Practice parameter

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 (JTFPP), 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,

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 this 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, dermographia, and dermographism) 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 *C1AS1* 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 leukocytoclasis. 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 character-istic of episodic angioedema with eosinophilia (Gleich syndrome). Hypereosinophilic syndrome should be considered when the peripheral total eosinophil count exceeds 1500/μL 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 (Melkersson-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, papulove-sicles, 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 nonprur-itic 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
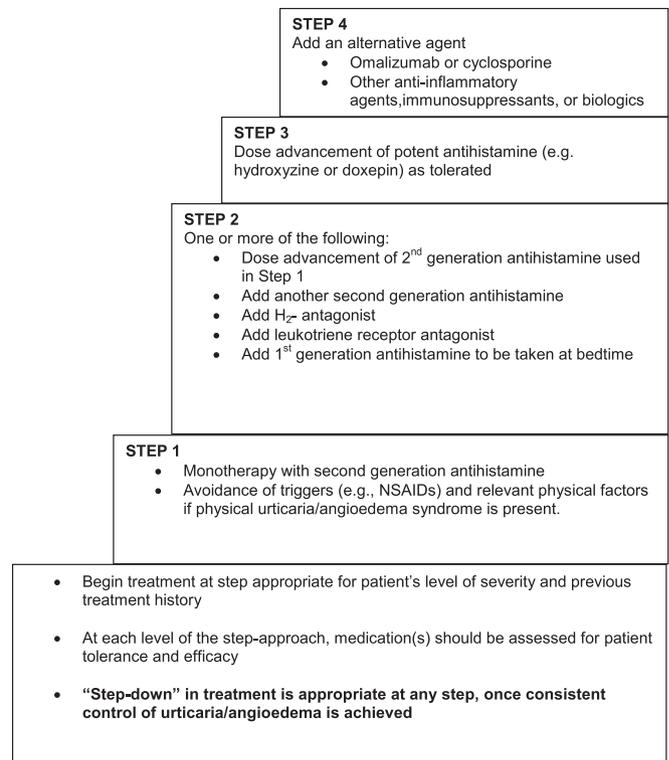
FIG 1. Step-care approach to the treatment for CU.

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 association 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.

To read the Practice Parameter in its entirety, please download the online version of this article from www.jacionline.org, www.jcaai.org, or www.allergyparameters.org. The reader is referred to the online portion of the document for more detailed discussion of the comments made in the printed version.

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 (JTFPP), 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, 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

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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 (GRADE) approach for critical appraisal of evidence to assess the therapeutic utility of cyclosporine for refractory chronic urticaria (CU)/angioedema. 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.[1]

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 chronic urticaria (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 are 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 are 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 (eg, ovarian tumors) as well as oral contraceptive use. 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 this 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 (APST) is unclear because evidence has not clearly demonstrated that this testing identifies a distinct subgroup of patients with CU. There are no definitive studies that demonstrate 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 APSTs 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 (TSH) 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 TSH 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 (ACE) 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 non-urticarial 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, dermographia, and dermographism) 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 *C1AS1* 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 leukocytoclasis. The hypocomplementemic urticarial vasculitis syndrome (HUVS) 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 (HES) should be considered when the peripheral total eosinophil count exceeds 1500/μL in the absence of other causes for peripheral eosinophilia. Cutaneous mast cell disorders that can present with urticaria-like lesions include urticaria pigmentosa (UP), 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 (EM) 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 (Melkersson-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, and 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 (NSAIDs), 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). H_1-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 (FDA)–approved doses, several treatment options can be used (step 2). Higher doses of second-generation antihistamines might provide more efficacy, but data are limited and conflicting

for certain agents. Addition of H_2-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: H_2-antihistamines, first-generation H_1-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 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, NSAIDs, 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 association 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 CU. 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. The evidence is weak that pseudoallergen-free diets improve CU; given the lack of evidence and burden of adhering to these diets, their use in patients with CU is not recommended. Other unproved therapies for CU, which are not recommended, include allergen immunotherapy, herbal therapies, vitamins, supplements, and acupuncture.

ACUTE URTICARIA (FIG 2)

Annotation 1: Patient presents with possible acute urticaria, angioedema, or both

Urticaria/angioedema is "acute" if it spans less than 6 weeks in duration. Such patients might have urticaria on a continual basis for days or weeks or might have acute recurring urticaria/angioedema caused by, for example, repeated exposure to an allergen (eg, drug or food) or physical factor (eg, cold).

In cases in which urticaria/angioedema is generalized, a patient might merit administration of immediate emergency treatment (eg, epinephrine) to manage laryngeal obstruction. In such instances a detailed history and physical examination for anaphylaxis should follow administration of treatment.

Annotation 2: Detailed history, including review of systems and physical examination

A comprehensive history and physical examination should be performed in an effort to identify a cause for acute urticaria/angioedema. This should include an inventory of possible factors that might explain the development of urticaria/angioedema. Exposures to a variety of potential triggers (including foods, drugs, infections, insect stings, and physical factors) and their temporal relationship to urticaria/angioedema should be

documented. The potential relevance of travel should also be assessed. Because the development of urticaria/angioedema might be a harbinger of certain infections, a history of relevant exposures (eg, blood transfusion) should be recorded. A comprehensive review of systems should also be carried out to investigate the presence of symptoms that could reflect an underlying connective tissue or other immune disorder.

The clinician should be encouraged to obtain objective assessments of the percentage of the body covered in hives, itch severity, and quality of life at the initial visit and each subsequent visit as a means for determining initial therapy and gauging response to therapy.[4-8]

Physical examination should focus on the extent and nature of urticarial lesions present, determine whether dermatographia is present, and include examination of the head, eyes, ears, nose, throat, neck, lymph nodes, lungs, heart, abdomen, and musculoskeletal system.

Annotation 3: Is the detailed history, physical examination, or both suggestive of an underlying cause?

Findings on physical examination and information gleaned from the comprehensive history might serve to focus the evaluation on a clear trigger for acute urticaria/angioedema. Examples of this would include the following:

1. a patient with hypertension in whom use of an angiotensin-converting inhibitor (ACE) inhibitor is associated with an acute episode of oropharyngeal angioedema;
2. a health care worker sensitized to latex in whom acute urticaria occurs in association with wearing powdered latex gloves;
3. a patient with increased liver enzyme levels who received a blood transfusion before onset of acute urticaria/angioedema; and
4. a patient with symptoms suggestive of hypothyroidism whose physical examination includes detection of thyromegaly.

Annotation 4: Specific evaluation

The information obtained from a comprehensive history, including review of systems and performance of physical examination, can direct subsequent work-up. For instance, a patient who describes acute recurrent urticaria/angioedema in association with consuming a specific food item is a candidate for performance of immediate hypersensitivity skin testing or determination of serum specific IgE antibody to the appropriate food or foods. Development of acute generalized urticaria/angioedema after Hymenoptera sting in an adult is an indication for further diagnostic evaluation to include immediate hypersensitivity skin testing, determination of serum specific IgE to Hymenoptera venoms, or both.

Annotation 5: Consider limited nonspecific evaluation

A limited laboratory diagnostic evaluation might include select blood tests, such as CBC with differential, erythrocyte sedimentation rate, TSH, and renal and liver profiles. Additional testing might be appropriate depending on the patient's history and physician's clinical assessment.

Annotation 6: Initial treatment

Remove or avoid factors that induce urticaria/angioedema. Once identifiable triggers to acute urticaria and angioedema have been eliminated, evidence supports the use of antihistamines as first-line therapy for persistent symptoms. Second-generation antihistamines are designed through chemical modifications

limiting transfer across the blood-brain barrier to have less sedating effects than first-generation antihistamines, such as diphenhydramine. A trial of a short course of oral corticosteroids can be considered if symptoms are severe or not resolving with antihistamine treatment. In patients presenting with acute urticaria who might have the potential for development of anaphylaxis (eg, food allergen or insect sting), injectable epinephrine should be prescribed.

Annotation 7: Is specific evaluation suggestive of an underlying cause?

If yes, then remove the inciting agent or manage/treat the underlying specific condition.

