

Clinical Evaluation and Treatment of Chronic Urticaria

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Abstract: Chronic urticaria is a common disease characterized by recurrent pruritic wheals with surrounding erythema for > 6 weeks. It is associated with a significant health care burden and affects patient quality of life. The etiology of chronic urticaria is often difficult to elucidate; however, known etiologies include autoimmune urticaria, physical urticarias (eg, cold, cholinergic, and delayed pressure urticaria), and idiopathic urticaria. The etiology is unknown in many patients, leading to a diagnosis of chronic idiopathic urticaria. The diagnosis of chronic idiopathic urticaria can be challenging for the primary care physician because of the disease's chronic symptoms. Diagnosis requires a detailed patient history and comprehensive physical examination, with additional testing tailored to the patient's history. Effective treatments include antihistamines, leukotriene receptor antagonists in combination with antihistamines, and oral immunomodulatory drugs, including corticosteroids, cyclosporine, dapsone, hydroxychloroquine, and sulfasalazine. Newer experimental therapies include intravenous immunoglobulin and omalizumab. This article reviews the pathophysiology, diagnosis, and treatment of chronic urticaria.

Keywords: etiology; autoimmune diseases; urticaria; antihistamine; nonsedating histamine H₁ antagonists; hives; angioedema

Introduction

Urticaria is estimated to affect 15% to 30% of the US population, with approximately 0.1% to 1% of these patients having chronic urticaria (CU).^{1,2} Chronic urticaria is characterized by individual pruritic wheals lasting < 24 hours and recurring for ≥ 6 weeks.¹ Chronic urticaria is further subdivided into physical urticarias, autoimmune urticaria, and chronic idiopathic urticaria (CIU) when no cause can be identified.^{1,2} An estimated 50% to 70% of CU cases are idiopathic.¹

Chronic urticaria is associated with a significant health care burden. Mean health care costs were estimated at \$2047 annually per patient in a burden of illness study comprising 50 CIU patients.³ These numbers are likely underestimated because patients on immunosuppressants were excluded.^{3,4} Medications account for > 60% of this cost, indirect costs (eg, missed school and work) account for approximately 16%, and the balance comprises laboratory costs, outpatient visit costs, and emergency department/hospital visit costs.³ As a result of the high cost of medications to treat CIU, low-income and uninsured or underinsured patients may be at risk for poorly controlled disease.³ Uncontrolled CU has been shown to have a significant negative impact on patient quality of life, similar to that of ischemic heart disease.⁵

Primary care physicians frequently encounter patients with urticaria, and the diagnosis can be challenging. During early presentation of the disease, clinical patterns are often not yet apparent. Furthermore, objective screening tools such as questionnaires are not well established. This review focuses on the pathophysiology, diagnosis, and treatment of CU.

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Case Study

A 30-year-old woman was referred to an allergy and immunology specialist due to a 2-month history of recurrent generalized hives and facial angioedema. The initial presentation of symptoms occurred a few hours after eating Chinese food, which included rice, chicken, and shrimp. Although she initially attributed her symptoms to MSG, the symptoms continued despite the elimination of MSG from her diet. Her only medication at the time of initial onset was an oral contraceptive, which was subsequently discontinued. Her hives were very pruritic and only temporarily improved with diphenhydramine (Benadryl®) treatment. She presented to a local emergency room for hives and swelling of her lips, and was treated with intravenous (IV) methylprednisolone (Medrol®) and diphenhydramine. She was sent home with a methylprednisolone dose pack. Although her symptoms resolved while on methylprednisolone, her hives returned a few days after completion of the methylprednisolone dose pack. The initial evaluation by her primary care physician included a radioallergosorbent test for food allergies, which was negative for all tested foods except for class II positivity for chicken and wheat. She subsequently avoided these foods with no improvement in her symptoms, and currently has generalized erythematous, raised wheals with excoriations, including lesions on her face and palms. The lesions are nontender but blanch with pressure and are extremely pruritic. She has no periorbital, tongue, or lip swelling. She is frustrated by these symptoms and

is concerned that her hives may either be induced by stress or due to a serious underlying disorder.

