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.

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. 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). 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. As opposed to acute urticaria, chronic urticaria is defined by recurrent episodes occurring at least twice weekly for 6 weeks. Urticaria occurring less frequently than this, over a long period, is more...
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. 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. 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. The severe effect of chronic urticaria on quality of life often is underestimated.

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). Results from a study in children demonstrated that autoimmune urticaria occurs in children in as many as 30% of chronic cases. 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). The IgG subclasses that appear to be pathogenic are IgG1; IgG3; and, to a lesser degree, IgG4 (though not IgG2). Complement activation augments histamine secretion by release of C5a. CAU has been reported to be associated with antithyroid antibodies (27% of cases) or autoimmune conditions such as vitiligo, rheumatoid arthritis, and pernicious anemia; and low vitamin B₁₂ levels. Patients with demonstrable histamine-releasing autoantibodies have a very strong association with HLA-DR4 and its associated allele HLA-DQ8.

Histologically, the 2 groups of urticaria are indistinguishable. Advanced techniques show a perivascular nonnecrotizing infiltrate of CD4+ lymphocytes consisting of a mixture of T_{H,1} and T_{H,2} subtypes, plus monocytes, neutrophils, eosinophils, and basophils. These cells are recruited because of interactions with C5a, cell priming cytokines, chemokines, and adhesion molecules. A recent study also found inflammatory cells and mediator up-regulation in uninvoluted CIU skin as a sign of prolonged and widespread “urticarial status.”

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. 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 and may be viewed as an exaggerated physiologic response. On average, dermographism runs a course of 2 to 3 years before usually resolving spontaneously.

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. An increased level of interleukin 6 has been found in suction blister fluid over induced lesions. 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. The response to antihistamines often is poor, and oral corticosteroids may be needed for disease control.

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. Fifty percent of patients are atopic. 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, but how this leads to urticaria is unclear. The routine treatment is with low-sedation H₁-type antihistamines, with or without an anxiolytic such as oral propranolol. In severe cases, the anabolic steroid stanzolol has been used.

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. 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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Group/Sex at Highest Risk</th>
<th>Aggravating Factors and Associations</th>
<th>Specialized Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ordinary Urticaria</strong></td>
<td></td>
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<tr>
<td>Chronic idiopathic urticaria</td>
<td>Women (2:1 ratio)</td>
<td>Aspirin, NSAIDs, ACE inhibitors, codeine</td>
<td>H₂-antagonists/doxepin hydrochloride</td>
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<tr>
<td>Chronic autoimmune urticaria</td>
<td></td>
<td>Dietary pseudoallergens</td>
<td>Low pseudoallergen diet</td>
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<tr>
<td></td>
<td></td>
<td>Infections</td>
<td>Leukotriene antagonists/nifedipine, short-term corticosteroids/thyroixine, immunosuppressive therapy</td>
</tr>
<tr>
<td><strong>Physical Urticaria</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Dermographism</td>
<td>Young adults/women</td>
<td>Skin stroking</td>
<td>Avoidance, PUVA/UVB</td>
</tr>
<tr>
<td>Delayed-pressure urticaria</td>
<td>Young adults/men</td>
<td>Vertical pressure</td>
<td>Avoidance of sharp edges and use of gel-filled soles, short-term corticosteroids, leukotriene antagonists/dapsone</td>
</tr>
<tr>
<td>Cholinergic urticaria</td>
<td>Young adults</td>
<td>Rise of body core temperature</td>
<td>Danazol/stanazolol</td>
</tr>
<tr>
<td>Cold urticaria</td>
<td>Children/young adults</td>
<td>Skin cooling</td>
<td>Induction of physical tolerance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infections</td>
<td>3-wk trial with penicillin, leukotriene antagonists, short-term corticosteroids</td>
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<tr>
<td>Adrenergic urticaria</td>
<td>Stress</td>
<td></td>
<td>Propranolol</td>
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<tr>
<td>Aquagenic urticaria</td>
<td>Young adults/women</td>
<td>Water of any temperature</td>
<td>Avoidance</td>
</tr>
<tr>
<td>Exercise-induced anaphylaxis</td>
<td>Young adults</td>
<td>Physical exercise</td>
<td>Avoid food before exercise</td>
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<tr>
<td></td>
<td></td>
<td>Diet and drugs</td>
<td>Food diary</td>
</tr>
<tr>
<td>Localized heat urticaria</td>
<td>Localized heat</td>
<td></td>
<td>Hardening through repeated heat exposure</td>
</tr>
<tr>
<td>Solar urticaria</td>
<td>Young adults/women</td>
<td>UV light±visible light</td>
<td>Photohardening, doxepin hydrochloride</td>
</tr>
<tr>
<td>Vibratory urticaria</td>
<td>Vibratory forces</td>
<td></td>
<td>Avoidance</td>
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</tbody>
</table>
Urticaria

are affected. The cause is unknown, but a serum factor, possibly IgM or IgE, has been implicated. A heterozygous deficiency of the protease inhibitor α1-antichymotrypsin has been demonstrated and may be etiologically important in some patients. The prognosis is good, with spontaneous improvement in an average of 2 to 3 years.