Annotation 8: Manage specific condition

If no response to specific treatment, then refer to Annotation 6.

Annotation 9: Follow-up in 2 to 6 weeks as symptoms and treatment response dictate

Management of urticaria/angioedema requires frequent follow-up visits to determine whether the intervention, treatment, or both is effective. This allows the physician to make additional recommendations for improving control if necessary. Modifying treatment (step down or discontinue) based on patient response is necessary after 2 to 6 weeks to determine whether hives are persistent and likely to become chronic.

Summary Statement 1: Acute urticaria and angioedema are differentiated from chronic urticaria and angioedema (CUA) based on duration of illness. (D)

The presence of urticaria and angioedema with a 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 sections on autoimmune urticaria, physical urticaria, and CU), such patients should be periodically re-evaluated until a diagnosis is clarified. The distinction of 6 weeks as a dividing interval between acute urticaria and CU, although somewhat arbitrary, is useful because the most common cause of acute urticaria and angioedema, particularly in children, is transient viral infection.[9-16] For this reason, acute urticaria, in contrast to CUA, can often be associated with a specific cause or trigger.

Summary Statement 2: Acute urticaria and angioedema should be differentiated from anaphylaxis. (D)

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. A diagnosis of urticaria/angioedema is made when episodes are primarily limited to the superficial and/or deeper dermis (including mucosal and submucosal tissue) but is not associated with other systemic symptoms.

Summary Statement 3: Epinephrine should be prescribed if the diagnosis of anaphylaxis has not been excluded. (D)

It is important to exclude anaphylaxis in patients presenting with acute urticaria. Like urticaria, anaphylaxis can be associated with specific triggers, such as foods[17,18] or medications, or can be idiopathic.[17-20] Physicians should prescribe epinephrine for patients with acute urticaria/angioedema in whom a diagnosis of anaphylaxis is suspected.[19]

Summary Statement 4: Acute urticaria and angioedema are often but not always related to mast cell and basophil activation from multiple triggers, which include IgE- and non–IgE-mediated mechanisms. (LB)

Mast cells and basophils responsible for acute urticaria and angioedema contribute both to immunity to parasitic infections and inactivation of snake and spider venom.[21-24] Because of the critical role of these cells in the innate and acquired immune response, they express multiple receptors responding to specific antigens, as well as multiple and often nonspecific triggers, such as changes in blood pressure and immunologic activation. Thus it is likely that a variety of different receptors on mast cells, including receptors for complement fragments, circulating immune complexes binding IgG and IgM, and cytokines, might cause mast cell activation in patients with acute urticaria and angioedema in addition to the classical allergic pathways mediated through IgE.[12,25-28]

For example, a specific mast cell or basophil receptor for proteases, including those in dust mite antigens and enzymatic proteins, such as papain, might account for IgE-independent activation of these cells through proteases in aeroallergens and foods, as well as proteases generated by the complement response to infectious agents. This might also suggest a role for serum proteases in patients with acute urticaria.[29]

Summary Statement 5: Acute urticaria and angioedema are more frequently associated with identifiable conditions. When this disorder becomes chronic, it is less likely to be associated with an identifiable cause. (D)

Acute urticaria can be considered a symptom of many diseases rather than a disease itself.[28] The possible causes of acute urticaria/angioedema include physical factors, allergens (eg, food and medication), toxins or sensitizers, and viral or other infections (Table I).[9-13,15,16,30] Exacerbations of physical urticaria causing mast cell activation in the absence of chronic inflammation can be mistaken for acute urticaria. Allergic urticaria associated with specific IgE bound to mast cells can be identified by focused skin testing or laboratory immunoassay.[2,10,17,18,31-34] Acute urticaria can be triggered by ingesting high levels of histamine and other vasoactive amines in scombroid fish.[35-37] Urticaria caused by a toxic reaction from scombroid fish can usually be identified by the clinical history, often with multiple patient reports of symptoms localized to a particular restaurant or dish. Inflammation from parasitic or other acute nonviral infections can also trigger acute urticaria.[38,39] Other less common conditions that can present as acute urticaria or CU, angioedema, or both are discussed in the "Differential diagnosis" section.

Skin testing or laboratory evaluation for allergy to foods, food additives, or aeroallergens not supported by a specific history compatible with IgE-mediated pathogenesis has not been associated with improved outcomes of care and is not recommended. Because acute urticaria and angioedema will usually resolve spontaneously, laboratory evaluation for chronic illness not supported by the clinical history or physical examination and elimination diets are not recommended. Although many cases of acute urticaria are caused by viral or other infectious illness,[9-13,15,16,30] extensive evaluation for specific viral pathogens (or antiviral therapy) is not indicated unless suggested by the clinical history.

In contrast to CU, skin testing or immunoassay to identify specific triggers for acute urticaria and angioedema can be helpful if an allergic cause is suggested based on the patient's history.[17,20] Skin testing in this scenario would usually be done after the resolution of acute hives with suspension of antihistamines or through serologic testing in the presence of significant dermatographism. It is important to investigate the possibility of hidden

allergens, such as latex or foods,[27,33,40-42] in the evaluation of patients with acute urticaria through a combination of history, immunoassay, and prick and patch testing. More unusual food contact or aeroallergen triggers to acute urticaria, such as reaction to fish food in tropical fish breeders or foods in food handlers, can also appear as acute (or chronic) urticaria and should be investigated if there is a suggestive clinical or occupational history.[34,43]

Summary Statement 6: 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. (C)

Acute urticaria is usually not associated with evidence of chronic inflammation or cellular infiltrates of the skin. For this reason, skin biopsy is rarely indicated as long as the lesions are typical of urticaria (ie, duration <24 hours without bruising or purpura).[31] A skin biopsy might be indicated if symptoms and examination suggest mastocytosis, either congenital or acquired, or there is suspicion of urticarial vasculitis.[44] Most often, acute urticaria is a self-limiting condition that will resolve spontaneously in less than 6 weeks, and extensive evaluation for causes not suggested by the history or physical examination is not cost-effective and has not been associated with improved outcomes.[31,45]

Summary Statement 7: Common causes of acute urticaria and angioedema, including medications and foods, should be identified by a detailed history and eliminated, if possible. (C)

Management of acute urticaria and angioedema should be directed at identifying specific triggers (eg, foods and medications), as suggested based on the history, and focused testing combined with symptomatic relief.[31] A recently recognized syndrome of acute urticaria/angioedema with a delay of 3 to 6 hours after the ingestion of beef, pork, lamb, or venison has been recognized.[46] The mechanism for this delayed reaction is not understood. Urticaria or angioedema caused by medications requires a careful history. For instance, ACE inhibitors can cause angioedema after months or even years of therapy[47-49]; over-the-counter medications, such as aspirin or NSAIDs, or herbal remedies containing aspirin or aspirin-like drugs, can be associated with acute relapsing urticaria/angioedema, and this exposure might not be reported to physicians without specific questioning.[20,37,50-55] Aspirin and NSAIDs should be avoided, as feasible, with substitution of an equally efficacious alternative (eg, acetaminophen or a selective COX-2 inhibitor) not commonly associated with urticaria.[52,55]

Summary Statement 8: In most cases antihistamines are efficacious for therapy of acute urticaria and angioedema. (B)

Once identifiable triggers to acute urticaria and angioedema have been eliminated, high-quality evidence supports the use of antihistamines as first-line therapy.[56-61] The clinician should be encouraged to obtain objective assessments of percentage of body covered in hives, itch severity, and quality of life at the initial visit and each subsequent visit as a means for determining initial therapy and gauging response to therapy.[4-8] Second-generation antihistamines are designed through chemical modifications limiting transfer across the blood-brain barrier to have less sedating effects than first-generation antihistamines (eg, diphenhydramine).