Overview of Urticaria

Urticaria is characterized by pruritic, cutaneous, polymorphic wheals (Figure 1).⁶ These lesions may be round or irregularly shaped and range in size from a few millimeters to several centimeters.⁷ Urticarial lesions may appear anywhere on the body, and individual lesions typically resolve spontaneously within 24 hours.⁶ The intensity of pruritus varies but can be debilitating enough to require emergency room care.⁷ Approximately 40% to 50% of patients with CU also experience angioedema typically lasting < 24 hours, but large swellings tend to last longer.^{6,7}

Classification of urticaria is primarily based on the duration of recurrent episodes and disease etiology (Table 1).⁷ Most patients experience urticarial lesions daily or several days per week during episodes.⁸ In acute urticaria, episodes last < 6 weeks and are most commonly attributable to food, infection, or medication, whereas in CU, episodes last > 6 weeks and are most commonly idiopathic.⁷

Etiologies of CU

Although a large percentage of patients with CU have no known cause for their disease, several subtypes of CU based on autoimmune or pathogenic components have been identified.

Figure 1. A typical case of chronic urticaria characterized by pruritic cutaneous wheals with pale, raised centers.



Table 1. Classification of Urticaria⁷**Chronic Urticaria/Angioedema**

Autoimmune

Idiopathic

Physical

Cholinergic

Delayed pressure

Solar

Cold

Vibratory

Aquagenic

Presumed immune complex-induced

Thyroid disease

Urticarial vasculitis

Malignancy-associated

Collagen vascular disease-associated

Adapted with permission from *Prim Care*.⁷**Autoimmune Urticaria**

Autoimmune urticaria represents approximately 40% of all CU cases.⁹ In 25% to 60% of patients with chronic autoimmune urticaria, the disease is characterized by the presence of autoantibodies (IgG) to the alpha subunit of the high-affinity IgE receptor (FcεRI), which induces the release of histamine through direct actions on the alpha subunit of the receptor.^{10,11} Patients with autoimmune urticaria have more severe CU judging from wheal counts, extent of distribution of wheals, itch scores, and frequency of systemic symptoms. Additionally, patients with autoimmune urticaria were more likely to require second-line treatment.¹²

An autologous serum skin test (ASST) is often used to differentiate autoimmune urticaria from other types of CU.¹³ By intradermally injecting the patient's own serum into the forearm, this test identifies functional autoantibodies against FcεRIα.^{12–14} The ASST causes a wheal-and-flare reaction in up to 60% of patients with CIU, suggesting an induction of histamine-releasing activity from basophils.¹³ Although used infrequently, the ASST can be used to identify autoimmune urticaria; however, it has low sensitivity, specificity, and predictive values in CU. Another test that may be used is the in vitro histamine release assay. In this assay, basophils or mast cells in normal donors are stimulated with sera from a CU patient, and the released histamine is measured by fluorometric methods or immunoassays.¹⁴ This test is available commercially; its utility in the management of CU at this time is primarily to help the patient accept that CU is not due to exogenous triggers (eg, allergens).

Physical Urticarias**Cold Urticaria**

Cold urticaria, representing 5% to 30% of physical urticarias, is often idiopathic.⁸ Lesions appear within minutes on areas of the body exposed to cold.⁸ Systemic reactions can occur following total-body cooling, such as outdoor swimming and ingestion of cold drinks, and patients should be made aware of these risks.⁸ Diagnosis can be made by placing an ice cube on the forearm of the patient; an urticarial lesion will develop on rewarming.⁸ In addition, laboratory studies, including cryoglobulins and cold agglutinins, can be helpful in making a diagnosis.

Cholinergic Urticaria

Cholinergic urticaria occurs in response to stimuli that raise the core temperature of the body, including exercise, warm weather, spicy/hot food or drinks, or stress.¹⁵ Cholinergic urticaria represents approximately 30% of physical urticarias and 3% to 5% of CUs.⁸ The condition occurs more often in adolescents and is characterized by smaller wheals (1–3 mm) that are sometimes macular.^{6,8} Other cholinergic-mediated symptoms may occur, such as lacrimation, salivation, diarrhea, and wheezing.^{6,8} Diagnosis is made via an exercise challenge test or immersion in hot water (44°C).⁸

