

# Chronic Urticaria

## It's More Than Just Antihistamines!

Randy D. Danielsen, PhD, PA, DFAAPA, PA-C Emeritus, Gabriel Ortiz, MPAS, PA-C, DFAAPA, Susan Symington, MPAS, PA-C, DFAAPA

The discomfort caused by an urticarial rash, along with its unpredictable course, can interfere with a patient's sleep and work/school. Adding to the frustration of patients and providers alike, an underlying cause is seldom identified. But a stepwise treatment approach can bring relief to all.

### Randy D. Danielsen

is Professor and Dean of the Arizona School of Health Sciences, and Director of the Center for the Future of the Health Professions at A.T. Still University in Mesa, Arizona.

### Gabriel Ortiz

practices at Breathe America El Paso in Texas and is a former AAPA liaison to the American Academy of Allergy, Asthma & Immunology (AAAAI) and National Institutes of Health/National Asthma Education and Prevention Program—Coordinating Committee.

### Susan Symington

has practiced in allergy, asthma, and immunology for more than 10 years. She is the current AAPA liaison to the AAAAI and is President-Elect of the AAPA-Allergy, Asthma, and Immunology subspecialty organization.

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### LEARNING OBJECTIVES

- Differentiate between acute and chronic urticaria.
- List common history questions required for the diagnosis of chronic urticaria.
- Explain a stepwise plan for treatment of chronic urticaria.
- Describe serologic testing that should be ordered for chronic urticaria.
- Demonstrate knowledge of when to refer patients to a specialist for alternative treatment options.



Urticaria, often referred to as *hives*, is a common cutaneous disorder with a lifetime incidence between 15% and 25%.<sup>1</sup> Urticaria is characterized by recurring pruritic wheals that arise due to allergic and nonallergic reactions to internal and external agents. The name *urticaria* comes from the Latin word for “nettle,” *urtica*, derived from the Latin word *uro*, meaning “to burn.”<sup>2</sup>

Urticaria can be debilitating for patients, who may complain of a burning sensation. It can last for years in some and reduces quality of life for many. Recently, more successful treatments for urticaria have emerged that can provide tremendous relief.

It is important to understand some of the ways to diagnose and treat patients in a primary care setting and also to know when referral is appropriate. This article will discuss the diagnosis, treatment, and referral process for patients with chronic urticaria.

### PATHOPHYSIOLOGY

Hives most commonly arise from an immunologic reaction in the superficial skin layers that results in the release of histamine, which causes swelling, itching, and erythema. The mast cell is the major effector cell in the pathophysiology of urticaria.<sup>3</sup> In immunologic urticaria, the antigen binds to immunoglobulin (Ig) E on the mast cell surface, causing degranulation and release of histamine, which accounts for the wheals and itching associated with the condition. Histamine binds to H<sub>1</sub> and H<sub>2</sub> receptors in the skin to cause arteriolar dilation, venous constriction, and in-

**TABLE 1**  
**Etiology of Urticaria**

Type	Examples
Infectious disease	Viral infection*; hepatitis; infectious mononucleosis; bacterial, parasitic, or fungal infection
Medications	Penicillin and other antibiotics, aspirin, insulin, vaccines, allergy injections, morphine, meperidine, codeine, NSAIDs, ACE inhibitors
Environmental allergens	Grass, animal dander or saliva, insect stings
Foods	Eggs, milk, wheat, soy, peanuts, tree nuts, fish, shellfish
Autoimmune or noninfectious causes	Autoimmune hives†, collagen vascular disease, malignancy, thyroid disease, hormonal changes
Physical agents	Cold, heat, sunlight, pressure, vibration, exercise
Psychologic factors	Stress, anxiety

\* Most common cause of acute urticaria.

† Most common cause of chronic urticaria.

Sources: Arizona Asthma & Allergy Institute<sup>5</sup>; Wanderer. *Hives: The Road to Diagnosis and Treatment of Urticaria*. 2004.<sup>7</sup>

creased capillary permeability, accounting for the accompanying swelling.<sup>3</sup> Not all urticaria is mediated by IgE; it can result from systemic disease processes in the body that are immune related but not related to IgE. An example would be autoimmune urticaria.

