blockade and in whom disability due to the disease warrants consideration of corticosteroid therapy. Although controlled studies of the long-term use of corticosteroids have not been conducted, there is truly no question regarding their efficacy. [1] However, the incidence of side effects is substantial if the dose, the duration of use, or both are too great; in addition, their use may trigger diabetes or hypertension in patients at increased risk for these diseases.

Experimental Therapies

The best studied immunosuppressive therapy for chronic urticaria is cyclosporine,

although studies have been uncontrolled and have involved only a small number of patients. A low dose (2.5 to 3 mg per kilogram of body weight per day) appeared to be effective and corticosteroid sparing, [25] whereas a larger dose (6 mg per kilogram) was quite effective but was associated with severe side effects that precluded its continued use. [26]

A single case report indicated that sulfasalazine was effective for chronic urticaria, and case reports have suggested that hydroxychloroquine or dapsone might also be effective, but blinded studies involving a large number of patients have not been conducted. Plasmapheresis has been advocated for the subgroup of patients with demonstrable antibodies against the IgE receptor, [27] but this approach is impractical for long-term treatment. Intravenous immune globulin was effective in one small study, [28] but this report has not been confirmed. Treatment with levothyroxine has been proposed in patients with antithyroid antibodies, even if the patient is euthyroid. [29] Such treatment, however, carries a risk of inducing hyperthyroidism, and its efficacy has not been proved. [3]

Areas of Uncertainty

We need to document whether high doses of antihistamines, particularly the nonsedating types, are superior to lower doses. Leukotriene-receptor antagonists need to be evaluated in combination with antihistamine regimens, rather than in placebo-controlled trials. Long-term studies of corticosteroids are needed to clarify the dose range that yields the maximal benefit with the fewest side effects, and to compare the effect of these agents when they are used alone and when they are added to other regimens. Further studies of experimental agents such as cyclosporine or perhaps tacrolimus are needed to assess their safety and efficacy as corticosteroid-sparing agents.

Guidelines

A "practice parameter" for the diagnosis and management of acute and chronic urticaria was published in 2000 [\[30\]](#); it emphasizes the conditions that need to be considered in the differential diagnosis, such as urticarial vasculitis, connective-tissue disorders, systemic mastocytosis, and idiopathic anaphylaxis.

Summary and Recommendations

In a patient with chronic urticaria who has no signs or symptoms suggestive of an underlying condition, laboratory testing is not indicated, other than measurement of serum thyrotropin levels and antithyroid antibodies to rule out associated thyroid disease. These are the only tests I would recommend for the patient described in the vignette. Although there is no single right way to manage chronic urticaria and angioedema, there is general agreement that nonsedating antihistamines are the first choice for treatment. When severe urticaria, severe angioedema, or both are present, I believe that the older antihistamines are more effective than the newer ones, when maximal doses of these agents are given (e.g., 100 to 200 mg of hydroxyzine or diphenhydramine per day) ([Table 1](#)). For patients with severe angioedema (involving swelling of the face, tongue, and pharynx), diphenhydramine is particularly effective.

Drug	Usual Dose	Maximum Dose	Box 30/2/02
H₁-receptor antagonists			
Non-sedating			
Fexofenadine (Allegra)	180 mg/day	180 mg/day	Mild sedation in maximal dose
Loratadine (Claritin)	10 mg/day	20 mg/day	Mild sedation in maximal dose
Cetirizine (Zyrtec)	10 mg/day	20 mg/day	Mild sedation
Sedating			
Hydroxyzine (Atarax)	10 mg 4 times a day	50 mg 4 times a day	Sedation, dry mouth, dizziness
Diphenhydramine (Benadryl)	25 mg twice a day	50 mg 4 times a day	Sedation, dry mouth, dizziness
Cephradrine (Pavane)	4 mg 4 times a day	8 mg 4 times a day	Sedation, dry mouth, dizziness, increased appetite
H₂-receptor antagonists			
Cimetidine (Tagamet)	400 mg twice a day	800 mg twice a day	Headache, gastroenteritis
Ranitidine (Zantac)	150 mg twice a day	300 mg twice a day	Headache, rare cases of thrombocytopenia
Famotidine (Pepcid)	20 mg twice a day	40 mg twice a day	Headache, diarrhea
H₂ and H₁-receptor antagonists			
Desogrel (Oxygent)	40 mg 4 times a day	160 mg 4 times a day	Sedation, dry mouth, dizziness, blurred vision, visual disturbances
Leukotriene antagonists			
Zileuton (Zileuton)	600 mg twice a day		Headache, rare cases of hepatitis
Montelukast (Singulair)	10 mg/day		Headache, Churg-Strauss syndrome in rare cases
Corticosteroids*			
Prednisone	20 mg every other day, with gradual tapering		Weight gain, acne, osteoporosis, etc.
Methylprednisolone (Medrol)	16 mg every other day, with gradual tapering		Weight gain, acne, osteoporosis, etc.

Table 1. Medications Used to Treat Chronic Urticaria and Angioedema.

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Although patients become accustomed to the sedating effects of these drugs after about a week, their performance on various tests, such as driving, after a single 50-mg capsule of diphenhydramine [31] reflects a decreased reaction time and decreased steadiness; these effects are similar to the effects produced by alcohol. Yet the effect of long-term treatment with hydroxyzine or diphenhydramine at a dosage of 50 mg four times a day has not been assessed. H₂-receptor antagonists have very few side effects and may be useful as adjunctive therapy. Leukotriene antagonists are also considered safe and are worth trying. The goal is to maximize function (e.g., the patient's ability to work or attend school) and minimize the use of systemic corticosteroids.