Delayed Pressure Urticaria

Delayed pressure urticaria represents approximately 2% of CU cases, although anywhere from 2% to 40% of patients with CIU are reported to also have delayed pressure urticaria.^{6,8} Delayed pressure urticaria is characterized by development of cutaneous erythema and edema, often with subcutaneous swelling, after application of pressure to the skin.⁸ Itchy and painful urticarial lesions occur as early as 30 minutes to 12 hours after a pressure stimulus (eg, bra or shoulder straps, leaning against furniture, seat belts, tight clothing).^{6,15} Swelling may occur in the hands and feet as a result of carrying bags, using tools, walking, jogging, or wearing tight shoes.⁸ Delayed pressure urticaria frequently occurs in association with other physical urticarias: dermatographism, CU, and angioedema. The appearance of a palpable lesion at least 30 minutes after any form of pressure challenge is a positive response. Delayed pressure urticaria is often resistant to antihistamines and many anti-inflammatory medications; oral steroids may be helpful but side effects limit their long-term use.¹⁶

Rare Forms of Urticaria

Solar urticaria is a rapid wheal response, usually within 10 minutes of exposure to ultraviolet or visible light. The wheals are itchy but are limited to exposed areas of the body. Wheals typically resolve in < 2 hours.¹⁷ Aquagenic urticaria occurs in response to skin contact with water, regardless of temperature.¹⁷ Response is rapid, with wheals appearing on the upper trunk, face, and neck within minutes of exposure. Symptoms typically resolve within 2 hours.¹⁷ Vibratory angioedema is characterized by erythematous swelling in response to a vibratory stimulus.¹⁷ The swellings occur within 10 minutes of stimulus exposure and resolve within 2 hours.

Urticarial Vasculitis

Urticarial vasculitis (UV) may present as episodes of urticaria with a histologic diagnosis of vasculitis¹⁸ and should be considered in differential diagnosis when evaluating patients with CU. The disease is predominant in females (60%–80% of cases), with a peak incidence in the fourth decade of life.^{18,19} Urticarial vasculitis lesions have a burning, painful, or tender sensation, in contrast to the largely pruritic urticaria in CU; however, pruritic lesions have also been reported in UV. Lesions are more prominent on the lower extremities than on the trunk or arms and typically last from 24 to 72 hours.^{18,20} Lesions may resolve with hyperpigmentation or purpura, and angioedema may occur.²⁰ Many patients with UV have systemic involvement, including arthralgia/arthritis, obstructive lung disease, fever, uveitis, renal disease, or gastrointestinal or neurologic problems.^{18–20} Diagnosis of UV often necessitates a skin biopsy showing leukocytoclastic vasculitis on histopathology and low complement levels on serology.²⁰ Urticarial vasculitis is typically idiopathic but may be associated less commonly with connective tissue diseases (eg, systemic lupus erythematosus, Sjögren's syndrome), serum sickness, and, rarely, with infections or medications.^{18,20}

Pathophysiology of CU

While the pathogenesis of CU, regardless of the etiology, has not been fully elucidated, mast cells are the primary effector cells.²¹ These cells are widely distributed in the skin, intestinal mucosa, alveolar wall, and nasal mucosa. The inflammatory process begins with mast cell degranulation and the release of inflammatory mediators.²² Histamine plays a central role along with proinflammatory cytokines, chemokines, and chemokine receptors.^{9,21} The cellular infiltrate from wheals of patients with CU contains a milieu of inflammatory mediators including interferon gamma (IFN- γ), interleukin-4 (IL-4), IL-5, IL-8, eotaxin-specific receptor CCR3, Mig receptor

CXCR3, intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), endothelial-leukocyte adhesion molecule (ELAM), and CD4 lymphocytes.²¹ These inflammatory mediators are also present in unaffected skin, suggesting an overall activation of the immune system in patients with CU.²¹

Mast cell degranulation may occur either by activation via high-affinity IgG autoantibodies to Fc ϵ RI α , or less commonly, by IgG anti-IgE autoantibodies.^{9,23} Both anti-Fc ϵ RI and anti-IgE antibodies are able to cause direct cross-linking of adjacent Fc ϵ RI receptors, inducing mast cell and basophil activation and release of histamine and other proinflammatory mediators.²⁴ In some patients with CU, reduction of IgE levels has become a target for drug therapy.⁹

Basophils are also implicated in CU, but their role is still unclear.^{23,25} Basopenia has been correlated with disease activity; basophils may be recruited to lesional sites in patients with CU or may be reduced by degranulation.²⁵ Among patients with CU, significant enhancement of basophil function on disease remission has been seen as independent of the presence of autoantibodies.²³

