

The diagnosis and management of acute and chronic urticaria: 2014 update

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These parameters were developed by the Joint Task Force on Practice Parameters (JTFFPP), representing the American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology. The AAAAI and ACAAI have jointly accepted responsibility for

establishing “The diagnosis and management of acute and chronic urticaria: 2014 update.” This is a complete and comprehensive document at the current time. The medical environment is a changing environment, and not all recommendations will be appropriate for all patients. Because this document incorporated the efforts of many participants,

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no single individual, including those who served on the JTFPP, is authorized to provide an official AAAAI or ACAAI interpretation of these practice parameters. Any request for information about or an interpretation of these practice parameters by the AAAAI or ACAAI should be directed to the Executive Offices of the AAAAI, the ACAAI, and the Joint Council of Allergy, Asthma & Immunology.

The JTFPP understands that the cost of diagnostic tests and therapeutic agents is an important concern that might appropriately influence the work-up and treatment chosen for a given patient. The JTFPP recognizes that the emphasis of our primary recommendations regarding a medication might vary, for example, depending on third-party payer issues and product patent expiration dates. However, because a given test or agent's cost is so widely variable and there is a paucity of pharmacoeconomic data, the JTFPP generally does not consider cost when formulating practice parameter recommendations. In extraordinary circumstances, when the cost/benefit ratio of an intervention is prohibitive, as supported by pharmacoeconomic data, commentary might be provided. These parameters are not designed for use by pharmaceutical companies in drug promotion.

The JTFPP is committed to ensuring that the practice parameters are based on the best scientific evidence that is free of commercial bias. To this end, the parameter development process includes multiple layers of rigorous review. These layers include the workgroup convened to draft the parameter, the task force reviewers, and peer review by members of each sponsoring society. Although the task force has the final responsibility for the content of the documents submitted for publication, each reviewer comment will be discussed, and reviewers will receive written responses to comments, when appropriate.

To preserve the greatest transparency regarding potential conflicts of interest, all members of the JTFPP and the practice parameter workgroups will complete a standard potential conflict of interest disclosure form, which will be available for external review by the sponsoring organization and any other interested individual. In addition, before confirming the selection of a Work Group chairperson, the Joint Task Force will discuss and resolve all relevant potential conflicts of interest associated with this selection. Finally, all members of parameter workgroups will be provided a written statement regarding the importance of ensuring that the parameter development process is free of commercial bias.

Practice parameters are available online at www.jcaai.org and www.allergyparameters.org. (J Allergy Clin Immunol 2014;133:1270-7.)

Key words: Acute urticaria, chronic urticaria, autoimmune, skin rash, food allergies

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CLASSIFICATION OF RECOMMENDATIONS AND EVIDENCE**Category of evidence**

- Ia Evidence from meta-analysis of randomized controlled trials
- Ib Evidence from at least 1 randomized controlled trial
- IIa Evidence from at least 1 controlled study without randomization
- IIb Evidence from at least 1 other type of quasiexperimental study
- III Evidence from nonexperimental descriptive studies, such as comparative studies
- IV Evidence from expert committee reports or opinions or clinical experience of respected authorities or both

Strength of recommendation

- A Directly based on category I evidence
- B Directly based on category II evidence or extrapolated recommendation from category I evidence
- C Directly based on category III evidence or extrapolated recommendation from category I or II evidence
- D Directly based on category IV evidence or extrapolated recommendation from category I, II, or III evidence
- E Based on consensus of the Joint Task Force on Practice Parameters
- LB Laboratory based

In this parameter we have also used the Grading of Recommendations Assessment, Development and Evaluation approach for critical appraisal of evidence to assess the therapeutic utility of cyclosporine for refractory chronic urticaria (CU)/angioedema (CU). The decision to include this analysis was made at the time the workgroup for this parameter was convened. Cyclosporine was selected because this was the only agent for patients with refractory CU for which more than 1 randomized controlled trial had been published.

