



An Update on Acute and Chronic Urticaria for the Primary Care Provider

Umer Najib & Javed Sheikh

To cite this article: Umer Najib & Javed Sheikh (2009) An Update on Acute and Chronic Urticaria for the Primary Care Provider, Postgraduate Medicine, 121:1, 141-151, DOI: [10.3810/pgm.2009.01.1966](https://doi.org/10.3810/pgm.2009.01.1966)

To link to this article: <https://doi.org/10.3810/pgm.2009.01.1966>



Published online: 13 Mar 2015.



Submit your article to this journal [↗](#)



Article views: 30



Citing articles: 4 View citing articles [↗](#)

An Update on Acute and Chronic Urticaria for the Primary Care Provider

Umer Najib, MD¹

Javed Sheikh, MD¹

¹Division of Allergy and Inflammation, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Abstract: Urticaria is a common dermatologic condition seen by primary care physicians. Urticaria can result in significant morbidity and a dramatic decline in quality of life. Acute urticaria is mostly an allergic or IgE-mediated reaction and tends to be self-limited, while chronic urticaria generally does not exhibit any specific external cause and is therefore considered idiopathic. Evidence suggests that up to 30% to 50% of idiopathic cases may be autoimmune and/or related to mast cell/basophil abnormalities. There is further evidence of an autoantibody to the high-affinity receptor for IgE (FcεRI), specifically binding to the α-chain (FcεRIα), which may be pathogenic. The treatment regimen for urticaria needs to be individualized as the severity and clinical pattern can vary considerably between patients. Histamine antagonists are the mainstays of therapy. For more severe or persistent cases, there are few Food and Drug Administration (FDA)-approved options, and there are limited data from controlled trials. Further research is required to develop safe and more effective agents for this disease.

Keywords: urticaria; autoimmune; basophil; mast cell; FcεRI autoantibodies; hives; antihistamines

Introduction

Urticaria is a common dermatologic condition seen by primary care physicians. Most cases of urticaria are of short duration, but when urticaria becomes chronic, it can be a very frustrating condition for the patient and physician. The disability and distress caused by urticaria can lead to serious quality of life impairment. One study found that the level of quality of life impairment experienced by patients with chronic urticaria (CU) can be comparable to that experienced by patients with cardiovascular disease.¹

Urticaria, or hives, is classified as either acute or chronic. Recurrent urticaria lasting < 6 weeks is considered acute, whereas it is considered chronic when symptoms have been continuously or intermittently present for > 6 weeks.² Urticaria occurs in 15% to 25% of the population at some point in their lives and is most often acute.² Only 30% of these cases go on to become chronic.² The average duration of CU is 3 to 5 years.³ However, there is considerable variation in duration and some patients can continue to experience symptoms for ≥ 20 years.³ When no underlying cause is found, CU has been referred to as chronic idiopathic urticaria (CIU), which comprises 80% to 90% of patients with CU.⁴ Evidence shows that 30% to 50% of patients with CIU demonstrate evidence of autoimmunity, while the remaining 50% to 70% do not have autoimmune features.⁴ Chronic idiopathic urticaria affects up to 3% of the population, and up to 20% of these patients can have symptoms > 10 years.⁴ Urticaria affects both genders and all races. Acute urticaria is more common in children and young adults while CU is more common in adults. Chronic idiopathic urticaria has a female to male ratio of 4:1 and is most prevalent in middle-aged adults.⁴

Correspondence: Javed Sheikh, MD, Clinical Director, Division of Allergy and Inflammation, Clinical Director, Center for Eosinophilic Disorders, Beth Israel Deaconess Medical Center, Assistant Professor of Medicine, Harvard Medical School, One Brookline Place, Suite 623, Brookline, MA 02445.
Tel: 617-278-8100
Fax: 617-278-8101
E-mail: jsheikh@bidmc.harvard.edu

Approximately 50% of patients with urticaria present with associated angioedema, which is a condition that involves swelling of the deep dermal and subcutaneous/submucosal tissues.⁴ About 40% of patients present only with urticaria, while 10% have isolated angioedema.⁴

Clinical Presentation

Urticaria usually presents as edematous pink or red wheals of variable size and shape, with surrounding erythema. The lesions, which are often described as welts or hives, are generally pruritic.⁵ A painful or burning sensation may be described in some cases.⁶ Such lesions are often associated with angioedema or vasculitis.⁶

Angioedema appears as brawny, non-pitting edema typically without well-defined margins and without erythema.⁷ It is usually not distributed in the dependent parts of the body (in contrast to most other types of edema) and may involve the lips, tongue, eyelids, and genitalia.⁷

Dermographism is often observed in conjunction with CU. With dermatographism, wheals can be created or “written” on the skin by stroking or scratching the skin.⁸ A linear response occurs on the skin after stroking because of reflex vasodilation. An exaggerated response, accompanied by itching, leads to the development of erythema and hives.⁸ Dermographism is considered a common physical trigger for urticaria and accompanies CIU in approximately 50% of cases.⁴ The presence of dermatographism might aid the clinician in making the diagnosis of CIU, helping to distinguish CIU from masquerading conditions.

Patients with CU also may report pressure-induced hives, which can occur with elastic or tight clothing. Cholinergic urticaria presents as diffuse erythema and elevated, pale monomorphic urticarial lesions that have a pinpoint appearance.⁹ In addition, patients with cholinergic urticaria can have more generalized cholinergic manifestations, such as wheezing, salivation, syncope, or lacrimation, but this is unusual.⁹

Individual urticarial lesions usually fade within 24 hours, but new lesions may be developing continuously.⁴ With delayed pressure urticaria, lesions may last as long as 48 hours. In contrast, the lesions of urticarial vasculitis may last for several days or more.¹⁰ Therefore, if lesions are found to last > 48 hours, this would prompt consideration of a skin biopsy to evaluate for possible urticarial vasculitis. Other clinical features of urticarial vasculitis, which may or may not be present, include palpable and non-blanching purpura and residual hyperpigmented changes after lesions fade.