Although first-generation antihistamines are rapidly acting and effective for occasional symptoms, 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,

although these impairments are less evident or not evident in second-generation antihistamines as a class. With first-generation antihistamines, prominent anticholinergic effects, including dryness of the mouth and eyes, constipation, inhibition of micturition, and potential provocation of narrow-angle glaucoma, can occur. Because of co-occurring conditions (eg, increased intraocular pressure, benign prostatic hypertrophy, and pre-existing cognitive impairment) that can increase the potential risk associated with regular or even intermittent use, first-generation antihistamines should be prescribed with caution in older adults.[62-86]

Other studies have shown that with regular use, tolerance to the sedating effects of first- generation antihistamines can develop.[31,87-90] Antihistamines might interact unpredictably with other medications or alcohol, and patients might prefer first-generation antihistamines for their sedating properties in cases in which urticaria interferes with sleep. Moreover, higher than FDA-approved doses of some second-generation antihistamines can cause sedation. When agents that can cause drowsiness or impair performance are prescribed, adult patients and parents of patients who are children should be made aware of this potential side effect.

Multiple studies have compared first- and second-generation antihistamines, which differ in *in vivo* and *in vitro* in parameters such as histamine receptor binding affinity, onset of activity, and metabolism.[31,87-90] Second-generation antihistamines are effective in patients with acute urticaria when used on a regular basis and titrated to an effective dose in most patients, with reassuring long-term safety, even in small children.[15] Individual patient responses to different antihistamines can vary, both with respect to efficacy and dose-related sedation and impairment of performance. For this reason, management frequently entails periodic follow-up to monitor efficacy and untoward effects of medications and to individualize dosing of medication to optimize response to therapy.

Other medications with potent antihistaminic activity, such as doxepin, might have efficacy for patients for whom conventional (or graduated) doses of FDA-approved antihistamines lack sufficient efficacy. Histamine 2 blockers, in combination with H_1-antihistamines, might be considered as an additional therapeutic option; however, the evidence supporting this combination is weak.[31]

Summary Statement 9: In severe cases oral corticosteroids might be necessary to treat acute urticaria and angioedema. 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. (C)

A trial of a short course of oral corticosteroids can be considered if symptoms are severe or not resolving with antihistamines.[31,91] A randomized controlled study in adults demonstrated that time to resolution of acute urticaria was decreased with addition of oral corticosteroids to antihistamines in an emergency department setting.[92] A small study in both adults and children showed more rapid resolution of acute urticaria with oral corticosteroids in comparison with antihistamines.[93] However, these findings suggesting a benefit of oral corticosteroids for acute urticaria are not sufficient to warrant routine use of oral corticosteroids rather than antihistamines.[28,94]

Use of oral corticosteroids for acute urticaria/angioedema[95] is common in an adult emergency department setting. Dose-related

side effects of oral corticosteroids, such as adrenal suppression, effects on growth, or bone mineralization, are unlikely with short-term use (<2 weeks); however, patients should be aware of possible changes in mood, gastric upset, and transient weight gain in association with a brief course of oral corticosteroids. Optimal oral corticosteroid dosing has not been determined in controlled studies. Because oral corticosteroid dosing and responses will vary significantly and unpredictably, patients receiving oral corticosteroid therapy should be clinically monitored for response to therapy, side effects, and effects on comorbid conditions, such as hypertension and diabetes.

DIAGNOSIS AND MANAGEMENT OF CHRONIC URTICARIA AND ANGIOEDEMA (FIG 3)

Annotation 1: Patient presents with history suggestive of CU, angioedema, or both

Patients who present with episodes of urticaria, angioedema, or both that persist for greater than 6 weeks have CU, angioedema, or both. Patients who have had recurring or periodic urticaria, angioedema, or both can also be considered to have CU, angioedema, or both depending on the frequency and timing of episodes (eg, progesterone-associated dermatosis). Episodes of acute urticaria are usually short lived. Patterns of development will help clinicians to define the cause in most of the recurrent episodes of acute urticaria (eg, food, drug, insect sting, and contact).

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 sensation might be described in some cases (such lesions can be associated with angioedema or 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 purpuric and can last for several days or more, often followed by residual hyperpigmented changes, although in some cases lesions might be more evanescent, as seen in ordinary CU. Systemic symptoms of joint pain, fatigue, or shortness of breath might be present. Angioedema typically appears as brawny nonpitting edema, typically without well-defined margins and erythema. Commonly, areas affected by angioedema include the lips, tongue, eyelids, and genitalia.

Annotation 2: Does patient have angioedema only?

In 40% to 50% of patients with urticaria, angioedema will also be a part of the spectrum. When angioedema occurs alone, the decision point should shift toward the angioedema algorithm pathway (Box 3 in Fig 3). In most instances the angioedema that occurs alone can last for greater than 24 hours and be nonpruritic. Otherwise, if urticaria occurs at any point, proceed with Box 4.

Annotation 3: Consider medications, C1-inhibitor syndromes, or conditions that mimic angioedema

As with urticaria, an underlying cause for the angioedema might not be apparent despite adequate history, physical, laboratory, and radiologic evaluation. Episodic angioedema, particularly in combination with a positive family history, warrants evaluation for C1-inhibitor deficiency with measurement of C4 and possibly C1-inhibitor antigen and function. Complement abnormalities warrant respective laboratory evaluations for autoimmune disease, malignancies, or C1-inhibitor deficiency. For a patient taking an ACE inhibitor, drug discontinuation and replacement with an equally efficacious alternative

agent should be considered. Excluding physical causes of angioedema (eg, pressure and vibratory) is important in defining treatment. Persistent angioedema of the lips might be a manifestation of Melkersson-Rosenthal syndrome or contact dermatitis. Obtaining a CBC with differential is important in defining episodic angioedema with eosinophilia. Thyroid ophthalmopathy (swelling of the inner aspect of the eyelids) might be mistaken for angioedema in patients with hypothyroidism. Swelling that occurs in the upper torso/face might be due to superior vena caval syndrome, which could be confirmed by using chest radiography.

Annotation 4: Are the history, review of systems, and physical examination consistent with CU?

The history, review of systems, and physical examination can be very important in determining whether CU is truly CU versus a masquerading diagnosis and aid in directing any further laboratory or other diagnostic work-up. If the history, review of systems, and physical examination point away from CU as the diagnosis, then alternative diagnoses should be considered (go to Box 5). If the patient's urticaria, angioedema, or both are exclusively or primarily triggered by an external physical trigger, then the diagnosis is likely a primary physical urticaria/angioedema syndrome, and the work-up should proceed to Box 6. If the urticaria/angioedema is only partially triggered by physical factors or not at all, then it likely fits under the category of CU, and the work-up should progress to Box 10.

Annotation 5: Consider alternative diagnoses

Consider alternative diagnoses (see the "Differential diagnosis" section).

Annotation 6: Does the history suggest physical urticaria? Is there a physical component to the urticaria, angioedema, or both?

Depending on the particular physical factor suspected as the trigger of urticaria or angioedema, in the context of a compatible history, physical examination, or both, physical challenge procedures can be used to confirm the diagnosis (go to Box 7).

Annotation 7: Consider appropriate challenge testing for physical urticaria

If the diagnosis is confirmed by physical challenge testing, the diagnosed physical urticaria/angioedema condition should be managed with a combination of avoidance measures, as appropriate (eg, cold, pressure, and vibration). This will likely also lead to prescribing medications similar to patients with "nonphysical" CU (see the CU treatment algorithm, Fig 1).

Annotation 8: Does the history or physical examination suggest vasculitis?

Urticarial vasculitis is a condition separate from urticaria. These lesions often, but not always, persist for greater than 24 to 48 hours; can be more burning or painful than pruritic; and might leave a discoloration (eg, sprinkled nutmeg appearance) after the wheal resolves. The evaluation becomes focused on vasculopathies if a diagnosis of urticarial vasculitis appears likely. A biopsy is important for confirming the diagnosis of vasculitis (go to Box 9).