The coagulation cascade has been implicated in CU via thrombin generation.²⁴ Thrombin functions as an inflammatory mediator by increasing vascular endothelium permeability and inducing mast cell degranulation, with subsequent release of histamine.^{14,26} Its effects on vascular permeability are abolished if mast cell granules are depleted or inhibited by antihistamines.²⁶ Thrombin produces direct effects on vascular endothelium as well as indirect effects via the release of inflammatory mediators.²⁷ In a recent study, patients with CU had significantly elevated mean plasma levels of prothrombin fragment and factor VIIa compared with healthy controls; these increased levels correlated with a more severe disease state.²⁴ Factor XIIa levels, however, were similar in both groups.²⁴

Evaluation

The diagnosis of urticaria can be difficult because of the intermittent and varied nature of the symptoms. For example, CU may be associated with classic or fixed atypical urticarial lesions and can be caused by a number of systemic conditions, such as infections, connective tissue disorders, autoimmune diseases, endocrine disorders, and, rarely, cancer.^{28,29} As a number of conditions are associated with the erythematous, edematous, pruritic plaques characteristic of CU, other disease processes must be ruled out to ensure an accurate diagnosis. The differential diagnosis of CU includes conditions with classic urticarial lesions, such as cryopyrin-mediated autoinflammatory disorders and

Schnitzler syndrome, and conditions with fixed atypical urticarial lesions, such as cutaneous lupus erythematosus, Sweet syndrome, and bullous pemphigoid.²⁹ The difficulty of diagnosis necessitates that clinicians obtain a complete history and conduct a comprehensive physical examination. The importance of a history-based diagnosis was demonstrated in a prospective study that compared the effectiveness of a comprehensive history plus either limited or extensive laboratory testing.³⁰ Symptom history should include information about the frequency, duration, patterns of recurrence, site of occurrence, and precipitating and relieving factors.³¹ The history may reveal an immunologic cause such as foods (albeit a very rare cause of CU) or medications. Nonimmunologic causes include physical urticarias caused by trauma, pressure, exercise, extreme temperatures, water, or direct degranulation of mast cells.²⁹ A detailed family history is important when considering connective tissue disorders or complement deficiencies. A complete physical examination is required to characterize lesions (if present) and rule out other causes of urticaria.

Although diagnosis is historically based on history and physical examination alone, additional tests are available if necessary (eg, histamine release assay, skin-prick testing, erythrocyte sedimentation rates, thyroid function and antibody testing, skin biopsy, measurement of cryoglobulins, complement levels). The physician should employ a stepwise approach to testing based upon the patient's history; an algorithm similar to that of the British Society for Allergy and Clinical Immunology (BSACI) can be utilized as a guide to test selection.^{28,31} In most cases, the etiology remains unknown (ie, CIU) despite a thorough history, physical examination, and additional testing.^{29,32}

Therapy Antihistamines

Antihistamines (H_1 histamine receptor antagonists) are first-line therapy for urticaria (Figure 2) due to the presence of histamine in the skin of most CU patients.^{31,33} Both first- and second-generation H_1 receptor antihistamines are effective at relieving most CU symptoms, such as itching, redness, number, size, duration of wheals, and number of episodes.^{34,35} Antihistamines should be taken on a daily schedule for optimal response, not only as needed for relief of symptoms.³⁶

First-generation H_1 receptor antihistamines (eg, chlorpheniramine, diphenhydramine, and hydroxyzine) lack specificity for H_1 histamine receptors and cross the blood-brain barrier.³³ As a result, patients often experience numerous adverse effects,³³ including dry mouth, headache, and urinary retention due to anticholinergic effects, as well as sedation and cognitive impairment due to cerebral histamine receptor binding.³³ These adverse effects led to the development of the second- and third-generation antihistamines

(fexofenadine, loratadine, desloratadine, cetirizine, and levocetirizine). Second-generation antihistamines effectively decrease CU symptoms with reduced adverse effects compared with first-generation antihistamines.^{33,37,38}

Although trials have been conducted to compare second-generation antihistamines with first-generation antihistamines, there are no trials that suggest one of the second-generation antihistamines is superior to any of the others.^{34,35,39,40} Some patients with CU remain unresponsive to H_1 receptor antihistamines, possibly because of the presence of lymphocytes, monocytes, neutrophils, or eosinophils in the perivascular dermal infiltrates.⁴¹ Such refractory disease necessitates the utilization of additional therapies.