Pathophysiology

Urticaria manifests as skin lesions and pruritus caused by an allergic or nonallergic mechanism. Mast cells and basophils are the primary effector cells in urticaria.¹¹ Histamine, although not the only mediator, is thought to be the most important biochemical mediator in urticaria.¹² It is known to cause the classic wheal-and-flare response that is observed with urticaria and with positive results on allergy skin tests. The classic allergic response that occurs with allergen-triggered urticaria is characterized by release from mast cells of histamine, leukotriene C₄, and prostaglandin D₂.¹³ This activation of mast cells occurs when adjacent immunoglobulin E (IgE) molecules, which are bound to the surface of mast cells by the high-affinity receptors for IgE (FcεRI), are cross-linked by allergens. The release of these mediators leads to quick onset of vasodilatation and subcutaneous and intradermal leakage of plasma from postcapillary venules, which in turn lead to pruritus. There can also be a more delayed (4–8 hours) secretion of inflammatory cytokines (tumor necrosis factor, interleukin [IL]-4, and IL-5) that leads to an inflammatory infiltrate and longer lasting lesions, somewhat analogous to the allergen-induced, late-phase response that occurs in asthma. Histamine and other mediators can be released by other nonallergic mechanisms (ie, independent of allergen-induced activation of mast cells). For example, neuropeptides are known to cause mast cell degranulation by a nonallergic mechanism and may well be involved in dermatographism and in emotional exacerbation of urticaria. This phenomenon does not require specific IgE to any particular allergen. Basophils also possess the high-affinity IgE receptor and studies suggest that basophils may have an altered histamine release and recruitment in at least some patients with CU.¹⁴

Acute urticaria is mostly an allergic or IgE-mediated reaction and tends to be self-limited. Typically, acute urticaria is a hypersensitivity reaction to foods, drugs, insect bites, or contact with pets. The predominant foods that cause urticaria are milk, eggs, peanuts, tree nuts (eg, walnuts, hazelnuts, and almonds), finfish, and shellfish. Although uncommon, the antioxidant food preservatives butylated hydroxyanisole and butylated hydroxytoluene have also been shown to trigger urticaria.¹⁵ Inflammatory processes produced by viral illness, particularly in children, can also quite commonly cause acute urticaria. Drugs most commonly implicated in drug-induced urticaria include penicillins, sulfonamides, muscle relaxants (used with anesthesia induction), diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs).

It is important to note that many cases of drug-induced urticaria and other forms of urticaria can occur by an IgE-independent (nonallergic) mechanism. For instance, some drugs (eg, opioids, NSAIDs), radiocontrast dye, viral infections (eg, hepatitis B and C, Epstein-Barr, and herpes) or ingestion of fish contaminated by histamine-producing bacteria (eg, scombroid food poisoning) can produce urticaria by an IgE-independent mechanism. Nonsteroidal anti-inflammatory drugs have been reported to induce urticaria by either IgE-mediated or IgE-independent mechanisms. True IgE-mediated allergy to an NSAID is rare and is usually specific to a single agent, and other NSAIDs may be well tolerated by the patient. In contrast, IgE-independent NSAID-triggered urticaria is fairly common. It is thought to occur due to manipulation of the kinin-prostaglandin pathways by NSAIDs. In such patients, all typical NSAIDs would be expected to trigger urticaria. Selective cyclooxygenase-2 (COX-2) inhibitors generally do not induce urticaria in patients who are sensitive to NSAIDs, although there can be exceptions.¹⁶

Although a lymphocytic infiltrate is commonly found in the lesions of both acute and chronic types of urticaria, some CU lesions have a mixed cellular infiltrate, ie, a mixture of lymphocytes, polymorphonuclear leukocytes (PMNs), and other inflammatory cells.¹⁷ A minority of patients with particularly severe or atypical CU are found to have urticarial vasculitis on skin biopsy, with lesions characterized by vascular destruction, fibrinoid necrosis, and immune complex deposition.¹⁰

Autoantibodies Found in Chronic Urticaria

Evidence suggests that 30% to 50% of patients with CU have autoantibodies to the α -chain of the high affinity receptor for IgE (Fc ϵ RI α).¹⁷ It is hypothesized that these autoantibodies are present in the circulation of these patients and lead to the activation of infiltrating basophils or skin mast cells, thereby causing hives. Conclusive evidence of this mechanism is still lacking. In other words, these autoantibodies are thought to “short-circuit” the IgE-mast cell system, activating IgE without any need for allergen-specific IgE to be bound to the IgE. Therefore, a good proportion of chronic idiopathic urticaria is now thought to be an intrinsic autoimmune condition rather than an allergy. Further evidence supporting an autoimmune basis for urticaria in some patients is a close association with thyroid autoimmunity.¹⁸ Despite the apparent presence of 2 different CIU subgroups (based on the presence or absence of specific autoantibodies), studies have noted only a few differences in clinical presentation,¹⁹ histology,^{20,21} or response

to therapy between patients of the 2 subgroups, and have found that skin biopsy specimens of wheals from CU patients show a similar pattern of infiltration with eosinophils, neutrophils, basophils, and lymphocytes regardless of whether the CU is associated with autoantibody presence or not.^{20,21}

A diagnostic test called the autologous serum skin test (ASST), which is now often used by allergists and some dermatologists, was developed as a result of 2 decades of investigations in which the investigators were able to demonstrate that intradermal injection of autologous serum caused an immediate wheal-and-flare response in some patients with CU,²² and that this process seemed to occur only during disease activity but not remission.^{23,24} Further evidence demonstrated that many of these patients appeared to have circulating serum histamine-releasing factors, meaning that the serum from these patients was able to cause histamine release in an in vitro laboratory model of basophil or mast cell activation.^{22,25,26} This in-vitro histamine release also occurred with purified IgG fractions of the serum in the majority of the patients, suggesting that the histamine-releasing factor in most cases was an IgG antibody.^{19,25} Investigations further demonstrated that the histamine-releasing IgG antibody appeared to be an autoantibody to the α -chain of the high-affinity IgE receptor (Fc ϵ RI α) in the majority of such patients.^{12,27} However, in a small number of cases, the serum with histamine-releasing activity has no evidence of autoantibody to Fc ϵ RI α , and in these cases it is thought that the serum contains autoantibodies to the IgE molecule itself.^{27,28}

Studies have shown that there may be both false-positive (due to formation of other vasoactive mediators while processing the serum) and false-negative (due to degradation of the histamine-releasing factor or autoantibody) results with the ASST.²⁹ Similarly, several recent studies have noted that serum samples from patients without CU can also induce positive ASST results^{30,31} and in vitro histamine release from donor basophils.³² The current gold standard for detecting clinically relevant autoantibodies is a laboratory test referred to as the functional in-vitro donor basophil histamine release assay.^{33,34} At the time of writing this article, there are 2 reference laboratories in the United States that commercially offer such a test: IBT Reference Laboratory (with the test referred to as the CU Index™) and Clinical Reference Laboratories at National Jewish Medical and Research Center (with the test referred to as the anti-Fc ϵ RI antibody).^{35,36} However, the exact clinical role of these tests has not yet been established in the literature.