Annotation 9: If the skin biopsy is diagnostic for vasculitis, manage vasculitis; if negative, then proceed to Box 10

Classic elements in the histopathology of a skin biopsy specimen to diagnose vasculitis include fibrinoid necrosis, leukocytoclasis, and infiltration of the small-vessel walls by neutrophils. Low complement component (C3 and C4) levels suggest hypocomplementemic urticarial vasculitis, which should

prompt evaluation of renal, connective tissue, and pulmonary systems. In cases of CU with a high suspicion for cutaneous vasculitis with a negative biopsy result, repeat biopsy for hematoxylin and eosin staining and direct immunofluorescence of lesions, preferably within 24 hours of onset and reviewed by a dermatopathologist, might be warranted. If vasculitis is confirmed, management generally requires use of an immunosuppressant medication. The antihistamine and anti-inflammatory agents used for CU, as well as nonsteroidal anti-inflammatory agents, such as indomethacin, can have some benefit as adjuncts in vasculitis but usually lack complete efficacy as monotherapy. If a biopsy result is negative, go to Box 10.

Annotation 10: Are history, physical examination, and/or basic laboratory tests indicative of an underlying cause?

If the history and results of physical examination are consistent with CU, the odds of identifying an underlying condition as the cause of CU are quite low. However, as noted in Table II, consensus recommendations favor performance of limited laboratory testing to confirm or rule out an underlying condition, such as infection, autoimmune disease, or an endocrine disorder, although no testing might also be appropriate based on the physician's judgment in the context of patient circumstances. If the answer to Box 10 is yes, proceed to Box 11 to address the specific condition. If no, proceed to Box 12 for initiation of pharmacotherapy. The term "chronic idiopathic urticaria" is appropriate for cases in which no underlying cause can be identified for CU. History taking and physical examination should be performed, keeping in mind the various possible causes of CU and that the vast majority of cases will fall into the idiopathic category (which includes "autoantibody-associated urticaria"). If the history or physical examination generates suspicion for an underlying medical condition associated with CU, this can be investigated further. If a physical urticaria/angioedema condition is suspected, this can be evaluated further with specific challenge tests. The evaluation of physical urticarias might include some laboratory evaluation (eg, measurement for cryoglobulins in patients with cold urticaria). An extensive laboratory work-up, including skin testing to inhalants and foods, is of limited use and not recommended. There is no correlation between the number of screening laboratory tests done and detection of an underlying diagnosis in patients whose presentation is consistent with CIU. Autoantibody-associated urticaria refers to the presence of autoantibodies in conjunction with urticaria. Even though autoantibody-associated urticaria can be differentiated from CIU by the presence of an autoantibody or autoantibodies, the cause and therapeutic and prognostic value of this autoantibody or autoantibodies have not been established. For this reason, autoantibody-associated urticaria should be considered a subset of CIU. Treatment of CIU should follow the step-care treatment approach outlined in Fig 1.

Annotation 11: Evaluate and manage specific conditions

Eliminate or treat an underlying cause, if identified. Remove or minimize factors that can augment or induce urticaria/angioedema.

Annotation 12: Management of CU/angioedema and periodic reassessment for underlying cause and response to therapy

Management entails realistic expectations, daily use of medications, appropriate avoidance measures, and regular follow-up. The treatment algorithm (Fig 1) defines what can be considered for patients with CU.

Patients with CU require regular medications to suppress the tendency for urticaria/angioedema. Periodic reassessment is important to determine response to therapy and to evaluate clinical changes over time. Further work-up might be needed to rule out underlying causes or development of concomitant conditions that can manifest later in the clinical course.

A more detailed evaluation might be warranted for selected patients. Such re-evaluation could include additional laboratory testing or skin biopsy. If a biopsy is considered, consider conditions that might require special testing (eg, immunofluorescence for bullous diseases and special staining for mast cell disease) and coordinate this with a dermatopathologist to ensure the correct media for the specimen is used.

Objective assessments of the percentage of the body covered in hives, itch severity, and quality of life at the initial visit and each subsequent visit[4-8] are also important to evaluate medication requirements and quality-of-life issues for the patient and his or her family. Complicating factors, such as use of nonsteroidal anti-inflammatory agents, which can aggravate urticaria, or an ACE inhibitor in a patient with episodic angioedema complicating his or her clinical course, are examples of medications that might compromise patient outcomes. Lack of salutary response to antihistamines taken regularly can also suggest that further evaluation for an alternative condition is warranted. Informing the patient of the need for reassessment and the value of the visit might enhance compliance for follow-up.

Summary Statement 10: CU is defined as urticaria that has been continuously or intermittently present for at least 6 weeks. (D) The duration of CU varies considerably; however, physical urticarias tend to persist the longest, often for many years. (C)

Urticaria/angioedema persisting for 6 weeks or longer is designated as chronic. When no underlying cause is found, CU has been referred to as CIU.[96] The prevalence of CU in the general population has been estimated to range from 0.5% to 5%[97-99]; however, the true point prevalence, cumulative prevalence, and lifetime prevalence of CU have not been established. Incidence has been estimated at 1.4% per year.[100] Studies have generally shown an increased prevalence in female subjects, with the female/male ratio of patients with CU ranging from 7:3 to as high as 4:1.[97,99] Data on the natural history of CU are limited and vary based on the type of center, referral patterns, and type of urticaria. Physical urticarias tend to have a longer duration than CIU, typically persisting for many years.[101,102]

Summary Statement 11: Some patients with CU might have both urticaria and angioedema, occurring simultaneously or separately. (C)

The majority of patients with CU have both urticaria and angioedema, although a minority have either urticaria or angioedema alone.[99,103] Patients with angioedema without concomitant urticaria might merit further evaluation to rule out C1-inhibitor deficiency or might be candidates for suspension of an ACE inhibitor (or angiotensin receptor blocker).

Summary Statement 12: Skin mast cells are the most important cells in patients with CU, and histamine is the predominant mediator, although other cells and mediators also play a key role. [LB] 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 for CUA severity. (C)

Histamine is the most important biochemical mediator in patients with urticaria.[96] It is known to cause the classic wheal-and-flare response seen with urticaria and allergen-provoked

wheal-and-flare reactions. Histamine is present in fluid taken from urticarial wheals.[104] Histamine and the other mediators can be released by other nonallergic mechanisms. For example, neuropeptides are known to cause mast cell degranulation.[104] In addition to histamine, other mast cell mediators, particularly the cysteinyl leukotrienes, are also thought to play a role in urticaria.[104]

Mast cells (tryptase and chymase) are the major histamine-releasing cells of the skin. Numbers of mast cells can be increased in urticarial lesions compared with unaffected skin.[104] Basophils have also been found in skin lesions, and basophil abnormalities might play a role in patients with CU.[105,106] Some patients with CU have lower circulating basophil counts and basophils that are hyporesponsive to nonspecific stimulation through FcεRI.[105,107] Other inflammatory cells are commonly recruited into the lesional areas in patients with urticaria, particularly in those with CU.[104] A predominantly lymphocytic infiltrate can be found in the lesions of patients with both the acute and chronic types of urticaria. Many patients demonstrate urticarial lesions that have a mixed cellular infiltrate: a mixture of lymphocytes, PMNs, and other inflammatory cells. The mixed infiltrate is similar to the histopathology of the allergic late-phase response.[108] Some overlap with features of vasculitis can occur.[109] The lesions of urticaria can be triggered by IgE-mediated and non–IgE-mediated mechanisms.[110]

Activation of the coagulation cascade, including increased levels of prothrombin fragment F1+2 and D-dimer, has been described in patients with CU[111-113] and might be a marker for CU severity.[112-115] A systematic review[116] concluded that based on the small sample size in a number of these studies and the lack of consistency of this association, including differences with measuring D-dimer levels by using a latex agglutination immunoassay or an ELISA, additional studies are required to establish these markers as prognostic aids for identifying patients with CU who are at risk for a more severe course of disease. If identified reliably, the potential value of such markers is substantial because patients with more severe CU might also be more likely to have longer disease duration[117,118] and would be candidates for earlier initiation of alternative agents (see below).

Summary Statement 13: Evaluation of a patient with CU should involve consideration of various possible causes. Most cases do not have an identifiable cause. (C)

Although IgE-mediated reactions to a particular allergen are much more likely to be possible causes of acute urticaria, such reactions might also merit consideration in properly selected patients with CU. IgE-mediated reactions can result from foods, drugs, or other allergens. However, these are rare causes for CU.[119,120] If such a cause is found to be responsible for recurring urticaria, withdrawal of the exposure would lead to resolution of urticaria, and this type of urticaria might be better classified as recurrent acute urticaria.