Urticaria commonly occurs with angioedema, which is marked by a greater degree of swelling and results from mast cell activation in the deeper dermis and subcutaneous tissue. Either condition can occur independently, however. Angioedema typically affects the lips, tongue, face, pharynx, and bilateral extremities; rarely, it affects the gastrointestinal tract. Angioedema may be hereditary, but its nonhereditary causes can be similar to those of urticaria.<sup>3</sup> For example, a patient could be severely allergic to cat dander and, when exposed to this allergic trigger, develop swelling of the lips, facial edema, and flushing.

### FORMS OF URTICARIA

Urticaria can be broadly divided based on the duration of illness: less than six weeks is termed *acute urticaria*, and continuous or intermittent presence for six weeks or more, *chronic urticaria*.<sup>4</sup>

Acute urticaria may occur in any age

group but is most often seen in children.<sup>1</sup> Acute urticaria and angioedema frequently resolve within a few days, without an identified cause. An inciting cause can be identified in only about 15% to 20% of cases; the most common cause is viral infection, followed by foods, drugs, insect stings, transfusion reactions, and, rarely, contactants and inhalants (see Table 1).<sup>1,5</sup> Acute urticaria that is not associated with angioedema or respiratory distress is usually self-limited. The condition typically resolves before extensive evaluation, including testing for possible allergic triggers, can be done. The associated skin lesions are often self-limited or can be controlled symptomatically with antihistamines and avoidance of known possible triggers.<sup>1</sup>

Chronic urticaria, sometimes called *chronic idiopathic urticaria*, is more common in adults, occurs on most days of the week, and, as noted, persists for more than six weeks with no identifiable triggers.<sup>6</sup> It affects about 0.5% to 1% of the population (lifetime prevalence).<sup>3</sup> Approximately 45% of patients with chronic urticaria have accompanying episodes of angioedema, and 30% to 50% have an autoimmune process involving autoantibodies against the thyroid, IgE, or the high-affinity IgE receptor

**FIGURE 1**  
**Dermatographism**



From the Latin for “write on skin,” dermatographism is another name for *pressure urticaria*, in which pressure applied to skin causes increased release of histamine and subsequent development of wheals and itching.

Source: Dr P. Marazzi/Science Source.

(FcR1).<sup>3</sup> The diagnosis is based primarily on clinical history and presentation; this will guide the determination of what types of diagnostic testing are necessary.

Chronic urticaria requires an extensive, but not indiscriminate, evaluation with history, physical examination, allergy testing, and laboratory testing for immune system, liver, kidney, thyroid, and collagen vascular diseases.<sup>3</sup> Unfortunately, an identifiable cause of chronic urticaria is found in only 10% to 20% of patients; most cases are idiopathic.<sup>3,7</sup>

Several forms of chronic urticaria can be precipitated by physical stimuli, such as exercise, generalized heat, or sweating (cholinergic urticaria); localized heat (localized heat urticaria); low temperatures (cold urticaria); sun exposure (solar urticaria); water (aquagenic urticaria); and vibration.<sup>1</sup> In another form (pressure urticaria), pressure on the skin increases histamine release, leading to the development of wheals and itching; this form is also called *dermatographism*, which means “write on skin” (see Figure 1). These types of urticaria should be evaluated and treated by a board-certified allergist, as

there are special evaluations that can confirm the diagnosis.

## CLINICAL FEATURES

The main feature of urticaria is raised skin lesions that appear pale to pink to erythematous and most commonly are intensely pruritic (see Figure 2). These lesions range from a few millimeters to several centimeters in size and may coalesce.

Characteristically, evanescent old lesions resolve, and new ones develop over 24 hours, usually without scarring. Scratching generally worsens dermatographism, with new urticaria produced over the scratched area. Any area of the body may be involved.

The lesions of early urticaria may vary in size and blanch when pressure is applied. An individual hive may last minutes or up to 24 hours and may reoccur intermittently on various sites on the body for an unspecified period of time.<sup>1,6</sup>

## DIFFERENTIAL DIAGNOSIS

Other dermatologic conditions may be mistaken for chronic urticaria. Common rashes that may mimic it include anaphylaxis, atopic dermatitis, medication allergy or fixed drug eruption, ACE inhibitor-related angioedema, mastocytosis, contact dermatitis, autoimmune thyroid disease, bullous pemphigoid, and dermatitis herpetiformis.

