

# Evaluating Chronic Urticaria Patients for Allergies, Infections, or Autoimmune Disorders

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## Abstract

Urticaria is a common disorder affecting one-fifth of the world's population. The pathophysiology is characterized by an increased propensity for mast cell degranulation with the release of potent mediators into the dermal and subdermal tissues with resulting vasoactive, chemotactic, and inflammatory effects. The final clinical manifestation of the typical urticarial lesion is the effect of several diverse effects and causes. The general classification is acute, chronic, and physical urticaria. In general, allergenic triggers can be identified in between 60–80% of acute urticarias. Physical urticarias are characterized by the onset after the specific inciting stimulus, which can reproduce the characteristic lesion which is usually of shorter duration (with the exception of delayed pressure urticaria). Chronic idiopathic urticaria is associated with thyroid autoimmunity and, more recently, anti-mast cell receptor antibodies. An extensive work-up is usually not indicated or helpful in identifying a cause. Food or other allergens are rare causes of this type of presentation.

The evaluation and work-up is dependent on clues identified by history. The treatment is removal of specific and non-specific triggers and the use of symptomatic medications generally attenuating the mediator effects.

**Index Entries:** Acute; chronic physical; cost-effective; triggers, specific, non-specific.

## Introduction

Urticaria is a common disorder that affects more than one-fifth of the world population. The characteristic urticarial lesion is a wheal-

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Table 1  
Causes of Chronic Urticaria

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|                                                                                   |
|-----------------------------------------------------------------------------------|
| Idiopathic and/or autoimmune type associated with anti-IgE-receptor auto-antibody |
| Urticarial vasculitis (relatively rare)                                           |
| Physical urticaria                                                                |
| Dermatographism                                                                   |
| Cholinergic (heat-induced) urticaria                                              |
| Cold-induced urticaria                                                            |
| Delayed-pressure urticaria (DPU)                                                  |
| Solar urticaria                                                                   |
| Vibratory urticaria/angioedema                                                    |
| Aquagenic urticaria                                                               |

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and-flare reaction, also known as “hives.” Lesions vary from a few millimeters to several centimeters in diameter. Lesions may coalesce and produce “giant urticaria.” Angioedema is a deeper and more localized edematous process that is often associated with urticaria.

Urticaria is classified as acute, chronic, or physical urticaria. Acute urticaria is defined as hives that occur intermittently for less than 6 wk in duration. This is the most common presentation, representing about 80% of urticaria. An identifiable allergenic trigger is more commonly found within this subset, often caused by an allergy to a food or drug. Chronic urticaria (1–3) is defined as hives occurring at least three times weekly for a period of more than 6 wk in duration. Allergy is only rarely proven as a cause of chronic urticaria. Physical urticaria (4–7) is the variant, in which physical stimuli trigger urticarial responses (Table 1). Urticaria is a multifactorial disorder, comprising several subsets with different pathophysiologic mechanisms. The final common manifestation is the development of the typical urticarial lesion—a direct result of mast-cell degranulation with the release of potent vasoactive and inflammatory mediators.

The primary process in urticaria is edema, resulting from plasma transudation caused by increased subdermal and capillary permeability. Surrounding vasodilatation results from cutaneous antidromic neural stimulation and release of substance P (SP), which leads to reflex erythroderma—the flare response. Stimulation of free nerve endings by chemical mediators causes the clinical symptoms of itching and burning. Typical urticarial lesions completely resolve in a period lasting from a few minutes to hours.

The central role of mast cells in immediate hypersensitivity, and specifically urticaria, is well-established. Mast cells have high-affinity IgE receptors, of which about 10% are occupied. Mast cells are 10–13  $\mu\text{m}$  in diameter, and are found in loose connective tissue around blood

vessels approximately 7000 in number. Mast cells can respond to immunologic, non-immunologic, and physical stimuli. In classic allergic reactions, mast-cell-mediator release occurs when IgE molecules bound to the cell-surface receptors are bridged by specific antigens. The translation of the surface signal and perturbation of the resting mast cell is associated with complex biochemical events, and results in granular fusion and exocytosis.

Immunologically mediated urticarial reactions may be associated with the activation and release of complement split products, including C3a, C4a, and C5a. These anaphylotoxins also activate mast cells through specific surface receptors. Other pathways, including the kinin/bradykin cascade, may amplify the inflammatory urticarial response, and may be involved in the pathogenesis of specific subgroups of urticaria.

The exact role of lymphocytes in urticaria is unclear. Receptors on mast cells have been described for other antigens, which may explain the association of urticaria with viral infections and thyroid autoimmunity. Non-immunologic agents that are capable of causing urticaria include radiographic contrast media (RCM), drugs such as opiates, and neuropeptide-induced mast-cell activation and degranulation. Physical stimuli—both immunologic and non-immunologic mechanisms—cause mast-cell activation.