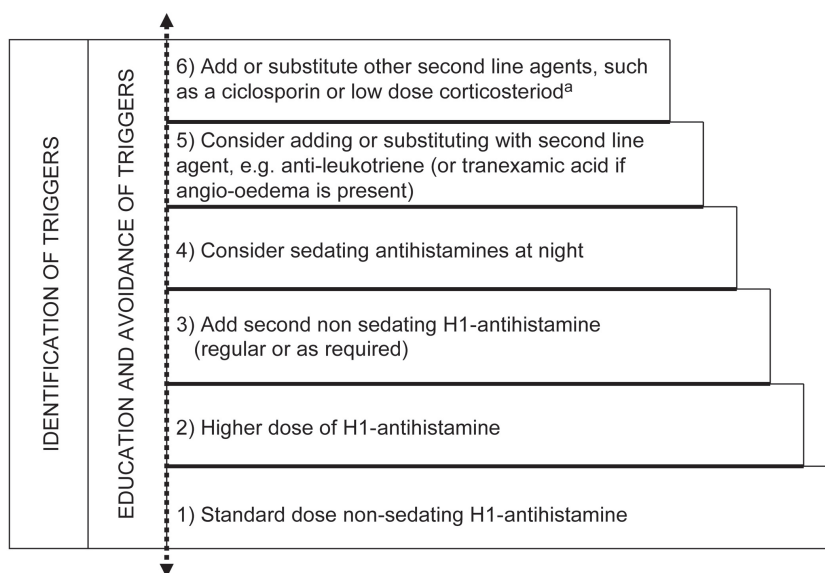
Newer Second-Generation Antihistamines

Desloratadine (Clarinet[®]), the principle active metabolite of loratadine (Claritin[®]), is a nonsedating, selective antagonist of peripheral H_1 receptors. The efficacy of desloratadine alone and in combination with the leukotriene receptor antagonist montelukast in patients with CIU has been demonstrated in several trials.⁴² In a randomized, double-blind, placebo-controlled trial, 226 patients with CU received either desloratadine 5 mg daily or placebo. Compared with placebo patients, those receiving desloratadine had significant improvements from baseline in pruritus scores, total symptom scores, and joint patient/physician assessment of overall treatment response. Improvements were seen on the first assessment (treatment day 2) and throughout the study.⁴³

Levocetirizine (Xyzal[®]) is the active optical isomer of cetirizine (Zyrtec[®]) and has a 2-fold higher affinity for H_1 histamine receptor compared with cetirizine.⁴⁴ The efficacy of levocetirizine was demonstrated in a randomized, double-blind, placebo-controlled trial in which 166 patients with moderate-to-severe CIU received either levocetirizine 5 mg or placebo for 4 weeks.⁴⁵ Patients who received levocetirizine had a significant decrease in mean pruritus severity score, duration of pruritus, number of wheals, and size of wheals at 1 and 4 weeks of treatment compared with patients receiving placebo; they also had greater improvement in quality of life, as measured by the Dermatology Life Quality Index (DLQI), and used fewer concomitant medications during the treatment period.

Levocetirizine and desloratadine have been compared in head-to-head clinical studies. The efficacy of levocetirizine 5 mg and desloratadine 5 mg was compared in a multicenter, randomized, double-blind, parallel-group trial in which 886 patients with CIU received either levocetirizine or desloratadine daily for 4 weeks.⁴⁶ Patients in both treatment groups had a decrease in the severity of pruritis from baseline. Sig-

Figure 2. Stepwise treatment strategy for patients with CU. Management of CU is based on severity of disease and response to treatment. Treatment is accelerated in patients with severe disease and withdrawn on symptom resolution.³¹



^aLow-dose daily corticosteroid (5–10 mg/day) or low-dose, alternative-day corticosteroid (15–20 mg every other day) could be considered.