The practice parameter developmental process

The Joint Task Force on Practice Parameters. The Joint Task Force on Practice Parameters (JTFPP) is a 13-member task force consisting of 6 representatives assigned by the AAAAI, 6 by the ACAAI, and 1 by the Joint Council of Allergy and Immunology. The JTFPP oversees the development of practice parameters, selects the workgroup chair or chairs, and reviews

drafts of the parameters for accuracy, practicality, clarity, and broad utility of the recommendations for clinical practice.

The Urticaria Practice Parameter Workgroup. The workgroup was formed by the JTFPP to develop a practice parameter to address the diagnosis and treatment of urticaria with or without angioedema. The chair, Jonathan Bernstein, MD, invited workgroup members to participate in the parameter development. The charge to the workgroup was to use a systematic literature review in conjunction with consensus expert opinion and workgroup-identified supplementary documents to develop practice parameters that provide a comprehensive approach for the assessment and management of urticaria with or without concomitant angioedema. The diagnosis and management of angioedema without concomitant urticaria has been addressed in a separate parameter.

Protocol for selecting, grading, and reviewing evidence. A search of the medical literature was performed for a variety of terms that were considered relevant to this practice parameter. Literature searches were performed on PubMed, Google Scholar, and the Cochrane Database of Systematic Reviews. All reference types were included in the results. References identified as relevant were searched for relevant references, and those references were searched for relevant references as well. In addition, members of the workgroup were asked for references that were missed by this initial search. Published clinical studies were rated by category of evidence and used to establish the strength of the recommendations.

The parameter was subsequently appraised by reviewers designated by the national organizations of the AAAAI and ACAAI. On the basis of this process, this parameter represents an evidence-based, broadly accepted consensus document.

These parameters are also available online at www.jcaai.org and www.allergyparameters.org.

EXECUTIVE SUMMARY

Acute urticaria and angioedema are differentiated from CU based on the duration of illness. Urticaria and angioedema with duration of less than 6 weeks is termed acute urticaria.^{2,3} If urticaria of less than 6 weeks' duration has features suggesting it might progress to a chronic illness (see the sections on autoimmune, physical, and CU), such patients should be periodically re-evaluated until a diagnosis is clarified. Acute urticaria and angioedema should be differentiated from anaphylaxis. Urticaria/angioedema associated with signs and symptoms in organs other than the skin, such as the pulmonary tract (wheezing and cough), gastrointestinal system (vomiting and diarrhea), nervous system (dizziness and loss of consciousness), or cardiac system (changes in blood pressure or heart rate), can occur in patients with anaphylaxis. Epinephrine should be prescribed if the diagnosis of anaphylaxis has not been excluded. Acute urticaria and angioedema is often but not always related to mast cell and basophil activation from multiple triggers, which include IgE-mediated and non-IgE-mediated mechanisms. These cells play a broad critical role in the innate and acquired immune response because they express multiple receptors responding to specific antigens, as well as complement fragments, circulating immune complexes binding IgG and IgM, cytokines, changes in blood pressure, and immunologic activation. Thus it is likely that mast cell activation in patients with acute urticaria and angioedema occurs through multiple pathways in addition to IgE. The presence of a specific mast cell or basophil receptor for

proteases might account for IgE-independent activation of these cells through proteases in aeroallergens, foods, and enzymes, as well as by proteases generated by the complement response to infectious agents. Acute urticaria and angioedema is more frequently associated with identifiable conditions. When this disorder becomes chronic, it is less likely to be associated with an identifiable cause. Because acute urticaria and angioedema will usually resolve spontaneously, laboratory evaluation for chronic illness is also not required unless supported by the clinical history or physical examination. Furthermore, empiric elimination diets (not guided by history and testing) are not recommended. Although many cases of acute urticaria are caused by viral or other infectious illnesses, extensive evaluation for specific viral pathogens or antiviral therapy is not indicated unless suggested by the clinical history.