Non–IgE-mediated release of mast cell mediators can also occur as a cause of both acute urticaria and CU, an example being urticaria caused by aspirin or other NSAIDs.

A number of chronic infectious processes have been reported in the literature as causes of CU. The incidence of each of these has not been well established. Examples of reported infections include viral infections, such as hepatitis B and C, EBV, and herpes simplex virus, and helminthic parasitic infections. There are no convincing data implicating occult infections, such as *H pylori*, chronic sinusitis, and cutaneous fungal infections,[121-124] as causes of CU.

CU has been reported with a number of systemic conditions, many of which have a complement-mediated or immunologic basis. These include specific complement component deficiency; cryoglobulinemia (eg, with hepatitis C and chronic lymphocytic leukemia); serum sickness or other immune-complex mediated processes; connective tissue diseases, such as 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 (eg, ovarian tumors) as well as oral contraceptive use.

CU triggered exclusively by specific physical causes (eg, heat, cold, pressure, and vibration) is considered a distinct entity. However, physical urticaria/angioedema can occur concomitantly in patients with CIU.

Autoantibody-associated urticaria refers to the presence of autoantibodies in conjunction with urticaria. Autoantibody-associated urticaria can be considered a subset of CIU. However, even though autoantibody-associated urticaria can be differentiated from CIU by the presence of an autoantibody or autoantibodies, the etiologic, therapeutic, and prognostic value of this autoantibody or antibodies has not been determined.

Summary Statement 14: Numerous autoimmune disorders, including SLE, dermatomyositis and polymyositis, Sjögren syndrome, type 1 diabetes, rheumatoid arthritis, celiac disease, and Still disease, have been associated with CU. (C)

Urticaria can be a presenting symptom of an underlying autoimmune disorder, such as rheumatoid arthritis, adult-onset Still disease, SLE, Sjögren syndrome, type 1 diabetes mellitus, celiac disease, and polymyositis or dermatomyositis. This emphasizes the need to consider atypical and uncommon presentations of these conditions.[125-130] The mechanisms for these associations have not been determined.

Summary Statement 15: Serology to diagnose 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. (B)

A number of cross-sectional studies have investigated whether patients with CU are more prone to autoimmune disorders. Ryhal et al[131] compared results of testing on sera from 25 consecutive patients referred for urticaria with those of 75 subjects being treated for other conditions. Antibodies to thyroid peroxidase (also known as thyroid microsomal antibody) and rheumatoid factor were found more commonly in sera from patients with CU ($P < .01$ and $P < .05$, respectively) compared with control sera. However, there was no difference in the prevalence of other autoantibodies between the 2 groups. The autoantibody test panel included anti-thyroglobulin, anti-sDNA, anti-Ro/anti-La ribonucleic acid antibodies found in Sjogren's syndrome, extractable nuclear antigen profile, anti-cardiolipin, anti–β_2-glycoprotein 1, anti-myeloperoxidase, anti–proteinase 3, anti–smooth muscle, anti-nuclear antibodies, anti-human lysosome-associated membrane protein, and anti-bactericidal permeability-increasing protein. These data imply that broad nonspecific autoantibodies are not commonly found in patients with CU.

Summary Statement 16: Thyroid autoantibodies are frequently identified in patients with CU. (C) The clinical relevance of these tests for patients with CU has not been established.

The relationship between CU and thyroid autoantibodies was originally suggested by a number of clinical observational

reports. Leznoff et al[132] reported 17 (12.1%) of 140 patients consecutively seen with CU versus 27 (5.6%) of 477 patients without CU had thyroid autoantibodies manifested as high titers of thyroid microsomal antibodies. Eight of these patients were subsequently found to have a goiter or thyroid dysfunction, and all 17 of the patients with CU with thyroid autoantibodies also had angioedema. An extension of this initial observation confirmed that 90 (14.4%) of 624 of consecutive patients with CU had evidence of thyroid autoantibodies, which was larger than the number calculated by chance alone in the normal population.[133] Fewer reports regarding thyroid autoantibodies and CU are available in children. One study found that 8 (4.3%) of 187 children and adolescents with CU had thyroid autoantibodies, and interestingly, all were female.[134] Although thyroid autoantibodies are identified more frequently in patients with CU compared with the general population, there is no clear evidence that management of CU or the course of CU differs in this subgroup, nor is there persuasive evidence that administration of thyroid hormone supplementation in such cases is associated with improved outcomes. 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.

Summary Statement 17: Chronic urticarial vasculitis, associated with low or normal complement levels, can present as a primary autoimmune disorder or develop secondary to an autoimmune disorder, such as SLE. (B)

Case series have been reported describing patients with normal or decreased complement levels and CU-like lesions. Urticarial vasculitis is a rare entity characterized by nonblanching lesions that usually last longer than 24 hours and leave residual marks. They are often painful lesions and have most commonly been associated with SLE, juvenile rheumatoid arthritis, hepatitis B or C, cryoglobulinemia, and paraproteinemia.[135] The diagnosis of this condition should be confirmed by a biopsy demonstrating leukocytoclastic vasculitis. This condition has also been described as a primary condition in patients presenting concurrently with angioedema, ocular inflammation, glomerulonephritis, and obstructive lung disease.[136,137]

Summary Statement 18: Urticarial vasculitic lesions can sometimes be evanescent, lasting less than 24 hours, which is similar to CU. For this reason, urticarial vasculitis cannot be completely excluded based on the history of lesions spanning less than 24 hours. (B)

A recent study investigating the clinical characteristics of idiopathic urticarial vasculitis examined skin biopsy specimens obtained from 312 subjects with treatment-unresponsive CU, of whom 47 were given a histologic diagnosis of urticarial vasculitis.[138] Biopsy specimens were obtained irrespective of the clinical features of wheal eruption; other diseases known to be associated with small-vessel vasculitis were previously excluded. Among the patients with urticarial vasculitis, individual wheals lasted less than 24 hours in 57.4% of patients, and pain or tenderness was reported by only 8.6% of patients.[138,139] These data imply that patients whose urticarial lesions span 24 hours or less might still have urticarial vasculitis.

Summary Statement 19: 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. (C)

H pylori has been associated with CU in a number of studies.[140-144] Other infectious agents have been associated with CU in case reports or case series. Early case studies demonstrated an association between the presence of *H pylori* and urticaria and suggested this association might be more prevalent in patients with a positive ASST result.[140-142] However, more recent studies did not confirm such a relationship between ASST and *H pylori*.[143,145] A systematic review[146] found that evidence supporting the utility of testing for and treating *H pylori* in patients with CU has yielded conflicting results and suffers from substantial methodological limitations. For this reason, routine testing for *H pylori* is not recommended.

Case studies have suggested an association between celiac disease and CU in children.[147,148] However, 2 case-control studies conducted in 2005 arrived at different conclusions; one found an association, and one did not.[149,150] Additional studies are required to substantiate an association between celiac disease and CU.