Nonautoimmune Subgroup of CU

Patients with CU who do not have autoantibodies to FcεRIα or IgE usually have no identifiable cause for their hives and comprise the remaining 50% to 70% of patients with CIU. There is now increasing evidence that there may be abnormalities in number, structure, or function of basophils or mast cells in at least some of these patients, but there is much to be learned about the pathophysiology in this subgroup.¹⁴ For example, patients with CU have been found to have lower circulating basophil counts and basophils that are hyporesponsive to nonspecific stimulation through FcεRI.^{26,37} It has also been shown that patients with CU and histamine-releasing serum

activity have lower basophil counts than CU patients without releasing activity.³⁸ Future investigations in this area will help to further explain the pathogenesis of urticaria in patients without autoantibodies to FcεRIα or IgE.

External Causes of Urticaria

When urticaria is not idiopathic, other major causes, such as food and drugs, should be considered (Table 1). As described previously, food allergy, which is often a consideration in acute urticaria—particularly in children—is rarely a factor in CU. Drug sensitivities, which are commonly implicated in acute urticaria, can be a cause of CU as well when the

Table 1. Causes of Urticaria

	Acute Urticaria
Allergic reactions (may also rarely cause chronic urticaria)	– Foods (especially for children) – Food additives/preservatives (rare) – Drugs – Insect bites – Others (eg, venom, animal saliva, latex)
Nonallergic release of mediators (may also rarely cause chronic urticaria)	– Drugs • Nonsteroidal anti-inflammatory drugs • Angiotensin converting enzyme inhibitors • Opiates • Succinylcholine – Acute infections – Venoms – Radiocontrast media
Infections	Chronic Urticaria – Viral • eg, hepatitis B and C, Epstein-Barr, and herpes – Parasitic – Limited evidence • <i>Helicobacter pylori</i>, sinusitis, cutaneous fungal, other occult infections
Systemic illnesses/conditions	– Complement deficiencies – Cryoglobulinemia • eg, with hepatitis C, chronic lymphocytic leukemia – Serum sickness • or other immune complex-mediated processes – Rheumatologic • eg, systemic lupus, rheumatoid arthritis – Thyroid disease – Neoplasm • eg, chronic lymphocytic leukemia – Other endocrine • eg, tumors, ovarian, oral contraceptives
Physical	– Heat, cold, pressure, vibratory, cholinergic, solar, aquagenic, dermatographism, exercise-induced urticaria/anaphylaxis
Chronic idiopathic	– 80%–90% of all chronic urticaria – Excludes all of the above etiologies – No known antigenic stimulus – Up to 40%–60% may be autoimmune – New data: mast cell/basophil defects

drug is taken daily, so medication history is important. Cholinergic urticaria occurs following exercise or exposure to heat, when there is a rise in the basal body temperature.⁹ Cold urticaria and solar urticaria usually manifest after exposure to a cold stimulus and sunlight, respectively. In an event of massive total body exposure (eg, swimming, in the case of cold urticaria), hypotension or death can occur.³⁹ Delayed pressure urticaria usually manifests 4 to 6 hours after prolonged pressure has been applied (eg, tight clothing).⁴⁰ As discussed previously, up to 90% of cases of CU can be classified as idiopathic, but recent studies have shown that 30% to 50% of these cases have an autoimmune component.¹⁷

Some investigators have shown an association between CU and chronic infections, which include *Helicobacter pylori* gastric infection, tinea pedis, cholecystitis, hepatitis, sinus infections, and dental abscesses, but the evidence is controversial. Additionally, a significant proportion of patients with CU are found to have concomitant thyroid autoimmunity.¹⁸ These patients have autoantibodies directed against thyroid proteins but may be euthyroid. Some patients with these thyroid autoantibodies also have autoantibodies to FcεRIα, but others do not.⁴¹ Some authors have found that treating these euthyroid patients with thyroxine leads to an improvement in urticaria,⁴² but other authors have not been able to reproduce this finding⁴³ and there are no large, blinded, placebo-controlled trials of thyroxine for treatment of urticaria.

Differential Diagnosis

The conditions that may be confused with urticaria include flushing disorders, angioedema, erythema multiforme (lesions last longer), bullous pemphigoid, dermatitis herpetiformis, papular urticaria (eg, insect bites), exercise-induced anaphylaxis, exercise-induced/food-associated anaphylaxis, mastocytosis/urticaria pigmentosa, urticarial vasculitis, and pruritic urticarial papules and plaques of pregnancy (PUPPP), which is also referred to as polymorphic eruption of pregnancy (PEP).⁴ Urticarial vasculitis, which can be considered to be an extreme form of CU, can be seen in conjunction with systemic lupus erythematosus (SLE), juvenile rheumatoid arthritis (JRA), hepatitis B or C, and paraproteinemias.^{7,10}

Angioedema presenting without urticaria is a unique situation where the following diagnoses should be considered: angioedema due to hereditary C1-inhibitor deficiency, angioedema due to acquired C1-inhibitor deficiency, angioedema associated with angiotensin-converting enzyme inhibi-

tors, and primary vascular processes, such as the superior vena cava syndrome.⁴⁰

Evaluation

The evaluation of urticaria begins with a detailed history and physical examination. For acute urticaria and CU, history should include details of the hives in relation to foods, medications (including herbals, supplements), infections, occupational exposures, physical triggers, insect stings, and contact exposures, as well as a complete review of systems.⁴⁴ For patients with CU, key elements include duration of the episodes, duration of individual lesions, nature of the lesions, and presence of angioedema. Some herbal products that have been associated with urticaria include cranberry, echinacea, hypericum, willow, garlic, glucosamine, ginger, horseradish, phytoestrogen, royal jelly, propolis, and valerian.^{45,46} At times, topical use of herbal soap may cause urticaria.⁴⁷ However, if the history does not raise suspicion of one of these triggers based on timing of the onset of urticaria with the start of a food or herbal product, it is rare to have an occult food, herbal, or food additive trigger. Data suggest that such an occult cause of CU is found in no more than 2% to 3% of cases.⁴ For these reasons, having the patients complete a detailed and prolonged diary of foods or food additives, or undergo complex elimination diets are rarely helpful.