For acute urticaria, skin testing or immunoassays to identify specific triggers for acute urticaria and angioedema can be helpful if an allergic cause is suggested by history. Skin testing in this scenario would usually be done after the resolution of acute urticaria and after suspension of antihistamines or through serologic testing in the presence of significant dermatographism. Although skin biopsy is not indicated in most cases of acute urticaria and angioedema, it might occasionally be useful for differentiating this condition from other inflammatory disorders. Common causes of acute urticaria and angioedema, including medications and foods, should be identified by a detailed history and eliminated, if possible. For treatment of acute urticaria and angioedema, antihistamines are efficacious in most cases and recommended as first-line therapy. Although first-generation antihistamines are rapidly acting and effective, in both pediatric and adult patients they can be associated with sedation and impaired motor skills because of their ability to cross the blood-brain barrier, whereas these impairments are less evident or not evident with second-generation antihistamines as a class. When agents that can cause drowsiness or impair performance are prescribed, adult patients and parents of child patients should be made aware of this potential side effect. In patients with poor response to antihistamines, a brief course of oral corticosteroids might also be required while attempting to eliminate suspected triggers and develop an effective treatment plan.

CU is defined as urticaria that has been continuously or intermittently present for at least 6 weeks. The duration of CU varies considerably; however, physical urticarias tend to persist the longest, often for many years. The prevalence of CU in the general population has been estimated to range from 0.5% to 5%; however, the true point prevalence, cumulative prevalence, and lifetime prevalence of CU have not been established. The incidence of CU has been estimated at 1.4% per year. Some patients with CU might have both urticaria and angioedema, occurring simultaneously or separately. Pathogenically, the skin mast cells are the most important cell in patients with CU, and histamine is the predominant mediator, although other cells and mediators also play a key role. A predominantly lymphocytic infiltrate can be found in the lesions of both patients with acute and those with chronic types of urticaria. However, many patients demonstrate urticarial lesions that have a mixed cellular infiltrate: a mixture of lymphocytes, PMNs, and other inflammatory cells. Activation of the coagulation cascade, including increased prothrombin fragment F1+2 and D-dimer levels, has been described in patients with CU and might be a marker of CU with angioedema severity.

Evaluation of a patient with CU should involve consideration of various possible causes, although most cases do not have an identifiable cause. Rarely, IgE-mediated reactions from foods, drugs, or other allergens might result in CU. A number of chronic infectious processes have been reported, including viral infections, such as hepatitis B and C, EBV, and herpes simplex virus; *Helicobacter pylori* infections; and helminthic parasitic infections. CU has been reported with a number of other systemic conditions, many of which have a complement-mediated or immunologic basis, including specific complement component deficiencies; cryoglobulinemia (eg, with hepatitis C and chronic lymphocytic leukemia); serum sickness or other immune-complex mediated processes; connective tissue diseases, such as systemic lupus erythematosus (SLE) and juvenile rheumatoid arthritis; thyroid disease (with both hypothyroidism and hyperthyroidism being associated); neoplasms (particularly lymphoreticular malignancy and lymphoproliferative disorders); and other endocrine disorders or hormonal therapies (eg, ovarian tumors and oral contraceptive use, respectively). Autoantibody-associated urticaria refers to the presence of autoantibodies (eg, thyroid autoantibodies and IgE receptor autoantibodies) in conjunction with urticaria and can be considered a subset of chronic idiopathic urticaria (CIU). However, the etiologic, therapeutic, and prognostic value of these autoantibodies has not been determined.

Numerous autoimmune disorders, including SLE, dermatomyositis and polymyositis, Sjögren syndrome, and Still disease, have been associated with CU. However, serology to diagnose these underlying autoimmune diseases (eg, connective tissue disease) is not warranted in the initial evaluation of CU in the absence of additional features suggestive of a concomitant autoimmune disease. Thyroid autoantibodies are frequently identified in patients with CU. However, because the clinical relevance of these autoantibodies for evaluation and treatment of patients with CU has not been established, routine testing for thyroid autoantibodies is not recommended.