Summary Statement 20: Malignancies, such as lymphoproliferative diseases and Schnitzler syndrome, can present with CU. (C)

The clinician should be aware that although rare, malignancies can present with CU. There are case reports describing CU in association with a number of different malignancies, including Schnitzler syndrome, Waldenstrom macroglobulinemia, Hodgkin disease, hairy cell leukemia, and piloleiomyomas.[151-155] A case of Schnitzler syndrome was described in which the patient produced IgG$_3$ antibodies against dermal microvascular endothelial and mast cells and IgG$_2$ to the FcεR1α subunit, suggesting T$_H$1-induced autoantibodies.[151]

Summary Statement 21: Approximately 30% to 50% of patients with CU produce specific IgG antibodies against the FcεR1α subunit component of the high-affinity IgE receptor. (C)

Up to 60% of patients with CU can have autoantibodies to FcεRIα or IgE itself; 30% to 50% of patients with CU produce specific IgG antibodies against the FcεRIα subunit component of the high-affinity IgE receptor and 10% to the IgE molecule itself. Patients with autoantibody-associated urticaria might produce specific IgG antibodies to FcεRIα or the low-affinity FcεRII (CD23) receptor on mast cells, basophils, or eosinophils. Patients with autoantibody-associated urticaria can also have histamine-releasing autoantibodies or IgG antibodies directed against IgE. The proposed mechanism of autoimmune-induced CU is due to cross-linking of IgE receptors by an IgG antibody to the FcεRIα subunit, resulting in the release of bioactive mediators, such as histamine.[156-158] The presence of thyroid autoantibodies might be more frequently found in patients with CU with anti-IgG antibodies to the FcεRIα subunit; a cause-and-effect relationship between these antibodies has not been established.[159]

Summary Statement 22: The utility of the ASST and APST is unclear because evidence has not clearly demonstrated that this testing identifies a distinct subgroup of patients with CU. Current evidence does not support routine performance of ASSTs or APSTs in patients with CU. (C)

The ASST and APST have been proposed as useful screening tests for identifying patients with autoantibody-associated urticaria. Assays developed to measure autoantibodies against the α-chain of the high-affinity IgE receptor might be hindered by the presence of natural IgE antibodies bound to these receptors. Artificial removal of IgE from the receptor by using lactic acid

stripping results in high levels of antibodies against the high-affinity IgE receptor, regardless of whether they are pathogenic.[160] A recent study comparing the 2 *in vitro* tests, basophil histamine release and CD63 upregulation, which measure IgG autoantibodies to IgE or IgE receptors, found a strong correlation between these 2 assays, but histamine release was more sensitive.

A positive ASST result does not consistently correlate with results of *in vitro* assays.[161] Positive ASST results have been observed in patients with allergic rhinitis and healthy control subjects without CU.[14] The cellular infiltrate of patients with CU with and without autoantibodies does not differ nor is there a difference in T_H2 cytokine profiles in skin lesions between patients with CU with and without FcεRI autoantibodies.[108,162] These and other findings suggest that positive ASST results might not identify a distinct subgroup or influence the management of CU. For this reason, current evidence does not support routine performance of ASSTs or APSTs in patients with CU.

Summary Statement 23: There are no definitive studies that demonstrate 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. (C)

Double-blind, placebo-controlled trials initially reported efficacy with cyclosporine in patients with a positive ASST result.[163-165] However, benefit was subsequently also reported in patients with negative ASST results.[166] Treatment with hydroxychloroquine has been demonstrated to be efficacious, irrespective of a positive or negative ASST result.[167] One randomized double-blind, placebo-controlled study demonstrated that combination therapy with zafirlukast and cetirizine was more efficacious in patients with positive ASST results compared with those with negative ASST results.[4] One case report described complete resolution of CU in a patient with a positive ASST result refractory to all medications after treatment with intravenous cyclophosphamide. The patient's ASST result converted from positive to negative after treatment. This case supports the functional importance of the FcεRIα subunit antibody because treatment with cyclophosphamide, which specifically targets antibody-producing B cells, resulted in complete resolution of hives and conversion from a positive ASST result to a negative ASST result.[168] A subsequent case report with oral cyclophosphamide confirmed this observation.[169] More recently, a case of successful treatment with rituximab in a patient with refractory chronic autoimmune urticaria caused by IgE receptor autoantibodies was reported.[170] More studies are needed to further substantiate the contention that documentation of a positive ASST result has clinical relevance for CU management.

Summary Statement 24: 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. (LB)

$CD45RO^+$ and $CD4^+/CD45RO^+$ cells correlate with the wheal diameter of ASST result in patients with CU, suggesting that memory T cells might play a role in the pathogenesis of CU.[171] Soluble CD40 ligand, a marker present in patients with autoimmune diseases, was found to be increased in patients with CU with positive ASST results compared with that seen in patients with positive ASST results. This suggests that soluble CD40 ligand is involved in immune activation of mast cells and leukocytes in patients with CU with positive ASST results.[172] Basophil response and autoantibodies remain stable in patients with active

CU; however, as patients with CU evolve into a state of remission, basophil function is enhanced, whereas autoantibody levels do not change.[173]

Patients with CU might have underlying structural and/or functional mast cell and/or basophil defects.[105,106,174,175] The clinical role of these mast cell and/or basophil phenotypes is not yet known. Increased expression of the cytoplasmic phosphatase Src homology domain 2–containing inositol phosphatase has been reported as a possible explanation for decreased basophil hyporesponsiveness to nonspecific stimulation (with polyclonal anti-IgE),[107] but the role (if any) of this increased phosphatase expression in the pathophysiology of CU is not yet known, and decreased responsiveness of basophils might be a consequence of having urticaria rather than its cause.[119] Some studies suggest that the same phenotypes of CU and autoantibody-associated CU might be present in similar proportions in pediatric patients as well.[176,177] It is hypothesized that these autoantibodies are present in the circulation and lead to activation of infiltrating basophils or skin mast cells, thereby causing urticaria/angioedema, although conclusive evidence of this mechanism is still lacking.

These autoantibodies might "short circuit" the IgE–mast cell system, activating high-affinity IgE receptors without any need for allergen-specific IgE to be bound to the IgE receptors.[109] Thus far, despite the presence of 2 different CU phenotypes (based on the presence or absence of specific autoantibodies), studies have noted minimal differences in clinical presentation,[178] histology,[108,179] or response to therapy between patients of the 2 subgroups and have found that skin biopsy specimens of wheals from patients with CU show a similar pattern of infiltration with eosinophils, neutrophils, basophils, and lymphocytes, regardless of whether the CU is associated with presence of autoantibodies.[108,109,179]

Summary Statement 25: For patients with CU who present with an 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. (C) Targeted laboratory testing based on history or physical examination findings is appropriate, and limited laboratory testing can be obtained. (E)

An external cause cannot be identified in the overwhelming majority of patients with CU.[103,180] The source literature from which the estimate of 80% idiopathic was likely generated[103] might have overestimated the number of cases with an identifiable cause; for this reason, the percentage of cases that are "idiopathic" is probably greater than 80%.[181] Patients for whom a cause is not identified have been labeled as having CIU.[110] Laboratory abnormalities identified in routine extensive testing have not been shown to lead to changes in management associated with improved patient care outcomes.[182] With rare exception, CU is not related to IgE-mediated responses to inhalant or food allergens; accordingly, routine performance of skin or *in vitro* testing to assess the presence of IgE-mediated potential to inhalants or foods is also not cost-effective and not recommended. Targeted laboratory testing based on history and/or physical examination (eg, obtaining TSH in a patient with weight gain, heat/cold intolerance, and thyromegaly) is recommended. Limited laboratory testing in patients with CU with an unremarkable history and physical examination 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.

Key aspects of patient evaluation are summarized in Table II.

Summary Statement 26: The initial patient evaluation should be focused to determine (through history and physical examination) whether the lesions that patients described are consistent with CU. (D)

The lesions of CU 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.[96] Individual urticarial lesions usually fade within 24 to 48 hours, but new lesions can develop simultaneously at other skin sites.[96] In contrast, vasculitis lesions are palpable and usually nonblanching. Such lesions can span several days or more and are often followed by residual hyperpigmented changes, although in some cases lesions might be more evanescent, similar to ordinary CU.[184] Angioedema typically appears as nonpruritic, brawny, nonpitting edema, typically without well-defined margins and without erythema. Common areas affected by angioedema include the lips, tongue, eyelids, and genitalia.[136] As recommended for acute urticaria, the clinician should obtain objective assessments of the percentage of the body covered in hives, itch severity, and quality of life at the initial visit and at each subsequent visit as a means for determining initial therapy and gauging response to therapy.[4-8] Photographic documentation of prior episodes might assist the clinician in determining that the patient's self-reported lesions are consistent with urticaria, angioedema, or both.

Summary Statement 27: 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. (C)

History taking and physical examination should be performed, keeping in mind the various possible causes of CU but also recognizing that the vast majority of cases are idiopathic.[96,109,136,175,185] If the history or physical examination generates suspicion for any of the possible underlying medical conditions associated with CU, these can be investigated further.

