

# Urticaria and Angioedema: Clinical Spectrum and Management

*Siba P. Raychaudhuri, MD*  
*Sandeep Sharma, MD*

**U**rticaria (also known as hives) and angioedema are cutaneous manifestations of localized edema. They are common skin diseases that typically result from the same pathophysiologic processes. The primary difference between the disorders is that urticaria is associated with localized edema involving the upper dermis, whereas angioedema is associated with localized edema involving deeper layers of the skin, as well as subcutaneous and submucosal tissues. The diseases can affect persons of any age but most commonly affect young adults.<sup>1</sup> Episodes of urticaria and/or angioedema persisting for fewer than 6 weeks are considered acute, whereas episodes persisting 6 weeks or more are considered chronic.<sup>1-5</sup> Approximately 15% to 25% of Americans will experience at least a single episode of urticaria or angioedema during their lives.<sup>6</sup> This article reviews the etiology, pathogenesis, clinical manifestations, diagnosis, and treatment of these skin disorders.

## ETIOLOGY AND PATHOGENESIS

Most cases of urticaria and angioedema are idiopathic.<sup>1-7</sup> However, causes are more often identifiable in acute than in chronic cases.<sup>8,9</sup> Allergies to various exogenous and endogenous agents have been suspected, including hypersensitivity to food additives or drugs.<sup>9-13</sup> Hidden or overt infections (eg, intestinal parasitic infections, hepatitis), abdominal disorders, and sometimes mental stress may also cause the diseases.<sup>10,14-17</sup> Additionally, urticaria and angioedema have been associated with hereditary, metabolic, autoimmune, and malignant conditions, as well as physical stimuli (eg, cold, heat, sunlight, friction).

The degranulation of mast cells, which may be induced by immunologic or nonimmunologic mechanisms, and the subsequent release of histamine and various cytokines (leading to edema) are important factors in the pathogenesis of urticaria and angioedema.<sup>18</sup> Nonallergic mast cell activation may occur via substances such as neuropeptides (eg, substance P), drugs (eg,

morphine, codeine, vancomycin), foods (eg, strawberries), and radiocontrast media. Allergic mast cell activation occurs via the linkage of 2 adjacent  $\alpha$ -subunits of high-affinity IgE receptors on a mast cell. The mode of activation of mast cells in cases of urticaria and angioedema caused by physical stimuli is not well understood, but in some patients with urticaria caused by cold, sunlight, or the stroking of skin with a dull object (ie, dermatographism), a transferable IgE-like factor has been identified. In these patients, the physical stimulus may induce a neoantigen that could stimulate IgE production directed specifically against it.<sup>2</sup>

In approximately 30% of patients with chronic idiopathic urticaria, circulating IgG antibodies directed against high-affinity IgE receptors were detected on mast cells.<sup>19,20</sup> Subsequent to this observation, it was reported that immunomodulatory drugs such as cyclosporine may be helpful in severely affected patients with treatment-resistant chronic idiopathic urticaria.<sup>21</sup> The response to immunomodulation and the recent finding of an association with HLA-DR4 support the notion of there being an autoimmune basis to chronic idiopathic urticaria in some patients.<sup>22</sup>

## CLINICAL MANIFESTATIONS

A description of urticaria appears in the writings of Hippocrates, dating back to the 4th century BC. With regard to the characteristic lesions of urticaria, Heberden wrote the following nearly 200 years ago:

The little elevations upon the skin in the 'nettle' rash often appear involuntarily, especially if the skin be rubbed, or scrubbed, and seldom stay many hours in the same place, and sometimes

---

*Dr. Raychaudhuri is Director, Clinical Immunology, Psoriasis Research Institute, Palo Alto, CA; and Clinical Assistant Professor, Department of Medicine, University of California, Davis, CA. Dr. Sharma is a Chief Resident, Department of Dermatology, All India Institute of Medical Science, New Delhi, India.*

**Table 1.** Classification of Urticaria

**Clinical classification by duration of disease**

Acute (< 6 weeks)

Chronic (≥ 6 weeks)

**Etiologic classification**

Immunologic

IgE dependent\*

Autoimmune†

Immune-complex mediated ‡

Contact

Complement dependent§

Nonimmunologic

Direct mast cell-releasing agents||

NSAIDs, ACE inhibitors

Physical¶

Dermatographism

Delayed pressure

Vibratory

Cold

Localized heat

Solar

Cholinergic

Aquagenic

Idiopathic

ACE = angiotensin-converting enzyme; NSAIDs = nonsteroidal anti-inflammatory drugs.

\*Type I hypersensitivity reaction.

†Autoantibodies against IgE or the high-affinity IgE receptor.

‡Urticarial vasculitis.

§C1-esterase inhibitor deficiency.

||Opiates, radiocontrast media.