The physical examination should exclude possible physical triggers if suggested by the history. A primary care physician can easily evaluate for the presence of dermatographism by scratching the skin with the curved end of a tongue blade, and then observing for the development of a wheal-and-flare reaction in the subsequent 5 to 10 minutes. More sophisticated physical challenge tests, which include challenge with an ice cube, heat, pressure, light, exercise, and vibration, are sometimes performed in the specialty setting if needed to confirm physical urticaria.

Laboratory evaluation is usually not warranted in patients with acute urticaria. Routine laboratory evaluation/screening tests for CU is a controversial topic. Many specialists order only a few select screening labs for patients who have CU with no apparent etiology. Common screening lab tests that may be ordered include complete blood count with differential (to include evaluation of total eosinophil count) and erythrocyte sedimentation rate. Less commonly, some specialists will routinely perform a basic metabolic panel and liver enzymes on all patients with CU. Some experts advocate measurements of antithyroid antibodies (antimicrosomal and antithyroglobulin antibodies). Thyroid studies can be considered, particularly in women, or in patients with a family history of thyroid disease

or other autoimmune diseases.⁴ Evaluation of the complement system should be considered in patients with prominent angioedema and in patients with urticarial lesions lasting > 24 hours. Most experts agree that further testing should be done only based on specific positive findings from the history and physical examination. If any specific disorder is suspected, a targeted laboratory evaluation is warranted.

Allergists in specialty clinics may order allergy skin tests if there is suspicion of food allergy, stinging insect hypersensitivity, or severe allergy to pollen, cats, or latex as a cause of urticaria. This may come up in the evaluation of acute urticaria, but rarely is a concern with CU unless the history is suspicious. Skin testing can be done to help establish hypersensitivity to a limited number of antibiotics as well. Patients with cold urticaria warrant evaluation for cold agglutinins and cryoproteins, since they are found in 5% of cases. The presence of a cryoglobulin suggests an underlying cause such as chronic hepatitis (B or C) or lymphoreticular malignancy. Assays for serum histamine-releasing factors, and evaluation for specific autoantibodies (anti-IgE receptor and anti-IgE) are done by some research centers,^{34–36} but their utility in clinical practice is without a substantial evidence base. Skin biopsy should be considered if there are any atypical features that might raise the suspicion of vasculitis, such as non-blanching lesions which may last for > 48 hours and may leave residual marks, predominance of pain in the lesions (with or without burning) rather than pruritus, associated petechiae or purpura, and presence of systemic symptoms such as fever, arthralgia, or arthritis.¹⁰ In contrast, however, is usually not clinically helpful with routine urticaria without those features.

The diagnostic work-up for CU is summarized in Table 2. An algorithm for diagnosis and management of acute and CU in the primary care setting is presented in Figure 1.

Treatment

The treatment regimen for urticaria needs to be individualized as the severity and clinical pattern can vary considerably. As with other allergic conditions, if a specific trigger of urticaria can be identified (eg, physical stimuli, specific foods, medications, and topical sensitizers), optimal treatment would involve the avoidance of that specific trigger. If urticaria is ongoing, food supplements and drugs that are nonessential should be discontinued. Patients can keep a food diary to identify suspect foods, which can then be eliminated. As explained earlier, some cases of urticaria may be caused exclusively by nonallergic triggers, and in other cases, urticaria may be chronic but nonallergic triggers will lead to exacerbations.

Nonallergic triggers include aspirin, other NSAIDs,^{48,49} opiates, and alcohol. The patient must be educated that such agents may produce a temporary exacerbation. Psychosocial stress plays a part in many patients by exacerbating urticaria, although the mechanism for this is unclear.⁵⁰

Acute Urticaria

Acute urticaria is usually self-limited. In general, the main goal of treating patients with acute urticaria is supportive, aiming to suppress clinical manifestations. The treatment is therefore based on the extent, intensity, and duration of the symptoms and should be adapted based on response and course of the urticaria. The most commonly used medications are second-generation H₁-receptor antagonists (antihistamines) or glucocorticoids, alone or in combination when necessary. H₁-receptor antagonists are widely considered the first-line agents for acute urticaria. Second-generation H₁-receptor antagonists are generally preferred over first-generation H₁-receptor antagonists, as discussed further in the next section, but first-generation agents can be added in refractory cases. The hives are often treated symptomatically until they resolve spontaneously. Patients with life-threatening angioedema or anaphylaxis should always have access to epinephrine and be instructed to use it if needed.

Chronic Urticaria

As in acute urticaria, H₁-receptor antagonists are considered the first-line treatment of CU. While the older first-generation H₁ antagonists (Table 3) are effective in reducing the symptoms and number of lesions of urticaria, they may lead to side effects such as sedation, cognitive impairment, dry mouth, and urinary retention. Because of these side effects, chronic or around-the-clock use may not be desirable. The newer, second-generation H₁ antagonists (Table 4) are generally less sedating. Use of some of these drugs (eg, loratadine, fexofenadine, desloratadine) does not result in increased rate of sedation (compared with placebo) at the recommended doses and are thus considered to be nonsedating. Some of the second-generation agents (eg, cetirizine, levocetirizine) can produce sedation in a minority of patients.^{51–53} Although not to the same degree as seen with first-generation agents,^{51,52} these drugs have been labeled by some clinicians as minimally sedating. Second-generation agents are often used for chronic or around-the-clock treatment, while the first-generation agents are reserved for severe cases or acute exacerbations. Some clinicians recommend the use of a second-generation agent during the day, with a dose of a first-generation agent at night. Since patients with clinically severe urticaria often

Table 2. Diagnostic Work-Up for Urticaria**History and Physical Examination**

- Onset (eg, timing of symptoms with change in living conditions or exposures)
- Frequency, duration, severity, and localization of wheals and itching
- Dependence of symptoms on the time of day, day of the week, season, menstrual cycle, etc.
- Known precipitating factors of urticaria (physical stimuli, exertion, stress, food, medications)
- Occupation and leisure activities
- Associated angioedema, systemic manifestations (headache, joint pain, gastrointestinal symptoms, etc.)
- Known allergies, intolerances, infections, systemic illnesses, or other possible causes
- Family history of urticaria and atopy
- Degree of impairment of quality of life
- Response to prior treatment
- Detailed physical examination (with special attention to dermatographism)

Laboratory Evaluation (Chronic Urticaria)▪ **Routine evaluation**

- Complete blood count with differential
- Sedimentation rate
- Some clinicians routinely perform chemistry and hepatic panels

▪ **Additional routine evaluation by some specialty centers**

- Thyroid-stimulating hormone, antimicrosomal antibodies, and antithyroglobulin antibodies
- Functional autoantibody assay

▪ **Additional tests, likely to be helpful only if a specific diagnosis or entity is raised by the history, physical examination, and/or initial screening laboratory work-up**

- Complement system: eg, C3, C4, and CH₅₀
- Stool analysis for ova and parasites
- *Helicobacter pylori* work-up (limited evidence)
- Hepatitis B and C work-up
- Sinus radiography (if symptomatic)
- Antinuclear antibody
- Rheumatoid factor
- Cryoglobulin levels
- Other imaging studies
- Skin tests
- Physical challenge tests
- Skin biopsy
- Urinalysis

do not respond to these medications when they are given in the approved doses, some clinicians have recommended giving them in up to twice the Food and Drug Administration (FDA)-approved dose, although clinical evidence is limited for this practice.