Chronic urticarial vasculitis associated with low or normal complement levels might present as a primary autoimmune disorder or develop secondary to an autoimmune disorder, such as SLE. Urticarial vasculitic lesions might sometimes be evanescent, lasting less than 24 hours, similar to CU; for this reason, urticarial vasculitis cannot be completely excluded based on the history of lesions spanning less than 24 hours. The diagnosis of this condition should be confirmed by a biopsy demonstrating the presence of leukocytoclastic vasculitis.

The co-occurrence of CU with a number of conditions, including *H pylori* infection and celiac disease, has been reported. However, evidence does not support testing for these conditions in a patient with CU with an otherwise unremarkable history and physical examination. Moreover, there are no convincing data demonstrating that treatment based on abnormal test results consistent with these conditions being present leads to improvement or change in the course of CU. Patients with malignancies, such as lymphoproliferative diseases and Schnitzler syndrome, can also present with CU.

Approximately 30% to 50% of patients with CU produce specific IgG antibodies against the FcεRIα subunit component of the high-affinity IgE receptor, and approximately 5% to 10% produce IgG antibodies against IgE itself. The utility of the autologous serum skin test (ASST) and the autologous plasma skin test is unclear because evidence has not clearly demonstrated that this testing identifies a distinct subgroup of patients with CU.

There are no definitive studies demonstrating that patients with refractory CU and a positive ASST result respond differently to certain medication regimens compared with those patients with CU with a negative ASST result. Current evidence does not support routine performance of ASSTs or autologous plasma skin tests in patients with CU. The pathogenesis of autoantibody-associated urticaria remains elusive, but *in vitro/ex vivo* studies demonstrate a role for T cells, sCD154 (sCD40 ligand), and basophil histamine responsiveness.

For patients with CU who present with otherwise unremarkable history and physical examination findings, skin or *in vitro* testing for IgE to inhalants or foods and/or extensive laboratory testing are not recommended because such testing is not cost-effective and does not lead to improved patient care outcomes. Targeted laboratory testing based on history or physical examination findings is appropriate, and limited laboratory testing can be obtained. Limited laboratory testing includes a CBC with differential, sedimentation rate, and/or C-reactive protein, liver enzyme, and thyroid-stimulating hormone measurement. In patients with CU with an unremarkable history and physical examination, limited laboratory testing might be appropriate to identify the infrequent or rare case in which CU is a manifestation of an underlying condition that might not be discernible based on history or physical examination findings or to provide “reassurance value” for the patient and his or her family members.

The initial patient evaluation should be focused to determine (through history and physical examination) whether the lesions that patients describe are consistent with CU. CU lesions are typically edematous pink or red wheals of variable size and shape with surrounding erythema and are generally pruritic. A painful or burning dysesthesia is not characteristic of CU and suggests the presence of cutaneous vasculitis. Individual urticarial lesions usually fade within 24 to 48 hours, but new lesions might be developing simultaneously at other skin sites. In contrast, vasculitis lesions are palpable and usually nonblanching, spanning several days or more and often followed by residual hyperpigmented changes, although in some cases lesions might be more evanescent, similar to ordinary CU. Angioedema typically appears as nonpruritic, brawny, nonpitting edema, typically without well-defined margins and without erythema. The medical work-up of a patient with CU should be done, keeping in mind that CU is of undetermined cause in the majority of cases.

After a thorough history and physical examination, no diagnostic testing might be necessary for some patients with CU; however, limited routine laboratory testing can be performed to exclude underlying causes. Targeted laboratory testing based on clinical suspicion is appropriate. Extensive routine testing for exogenous and rare causes of CU or immediate hypersensitivity skin testing for inhalants or foods is not warranted. Routine laboratory testing in patients with CU whose history and physical examination lack atypical features rarely yields clinically significant findings. Screening for thyroid disease is of low yield in patients without specific thyroid-related symptoms or a history of thyroid disease. Increased levels of anti-thyroglobulin or anti-thyroid antibodies in euthyroid (ie, normal thyroid-stimulating hormone levels) subjects are commonly detected, although the clinical implications of this finding are unclear. Although commercial assays are now available, the utility of testing for autoantibodies to the high-affinity IgE receptor or autoantibodies

to IgE has not been established. Whether detection of autoantibodies identifies a clinically unique population or will lead to a change in management is also currently unclear. Although some studies have suggested that a positive autoantibody test result might indicate a marker of increased disease severity, data are limited and might reflect the fact that these populations do not differ clinically and that these autoantibodies might represent an epiphenomenon. For these reasons, autoantibody-associated CU has been included under the diagnosis of CIU.