¶Some authors consider physical urticaria to be IgE dependent.

not many minutes. There is nobody exempt from 'them' and by far the greatest number experience no other evil from it besides the intolerable anguish arising from the itching....<sup>3</sup>

This clinical description of the disease is accurate even by today's standards.

Urticaria and angioedema may be associated with headache, dizziness, nausea, vomiting, abdominal pain, diarrhea, and arthralgias. In their most severe forms, they may be associated with anaphylaxis.

Urticaria presents as pruritic erythematous macules that develop into wheals consisting of pale-pink, edematous, raised areas of skin often with a surrounding flare. The lesions may occur anywhere on the body and may be multiple, of various sizes, and of various shapes (eg, rounded, annular, serpiginous, irregular). Without treatment, 50% of cases of urticaria can be expected to clear in approximately 6 months.<sup>23</sup> With treatment, wheals generally begin to resolve within 24 hours, and affected areas of skin usually return to their normal appearance.

Angioedema presents as pale or pink swellings, mainly on the face, affecting the eyelids and lips; however, other areas of the body, such as the ears, neck, hands, feet, and genitalia, may also be affected. Mucosal swellings occur inside the oral cavity on the buccal mucosa, tongue, pharynx, and larynx. The lesions may be preceded by an itching or tingling sensation but are not always pruritic.

Urticaria and angioedema represent a heterogeneous group of disorders. They may be arbitrarily classified by duration or according to the underlying triggering factors (Table 1).

**CLINICAL CLASSIFICATIONS**

**Acute Urticaria**

Acute urticaria is characterized by episodes of lesions for fewer than 6 weeks. Acute urticaria usually presents with large wheals and is often associated with angioedema; in more than 50% of patients, no cause is identified.<sup>24</sup>

**Acute allergic urticaria.** Acute allergic urticaria is more common in patients with atopy. It is caused by a reaction between an antigen and its specific IgE antibody. Acute urticarial reactions to drugs are common and usually occur within 36 hours of drug intake. Such reactions to food are not uncommon and may be caused by the basic nutrient, spices, coloring agents, or preservatives of the food substance.<sup>25</sup>

**Acute nonallergic urticaria.** Intolerance or anaphylactoid reactions to aspirin, nonsteroidal anti-inflammatory agents, or radiocontrast media can cause the release of histamine in nonimmune reactions. Other agents that cause the release of histamine through nonimmune reactions and lead to urticaria include morphine, codeine, tubocurarine, ciprofloxacin, rifampicin, and vancomycin.

**Chronic Urticaria**

Urticaria is defined as chronic if manifestations persist or recur for more than 6 weeks. Lesions may appear daily or could be intermittent. In many patients,

the periodic appearance of lesions may continue for years; some patients may go into spontaneous remission after several months. Approximately 37% of patients with chronic urticaria have an associated delayed-pressure urticaria.<sup>2</sup>

### Angioedema

Ordinary angioedema has the same multiple etiology as chronic urticaria, and as with chronic urticaria, a precise diagnosis is frequently not attained.<sup>7,26</sup> Almost any part of the body may be involved; common sites are the eyelids, lips, tongue, pharynx, and genitalia. The lesions are not always pruritic. In the acute form, the lesions usually last for a few hours, or occasionally, for 2 to 3 days. In the chronic form, the lesions persist for more than 6 weeks.

### ETIOLOGIC CLASSIFICATIONS

#### Immunologic IgE-Mediated Urticaria or Angioedema

Immunologic IgE-mediated urticaria or angioedema often occurs in persons who have atopy and usually occurs acutely. Specific antigens that provoke this form of urticaria or angioedema include nuts, shellfish, chocolate, and drugs. Some specific allergens and non-specific stimuli may activate local reactions, termed *recall urticaria*, at sites previously treated with allergen immunotherapy.<sup>27</sup>

#### Autoimmune Urticaria

At least 30% of patients with chronic idiopathic urticaria have circulating autoantibodies in the blood. These individuals are said to have autoimmune urticaria.<sup>6</sup> Intracutaneous injection of autologous serum can produce a wheal and erythema reaction. Autoantibodies of IgG type are directed against high-affinity IgE receptors or IgE.<sup>19,20,28</sup>

#### Urticarial Vasculitis

Urticarial vasculitis is thought to be caused by immune complex-mediated inflammation. It is important to recognize this disease because it is associated with other systemic diseases (eg, the Henoch Schönlein syndrome) and is amenable to treatment. If an urticarial lesion lasts longer than 24 hours in the same location, urticarial vasculitis should be suspected. Specific histopathology and immunofluorescence studies establish the diagnosis.