Summary Statement 28: After a thorough history and physical examination, no further diagnostic testing might be appropriate for 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. (C)

After a comprehensive history and careful physical examination, no further diagnostic testing might be appropriate for patients with CU. Limited laboratory testing can be performed to exclude underlying causes. Targeted laboratory testing based on clinical suspicion is appropriate.[186] Extensive routine testing for exogenous and rare causes of CU or immediate hypersensitivity skin testing for inhalants or foods is not warranted. There is no correlation that has been demonstrated between the number of screening laboratory tests done and detection of an underlying cause for CU. In one report extensive testing uncovered an otherwise undiscovered specific underlying disease process (ie, cutaneous vasculitis, thyroid disease, connective tissue disease, and paraproteinemia) in 1.6% of cases of CU.[186] A more recent study[182] found that although 17% of laboratory tests performed in 356 patients with CU were abnormal and 8.4% of patients subsequently underwent additional testing based on initial findings, only 1 patient had a change in management leading to improvement in CU based on findings from laboratory testing performed at initial evaluation. In 2 other reports a definite cause was found in only 5% or less of patients with CUA.[181,187] These data imply that routine laboratory testing in patients with CU whose history and physical examination lacks atypical features rarely yield clinically significant findings. Limited testing might be justified based on its "reassurance value"; however, extensive routine testing is not favorable from a cost-benefit standpoint and does not lead to improved patient care outcomes.

Summary Statement 29: Screening for thyroid disease is of low yield in patients without specific thyroid-related symptoms or history of thyroid disease. Increased levels of anti-thyroglobulin or anti-thyroid antibodies in euthyroid (ie, normal TSH) subjects are commonly detected, although the clinical implications of this finding are unclear. (C)

A significant proportion of patients with CU have increased levels of thyroid autoantibodies but are euthyroid.[109] Some patients with these thyroid autoantibodies also have autoantibodies to FcεRIα.[188] Some authors have found that treatment of these euthyroid patients with thyroxine can lead to an improvement in urticaria,[159] but other authors have not been able to reproduce this finding,[133] and to date, there are no large, blind, placebo-controlled trials of thyroxine for patients with CU.

Summary Statement 30: 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. (C)

In vitro assays (eg, the functional basophil histamine release assay or measurement of basophil surface activation marker expression with incubation in sera from patients with CU)[189-192] are commercially available to detect autoantibodies to FcεRI, and an ASST or APST might also be performed.[14,179,193-195] The test that best defines "autoantibody-associated urticaria" is not yet known.[196] The ASST does not consistently correlate with *in vitro* assays. Whether serum or plasma yields best results is unknown.[197] There can be both false-positive and false-negative results with the ASST.[198] Serum samples from patients without CU can also induce positive ASST results[14,195] and *in vitro* histamine release from donor basophils.[199] Therefore the role and accuracy of autoantibody testing (whether by means of ASST or *in vitro* functional antibody testing) in the clinical evaluation and management of CU is unclear. For this reason, patients with positive ASST results should be regarded as having CIU. ELISA-type assays to measure autoantibodies to FcεRI are considered unreliable, which is in contrast to the use of an assay that detects functionally active autoantibodies, as described above.[119,191] Currently, there are no published studies that provide the sensitivities, specificities, or positive or negative likelihood ratios for diagnosis of autoantibody-associated urticaria by using these assays.

Whether detection of autoantibodies identifies a clinically unique population or leads to a change in management is also currently unclear.[196] Some studies have suggested that a positive autoantibody test result might indicate a marker of increased disease severity, but these data are limited[200,201] and can reflect the fact that these populations do not differ clinically and that these autoantibodies might represent an epiphenomenon. For these

reasons, we have included autoantibody-associated CU under the diagnosis of CIU.

Summary Statement 31: Patients with recurrent angioedema in the absence of coexisting urticaria should be evaluated for hereditary angioedema, acquired C1-inhibitor deficiency, or ACE inhibitor–associated angioedema before a diagnosis of idiopathic angioedema is made. (C)

Hereditary angioedema, acquired C1-inhibitor deficiency, and ACE inhibitor–associated angioedema can be associated with severe angioedema and significant morbidity and mortality.[202-206] Evaluation and management of patients with these conditions are substantially different than management of patients with CIU.[207] When C1-inhibitor deficiency is suspected, measurement of the C4 level is recommended as the best initial screening test.[208] A normal C4 level during an episode of angioedema strongly suggests that a diagnosis of C1-inhibitor deficiency is unlikely.

For typical CU (whether with or without angioedema), obtaining routine testing for C4 levels, C1-inhibitor levels, or functional assays is not appropriate because C1-inhibitor deficiency is not characterized by concomitant urticaria.

Summary Statement 32: Skin biopsy can be performed when vasculitis is suspected, such as in patients with refractory CU, or when other nonurticarial immunologic skin diseases are a consideration. Routine skin biopsy specimens are not required in most cases of CU.[109,183] (D)

If vasculitis or another nonurticarial skin disease is suspected at the time of initial work-up or if they later become a consideration because of lack of response to the standard treatment for ordinary CU, then skin biopsy can be obtained. Routine skin biopsy is not recommended for patients with CU.[183]

Summary Statement 33: Immediate hypersensitivity skin or serologic testing for food or other allergens is rarely useful and not recommended on a routine basis. (D)

When immediate hypersensitivity skin testing is carried out, it is more often performed in properly selected patients with acute urticaria. It is rarely indicated in the evaluation of CU. For example, if acute urticaria is thought to be possibly caused by food allergy, stinging insect hypersensitivity, or severe allergy to pollen, cat, or latex, then skin testing would be indicated; however, these are unlikely causes of CU. Furthermore, skin testing is technically difficult in patients with CU. Dermographism might be present. Moreover, patients must withhold antihistamines for a sufficient period of time for testing to be valid.

An adverse reaction to a medication is rarely a cause of CU. Such cases of medication-induced urticaria might be either IgE mediated or non–IgE mediated. For many drugs, validated skin testing protocols have not been established. If favorable from a risk/benefit standpoint, a trial off the suspected agent, although replacing this with an equally efficacious structurally unrelated alternative, can be considered to confirm or rule out the drug as a cause of CU.

PHYSICAL URTICARIA/ANGIOEDEMA

Summary Statement 34: 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 these factors. Patients can present with isolated physical urticaria/angioedema (Table III) syndromes or a combination of syndromes but might also have concomitant CIU.

Patients with 1 or more physical urticaria/angioedema syndromes comprise an important subgroup of patients with CU. In these 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 these factors. These responses range in severity from mild reactions locally at the application of a physical stimulus to systemic mediator release with serious or potentially life-threatening reactions.[209]

Patients can have isolated physical urticaria/angioedema syndromes or a combination of syndromes and might also have concomitant CIU. Delayed pressure urticaria/angioedema (DPUA) can coexist with CIU. Dermatographism and cold urticaria/angioedema can co-occur with other physical urticaria/angioedema syndromes but could be present in isolation. Patients with CIU and a concomitant physical urticaria/angioedema syndrome might be less likely to respond to conventional pharmacotherapeutic interventions.[209-211]

On the basis of methodological limitations, the true prevalence of the physical urticaria/angioedema syndromes is difficult to precisely determine; however, the most common of these syndromes is dermatographism, which is estimated to occur in 2% to 5% of the general population.[212] Cholinergic urticaria accounts for approximately 5% of all cases of CU and 30% of all cases of physical urticaria.[213] The other physical urticaria/angioedema syndromes are uncommon, with cold urticaria reported to have a prevalence of 2% and solar urticaria having an estimated 0.4% prevalence. Patients with vibratory angioedema or aquagenic urticaria are rarely encountered.[209,211]

Aquagenic urticaria

Summary Statement 35: Aquagenic urticaria is a rare condition. Patients 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 applied to the skin of the upper body for 30 minutes. (C)