Doxepin, a tricyclic antidepressant, has potent H₁ and H₂ antihistaminic activity and can be used as well (although is not FDA-approved for urticaria).^{54,55} Sedation, which is the main disadvantage of this medication, can often be managed by starting at the lowest effective dose (Table 3)

every night and then slowly increasing the dose if needed and as tolerated. Additional problems with doxepin include dry mouth, urinary retention, and increased appetite.⁵⁵ While hydroxyzine and ciproheptadine have traditionally been used as the agents of choice for cold-induced urticaria, there is little experimental evidence to support the notion that specific H₁ antagonists may be more efficacious for certain types of urticaria.

Given that 15% of the histamine receptors of the skin are of the H₂-type, the addition of an H₂ antagonist (examples listed in

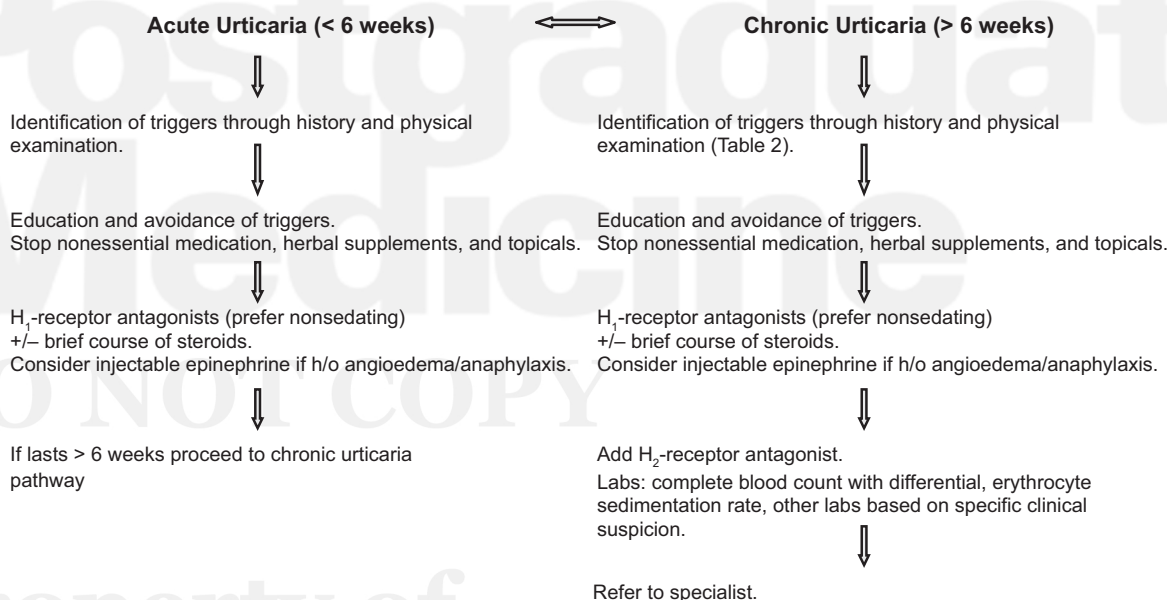
Figure 1. Algorithm for the evaluation and management of urticaria in the primary care setting.

Table 5) to an H₁ antagonist in treating CU can be more effective than an H₁ antagonist alone, as confirmed in some small trials,⁵⁶⁻⁵⁸ although data have been conflicting in others.⁵⁹

Corticosteroids

Systemic corticosteroids are usually considered in acute or CU that has not responded to H₁ antagonists. Although there are no large-scale, double-blind, placebo-controlled trials of the long-term use of corticosteroids in CU,⁶⁰ clinical experience suggests

that these drugs are highly efficacious in most patients if an adequate dose is used. Standard dosages (0.5–1.0 mg/kg/d) can be used for initial dosing, with subsequent tapering to maintain the desired response. A short course of corticosteroids (from a few days to up to 6 weeks) in acute urticaria is often helpful in achieving adequate symptom control.⁶⁰ Since corticosteroid doses that are high enough to be effective can have serious side effects if continued over the long term,

Table 3. Commonly Used First-Generation H₁ Antagonists

Drug	Recommended Adult Dosage	Recommended Pediatric Dosage	Comments
Chlorpheniramine (Chlor-Trimeton®)	4 mg PO every 4–6 h 10–20 mg per dose IV/IM/SC; not to exceed 40 mg/d	2–6 y: 1 mg PO every 4–6 h; not to exceed 4 mg/d. 6–12 y: 2 mg PO every 4–6 h; not to exceed 12 mg/d.	Pregnancy category B
Cyproheptadine (Periactin®)	2–4 mg PO 3 times daily	2–6 y: 2 mg 2 or 3 times daily. 7–14 y: 2–4 mg 2 or 3 times daily.	Historically has been considered a drug of choice for primary acquired cold urticaria
Diphenhydramine (Benadryl®)	25–50 mg every 4–6 h PO/IV/IM	5 mg/kg/d PO/IV/IM divided 3 or 4 times daily; not to exceed 300 mg/d	
Doxepin (Sinequan®)	10–150 mg/d PO at bedtime or divided 2 or 3 times daily	> 12 y: 10–50 mg/d PO at bedtime or divided 2 or 3 times daily and can increase gradually to 100 mg/d	Tricyclic antidepressant Begin with a low dose (10–25 mg at bedtime) first
Hydroxyzine (Atarax®, Vistaril®)	10–100 mg every 6–8 h PO/IM	0.6 mg/kg/dose PO every 6 h, 0.5–1 mg/kg/dose IM every 4–6 h	

Abbreviations: IM, intramuscularly; IV, intravenously; PO, orally; SC, subcutaneously.