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nificantly greater decreases in pruritis severity scores were seen in patients receiving levocetirizine compared with desloratadine during the first week and throughout the treatment period. Both patients and providers reported greater global satisfaction following treatment with levocetirizine compared with desloratadine. In another study, the efficacy of high-dose therapy for patients with poorly controlled CU was assessed by randomizing 80 patients to receive up to 20 mg of levocetirizine or desloratadine.⁴⁷ Both therapies were well tolerated, with complete response (ie, elimination of all signs and symptoms) seen in 73% of patients receiving levocetirizine and 33% of patients receiving desloratadine. Of the 73% of patients showing complete response with levocetirizine, 24% crossed over from the desloratadine group after failing to achieve a complete response.

Fexofenadine (Allegra®) is a nonsedating, long-acting, specific peripheral histamine H₁ receptor antagonist that is approved by the US Food and Drug Administration for the treatment of CIU symptoms at doses of 60 mg twice daily and 180 mg once daily. In a large US, multicenter, double-blind, randomized, placebo-controlled trial, 259 patients with CIU were randomized to receive placebo or fexofenadine 180 mg once daily. Compared with placebo, patients receiving fexofenadine demonstrated significant reductions in the number of wheals (least squares [LS] mean change from baseline, -0.40 vs -0.78, respectively) and in the severity of pruritis (LS

mean change from baseline, -0.57 vs -1.04, respectively).⁴⁸ Additionally, in an analysis of 2 identical, 4-week, placebo-controlled trials in patients with CIU, 169 patients receiving fexofenadine 60 mg twice daily reported clinically significant improvements in health-related quality of life, as measured by the DLQI, when compared with placebo.⁴⁹

Leukotriene Receptor Antagonists

Leukotrienes are important mediators of inflammation. Leukotriene receptor antagonists have been studied as second-line therapy for patients with CIU poorly controlled with antihistamines, and have shown only mild benefit. In a small study, patients with CIU and a suboptimal response to H₁ antihistamines received either cetirizine or cetirizine in combination with zafirlukast (Accolate®).⁵⁰ Only patients with positive ASSTs receiving combination therapy showed significant improvements in average physician therapy effectiveness scores (6.2 vs 4.9 for placebo) and average visual analog scale scores (29.2 vs 45.7 for placebo).⁵⁰ In a double-blind, placebo-controlled, crossover trial, zafirlukast monotherapy was ineffective in CIU patients. No significant improvements were observed in daily symptom scores or in the use of rescue antihistamines versus placebo.⁵¹ However, when montelukast (Singulair®) was studied as add-on therapy in a small cohort of patients on antihistamines, half of the cohort showed improvement, as assessed by the number and duration of wheals and degree of itching.⁵² Leukotriene receptor antagonists are

therefore best used in combination with antihistamines in a stepwise approach for refractory patients.³¹ A trial of 4 weeks is acceptable, and discontinuation is advised if there is no improvement.

H₂ Antagonists

The presence of H₂ histamine receptors in the skin and the frequency of refractory CU led to studies of the combination of H₁ and H₂ antihistamines. In a randomized, double-blind trial, 18 patients with refractory CIU received either hydroxyzine (Vistaril[®], Atarax[®]) alone or in combination with cimetidine (Tagamet[®]).⁵³ Patients receiving combination therapy had a significant decrease in itching and in the frequency, number, and size of hives.^{53,54} In a small study, 15 healthy volunteers not receiving antihistamines, corticosteroids, or immunosuppressants were administered levocetirizine or levocetirizine plus ranitidine (Zantac[®]). A prick test performed with histamine showed that combination treatment is more successful in inhibiting a histamine skin reaction compared with H₁ antihistamine alone.⁵⁵ However, treatment guidelines do not recommend the combination of H₁ and H₂ antihistamines in clinical practice, as other trials failed to demonstrate an advantage of this therapy in patients with CU.^{31,56,57}

Oral Corticosteroids

Low-dose oral corticosteroids (given either daily or on an alternate-day schedule) are sometimes used for CU patients who fail to respond to antihistamines.³¹ A brief course of corticosteroids may be beneficial in acute management.³⁸ However, the long-term use of steroids includes the risk of complications such as bone loss, increased blood sugar, hypertension, suppression of immunity, decreased growth in children, adrenal suppression, and cataracts.⁵⁸ The most recent urticaria evaluation and management guidelines from the British Association of Dermatologists recommend avoiding the use of oral corticosteroids in patients with CU.⁵⁹