There is an important role for alternate-day corticosteroid use in patients with severe disease. One approach has been outlined in a number of textbooks, [1] although it has not been evaluated in clinical trials. Prednisone is started at a dose of 15 to 20 mg every other day, and the dose is gradually tapered to 2.5 to 5.0 mg every three weeks, depending on the patient's response, and discontinued after four to five months. Side effects are minimized with the use of dietary discretion and exercise. Chronic urticaria improves with time, and the condition of many patients can then be

controlled without corticosteroids.

The patient described in the vignette may require not only the maximal dosage of an H₍₁₎-receptor antagonist (e.g., 50 mg of hydroxyzine four times a day), plus an H₍₂₎-receptor antagonist and a leukotriene antagonist, but also alternate-day corticosteroids if a satisfactory response is not achieved. Occasional episodes of severe facial or pharyngeal swelling can be treated with one or two doses of a corticosteroid, such as 40 to 60 mg of prednisone ([Table 1](#)).

Patients who require alternate-day corticosteroids for more than six months should be examined annually by an ophthalmologist (for cataracts and glaucoma) and should undergo bone-density testing annually. In my practice, daily corticosteroids are never used, and the dose of alternate-day corticosteroids rarely exceeds 20 mg ([Table 1](#)). Some patients have no responses to any of these approaches, or have a response only to prohibitively high doses of corticosteroids. Of the experimental options, 200 to 300 mg of cyclosporine per day appears to be the best, as long as renal function is closely monitored.

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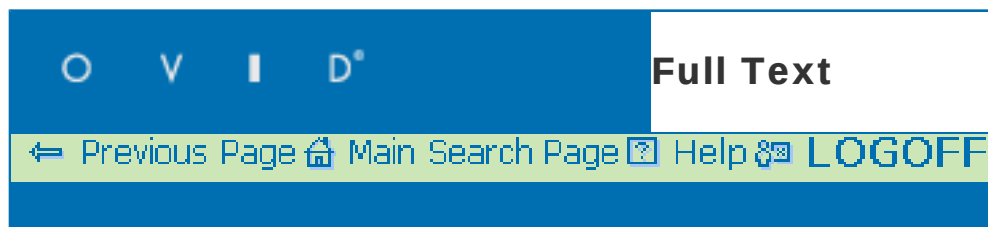
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Figure 1

Graphic

Figure 1. Typical Urticarial Lesions in a Patient with Chronic Urticaria. The lesions are erythematous, roughly circular, and sometimes confluent, with areas of central clearing.

From: Kaplan: N Engl J Med, Volume 346(3).January 17, 2002.175-179

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Figure 2

Graphic

Figure 2. Evidence of Dermatographism. Scratching the skin leads to a linear wheal within two minutes in a patient with dermatographism.

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Table 1

DRUG	INITIAL DOSE	MAXIMAL DOSE	SIDE EFFECTS
H₁-receptor antagonists			
Nonsedating			
Fexofenadine (Allegra)	180 mg/day	240 mg/day	Mild sedation at maximal dose
Loratadine (Claritin)	10 mg/day	20 mg/day	Mild sedation at maximal dose
Cetirizine (Zyrtec)	10 mg/day	20 mg/day	Mild sedation
Sedating			
Hydroxyzine (Atarax)	10 mg 4 times a day	50 mg 4 times a day	Sedation, dry mouth, dizziness
Diphenhydramine (Benadryl)	25 mg twice a day	50 mg 4 times a day	Sedation, dry mouth, dizziness
Cyproheptadine (Periactin)	4 mg 4 times a day	8 mg 4 times a day	Sedation, dry mouth, dizziness, increased appetite
H₂-receptor antagonists			
Cimetidine (Tagamet)	400 mg twice a day	800 mg twice a day	Headache, gynecomastia
Ranitidine (Zantac)	150 mg twice a day	300 mg twice a day	Headache, rare cases of transaminasemia
Famotidine (Pepcid)	30 mg twice a day	40 mg twice a day	Headache, diarrhea

ramotidine (Reproid)	20 mg twice a day	40 mg twice a day	Headache, diarrhea
H₁- and H₂-receptor antagonist			
Doxepin (Sinequan)	10 mg 4 times a day	50 mg 4 times a day	Sedation, dry mouth, dizziness, blurred vision, urinary retention
Leukotriene antagonists			
Zafirlukast (Accolate)	20 mg twice a day		Headache, rare cases of hepatotoxicity, Churg–Strauss syndrome
Montelukast (Singulair)	10 mg/day		Headache, Churg–Strauss syndrome in rare cases
Corticosteroids*			
Prednisone	20 mg every other day, with gradual tapering		Weight gain, striae, premature cataracts, easy bruising, osteoporosis, acne, aseptic necrosis, elevated blood pressure, hyperglycemia
Methylprednisolone (Medrol)	16 mg every other day, with gradual tapering		

*Prolonged daily use of corticosteroids, parenteral corticosteroids, or dexamethasone should be avoided. Angioedema of the face or tongue can be treated with 60 mg of prednisone, with 40 mg given the following day; treatment can then be stopped or the alternate-day dosing schedule can be resumed.

Table 1. Medications Used to Treat Chronic Urticaria and Angioedema.

From: Kaplan: N Engl J Med, Volume 346(3).January 17, 2002.175-179

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Version: rel10.2.0, SourceID 1.11354.1.53