Patients should be encouraged to bring pictures of the rash to the office visit, since the rash may have waned at the time of the visit and diagnosis based on the patient’s description alone can be challenging. Most rashes in the differential can be identified or eliminated through a careful history and complete physical exam. When necessary, serologic testing and skin punch biopsies can elucidate and confirm the diagnosis.

## EVALUATION

### History and physical examination

The medical history is the most important part of the evaluation of a patient with urticaria. The information that should be elicited and documented during the history is shown in Table 2 (page 40).

A general comprehensive physical exam

should be undertaken and the findings carefully documented. As noted, it can be helpful for patients to bring in pictures of the rash if the lesions wax and wane. It is also important to assess whether the urticarial lesions blanch when palpated, since this is a characteristic feature of acute and chronic urticarial lesions (but not of those with an autoimmune, cholinergic, or vasculitic cause). Thus, blanching of the wheal is a key finding on physical exam to discriminate between possible causes.<sup>8</sup> Lesions pigmented with purpuric areas that scar or last longer than 24 hours suggest urticarial vasculitis; other features that distinguish urticarial vasculitis from chronic urticaria are listed in Table 3 (page 41).<sup>2</sup>

### Laboratory evaluation

Although there is no consensus regarding appropriate laboratory testing, the following tests should be considered for patients with chronic urticaria after completion of a thorough history and physical exam: complete blood count (CBC) with differential; erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP); chemistry panel and hepatic panel; and thyroid-stimulating hormone, antimicrobial antibodies, and antithyroglobulin antibodies measurements.<sup>7</sup>

While the CBC is usually within normal limits, if eosinophilia is present, a workup for an atopic disorder or parasitic infection should be considered. If the ESR/CRP results are positive, consider ordering a larger antinuclear antibody (ANA) panel. Note: The utility of performing these tests routinely for chronic urticaria patients is unclear, as studies have demonstrated that results are usually normal. But it is important to order the appropriate tests to help you rule in or out a likely diagnosis.

Additional testing may be indicated by non-IgE or possible autoimmune findings on the history and/or physical exam. This can include a functional autoantibody assay (for autoantibodies to the high-affinity IgE receptor [FcR1]); complement analysis (eg, C3, C4, CH50), especially when concerned about hereditary angioedema; stool

**FIGURE 2**  
**Urticarial Lesions**



The main feature of urticaria is intensely pruritic, raised skin lesions that appear pale to pink to erythematous; they range from a few millimeters to several centimeters in size and may coalesce.

Source: Dr P. Marazzi/Science Source.

analysis for ova and parasites; *Helicobacter pylori* workup (there is limited experimental evidence to recommend this, however); hepatitis B and C workup; chest radiograph and/or other imaging studies; ANA panel; rheumatoid factor; cryoglobulin levels; skin biopsy; and urinalysis.<sup>7</sup>

Local urticaria can occur following contact with allergens via an IgE-mediated mechanism. If an allergen is suspected as a possible trigger, serologic testing to assess allergen-specific IgE levels that may be contributing to the urticaria can be performed in a primary care setting. The specific IgE levels most commonly assessed are for the endemic outdoor aeroallergens (eg, pets [cat, dog], dust mites); measurement of food-specific IgE levels can be ordered if a specific allergy is a concern. Allergy skin prick testing for immediate hypersensitivity and a physical challenge test are usually performed in an allergy office by board-certified allergists.