Newer Therapies

In a stepwise approach to treatment, once supratherapeutic doses and antihistamine combinations fail to abate symptoms, the use of immunomodulatory drugs is considered. The most extensive experience is with cyclosporine (Neoral[®]). In a randomized, double-blind trial, patients with severe refractory CU received daily cyclosporine or placebo, and were evaluated for daily urticaria activity scores of wheal numbers and itch. Significant improvement, defined as reduction of the weekly scores to < 25% of baseline, was seen with cyclosporine.⁶⁰ Similarly, in another study of 27 patients unresponsive to antihistamines, treatment with oral cyclosporine produced a significant reduction of urticaria activity scoring.⁶¹ Cyclosporine also decreases inflammatory cytokines in patients with CIU⁶¹ and inhibits mast cell and basophil degranulation.³¹

Dapsone, sulfasalazine (Azulfidine[®]), and hydroxychloroquine (Plaquenil[®]) have shown favorable activity in some patients with CU, but have only been tested in small trials and require monitoring of various parameters, including complete blood count and metabolic panels.⁶² These agents are reasonable second-line alternatives in patients who have failed antihistamines.

Colchicine is widely used in the treatment of gout; however, it has recently found a place in the treatment of several cutaneous diseases, including psoriasis, leukocytoclastic vasculitis, and urticarial vasculitis.⁴¹ Colchicine is believed to work by blocking neutrophil chemotaxis and reducing mast cell degranulation.⁴¹

The effect of IV immunoglobulin, a polyvalent antibody used for the treatment of several autoimmune disorders, was tested in 10 patients with severe CU and known histamine-releasing autoantibodies.⁶³ Patients receiving IV immunoglobulin had a significant improvement in urticarial activity scores and autologous intradermal skin tests. Intravenous immunoglobulin is considered a third-line therapy, as it is limited by cost and patient inconvenience without a better assurance of clinical benefit.

In a case series, 3 patients with refractory CU responded to the humanized monoclonal antibody omalizumab (Xolair[®]), which binds to free IgE and may interfere with binding of autoantibodies to cells.⁶⁴ Omalizumab seems promising based on speculation that CU patients with circulating IgE or IgE-receptor autoantibodies might experience a benefit; however, its use is also limited by cost and inconvenience. Clinical trials are ongoing with omalizumab in patients with CU who have failed antihistamines.

Case Report Summary

The patient in our introductory case presentation was seen by an allergy and immunology specialist for further evaluation of her recurrent hives and facial angioedema. The specialist obtained a detailed history of the symptoms, her response to previous therapy, and any potential triggers, as well as a comprehensive medical and family history. In the case presented, extensive laboratory testing did not enhance the physician's ability to render a diagnosis. At the time of her evaluation, the patient had no systemic symptoms and no abnormal findings on physical examination. Physical urticarias and cryoglobulinopathies were ruled out based on her history and physical examination. Radioallergosorbent testing was likely not beneficial because of her negative clinical history of food allergies.

These careful evaluations led to a diagnosis of CU. The patient came to her initial consultation very anxious about her symptoms; she was fearful that she had a serious underlying disease or that her stress was causing her symptoms.

Although she still did not fully understand why she developed her symptoms, she was greatly relieved that a

diagnosis had been made and that the diagnosis was relatively common. A review of her previous treatments revealed that she was primarily treated with IV methylprednisolone and diphenhydramine in the emergency room but was sent home with only the methylprednisolone dose pack. The patient was also given short-acting or sedating antihistamines with steroids for symptom flares.

Based on the BSACI treatment algorithm, the patient was started on a long-acting, nonsedating antihistamine. She immediately reported an improvement in the incidence and severity of her symptoms and quality of life.

Conclusion

The diagnosis of urticaria, although challenging, can be accomplished in the primary care setting. A complete and detailed history and comprehensive physical examination are vital; these 2 steps will usually lead to a diagnosis. If the diagnosis remains elusive after these steps, additional testing can be performed in a stepwise manner based on the patient's history and according to the BSACI diagnostic algorithm; treatment options may also be derived from this guideline.³¹

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Conflict of Interest Statement

Luz Fonacier, MD discloses conflicts of interest with Alcon, Allerderm, Dyax, GlaxoSmithKline, Lev, and Novartis-Genentech. Marcella Aquino, MD and Bora Kim, DO disclose no conflicts of interest.

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