#### Contact Urticaria

Contact urticaria may occur after direct contact with a substance. It may be immunologic or nonimmunologic. A rash appears within minutes of contact. Proteins

from latex products are a major cause of IgE-mediated contact urticaria. A variety of food substances and food additives can also produce contact urticaria. The prick test or patch test reading 15 to 45 minutes after exposure is helpful for diagnosing the disorder.

### Papular Urticaria

Papular urticaria occurs as episodic, symmetrically distributed, itchy wheals that are caused by bites of insects such as mosquitoes, fleas, and bedbugs. A punctum is often visible on the wheal, which may blister.<sup>29</sup> This condition mainly occurs in children.<sup>30</sup>

### Physical Urticaria or Angioedema

Physical urticaria or angioedema is caused primarily by physical stimuli (eg, trauma, vibration, heat, cold, solar irradiation).<sup>31-33</sup> The characteristics of some types of physical urticaria or angioedema help in identifying the triggering factors. With a few exceptions, urticarial lesions develop in exposed skin areas shortly after exposure to the causative stimulus and disappear after a few hours.<sup>34</sup>

**Dermatographism.** In dermatographism (or dermographism), meaning “writing on the skin,” a wheal and flare reaction typically ensues within 2 to 5 minutes after the skin is stroked or rubbed with a dull object.<sup>34</sup> The wheals are typically linear in formation. The affected area of skin may itch in a minority of patients—that is, patients may have symptomatic dermatographism or factitious urticaria. The itching sensation usually fades within 30 minutes. Symptomatic dermatographism is easily diagnosed by using a dermatographometer.<sup>35</sup> Dermatographism may sometimes be caused by a drug reaction (eg, a reaction to penicillin)<sup>36</sup>; however, it is usually idiopathic.

Delayed dermatographism develops 3 to 6 hours after stimulation, either with or without an immediate reaction, and lasts 24 to 48 hours. Delayed dermatographism is closely related to delayed-pressure urticaria.<sup>37</sup>

Dermatographism is the most common form of physical urticaria.<sup>1</sup> The prevalence of dermatographism in the general population is 1.5% to 23.5%.<sup>32</sup> The prevalence of dermatographism among patients with chronic idiopathic urticaria is 22%.<sup>38</sup> Dermatographism can occur at any age, but the peak prevalence occurs in the second and third decades of life.

**Delayed-pressure urticaria.** With delayed-pressure urticaria, wheals occur at the site of sustained pressure (ie, pressure lasting for 4–8 hours or more) and usually remain for 12 to 72 hours.<sup>39</sup> Pressure-bearing areas (eg, skin under straps, watches, belts) are commonly affected. Delayed-pressure urticaria may develop on

the hands (after manual work), the buttocks (after sitting), and on feet (after walking). The condition may be accompanied by systemic symptoms of malaise as well as flu-like symptoms, arthralgia, myalgia, and leukocytosis. Delayed-pressure urticaria may occur alone or in association with chronic urticaria and constitutes less than 1% of all cases of urticaria.<sup>40,41</sup> However, it occurs to some degree in approximately 37% of patients with chronic idiopathic urticaria.<sup>38</sup>

**Vibratory angioedema and urticaria.** Vibratory angioedema may be familial or sporadic.<sup>42,43</sup> Any vibratory stimulus such as jogging or vigorous toweling may lead to the release of histamine and result in angioedema. Vibratory urticaria is a very rare form of urticaria.

**Cold urticarias.** The cold urticarias are induced by cold stimuli; cold air, water, drinks, or food, as well as other cold objects, can precipitate episodes of urticaria. Cold urticarias may be associated with headache, wheezing, shortness of breath, hypotension, and syncope. Collectively, cold urticarias represent 3% to 5% of all cases of physical urticarias<sup>34</sup>; they may coexist with other forms of physical urticaria.<sup>44</sup>

Idiopathic cold urticarias are the most common forms, comprising 96% of a series of patients with cold urticarias.<sup>43</sup> Among the idiopathic cold urticarias, immediate cold-contact urticaria is by far the most common form, occurring at any age but most frequently in young adults.<sup>2</sup> This form of cold urticaria presents with pruritus, erythema, and swelling confined to skin sites exposed to cold; the lesions develop 2 to 5 minutes or slightly later as the skin rewarms. Total body exposure to cold can cause anaphylaxis.<sup>34</sup>

Cold urticaria secondary to cryoglobulinemia is rare; cold urticaria occurs in only 3% of individuals with cryoglobulinaemia.<sup>45</sup> Other rare forms of acquired cold urticaria, described mainly in case reports, include systemic cold urticaria, localized cold urticaria, cold-induced cholinergic urticaria, cold-dependent dermatographism, and localized cold-reflex urticaria.<sup>1</sup>