## **Hypersensitivities and Chronic Urticaria**

Allergy is rarely implicated as the cause of chronic urticaria. Nevertheless, it is the focus of many patients, and in this respect, it is important to rule out environmental and food-allergy triggers to alleviate patient concerns. All subsequent investigations should be directed at information obtained from the history (8,9). The evaluation begins with a thorough, detailed history and review of systems to identify any possible triggers, such as foods, medications, and contact sensitivities. A history of multiple or repetitive insect stings/bites may suggest insect hypersensitivity as the cause of the chronic urticaria, especially if the symptoms are seasonal. A patient diary of symptom exacerbations and exogenous factors may be helpful.

A comprehensive medication history should be obtained, which includes all pharmaceuticals such as over-the-counter medications, vitamins, herbal remedies, and other “naturopathic” supplements. Angiotensin-converting enzyme (ACE) inhibitors (10), aspirin (11,12), other non-steroidal anti-inflammatory drugs (NSAIDs) (13,14) can exacerbate or trigger chronic urticaria (15,16). It is not uncommon for a patient to have taken antibiotics prior to the onset of an urticarial episode.

Although rare, the history may occasionally implicate a food or food additive (15–21), such as tartrazine, sodium benzoate, or salicylates as the cause of chronic urticaria. The temporal relationship of food ingestion and the appearance of symptoms should therefore be noted. However, it is difficult to confirm the diagnosis of food dye or preservative-induced urticaria. In order to prove causation, patients should have standard double-blind oral challenges to determine the relationship. Further evaluation of food allergy may include targeted food-specific prick tests or serum IgE-specific assays such as the radioallergosorbent test (RAST) (22) in patients with extensive involvement of the skin or those who require continuous antihistamine treatment. A standardized screening using skin tests with multiple food allergens is helpful only in rare cases.

The common occurrence of dermatographism makes interpretation of skin tests difficult, and false-positive skin tests may occur. Positive food-specific IgE tests would generally lead to further confirmatory food-elimination trials (23). A short yet strict trial elimination diet may be used in selected urticaria patients. Open-single or double-blinded placebo-controlled food or food-additive challenges may also be useful, but are difficult to interpret. However, some patients with positive oral provocation tests to additives show a marked improvement in symptoms on an additive-free diet (15).

An occupational history may identify work exposure to sensitizing antigens such as latex, which may be causing chronic symptoms, since the patient is exposed on an ongoing basis. Similarly, the history should also reveal the presence of contact-induced urticaria, because patients exposed on a recurrent basis may present with a chronic history. Patients with metal implants, such as dental bridges or joint prostheses, may have metal contact sensitivity (24–26). Patch testing should be performed as warranted by the history.

Physical urticarias, such as dermatographism, cold or pressure-induced urticaria, and solar and cholinergic urticaria, should be assessed by appropriate challenge testing as indicated by the history and physical examination (27–31) (Table 2).

## Infections and Chronic Urticaria

Chronic infection as an etiology for chronic urticaria is controversial. There is usually no convincing evidence to substantiate this link, and the association is based primarily on anecdotal evidence of case reports. Occasionally, however, chronic infections, such as chronic sinusitis, Trichophyton skin infections, or *Helicobacter pylori* infections are identified by history and physical examination and appropriate supporting laboratory tests, and if so, it should be appropriately treated.

Table 2  
Challenge Testing for Physical Urticarias (2)

|                                  |                                                                                                |
|----------------------------------|------------------------------------------------------------------------------------------------|
| Symptomatic dermatographism      | Light stroking of skin to cause immediate wheal-and-flare with itching                         |
| Cholinergic urticaria            | Inducible with hot shower or exercise; produces a characteristic papular urticaria             |
| Cold-induced urticaria           | Ice cube test—application of ice for 10 min results in a wheal within 5–10 min after removal   |
| Delayed-pressure urticaria (DPU) | Application of deep pressure to skin results in swelling after 1–5 h, deep and tender to touch |
| Solar urticaria                  | Expose the skin to light wavelengths by a 2.5-kW simulator (290–690 nm) for 30–120 s           |

Hepatitis C infection has been shown to manifest with a variety of skin diseases (32,33). The most commonly reported is the triad of leukocytoclastic vasculitis, cryoglobulinemia, and chronic Hepatitis C virus (HCV) infection. Therefore, patients with urticarial vasculitis should be tested for hepatitis B and C. The prodrome of Hepatitis B infection may present with a serum sickness-type of reaction, with urticaria the most predominant manifestation. However, the association between chronic urticaria and viral hepatitis is more controversial, and causation has been difficult to prove (34,35).

Other viral diseases have also been associated with chronic urticaria, including acquired cold urticaria with infectious mononucleosis (36,37). Common viral infections of childhood are often implicated as a cause of urticaria rather than the prescribed antibiotic. A complete immune-complex work-up should be performed in these patients with chronic viral infections if they have other symptoms of immune-complex disease, such as palpable purpura.

Some studies have linked chronic bacterial infections with chronic urticaria, possibly from bacterial activation of complement. For example, various studies have shown a high prevalence of *Helicobacter pylori* infection in patients with chronic urticaria, and occasional remission of skin lesions after eradication therapy. However, several recent case-control studies do not support a relationship between *Helicobacter pylori* infection and chronic urticaria (38–40).