Patients with recurrent angioedema in the absence of coexisting urticaria should be evaluated for hereditary angioedema, acquired C1 inhibitor deficiency, or angiotensin-converting enzyme inhibitor-associated angioedema before a diagnosis of idiopathic angioedema is made. Skin biopsy can be performed in patients with refractory CU and should be performed when vasculitis is suspected or when other nonurticarial immunologic skin diseases are a consideration. Routine skin biopsies are not required in most cases of CU. Immediate hypersensitivity skin or serologic testing for food or other allergens is rarely useful and not recommended on a routine basis.

In a subgroup of patients, a tendency exists to have urticaria, angioedema, or both as a result of the effect of environmental stimuli on inflammatory cells predisposed to respond to physical factors. Patients might present with isolated physical urticaria/angioedema syndromes or a combination of syndromes but might also have concomitant CIU.

Aquagenic urticaria is a rare condition. Subjects with aquagenic urticaria have hives (typically 1-3 mm in size) after direct contact of skin with any source of water independent of temperature. Aquagenic urticaria can be confirmed by the appearance of wheals at the site of challenge with a water compress at 35°C and applied to the skin of the upper body for 30 minutes.

Subjects with cholinergic urticaria have hives that are "pinpoint" (1-3 mm) and surrounded by large flares in association with an increase in core body temperature. Common provoking factors for cholinergic urticaria include exercise, sweating, emotional factors, and hot baths or showers. Provocative challenges that raise core body temperature, such as exercise and hot water immersion or methacholine intradermal challenge, have been considered for the diagnosis of cholinergic urticaria. However, the negative predictive value of these tests is not optimal, and lack of response cannot rule out the diagnosis. The severity of cholinergic urticaria ranges from mild pruritus to serious and potentially life-threatening reactions.

Subjects with cold urticaria have pruritus and swelling with exposure of the skin to a cold stimulus. Patients with cold urticaria might have systemic reactions associated with systemic cold exposure (eg, aquatic activities). The diagnosis of cold urticaria can be confirmed by applying a cold stimulus (eg, an ice cube on the forearm) to the patient's skin and observing a wheal-and-flare reaction during rewarming of the skin. The primary treatment for cold urticaria is avoidance of cold exposure, as feasible; however, prescribing pharmacotherapy is also frequently advisable. Some forms of cold urticaria might have a negative ice cube test result.

Subjects with delayed-pressure urticaria/angioedema experience swelling (which might be painful) with a delay of 4 to 6 hours after exposure of the skin to a pressure stimulus. In some cases the delay can be as long as 12 or even 24 hours after pressure exposure. Common provoking factors include working with tools, sitting on a bench, or wearing constricting garments.

Delayed-pressure urticaria/angioedema can be confirmed by a challenge with 15 pounds of weight suspended over a patient's shoulder for 10 or 15 minutes and monitoring for development of delayed angioedema. Development of angioedema in a delayed fashion at the site of pressure is considered a positive challenge result. Management of delayed-pressure urticaria and angioedema differs from that of other types of CU/angioedema, and it is often very difficult to treat. Additional pharmacotherapeutic treatment is frequently required along with avoidance measures. Conventional antihistamine dosing frequently lacks efficacy for achieving control of symptoms.