The diagnosis can be made by the application of an ice cube in a plastic bag onto the skin for 20 minutes; whealing occurs within 15 minutes. Sometimes, a more extensive local challenge such as immersion of an arm in cold water is required.<sup>43</sup> For the diagnosis of systemic cold urticaria, the body should be cooled by having the patient stand with loose clothing in a cold room (4°C) for 10 to 20 minutes. Generalized itching, wheals, and angioedema appear in 10 to 20 minutes.<sup>34</sup>

**Localized heat urticaria.** Localized heat urticaria is an unusual form of urticaria in which wheals develop within minutes after exposure to locally applied heat. There are 2 subtypes: immediate localized heat urti-

caria and delayed localized heat urticaria. In the immediate form, lesions develop after 5 minutes of the onset of the heat stimulus. In the delayed form, lesions develop after 1 to 2 hours of the heat stimulus.<sup>46</sup>

**Solar urticaria.** Solar urticaria is a rare form of urticaria in which pruritus, erythema, and wheals develop within 5 minutes of exposure to an appropriate wavelength of light<sup>47</sup>; it accounts for less than 1% of all urticarias.<sup>48</sup> The lesions usually fade 15 minutes to 3 hours after onset. It is most common in the third and fourth decades of life but can occur at any age.<sup>49</sup> This disorder is usually idiopathic but may be associated with systemic lupus erythematosus or erythropoietic protoporphyria.<sup>1</sup>

Phototesting is an important part of the evaluation of patients with solar urticaria. A reaction develops within 5 to 10 minutes of exposure of skin to natural sunlight or to a specific wavelength of a monochromator. The response to specific wavelengths on phototesting has allowed classification into subtypes. In one type, a response can be elicited by wavelengths of 285 to 320 nm; in another type, wavelengths between 400 to 500 nm cause a response.<sup>1</sup>

**Cholinergic urticaria.** Cholinergic urticaria is the second most common form of physical urticaria (after dermatographism).<sup>50</sup> It is also known as generalized heat urticaria and constitutes approximately 7% of all urticarias.<sup>34</sup> The cutaneous lesions are very characteristic: small (1–5 mm in diameter), scattered, punctate, pruritic wheals with surrounding flares. They begin from the face and neck and spread to other parts of the body. The lesions persist from a few minutes to 1 or 2 hours. Cholinergic itching without wheals has also been described.<sup>51</sup> The disorder may be associated with systemic symptoms such as headache, dizziness, abdominal cramps, wheezing, asthma, and syncope.<sup>50–52</sup> Urticaria not precipitated by heat may be associated with cholinergic urticaria.<sup>2</sup> Additionally, cholinergic angioedema has been reported.<sup>53</sup>

Precipitating stimuli include exercise, warm temperatures, ingestion of hot or spicy foods, and emotional stress. The disease occurs more commonly in persons age 23 to 28 years and may be worse in the winter.<sup>54</sup> Familial cases have also been reported.<sup>55</sup>

Confirmation of the diagnosis is performed with challenge tests; a warm bath at 40°C to 45°C for 10 to 20 minutes, jogging exercise up to 30 minutes, or running in place for 5 to 15 minutes provokes the characteristic lesions of cholinergic urticaria in almost 100% of cases. Intradermal injection of cholinergic agents (eg, methacholine) induce satellite wheals in only 30% to 50% of patients.<sup>34</sup> Cholinergic urticaria may coexist

with cold or localized heat urticaria, aquagenic urticaria, and vibratory angioedema. It is also found in association with dermatographism. Exercise-induced anaphylaxis may occur as a part of the cholinergic urticaria spectrum after severe exercise.<sup>56</sup>

**Aquagenic urticaria and aquagenic pruritus.** Aquagenic urticaria and aquagenic pruritus is a very rare disorder. Contact of skin with water of any temperature may result in small pruritic wheals resembling those of cholinergic urticaria.<sup>57</sup>

Aquagenic pruritus without urticaria is usually idiopathic but it can occur in elderly persons with dry skin and in patients with polycythemia vera, Hodgkin's disease, the myelodysplastic syndrome, and the hyper-eosinophilic syndrome.<sup>1</sup> Challenge test for aquagenic urticaria is performed by application of water compresses at approximately body temperature (37°C) for 30 minutes.

**Adrenergic urticaria.** Adrenergic urticaria occurs as wheals surrounded by a white halo that develop during emotional stress. The lesions can be elicited by the intracutaneous injection of noradrenaline.

#### **Hereditary Angioedema**

Hereditary angioedema is a rare disorder and accounts for only 5% of all cases of angioedema without urticaria and only approximately 1% of all cases of angioedema in general.<sup>2</sup> It is transmitted as an autosomal dominant trait.