Ninety-six percent of cases of cold urticaria are primary. The diagnosis of secondary acquired cold urticaria depends on being able to demonstrate cryoglobulins, cold agglutinins, or possibly cryofibrinogens. These findings should, in turn, lead to investigations for an underlying cause, such as hepatitis B or C infection, lymphoproliferative disease, or infectious mononucleosis.

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. Aquagenic urticaria is precipitated by skin contact with water of any temperature. 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; it usually disappears in less than one hour. Vibratory urticaria occurs after a vibratory stimulus and can be a hereditary autosomal dominant disorder or an acquired sporadic disease.

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. 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. 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%).

Normocomplementemic urticarial vasculitis usually is idiopathic, but hypocomplementemic urticarial vasculitis may be associated with underlying systemic lupus erythematosus, Sjögren syndrome, or cryoglobulinemia. Primary urticarial vasculitis can occasionally evolve into systemic lupus erythematosus. 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

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</thead>
<tbody>
<tr>
<td>Urticarial Vasculitis</td>
<td>Middle-aged women/men</td>
<td>Trauma and pressure</td>
<td>NSAIDs</td>
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<td></td>
<td>Infection</td>
<td>Systemic corticosteroids</td>
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<tr>
<td></td>
<td></td>
<td>Drugs (cimetidine, diltiazem hydrochloride)</td>
<td>Immunosuppressive therapy</td>
</tr>
<tr>
<td>Contact Urticaria</td>
<td></td>
<td>Direct contact</td>
<td>Avoidance, NSAIDs, antihistamines</td>
</tr>
<tr>
<td>Angioedema Without Wheals</td>
<td>Children and adolescents</td>
<td>C1 inhibitor deficiency</td>
<td>Purified C1 inhibitor concentrate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drugs (ACE inhibitors, NSAIDs)</td>
<td>Danazol/stanozolol, tranexamic acid</td>
</tr>
</tbody>
</table>

*NSAIDs indicates nonsteroidal anti-inflammatory drugs; ACE, angiotensin-converting enzymes; PUVA, psoralen plus UVA.
Diagnosis—The diagnosis of urticaria is primarily clinical; extensive laboratory tests are very rarely needed—only when indicated by the patient history. Some authors argue that laboratory investigations are unnecessary for mild ordinary urticaria responding to antihistamines. Taking a thorough patient history has been found to be almost as effective in identifying a cause as a complete diagnostic evaluation. In acute urticaria, if the history indicates a type I hypersensitivity reaction, confirmation is possible by a prick test or laboratory radioallergosorbent tests. 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. 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. Further investigations are guided by clinical suspicion, which may include a skin biopsy, autoimmune screening, urinalysis, serum cryoglobulins, and hepatitis B and C serology. 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. 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.

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. Aspirin and NSAIDs should be avoided because they aggravate symptoms in 30% of patients. 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. Avoiding dietary pseudoallergens, such as food coloring and natural salicylates, is controversial. This generally has only a small role unless proven by a double-blinded placebo-controlled challenge.

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. Antihistamines can be grouped into first-generation (sedating), second generation (minimally sedating), third-generation (nonsedating), and H2 antagonists. The physiologic and pharmacologic actions of histamine are mediated through 4 histamine receptor subtypes: H1, H2, H3, and H4. The erythema, wheal formation, and itching associated with urticaria are mainly due to activation of H1 receptors and the less contributory role of H2 receptors. Histamine H1 receptors are located presynaptically on postganglionic sympathetic norepinephric nerves, including sympathetics innervating the heart and blood vessels. The contribution of H4 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 H₂ and H₃ 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.¹ 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 H₁ 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 H₂ antagonist to conventional H₁ antihistamines may be helpful in some patients.³⁴⁷ Doxepin hydrochloride at low doses (10–50 mg) is used for its potent H₁ and H₂ 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 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 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.¹

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

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