Table 4. Commonly Used Second-Generation H₁ Antagonists

Drug	Recommended Adult Dosage	Recommended Pediatric Dosage	Comments
Cetirizine (Zyrtec®)	5–10 mg PO once per day	6–12 mo: 2.5 mg PO once per day. 12–23 mo: 2.5 mg PO once per day to 2 times daily. 2–5 y: 2.5–5 mg PO once per day or 2.5 mg PO 2 times daily. > 6 y: 5–10 mg PO once per day.	May cause sedation in approximately 10%–14% of patients. Pregnancy category B.
Desloratadine (Clarinet®)	5 mg PO once per day	Not established for children < 12 y	Rate of sedation similar to that with placebo. A metabolite of loratadine.
Fexofenadine (Allegra®)	60 mg PO 2 times daily	< 6 y: not established. 6–11 y: 30 mg PO 2 times daily.	Rate of sedation similar to that with placebo.
Loratadine (Claritin®)	10 mg PO once per day	2–5 y: 5 mg PO once per day. > 6 y: administer as in adults.	Rate of sedation similar to that with placebo. Pregnancy category B.
Levocetirizine (Xyzal®)	2.5–5 mg PO once per day	6–12 y: 2.5 mg PO once per day. > 12 y: as per adults.	Pregnancy category B.

Abbreviations: IM, intramuscularly; IV, intravenously; PO, orally; SC, subcutaneously.

these agents should be used only when absolutely needed in the treatment of CU.

Additional Pharmacotherapy Options

Additional pharmacotherapy options are used by specialists who treat patients with refractory urticaria (Table 6). The primary care physician will likely not be involved in the prescription of agents listed in Step 4 without specialist assistance. Most of these agents have little evidence in the form of clinical trials and are not FDA-approved for urticaria. Intravenous gammaglobulin (IVIG), plasmapheresis, and cyclosporine have been shown to be effective in urticaria in a limited number of studies.^{61–63} They can be a consideration in severe urticaria, particularly of the autoimmune type, that is unresponsive to medications. Colchicine and dapsone have also been reported to be useful for refractory urticaria and urticarial vasculitis.^{64,65} As discussed previously, the role of thyroxine in the treatment of CU is still uncertain.^{42,43} Since mast cells release a variety of mediators in addition to histamine, antileukotriene medications may be added;^{66,67} however, extensive clinical trials have not been performed,

so the usefulness of antileukotriene agents is still questionable. Early case reports and a clinical trial of omalizumab (monoclonal antibody to IgE) in CU appear promising, but considerable further study is needed.⁶⁸ Case reports suggest that hydroxychloroquine, nifedipine, sulfasalazine, azathioprine, and methotrexate may be useful in selected patients. Many of these medications are limited by their side effect profiles.

Conclusion

Urticaria is a common, debilitating condition seen by primary care physicians. Acute urticaria is usually due to a hypersensitivity reaction or part of a viral syndrome, while CU is generally idiopathic. Thirty percent to 50% of idiopathic cases may be autoimmune and/or related to mast cell/basophil abnormalities. Antihistamines remain the mainstay of pharmacotherapy for urticaria. In severe cases, referral to a specialist is warranted in order to minimize disease severity with more aggressive treatment. Although there are a number of treatment options for urticaria, further research is required to develop safe and more effective agents.

Table 5. Commonly Used H₂ Antagonists

Drug	Recommended Adult Dosage	Recommended Pediatric Dosage	Comments
Cimetidine (Tagamet®)	400 mg PO 2 times daily	Infants: 10–20 mg/kg/d divided every 6 h. Children: 10–20 mg/kg/d divided every 6 h.	Pregnancy category B
Ranitidine (Zantac®)	150 mg PO 2 times daily	1.5–2 mg/kg per dose PO 2 times daily	Pregnancy category B

Abbreviation: PO, orally.

Table 6. Proposed Algorithm for the Treatment of Chronic Urticaria**Begin at Step 1 and progress to higher steps only if needed. Treatment should be stepped down once control is achieved.**

Step 4	1. Chronic oral corticosteroids (titrated to lowest effective dose) 2. Cyclosporin A (for steroid sparing effects) 3. Consider other nonstandard therapies: colchicine, dapsone, sulfasalazine, hydroxychloroquine, intravenous gammaglobulin, plasmapheresis, interferon- α , methotrexate, cyclophosphamide, calcium-channel blockers, warfarin, ephedrine, terbutaline
Step 3	1. Consider increasing dose of H_1 -receptor antagonist 2. Consider multiple simultaneous H_1 -receptor antagonists 3. Doxepin (for additional antihistamine effect) 4. Antileukotriene 5. If evidence of thyroid autoimmunity, consider thyroxine
Step 2	H_2 -receptor antagonist in combination with H_1 -receptor antagonist
Step 1	H_1 -receptor antagonists (antihistamines)

Disclaimer

The drugs, doses, and treatments discussed are thought to be accurate by the authors as of the time of article submission. Any changes since that date are not reflected in this article.

Acknowledgments

No financial funding support was received for this article.

Conflict of Interest Statement

Javed Sheikh, MD discloses conflicts of interest with sanofi aventis and UCB. Umer Najib, MD discloses no conflicts of interest.