The disease is characterized by recurrent swellings of the skin and mucous membranes, typically throughout life, and is usually associated with nausea, vomiting, abdominal colic, and urinary symptoms. The lesions may develop spontaneously or after trauma, particularly dental trauma. Erythema and itching sensations in the swellings are usually absent but pain may be present. Onset is usually in early childhood<sup>58</sup> but it can begin during adulthood also. The attacks become worse at puberty and usually decrease in frequency and severity after the age of 50 and may even disappear totally.<sup>1</sup>

Without urticarial lesions, reticulate erythema may occur as a prodrome.<sup>59</sup> Laboratory findings reveal decreased levels of C1-esterase inhibitor in 85% of patients and dysfunctional inhibitor in 15% of cases. The level of complement C4 is nearly always low during, after, and to some extent between attacks or in asymptomatic carriers.<sup>2</sup> The C1-esterase deficiency should be detected by both antigenic and functional assays.

#### **Acquired C1-Esterase Inhibitor Deficiency Angioedema**

Clinically, acquired C1-esterase inhibitor deficiency angioedema can present very similarly to the hereditary

type of angioedema but the onset occurs in the fifth and sixth decades of life. The laboratory changes are similar except that C1 levels are also reduced. B-cell lymphoma, myeloma, Waldenström's macroglobulinemia, and chronic lymphocytic leukemia are the most common causes.<sup>59</sup>

#### **Angiotensin-Converting Enzyme Inhibitor-Induced Angioedema**

Angiotensin-converting enzyme inhibitors usually produce angioedema without urticaria.<sup>60</sup> The drugs can cause increased bradykinin levels, resulting in the lesions. Most cases occur within 3 weeks of starting treatment, but the disorder can occur at any time during treatment. It usually affects the face and oral mucosa and can cause serious breathing difficulties.

#### **DIAGNOSTIC EVALUATION**

Although a cause of urticaria and angioedema is often not found despite diagnostic efforts, a clinician should make every attempt to find the underlying etiology in each patient, because the identification and elimination of causal factors represent the best therapeutic program. The diagnostic evaluation of a patient with urticaria and/or angioedema includes a detailed history, physical examination, and laboratory studies. The history is a particularly valuable diagnostic tool. Inquiries should be made regarding difficulty in swallowing or breathing, systemic symptoms, and possible precipitating and aggravating factors.<sup>2</sup> The history should include a thorough search for all potential causes of the disorders. Each item of the history can be considered a diagnostic test that either increases or decreases the probability of establishing the diagnosis.<sup>61</sup>

If the history and physical examination indicate any underlying cause, then it is essential to perform the relevant laboratory tests. However, a screening test comprising a complete blood count, erythrocyte sedimentation rate analysis, urinalysis, and liver function tests is also justified.<sup>4</sup> Other tests, such as those for thyroid autoantibodies, may be included to the screening panel based on the clinical evaluation. Tests for physical urticarias should be performed on the basis of information obtained from the history and physical examination.

Skin biopsy may be helpful in detecting unsuspected urticarial vasculitis and mastocytosis. In patients with chronic idiopathic urticaria who have a poor therapeutic response to antihistamines, skin biopsy is appropriate.<sup>4</sup> It also may be warranted to refer such patients to specialized services for immunologic investigations. The routine skin prick test, however, is of very

little value, and the intradermal tests for drugs are limited to penicillin.

A food diary may be helpful, especially in intermittent urticaria. Positive skin test results for the role of foods in urticaria or angioedema must be associated with clinical improvement on withdrawal of the food from the diet and a return of clinical features of the diseases on reintroduction of the food. Positive test results must also be verified by double-blind food challenge.<sup>1</sup> A skin test with autologous serum to discern the presence of anti-IgE or anti-high-affinity IgE receptor antibodies is not recommended.

Some types of urticaria may be identified by their characteristic features, which aid in efforts to determine cause. Examples include cholinergic urticaria (small wheals with large surrounding flare), dermatographism (linear wheals), solar or cold-induced urticaria (localization of wheals to commonly exposed areas), and cryoglobulinemias or leukocytoclastic vasculitis (palpable purpura on lower extremities). There is no consensus in the literature concerning the extent to which the cause of chronic urticaria or angioedema should be investigated.

## TREATMENT

The identification and elimination of the cause of urticaria or angioedema represent the best therapy for a patient. However, when the underlying cause of urticaria or angioedema remains unknown, the treatment must be based on symptoms. When this is the case, the goal of treatment should not necessarily be to free the patient completely of the cutaneous manifestations of the diseases, but rather to help him or her to become comfortable enough to sleep at night and function during the day and have the lowest possible risk for adverse effects.<sup>3</sup> As during any treatment program, the physician should provide support and reassurance to the patient.