Subjects with dermatographia (also known as dermatographism, dermatographia, and dermatographism) promptly experience a wheal-and-flare response to pressure applied to the skin. Dermatographia can be confirmed by stroking the skin with a firm object, such as a tongue blade. Dermatographia is the most common form of physical urticaria and reported to be present in 2% to 5% of the general population, although only a minority of patients have symptoms to a degree that prompt medical attention.

Urticaria provoked by exercise can occur in patients with 2 conditions: cholinergic urticaria or exercise-induced anaphylaxis (EIAN). There are 2 groups of patients with EIAN: one group can have anaphylaxis provoked by exercise, and the second group can have anaphylaxis with exercise temporally related to ingestion of food or medication. Two subgroups of patients with food-dependent EIAN have been described: one group might have anaphylaxis when exercising in temporal proximity to ingestion of any type of food, and the another group might experience anaphylaxis with exercise in conjunction with prior ingestion of a specific food. It is important to distinguish EIAN from cholinergic urticaria. The diagnosis of EIAN can be confirmed by exercise challenge in a controlled environment, whereas cholinergic urticaria can be elicited by both exercise challenge and passive heating. Management depends on determining whether the patient has EIAN or cholinergic urticaria. If a food, drug, or another essential or modulating factor is identified, this should be avoided in the periexercise period. Patients with EIAN should carry injectable epinephrine, exercise with a partner, and wear medical identification jewelry.

Subjects with solar urticaria promptly (generally within 1-3 minutes) have urticaria with exposure of skin to sunlight. The diagnosis of solar urticaria can be confirmed with phototesting to various wavelengths of light.

Subjects with vibratory angioedema experience pruritus and swelling with exposure of the skin to a vibratory stimulus. This condition can be familial. Vibratory angioedema can be confirmed by demonstrating an exaggerated response after exposure of the skin to a vortex mixer.

Cryoglobulinemia is often found in many conditions that result in vasculitis. Autoinflammatory syndromes are a group of conditions that involve aberrant activation of mediators of the innate immune response with resultant fever and other symptoms. Cryopyrin-associated periodic syndromes (also referred to as cryopyrinopathies) are a group of syndromes that are characterized by abnormalities in the *CIAS1* gene, which encodes for the cryopyrin protein. Hypocomplementemic or normocomplementemic urticarial vasculitis is associated with decreased or normal complement levels (C1q, C4, and C3) and a biopsy that reveals vasculitis of dermal blood vessels with leukocytoclasia. The hypocomplementemic urticarial vasculitis syndrome is a more severe form of this condition associated with arthralgias,

glomerulonephritis, uveitis or episcleritis, recurrent abdominal pain, obstructive lung disease and urticaria, and/or angioedema. Swelling of the area in the medial portion of the upper eyes might be a sign of thyroid ophthalmopathy and misinterpreted as angioedema. Urticaria-like dermatoses can occur at various stages of pregnancy. Women who present with cyclical urticaria might have autoimmune progesterone-induced dermatitis. Episodic attacks of angioedema with weight gain are characteristic of episodic angioedema with eosinophilia (Gleich syndrome). Hypereosinophilic syndrome should be considered when the peripheral total eosinophil count exceeds $1500/\mu\text{L}$ in the absence of other causes for peripheral eosinophilia. Cutaneous mast cell disorders that can present with urticaria-like lesions include urticaria pigmentosa, mastocytomas, and telangiectasia macularis eruptiva perstans. Mast cell activation disorders can also present with urticaria and angioedema but usually have additional systemic symptoms. Erythema multiforme might resemble urticaria and might be due to viral infections (herpes), mycoplasma infection, or medications. Hepatitis B or C can be associated with urticarial vasculitis and should be considered in differential diagnosis, particularly for patients whose behaviors predispose for contracting a sexually transmitted disease, who have recently received a blood transfusion, or who have exposure to contaminated needles. Bullous pemphigoid can present initially with urticaria-like papules or small plaques that might be excoriated by the patient before noticeable blistering occurs. Persistent swelling of the lips without evidence of eczematous dermatitis might be a sign of cheilitis granulomatosa (Melkerrson-Rosenthal syndrome). Polymorphous light eruption differs from solar urticaria in that the onset usually occurs minutes to hours after sunlight exposure and the eruption, which occurs in different forms, including papules, papulovesicles, and plaques, lasts for days compared with solar urticaria, which is short-lived between exposures. Recall urticaria is a condition in which urticaria is observed at the site of a previous sting or injection after re-exposure to the same inciting factor. Patients with Schnitzler syndrome caused by an IgM or more rarely IgG monoclonal gammopathy present with nonpruritic urticaria (that spares the face), bone pain, and intermittent fever.