References

- O'Donnell BF, Lawlor F, Simpson J. The impact of chronic urticaria on the quality of life. *Br J Dermatol*. 1997;136(2):197–201.
- Kaplan AP. Urticaria angioedema. In: *Allergy: Principles and Practice*. Adkinson NF Jr, Busse WW, et al; eds. Philadelphia, PA: Mosby; 2003;1537–1558.
- Champion RH, Roberts SO, Carpenter RG, Roger JH. Urticaria and angioedema. A review of 554 patients. *Br J Dermatol*. 1969;81(8):588–597.
- Sheikh J. Urticaria. <http://emedicine.medscape.com/article/137362-overview.com>. Accessed December 18, 2008.
- Kaplan AP. Urticaria and angioedema. In: *Allergy: Principles and Practices*. Middleton E, Reed CE, Ellis EF, eds. St. Louis, MO: Mosby-Year Book; 1998;1104–1118.
- Charlesworth EN. Urticaria and angioedema: a clinical spectrum. *Ann Allergy Asthma Immunol*. 1996;76(6):484–495.
- Greaves M. Chronic urticaria. *J Allergy Clin Immunol*. 2000;105(4):664–672.
- Wong RC, Fairley JA, Ellis CN. Dermographism: a review. *J Am Acad Dermatol*. 1984;11 (4 pt 1):643–652.
- Hirschmann JV, Lawlor F, English JS, Louback JB, Winkelmann RK, Greaves MW. Cholinergic urticaria. A clinical and histologic study. *Arch Dermatol*. 1987;123(4):462–467.
- Davis MD, Brewer JD. Urticarial vasculitis and hypocomplementemic urticarial vasculitis syndrome. *Immunol Allergy Clin North Am*. 2004;24(2):183–213.
- Brodell LA, Beck LA, Saini SS. Pathophysiology of chronic urticaria. *Ann Allergy Asthma Immunol*. 2008;100(4):291–297.
- Hide M, Francis DM, Grattan CE, Hakimi J, Kochan JP, Greaves MW. Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. *N Engl J Med*. 1993;328(22):1599–1604.
- Jacques P, Lavoie A, Bédard PM, Brunet C, Hébert J. Chronic idiopathic urticaria: profiles of skin mast cell histamine release during active disease and remission. *J Allergy Clin Immunol*. 1992;89(6):1139–1143.
- Sheikh J. Autoantibodies to the high-affinity IgE receptor in chronic urticaria: how important are they? *Curr Opin Allergy Clin Immunol*. 2005;5(5):403–407.
- Goodman DL, McDonnell JT, Nelson HS, Vaughan TR, Weber RW. Chronic urticaria exacerbated by the anti-oxidant food preservatives, butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT). *J Allergy Clin Immunol*. 1990;86(4 pt 1):570–575.
- Zembowicz A, Mastalerz L, Setkowicz M, et al. Safety of cyclooxygenase 2 inhibitors and increased leukotriene synthesis in chronic idiopathic urticaria with sensitivity to nonsteroidal anti-inflammatory drugs. *Arch Dermatol*. 2003;139(12):1577–1582.
- Kaplan AP. Chronic urticaria: pathogenesis and treatment. *J Allergy Clin Immunol*. 2004;114(3):465–474.
- Leznoff A, Josse RG, Denburg J, Dolovich J. Association of chronic urticaria and angioedema with thyroid autoimmunity. *Arch Dermatol*. 1983;119(8):636–640.
- Zweiman B, Valenzano M, Atkins PC, Tanus T, Getsy JA. Characteristics of histamine-releasing activity in the sera of patients with chronic idiopathic urticaria. *J Allergy Clin Immunol*. 1996;98(1):89–98.
- Sabroe RA, Poon E, Orchard GE, et al. Cutaneous inflammatory cell infiltrate in chronic idiopathic urticaria: comparison of patients with and without anti-Fc ϵ RI or anti-IgE autoantibodies. *J Allergy Clin Immunol*. 1999;103(3 pt 1):484–493.
- Ying S, Kikuchi Y, Meng Q, Kay AB, Kaplan AP. TH1/TH2 cytokines and inflammatory cells in skin biopsy specimens from patients with chronic idiopathic urticaria: comparison with the allergen-induced late-phase cutaneous reaction. *J Allergy Clin Immunol*. 2002;109(4):694–700.
- Sabroe RA, Grattan CE, Francis DM, Barr RM, Kobza Black A, Greaves MW. The autologous serum skin test: a screening test for autoantibodies in chronic idiopathic urticaria. *Br J Dermatol*. 1999;140(3): 446–452.
- Grattan CE, Wallington TB, Warin RP, Kennedy CT, Bradfield JW. A serological mediator in chronic idiopathic urticaria—a clinical, immunological and histological evaluation. *Br J Dermatol*. 1986;114(5):583–590.
- Nguyen L, Sheikh J, Lin CK, et al. Serial basophil histamine release correlates with the clinical course in a patient with autoimmune urticaria. *J Allergy Clin Immunol*. 2000;104:S40–S41.