Antihistamines are the mainstay for controlling the symptoms of the diseases; however, if any specific antihistamine is not effective, an agent from a different pharmacologic class should be used. The use of 2 agents from different classes may be helpful in controlling symptoms<sup>62</sup>; combining drugs according to patient response and the least amount of adverse effects is important. Also, it may be useful for some patients with urticaria or angioedema to avoid aspirin, other non-steroidal anti-inflammatory drugs, and angiotensin-converting enzyme inhibitors. Antipruritic lotions and cool compresses may provide some temporary relief.<sup>1</sup> Oral disodium cromoglycate is ineffective in the treatment of chronic idiopathic urticaria, although a few patients with urticaria caused by food may have a favor-

able response to it.<sup>1</sup> Epinephrine, which is injected intramuscularly or subcutaneously, is the emergency treatment of nonhereditary angioedema causing respiratory symptoms.

## Antihistamines

Antihistamines are classified as H<sub>1</sub> receptor blockers and H<sub>2</sub> receptor blockers. H<sub>1</sub> receptor blockers are further classified as first generation and second generation. The first-generation H<sub>1</sub> receptor blockers are older antihistamines and are sometimes referred to as traditional or classic antihistamines. Second-generation H<sub>1</sub> receptor blockers are newer drugs, and unlike the first-generation agents, have nonsedative properties and reduced anticholinergic side effects.

Antihistamines cross the placenta and have a pregnancy category B classification. Thus, it is best for patients to avoid them during pregnancy, particularly during the first trimester. When an antihistamine is indicated for a patient, the choice of drug should be based on its effectiveness, the frequency by which it needs to be administered, and its adverse-effects profile.<sup>3-5</sup> The antihistaminic agent should initially be administered at a low dose; subsequently, the dose should be increased to a tolerable level. The drug should be taken on a regular basis and not as needed. The combination of a sedative antihistamine at bedtime and a nonsedative antihistamine in the morning may be very effective.<sup>3</sup> Sedative antihistamines such as hydroxyzine and pheniramine are absorbed well but are subject to tachyphylaxis. Nonsedative antihistamines such as cetirizine, loratadine, terfenadine, and fexofenadine do not have this disadvantage and can be administered in once-daily doses. Cetirizine may be mildly sedative in some patients.

In most patients, antihistamines are able to control symptoms but do not constitute a cure of the diseases. Moreover, symptoms may recur following a variable period of time after discontinuation of drug therapy.

**H<sub>1</sub> receptor blockers.** H<sub>1</sub> receptor blockers are the most commonly used drugs for the treatment of acute and chronic urticaria and angioedema. The binding of histamine to H<sub>1</sub> receptors lasts from 15 minutes to 24 hours. H<sub>1</sub> receptor blockers do not displace histamine once it is bound but will deter activation of the receptor by histamine.<sup>63</sup>

Terfenadine and astemizole are effective for treating the symptoms of urticaria and angioedema.<sup>64</sup> However terfenadine and astemizole can prolong the cardiac QTc interval and, rarely, produce serious irregular ventricular tachycardia. Because of these adverse effects, many clinicians have avoided the use of these drugs. Loratadine

(adult dose, 10 mg daily) and cetirizine (adult dose, 10 mg daily) do not have any effect on the QTc interval. Fexofenadine (adult dose, 120–180 mg daily) is also considered to be a safe and well-tolerated nonsedative antihistamine.<sup>65</sup> Desloratadine (adult dose, 5 mg daily), a new nonsedative H<sub>1</sub> receptor blocker, has anti-inflammatory properties. Desloratadine inhibits histamine and leukotriene C<sub>4</sub> release by human basophils; in addition, it also prevents secretion of interleukin 4 (IL-4) and IL-13, induced by anti-IgE.<sup>66</sup> Ketotifen not only is an H<sub>1</sub> receptor blocker but also inhibits the release of histamine and leukotrienes from human basophils as well as calcium uptake from the mast cells; thus, it stabilizes the mast cells. This drug was found to be useful in chronic, cold, and exercise-induced urticaria, as well as dermatographism.<sup>67,68</sup> Doxepin, a tricyclic antidepressant has potent H<sub>1</sub> (and H<sub>2</sub>) antihistaminic properties. Despite its sedative and anticholinergic side effects, use of doxepin at night can induce significant symptomatic relief.<sup>4,5</sup>

As mentioned previously, the use of antihistamines should be avoided in patients who are pregnant. If a sedative antihistamine must be used during pregnancy, chlorpheniramine, which is associated with the smallest amount of risk, may be used. In the nonsedative group, terfenadine and astemizole have been reported to be safe.<sup>69</sup>