Skin biopsy should be done on all lesions concerning for urticarial vasculitis (see Ta-

TABLE 2

**Key Components of Patient History in the Evaluation of Urticaria**

Component	Considerations
Onset	Timing of symptoms; any change in medication or other exposures?
Duration	Frequency, severity, and localization of wheals and itching; do they come and go within 24 h or last longer?
Patterns	Dependence of symptoms on the time of day, day of the week, season, menstrual cycle, etc
Precipitating factors	Physical stimuli, exertion, stress, food, medications
Activity	Relation of urticaria to occupation and leisure
Systemic manifestations	Associated angioedema; headache, joint pain, gastrointestinal symptoms
Possible triggers	Known allergies, intolerances, infections, systemic illnesses
Family history	Urticaria, atopy
Quality of life	Degree of impairment
Treatment	Response to prior attempts
Workup	Previous diagnostic studies and results

ble 4, page 42).<sup>2</sup> Biopsy is also important if the hives are painful rather than pruritic, as this may suggest a different cause. The clinician should consider more detailed lab testing and skin biopsy if urticaria does not respond to therapy as anticipated. Also, specific lab testing may be required screening for certain planned medical therapies (eg, glucose-6-phosphate dehydrogenase enzyme deficiency screening before dapsone or hydroxychloroquine therapy).<sup>3</sup>

### MANAGEMENT

#### Nonpharmacologic therapy

Treatment of the underlying cause, if identified, may be helpful and should be considered. For example, if a thyroid disorder is found on serologic testing, correcting the disorder may resolve the urticaria.<sup>9</sup> Similarly, if a complement deficiency consistent with hereditary angioedema is detected, there are medications to correct it, which can be life-saving.<sup>3</sup> Medications for treating

hereditary angioedema are best prescribed in an allergy practice.

If triggers are discovered, the patient must be made aware of them and advised to avoid them as much as possible; however, total avoidance can be very difficult. Other common potentiating factors—such as alcohol overuse, excessive tiredness, emotional stress, hyperthermia, and use of aspirin and NSAIDs—should be avoided.<sup>10</sup> These factors can worsen what is already triggering the urticaria and make it more difficult to treat; an example would be a patient who develops urticaria from a new household dog and is taking anti-inflammatory drugs for arthritis symptoms.

Topical agents rarely result in any improvement, and their use is therefore discouraged. In fact, high-potency corticosteroids may cause dermal atrophy.<sup>11</sup> Also, dietary changes are not indicated for most patients with chronic urticaria, because undiscovered allergy to food or food additives is not likely to be responsible.<sup>4</sup>

## Antihistamines

Antihistamines are the most commonly used pharmacologic treatment for chronic urticaria (see Table 4, page 42). H<sub>2</sub>-receptor blockers, taken in combination with first- and second-generation H<sub>1</sub>-receptor blockers, have been reported to be more efficacious than H<sub>1</sub> antihistamines alone for the treatment of chronic urticaria.<sup>6</sup> This added efficacy may be related to pharmacologic interactions and increased blood levels achieved with first-generation antihistamines. Increased doses of second-generation antihistamines—as high as four times the standard dose—are advocated by the 2014 Joint Task Force on Practice Parameters (JTFPP) for the diagnosis and management of acute and chronic urticaria.<sup>4</sup>

A stepwise approach to treatment is imperative. The JTFPP guidelines (available at [www.allergyparameters.org](http://www.allergyparameters.org)) are summarized below.

**Step 1:** Administer a second-generation antihistamine at the standard therapeutic dose (see Table 4, page 42) and avoid triggers, NSAIDs, and other exacerbating factors.

If symptom control is not achieved in one to two weeks, move on to

**Step 2:** Increase therapy by one or more of the following methods: increase the dose of the second-generation antihistamine used in Step 1 (up to 4x the standard dose); add another second-generation antihistamine to the regimen; add an H<sub>2</sub> blocker (ranitidine, famotidine, cimetidine); and/or add a leukotriene-receptor antagonist (montelukast 10 mg/d).

If these measures do not result in adequate symptom control, it's time for

**Step 3:** Gradually increase the dose of H<sub>1</sub> antihistamine(s) and discontinue any medications added in Step 2 that did not appear beneficial. Add a first-generation antihistamine (hydroxyzine, doxepin, cyproheptadine), which should be taken at bedtime due to risk for sedation.<sup>12</sup>

If symptoms are not controlled by Step 3 measures, or if the patient is unable to tolerate an increased dose of first-generation antihistamines, the urticaria is considered

**TABLE 3**  
**Distinguishing Urticarial Vasculitis From Chronic Urticaria**

Feature	Urticarial vasculitis	Chronic urticaria
<b>Wheal duration</b>	> 24 h*	< 24 h
<b>Purpura/pain/hyperpigmentation</b>	Yes	No
<b>Systemic signs</b>	Yes	Usually none
<b>Laboratory findings</b>	Increased ESR, acute phase reactants; decreased C3/C4 levels	Usually normal
<b>Leukocytoclasia or extravasulation of TBCs</b>	Yes	No
<b>Response to antihistamines</b>	Sometimes	Yes

\* Not always true.