25. Grattan CE, Francis DM, Hide M, Greaves MW. Detection of circulating histamine releasing autoantibodies with functional properties of anti-IgE in chronic urticaria. *Clin Exp Allergy*. 1991;21(6):695–704.
26. Sabroe RA, Francis DM, Barr RM, Black AK, Greaves MW. Anti-Fc(epsilon)RI auto antibodies and basophil histamine releasability in chronic idiopathic urticaria. *J Allergy Clin Immunol*. 1998;102(4 pt 1): 651–658.
27. Ferrer M, Kinét JP, Kaplan AP. Comparative studies of functional and binding assays for IgG anti-Fc(epsilon)RIalpha (alpha-subunit) in chronic urticaria. *J Allergy Clin Immunol*. 1998;101(5):672–676.
28. Tong LJ, Balakrishnan G, Kochan JP, Kinét JP, Kaplan AP. Assessment of autoimmunity in patients with chronic urticaria. *J Allergy Clin Immunol*. 1997;99(4):461–465.
29. Asero R, Lorini M, Chong SU, Zuberbier T, Tedeschi A. Assessment of histamine releasing activity of sera from patients with chronic urticaria showing positive autologous skin test on human basophils and mast cells. *Clin Exp Allergy*. 2004;34(7):1111–1114.
30. Mari A. Allergy-like asthma and rhinitis: a cross-sectional survey of a respiratory cohort and a diagnostic approach using the autologous serum skin test. *Int Arch Allergy Immunol*. 2004;133(1):29–39.
31. Guttman-Yassky E, Bergman R, et al. The autologous serum skin test in a cohort of chronic idiopathic urticaria patients compared to respiratory allergy patients and healthy individuals. *J Eur Acad Dermatol Venereol*. 2007;21(1):35–39.
32. Vasagar K, Vonakis BM, Gober L, Viksman A, Gibbons SP Jr, Saini SS. Evidence of in vivo basophil activation in chronic idiopathic urticaria. *Clin Exp Allergy*. 2006;36(6):770–776.
33. Soundararajan S, Kikuchi Y, Joseph K, Kaplan AP. Functional assessment of pathogenic IgG subclasses in chronic autoimmune urticaria. *J Allergy Clin Immunol*. 2005;115(4):815–821.
34. Kikuchi Y, Kaplan AP. Mechanisms of autoimmune activation of basophils in chronic urticaria. *J Allergy Clin Immunol*. 2001;107(6): 1056–1062.
35. Yasnowsky KM, Dreskin SC, Efaw B, et al. Chronic urticaria sera increase basophil CD203c expression. *J Allergy Clin Immunol*. 2006;117(6):1430–1434.
36. Sheikh J. Effect of omalizumab on patients with chronic urticaria: issues with the determination of autoimmune urticaria. *Ann Allergy Asthma Immunol*. 2008;100(1):88.
37. Saini S, Vasagar K, Huang F, Gibbons S, Vonakis BM. Signaling defects in basophils in chronic urticaria. *J Allergy Clin Immunol*. 2003;111:S178.
38. Grattan CE, Walpole D, Francis DM, et al. Flow cytometric analysis of basophil numbers in chronic urticaria: basophilia is related to serum histamine releasing activity. *Clin Exp Allergy*. 1997;27(12):1417–1424.
39. Wanderer AA. Cold urticaria syndromes: historical background, diagnostic classification, clinical and laboratory characteristics, pathogenesis, and management. *J Allergy Clin Immunol*. 1990;85(6): 965–981.
40. Amar SM, Dreskin SC. Urticaria. *Prim Care*. 2008;35(1):141–157.
41. Irinyi B, Széles G, Gyimesi E, et al. Clinical and laboratory examinations in the subgroups of chronic urticaria. *Int Arch Allergy Immunol*. 2007;144(3):217–225.
42. Rumbly JS, Katz JL, Schocket AL. Resolution of chronic urticaria in patients with thyroid autoimmunity. *J Allergy Clin Immunol*. 1995; 96(6 pt 1):901–905.
43. Leznoff A, Sussman GL. Syndrome of idiopathic chronic urticaria and angioedema with thyroid autoimmunity: a study of 90 patients. *J Allergy Clin Immunol*. 1989;84(1):66–71.
44. Joint Task Force on Practice Parameters. The diagnosis and management of urticaria: a practice parameter part I: acute urticaria/angioedema part II: chronic urticaria/angioedema. *Ann Allergy Asthma Immunol*. 2000;85(6 pt 2):521–544.
45. Mullins RJ, Heddle R. Adverse reactions associated with echinacea: the Australian experience. *Ann Allergy Asthma Immunol*. 2002;88(1):42–51.
46. Dibbern DA Jr. Urticaria: selected highlights and recent advances. *Med Clin North Am*. 2006;90(1):187–209.
47. Knight TE, Hausen BM. Melaleuca oil (tea tree oil) dermatitis. *J Am Acad Dermatol*. 1994;30(3):423–427.
48. Wong JT, Nagy CS, Krinzman SJ, et al. Rapid oral challenge-desensitization for patients with aspirin-related urticaria-angioedema. *J Allergy Clin Immunol*. 2000;105(5):997–1001.
49. Grattan CE. Aspirin sensitivity and urticaria. *Clin Exp Dermatol*. 2003;28(2):123–127.
50. Shertzer CL, Lookingbill DP. Effects of relaxation therapy and hypnotizability in chronic urticaria. *Arch Dermatol*. 1987;123(7):913–916.
51. Kalivas J, Breneman D, Tharp M, Bruce S, Bigby M. Urticaria: clinical efficacy of cetirizine in comparison with hydroxyzine and placebo. *J Allergy Clin Immunol*. 1990;86(6 pt 2):1014–1018.
52. Breneman DL. Cetirizine versus hydroxyzine and placebo in chronic idiopathic urticaria. *Ann Pharmacother*. 1996;30(10):1075–1079.
53. Breneman D, Bronsky EA, Bruce S, et al. Cetirizine and astemizole therapy for chronic idiopathic urticaria: a double-blind, placebo-controlled, comparative trial. *J Am Acad Dermatol*. 1995;33(2 pt 1): 192–198.
54. Harto A, Sendagorta E, Ledo A. Doxepin in the treatment of chronic urticaria. *Dermatologica*. 1985;170(2):90–93.
55. Goldsobel AB, Rohr AS, Siegel SC, et al. Efficacy of doxepin in the treatment of chronic idiopathic urticaria. *J Allergy Clin Immunol*. 1986;78(5 pt 1):867–873.
56. Monroe EW, Cohen SH, Kalbfleisch J, Schulz CI. Combined H₁ and H₂ antihistamine therapy in chronic urticaria. *Arch Dermatol*. 1981;117:404–407.
57. Harvey RP, Wegs J, Schocket AL. A controlled trial of therapy in chronic urticaria. *J Allergy Clin Immunol*. 1981;68(4):262–266.
58. Bleehen SS, Thomas SE, Greaves MW, et al. Cimetidine and chlorpheniramine in the treatment of chronic idiopathic urticaria: a multi-center randomized double-blind study. *Br J Dermatol*. 1987;117(1):81–88.
59. Cook LJ, Shuster S. Lack of effect of cimetidine in chronic-idiopathic urticaria. *Acta Derm Venereol*. 1983;63(3):265–267.
60. Kaplan AP. Clinical practice: Chronic urticaria and angioedema. *N Engl J Med*. 2002;346(3):175–179.
61. O'Donnell BF, Barr RM, Black AK, et al. Intravenous immunoglobulin in autoimmune chronic urticaria. *Br J Dermatol*. 1998;138(1):101–106.
62. Grattan CE, Francis DM, Slater NG, Barlow RJ, Greaves MW. Plasmapheresis for severe unremitting chronic urticaria. *Lancet*. 1992;339(8801):1078–1080.
63. Toubi E, Blant A, Kessel A, Golan TD. Low-dose cyclosporin in the treatment of severe chronic idiopathic urticaria. *Allergy*. 1997; 52(3):312–316.
64. Werni R, Schwarz T, Gschnait F. Colchicine treatment of urticarial vasculitis. *Dermatologica*. 1986;172(1):36–40.
65. Ruzicka T, Goerz G. Systemic lupus erythematosus and vasculitic urticaria. Effect of dapsone and complement levels. *Dermatologica*. 1981;162(3):203–205.
66. Netti E, Dambra P, D'Oronzio L, Loria MP, Ferrannini A, Tursi A. Comparison of montelukast and fexofenadine for chronic idiopathic urticaria. *Arch Dermatol*. 2001;137(1):99–100.
67. Asero R, Tedeschi A, Lorini M. Leukotriene receptor antagonist in chronic urticaria. *Allergy*. 2001;56(5):456–457.
68. Gober LM, Sterba PM, Eckman JA, Saini SS. Effect of anti-IgE (omalizumab) in chronic idiopathic urticaria (CIU) patients. *J Allergy Clin Immunol*. 2008;121. Abstract 566.