Chronic fungal infections such as *Candida* and tinea pedis (Trichophyton), as well as chronic parasitic infestations, have also been associated with chronic urticaria (41–45). Again, these are rare causative agents, and most fungal infections do not cause urticaria.

The patient's history should help to identify symptoms that may suggest the presence of underlying infections such as sinusitis or diarrhea. Preliminary blood work should include a complete blood count (CBC) and differential, sedimentation rate, and total hemolytic complement assay. An elevated eosinophil count may suggest the presence of occult parasitic infection. However, an extensive work-up for occult bacterial, viral, or fungal infections is not justified unless suggested by the history.

## **Autoimmunity and Chronic Urticaria**

Most cases of chronic urticaria are believed to be autoimmune, related to the autoantibody of the IgE receptor (*see* 46–49). As noted previously, chronic urticaria has been associated with many autoimmune disorders. For example, autoimmune thyroiditis can be identified in about 14% of cases of chronic urticaria (50), which is about three times the expected incidence. Other autoimmune associations include vitiligo, alopecia areata, pernicious anemia, and colitis (51–52). Definitive evidence for the autoimmune etiology of chronic urticaria came with the discovery of circulating autoantibodies against the high-affinity IgE receptor (FcεR1, alpha subunit) of mast cells (53–55).

The personal and family history may suggest the possibility of an autoimmune etiology, including signs and symptoms of autoimmune thyroiditis, systemic lupus erythematosus, and mixed connective-tissue disease. The history is more suggestive of an underlying autoimmune cause if urticarial vasculitis (56) is present. Urticarial vasculitis lesions differ from other urticarial lesions because they are palpable and purpuric, and persist for 24 h or longer. Lesion resolution often results in a residual pigmented change in the skin. There may be associated systemic symptoms such as low-grade fever, arthralgia, or arthritis, and gastrointestinal, pulmonary, or ocular complaints identified in the hypocompletemic urticarial vasculitis syndrome.

When systemic collagen vascular disease is suspected, useful tests may include erythrocyte sedimentation rate (ESR), complement assays, and cryoglobulins. If skin lesions have the appearance of urticarial vasculitis, a punch biopsy of the skin should be performed to confirm the diagnosis (57,58). Routine histopathology and immunofluorescence staining should be done. Biopsy of urticarial vasculitis shows polymorphonuclear infiltration within the walls of blood vessels and in the perivascular space. Cellular debris with leukocytoclasia is frequently observed, together with endothelial swelling, red blood cell (RBC) extravasation, and fibrin deposition. Immunofluorescence may determine the presence of fibrinogen, immunoglobulin, and/or complement deposition.

Evaluation of patients for thyroid autoantibodies (59,60) (anti-thyroglobulin and anti-thyroid peroxidase) and autoantibodies to high-

Table 3  
Diagnostic Evaluation of Chronic Urticaria

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- Is the urticaria triggered by physical stimuli?  
If YES, confirm with challenge testing (Table 2); other investigations unnecessary if no other systemic symptoms exist
  - Does the history suggest hypersensitivity to a food or drug as the cause of chronic urticaria?  
If YES, perform limited skin-prick tests/RAST based on history  
For foods, also consider food elimination trials or placebo-controlled food challenges
  - Does the history suggest contact sensitivity as the cause of chronic urticaria?  
If YES, perform patch testing based on history
  - Does the history suggest an infectious cause for chronic urticaria?  
If YES, perform investigation based on the history and physical examination.
  - The occasional patient with a history and physical examination suggestive of a collagen vascular disease should have directed laboratory evaluation:  
Complement assays (CH50, C3, C4, C1q precipitins)  
Cryoglobulin  
Erythrocyte sedimentation rate  
Anti-Nuclear Antibody (ANA)  
Rheumatoid factor  
Serum protein electrophoresis  
Quantitative immunoglobulins  
Skin biopsy
  - Does the history and physical examination suggest chronic idiopathic/auto-immune urticaria?  
Autologous serum skin test (detect anti-IgE-receptor autoantibody)  
Thyroid autoantibodies
- 

affinity IgE receptor of mast cells may be warranted. A skin test with autologous serum may reveal a wheal-and-erythema response, suggesting the presence of anti-IgE or anti-high-affinity IgE-receptor antibodies. Presently, mast-cell-receptor antibodies cannot be measured by routine laboratory evaluation.

**Diagnostic Evaluation of Chronic Urticaria**

In summary, chronic urticaria is only rarely caused by exogenous factors such as allergies or infections. However, if the history or physical examination suggests such an association, the patient should be examined with a focus on these aspects. A minority of patients will have an autoimmune disease underlying their chronic urticaria. Therefore, most diagnostic evaluations should focus on detecting this autoimmune process, especially if the patient has urticarial vasculitis or other systemic autoimmune features. Table 3 provides a summary of the

investigations that should be considered in the evaluation of chronic urticaria.

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