Abbreviations: ESR, erythrocyte sedimentation rate; TBCs, target-binding cells. Sources: Vazquez-López et al. *Rheumatology (Oxford)*. 2003<sup>8</sup>; Kaplan. *N Engl J Med*. 2002.<sup>9</sup>

refractory. At this point, the clinician should consider referral to an allergy specialist for

**Step 4:** Add an alternative medication, such as cyclosporine (an anti-inflammatory, immunosuppressive agent) or omalizumab (a monoclonal antibody that selectively binds to IgE).

It should be noted that while the recent FDA approval of omalizumab for treatment of chronic urticaria has been life-changing for many patients, the product label does carry a black box warning about anaphylaxis. Because special monitoring is needed (and prior authorization will likely be required by the patient's insurer), omalizumab is best prescribed in an allergy office.

It is not uncommon for patients with chronic urticaria to require multiple medications to control their symptoms. Once controlled, they will require maintenance and reevaluation on a regular basis.<sup>13</sup>

## When to refer

Clinicians must know when to refer a patient with chronic urticaria to an allergist/

**TABLE 4**  
**Categories of Antihistamines and Approved Dosing for Adults**

Medication	Dosage
<b>First-generation H<sub>1</sub> blockers</b>	
Chlorpheniramine	4 mg every 4-6 h up to 32 mg/d
Cyproheptadine	4 mg/d
Diphenhydramine	25-50 mg/d
Hydroxyzine	10-25 mg up to tid
Doxepin*	25-50 mg at bedtime
<b>Second-generation H<sub>1</sub> blockers</b>	
Cetirizine	10 mg QD-bid
Desloratadine	5 mg QD
Fexofenadine	180 mg QD-bid
Levocetirizine	5 mg QD-bid
Loratadine	10 mg QD-bid
<b>H<sub>2</sub> blockers</b>	
Cimetidine	300 mg bid
Famotidine	20 mg bid
Ranitidine	150-300 mg bid

\* Tricyclic antidepressant with potent antihistamine activity.

immunologist. Referral is indicated when an underlying disorder is suspected, when symptoms are not controlled with Steps 1 to 3 of the management guidelines, or when the patient requires repeated or prolonged treatment with glucocorticoids.

Unfortunately, out of frustration on both the provider and the patient side, glucocorticoids may be started, after determining that that is “all that works” for the patient. There appears to be a limited role for glucocorticoids, so they should be avoided unless absolutely necessary (ie, if there is no response to antihistamines).

If signs and symptoms suggest urticarial vasculitis, it is prudent to consider referral

to a specialist in rheumatology. Urticarial vasculitis requires a special skin punch biopsy to confirm the diagnosis.<sup>8</sup> The biopsy procedure may be performed by a primary care provider; if the clinician is not comfortable doing so, referral to an appropriate dermatology provider is indicated.

### PATIENT EDUCATION/ REASSURANCE

Effective patient education is critical, because patients often experience considerable distress as the symptoms of chronic urticaria wax and wane unpredictably. It is not uncommon for patients with this condition to complain of symptoms that interfere with work, school, and sleep. Reassurance can help to alleviate frustration and anxiety. Patients should understand that the symptoms of chronic urticaria can be successfully managed in the majority of patients, and that chronic idiopathic urticaria is rarely permanent, with about 50% of patients experiencing remission within one year.<sup>6</sup>

### CONCLUSION

The diagnosis of chronic urticaria is based primarily on the presentation, clinical history, and laboratory workup. Management of this chronic and uncomfortable condition requires the identification and exclusion of possible triggers, followed by effective patient education/counseling and a personalized management plan. By knowing when to suspect chronic urticaria, being familiar with the approach to evaluation and initial treatment, and knowing when referral to a specialist is indicated, primary care providers can help their patients find a path to relief. **CR**

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