First-generation H<sub>1</sub> receptor blockers are not recommended for newborns because of their increased susceptibility to experiencing antimuscarinic side effects with these drugs, such as central nervous system excitation (causing convulsions). Elderly patients are also susceptible to antimuscarinic side effects of first-generation H<sub>1</sub> receptor blockers, such as dry mouth and urinary retention. Antimuscarinic side effects are nonexistent or minimal with regard to second-generation H<sub>1</sub> receptor blockers, as well as H<sub>2</sub> receptor blockers. In older children, a paradoxical reaction characterized by hyperexcitability may occur with H<sub>1</sub> receptor blockers. The mydriatic effect of H<sub>1</sub> receptor blockers may cause a slight increase in intraocular pressure, requiring an adjustment of glaucoma therapy.<sup>70</sup>

**H<sub>2</sub> receptor blockers.** Cimetidine can antagonize experimentally produced (ie, histamine-induced) wheals. The simultaneous use of hydroxyzine with cimetidine was found to be more effective than hydroxyzine alone.<sup>71</sup> The addition of cimetidine 800 mg every day to a regimen of H<sub>1</sub>-receptor blockers in patients resistant to the latter was found to be very effective.<sup>72</sup> Some clinicians, however, did not find any benefit in their patients.<sup>73</sup> The addition of H<sub>2</sub> antagonists is helpful, especially if the patient demonstrates dermatographism<sup>74</sup> or flushing with the urticaria.<sup>75</sup>

### Immunosuppressive and Anti-inflammatory Drugs

With respect to immunosuppressive and anti-inflammatory drugs for the symptoms of urticaria or angioedema, there is no standardized guideline or recommendation. Systemic corticosteroids are sometimes indicated in severe acute urticaria and severe serum sickness. In patients with chronic urticaria, if the symptoms are unresponsive to antihistamines used in maximal dosages and are disabling in terms of the patient functioning at home or in the workplace, glucocorticosteroids and other immunomodulating agents (eg, methotrexate, cyclosporine, intravenous immunoglobulins) may be considered.<sup>1,4,5,76–78</sup> In a recent randomized double-blind study, cyclosporine was found to be effective in a group of patients with chronic urticaria who were not responding to antihistamines and who had a positive autologous serum skin test.<sup>21</sup> This observation further substantiates a role of histamine-releasing autoantibodies in the pathogenesis of chronic urticaria.

Anti-inflammatory agents such as dapsone, colchicine, and antileukotrienes have also been used in unremitting urticaria with some success. Some patients with thyroid autoantibodies may respond to small doses of thyroid hormone.

### β-Adrenergic Drugs

Terbutaline, a β-adrenergic agonist administered orally in a dose of 1.25 mg 3 times daily, was found to be very effective in alleviating the symptoms of urticaria as compared with cyproheptadine and dexchlorpheniramine.<sup>79</sup> However this drug is contraindicated in patients with hypertension, hyperthyroidism, and angina.

### Treatment of Hereditary Angioedema

In addition to the above treatment options, danazol and stanozolol are both beneficial in the treatment of hereditary angioedema. They correct the underlying biochemical deficiency by increasing the serum levels of C1-esterase inhibitor.<sup>80</sup> Danazol was of some benefit in cholinergic urticaria and led to a reduction in exercise-induced experimental wheals in some studies.<sup>1,4,5</sup> For patients with hereditary angioedema, tranexamic acid may be helpful as a prophylaxis for planned surgery or dental procedures. For acute life-threatening conditions, fresh frozen plasma or C1-inhibitor concentrate should be administered. Should these measures fail, intubation or tracheostomy may be necessary.

### CONCLUSION

The diagnosis of urticaria or angioedema is primarily clinical, and a carefully taken history, physical

examination, specific tests, and skin biopsy often provide useful information for the management of these disorders. Laboratory investigations should be individualized based on the information gathered from the patient's history and physical examination. A multitude of laboratory tests can be performed, but they often do not provide a diagnosis.

The dermal mast cells and their mediators play a central role in chronic urticaria. Various task forces have recommended antihistamines as the first line of drugs for the management for urticaria.<sup>4,5</sup> Lately, significant evidence has been accumulated to support a role of histamine-releasing autoantibodies in the pathogenesis of chronic idiopathic urticaria. Immunomodulating drugs such as corticosteroids and cyclosporine may be considered for severe unremitting urticaria of autoimmune origin.