Management of CU involves both nonpharmacologic and pharmacologic approaches. Nonsteroidal anti-inflammatory drugs, heat, and tight clothing might exacerbate CU in some patients, and avoidance of these factors might be beneficial. Pseudoallergens have been defined as substances that can induce intolerance reactions and include food additives, vasoactive substances, fruits, vegetables, and spices. The utility of a pseudoallergen-free diet for management of CU has not been convincingly demonstrated. Avoidance of pseudoallergens in the diet is not recommended. Potent topical corticosteroids might improve symptoms from delayed-pressure urticaria but have limited utility in the treatment of diffuse CU.

A step-care approach has been developed for the management of CU (Fig 1). H1 antagonists are effective in the majority of patients with CU but might not achieve complete control in all patients. Second-generation antihistamines are safe and effective therapies in patients with CU and are considered first-line agents (step 1). For patients not responding to monotherapy with a second-generation antihistamine at US Food and Drug Administration–approved doses, several treatment options can be used (step 2). Higher doses of second-generation

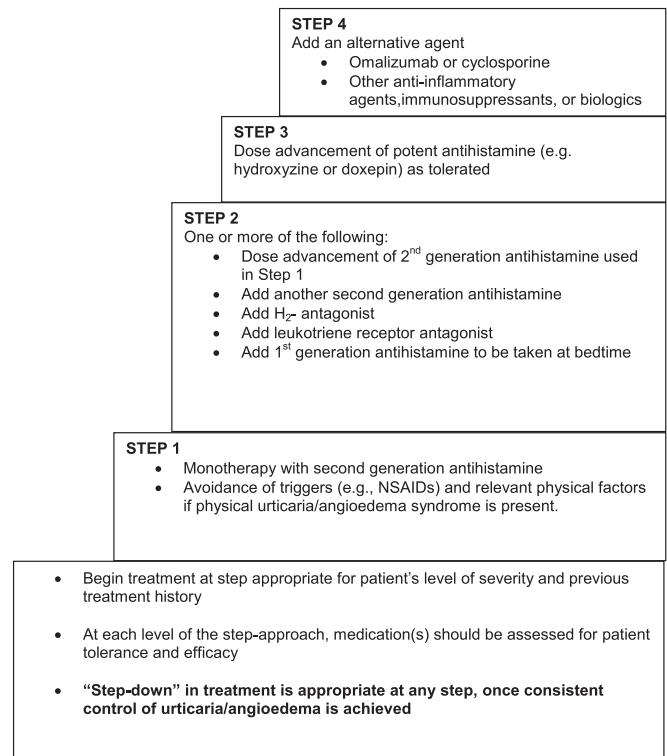


FIG 1. Step-care approach to the treatment for CU.

antihistamines might provide more efficacy, but data are limited and conflicting for certain agents. Addition of H₂ antagonists or leukotriene receptor antagonists can be considered for patients with CU with unsatisfactory responses to second-generation antihistamine monotherapy. First-generation antihistamines can also be considered in patients who do not achieve control of their condition with higher-dose second-generation antihistamines. Treatment with hydroxyzine or doxepin can be considered in patients whose symptoms remain poorly controlled with dose advancement of second-generation antihistamines and/or addition of 1 of more of the following: H₂ antihistamines, first-generation H₁ antihistamines at bedtime, and/or antileukotrienes (step 3). Systemic corticosteroids are frequently used for patients with refractory CU, but no controlled studies have demonstrated efficacy. In some patients short-term use (eg, 1-3 weeks' duration) might be required to gain control of their disease until other therapies can achieve control. Because of the risk of adverse effects with systemic corticosteroids, long-term use for treatment of patients with CU should be avoided as much as possible. Patients with CU whose symptoms are not adequately controlled on maximal antihistamine therapy (eg, step 3 care) might be considered to have refractory CU.