HP

## REFERENCES

1. Soter NA. Urticaria and angioedema. In: Freedberg IM, Fitzpatrick TB, editors. *Fitzpatrick's dermatology in general medicine*. 5th ed. New York: McGraw-Hill; 1999: 1409–19.
2. Black AK, Champion RH. Urticaria. In: Champion RH, Rook A, Wilkinson DS, Ebling FJG, editors. *Textbook of dermatology*. 6th ed. Oxford: Blackwell Science; 1998: 2113–39.
3. Beltrani VS. Urticaria and angioedema. *Dermatol Clin* 1996;14:171–98.
4. The diagnosis and management of urticaria: a practice parameter part I: acute urticaria/angioedema part II: chronic urticaria/angioedema. Joint Task Force on Practice Parameters. *Ann Allergy Asthma Immunol* 2000; 85:521–44.
5. Grattan C, Powell S, Humphreys F. Management and diagnostic guidelines for urticaria and angio-oedema. *Br J Dermatol* 2001;144:708–14.
6. Cooper KD. Urticaria and angioedema: diagnosis and evaluation. *J Am Acad Dermatol* 1991;25:166–74.
7. Greaves MW. Chronic urticaria [published erratum appears in *N Engl J Med* 1995;333:1091]. *N Engl J Med* 1995;332:1767–72.
8. Kumar SA, Martin BL. Urticaria and angioedema: diagnostic and treatment considerations. *J Am Osteopath Assoc* 1999;99:S1–4.
9. Kaplan AP. Urticaria and angioedema. In: Middleton E, editor. *Allergy: principles and practice*. 3rd ed. St Louis: CV Mosby; 1988:1377–401.
10. Juhlin L. Recurrent urticaria: clinical investigation of 330 patients. *Br J Dermatol* 1981;104:369–81.
11. Mathews KP. Urticaria and angioedema. *J Allergy Clin Immunol* 1983;72:1–14.
12. Malanin G, Kalimo K. The results of skin testing with food additives and the effect of an elimination diet in chronic and recurrent angioedema. *Clin Exp Allergy* 1989;19:539–43.
13. Kaeser P, Revely ML, Frei PC. Prevalence of IgE antibodies specific for food allergens in patients with chronic urticaria of unexplained etiology. *Allergy* 1994;49:626–9.
14. Raychaudhuri SP, Kaplan M. Chronic urticaria and hepatitis C. *Int J Dermatol* 1995;34:823–4.
15. Tebbe B, Geilen CC, Schulzke JD, et al. *Helicobacter pylori* infection and chronic urticaria. *J Am Acad Dermatol* 1996;34:685–6.
16. Rebora A, Drago F, Parodi A. May *Helicobacter pylori* be important for dermatologists? *Dermatology* 1995;191: 6–8.
17. Edward A, Nolph K. Streptococcus peritonitis with urticaria. *Perit Dial Int* 1991;12:214–5.
18. Schwartz LB. Mast cells and their role in urticaria. *J Am Acad Dermatol* 1991;25:190–203.
19. Hide M, Francis DM, Grattan CE, et al. Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. *N Engl Med* 1993;328: 1599–604.
20. Fiebiger E, Maurer D, Holub H, et al. Serum IgG autoantibodies directed against the alpha chain of Fc epsilon RI: a selective marker and pathogenetic factor for a distinct subset of chronic urticaria patients? *J Clin Invest* 1995;96:2606–12.
21. Grattan CE, O'Donnell BF, Francis DM, et al. Randomized double-blind study of cyclosporin in chronic 'idiopathic' urticaria. *Br J Dermatol* 2000;143:365–72.
22. Raulf-Heimsoth M, Chen Z, Rihs HP, et al. Analysis of T-cell reactive regions and HLA-DR4 binding motifs on the latex allergen Hev b 1 (rubber elongation factor). *Clin Exp Allergy* 1998;28:339–48.
23. Champion RH, Roberts SO, Carpenter RG, Roger JH. Urticaria and angioedema. A review of 554 patients. *Br J Dermatol* 1969;81:588–97.
24. Zuberbier T, Ifflander J, Semmler C, Henz BM. Acute urticaria: clinical aspects and therapeutic responsiveness. *Acta Derm Venereol* 1996;76:295–7.
25. Young E, Stoneham MD, Petrukevitch A, et al. A population study of food intolerance. *Lancet* 1994;343:1127–30.
26. Green GR, Koelsche GA, Kierland RR. Aetiology and pathogenesis of chronic urticaria. *Ann Allergy* 1965; 23:30–6.
27. Kelso JM, Hugh MY, Lin FL. Recall urticaria. *J Allergy Clin Immunol* 1994;93:949–50.
28. Niimi N, Francis DM, Kermani F, et al. Dermal mast cell activation by autoantibodies against the high affinity IgE receptor in chronic urticaria. *J Invest Dermatol* 1996;106: 1001–6.
29. Millikan LE. Papular urticaria. *Semin Dermatol* 1993; 12:53–6.
30. Jordaan HF, Schneider JW. Papular urticaria: a histopathologic study of 30 patients. *Am J Dermatopathol* 1997;19:119–26.
31. Breathnach SM, Allen R, Ward AM, Greaves MW. Symptomatic dermographism: natural history, clinical features, laboratory investigations and response to therapy.