A number of alternative therapies have been studied for the treatment of CU; these therapies merit consideration for patients with refractory CU (step 4). Omalizumab, approved by the FDA at both 150 mg and 300 mg doses for the treatment of CU patients unresponsive to H₁ antagonists 12 years of age and older, and cyclosporine have the greatest published experience for efficacy in patients with CU compared with all other alternative agents. The therapeutic utility of omalizumab for refractory CU has been supported by findings from large double-blind, randomized controlled trials and is associated with a relatively low rate of

clinically significant adverse effects. On the basis of this evidence, omalizumab should be considered for refractory CU if this is favorable from the standpoint of balancing the potential for benefit with the potential for harm/burden and cost and the decision to proceed is consistent with patients' values and preferences. There is evidence from observational studies with cyclosporine, including long-term use, that suggests cyclosporine is efficacious for patients with refractory CU and capable of inducing remission. There is also evidence for the efficacy of cyclosporine from randomized controlled trials; however, taken in the context of study limitations, potential harms, and cost, the quality of evidence from these randomized controlled trials supporting cyclosporine is low, leading to a weak recommendation for use of cyclosporine for refractory CU. Therefore clinicians need to carefully consider whether administration of cyclosporine is favorable from the standpoint of balancing the potential for benefit with the potential for harm and discuss this openly with patients to determine that the decision to proceed with a trial of cyclosporine is consistent with their values and preferences.

Many other alternative therapies have been used in patients with refractory CU; however, the level of evidence supporting their use is lower than with omalizumab or cyclosporine. Anti-inflammatory agents, including dapsone, sulfasalazine, hydroxychloroquine, and colchicine, have limited evidence for efficacy in patients with CU and some require laboratory monitoring for adverse effects. These agents are generally well tolerated and might be considered for properly selected patients with antihistamine-refractory CU. Other agents have been used in patients with refractory CU, including, but not limited to, theophylline, attenuated androgens, anticoagulants, nonsteroidal anti-inflammatory drugs, β -agonists, cyclophosphamide, gold, plasmapheresis, cromolyn, and nifedipine; however, these agents should be reserved for patients with refractory urticaria who have failed other anti-inflammatory, immunosuppressant, or biologic

agents. Other unproved therapies for CU, which are not recommended, include allergen immunotherapy, herbal therapies, vitamins, supplements, and acupuncture.

Multiple factors are involved in selecting an alternative agent in patients with refractory CU, including but not limited to the presence of comorbid factors, frequency of treatment-related visits, cost, rapidity of response, adverse effects, and the patient's values and preferences. The potential for harm and burden associated with a given alternative agent is extremely important and needs to be weighed against the patient's potential for benefit, current quality of life, and any adverse effects from current therapy for their CU.

The evidence that *H pylori* eradication leads to improvement of CU outcomes is weak and conflicting, leading to a weak recommendation for routine *H pylori* eradication for patients with chronic urticaria. There is a lack of high-quality evidence demonstrating the efficacy of thyroid hormone supplementation for euthyroid patients with CU with evidence of thyroid autoimmunity. For this reason, clinicians should be flexible in their decision making regarding the appropriateness of prescribing thyroid hormone in this setting. Thyroid hormone supplementation might merit consideration for euthyroid patients with CU with evidence of thyroid autoimmunity on an individualized basis. This will require careful assessment of the potential for benefit and potential for harm and burden associated with thyroid hormone supplementation, taking the patient's values and preferences into consideration and allowing the patient to participate actively in the decision-making process. Very limited data support the use of antiviral therapies in patients with CU, with concomitant herpetic infections or positive viral serologies.

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