Patients with aquagenic urticaria, a rare condition, have urticarial wheals within 30 minutes of direct skin contact with water, regardless of temperature.[214,215] Lesions are punctate, 1 to 3 mm in size, perifollicular, and similar in appearance to cholinergic urticaria. Cutaneous lesions can arise during a shower or bath and also with exposure to any source of water, including sea water, melting snow, or perspiration. Heterogeneity exists with respect to the ionic concentration, osmolarity, or both of the liquid capable of provoking a reaction: a patient with aquagenic urticaria has been described who was able to swim in the ocean without experiencing urticaria, whereas patients have also been described who exhibit reactions with hypertonic saline and tolerate distilled water without urtication.[216] Systemic symptoms, including headache and respiratory symptoms, can occur.[214,215] Familial and localized forms of aquagenic urticaria have also been reported.[216,217] Female subjects are affected more often than male subjects. Patients with aquagenic urticaria have no problem consuming water or other liquids. The condition generally begins after puberty but can have its onset in childhood.[218]

The pathogenic mechanism of aquagenic urticaria is not completely understood. It has been proposed that water acts not as an "antigen" itself but as a solvent vehicle for transport of

antigens from the stratum corneum to the dermis, where mast cell degranulation is triggered with release of histamine and other mediators.[219] Removal of the stratum corneum was associated with enhancement of response, implying that the reaction is determined or augmented by the degree of penetration of water beyond the stratum corneum layer of skin.[220] Basophil degranulation with histamine release on water challenge has been described, and intradermal injection of compound 48/80 (a mast cell activator) has elicited wheal formation in patients with aquagenic urticaria.[221,222] A role for acetylcholine, which can initiate sweating, has also has been proposed.[220] However, methacholine intradermal challenge does not elicit a response in patients with this condition.[222] Anticholinergic agents and antihistamines can attenuate or block cutaneous reaction, but this has not been observed consistently.[214]

It is important to distinguish this condition from aquagenic pruritus, which entails provocation of itching without wheal formation.[223] Aquagenic urticaria can be differentiated from cold urticaria by lack of response to an ice cube placed in plastic and applied to the skin. The lesions of patients with cholinergic urticaria and aquagenic urticaria are similar in appearance, and patients with both conditions can have cutaneous symptoms with exercise, in the latter case from perspiration. However, only patients with cholinergic urticaria will have lesions in response to heat, increased core body temperature, or emotional factors (see below). Cases of aquagenic and coexisting cold urticaria and cholinergic urticaria have been reported.[224,225]

Aquagenic urticaria can be confirmed by challenge with a water compress at 35°C applied to the skin of the upper body for 30 minutes.[215] Appearance of "pinpoint" hives at the site of challenge is a positive response. Immersion of a hand or distal upper extremity in water of variable temperature can also be performed to confirm the diagnosis.

Avoidance measures and antihistamines, with or without anticholinergic agents, are the initial treatment of choice. Refractory cases have been reported in which a favorable response was observed with use of barrier creams, selective serotonin reuptake inhibitors, or UV therapy.[215,225,226] One patient with concomitant infection with HIV who was resistant to antihistamine therapy responded dramatically to treatment with stanozolol.[227]

Cholinergic urticaria

Summary Statement 36: Patients 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. (B)

Summary Statement 37: Common provoking factors for cholinergic urticaria include exercise, sweating, emotional factors, and hot baths or showers. (B)

Summary Statement 38: Provocative challenges that increase 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. (D)

Cholinergic urticaria occurs as a result of an increase in core body temperature.[228] Cholinergic urticaria is one of the most common physical urticaria/angioedema syndromes and estimated to comprise at least 5% of all cases of CU.[103,229] In a study of 493 high school and college students examined by

using questionnaires and, in some cases, provocative challenges, 11.2% were found to have the condition.[213] The most common provoking factors for pruritus, urtication, or both were hot showers (71%), sweating (62%), sports (49%), and emotional factors (24%). The majority had limited mild symptoms and were "not troubled" by their condition; 87% did not regard this as a "disease." These findings imply that many patients with cholinergic urticaria do not seek medical attention for their cutaneous symptoms, and the true prevalence of this condition is likely underestimated.

Cholinergic urticarial lesions have a distinctive appearance: they initially appear as punctate or pinpoint (1-3 mm) in size and surrounded by large flares.[230] Lesions can be intensely pruritic. The flares can coalesce, forming large areas of erythema.

The diagnosis of cholinergic urticaria can be suspected based on history. Patients will have had urticaria triggered by factors that increase body temperature and will report the appearance of punctate wheals. Intradermal injection of 0.01 mg of methacholine in 0.1 mL of saline can lead to the appearance of 1 or more "satellite wheals" and can confirm the diagnosis.[231] However, as few as 1 in 3 patients with cholinergic urticaria will exhibit this "positive" response, and those who do, do not do so consistently.[232] Because of its poor negative predictive value, methacholine intradermal challenge might confirm but cannot rule out the diagnosis. Provocative challenges that increase core body temperature, including exercise or hot water immersion, might be associated with more optimal sensitivity. Partial immersion of a patient in a hot bath (42°C) to increase body temperature by 0.7°C or greater has been recommended.[210]

The pathogenesis of cholinergic urticaria generally involves an exaggerated cutaneous response to cholinergic substances. As with other physical urticaria/angioedema syndromes, studies of patients with cholinergic urticaria imply a heterogeneity of mechanisms exists in these patients. Secretion of larger amounts of acetylcholine, greater sensitivity to acetylcholine, impaired cholinesterase activity, hypohydrosis, and antigen-antibody reaction have been proposed as mechanisms.[231-234]

Summary Statement 39: The severity of cholinergic urticaria ranges from mild pruritus to serious and potentially life-threatening reactions. (C)

The severity of cholinergic urticaria varies from mild pruritus and urtication to systemic mediator release with generalized urticaria and angioedema, bronchospasm, and hypotension. Exercise on a treadmill while wearing a plastic occlusive suit resulted in not only cutaneous symptoms but also wheezing with decreases in spirometric parameters.[235] Episodes of cholinergic urticaria provoked by exercise might be difficult to distinguish from EIAn, as described below.[236]

Avoidance measures are important in the management of patients with cholinergic urticaria. Because these measures will frequently be incomplete, most patients benefit from regular use of antihistamines advanced as tolerated to achieve control of the condition. Compared with patients with CU without concurrent physical urticaria, patients with cholinergic urticaria who seek medical care experience significantly more impairment in quality of life that is comparable with that seen in patients with severe atopic dermatitis and greater than that observed in patients with other cutaneous disorders, including psoriasis, Behçet syndrome, and vitiligo.[229,237-240] For patients with cholinergic urticaria whose condition is poorly responsive to antihistamines, use of ketotifen, danazol, and omalizumab has been reported to have a

salutary effect in uncontrolled studies.[241-243] Anticholinergic agents do not have an established role in treatment.[244] Those patients with a tendency to experience severe episodes of cholinergic urticaria should receive a prescription for injectable epinephrine and be educated on its proper use.

Cold urticaria

Summary Statement 40: Patients with cold urticaria have pruritus and swelling with exposure of the skin to a cold stimulus. Patients with cold urticaria can have systemic reactions associated with systemic cold exposure (eg, aquatic activities). (B)

Patients with cold urticaria have localized pruritus, erythema, and edema after exposure to a cold stimulus. Symptoms are typically confined to cold-exposed areas and are generally maximal after the exposed skin is rewarmed. Patients typically have symptoms in the context of skin exposure to cold when outdoors, hand swelling when holding cold objects, or lip/pharyngeal symptoms when ingesting cold foods or beverages.[245,246] Laryngeal or abdominal symptoms are rare. Generalized urticarial reactions uncommonly occur after prolonged cold exposure. Extensive body surface area exposure to cold, such as with swimming, might trigger systemic symptoms, including headache, dyspnea, and hypotension. Fatalities caused by subsequent drowning have been reported.[247]

Several classification schemes have been proposed, with the most common classifying cold urticaria into familial versus acquired syndromes.[248] With regard to the acquired syndromes, primary acquired cold urticaria (ie, essential acquired cold urticaria, primary cold urticaria, or idiopathic cold urticaria) is the most common form. (For further discussion, see the "Differential diagnosis" section.) It affects patients of all ages, from infants to the elderly, and might resolve spontaneously, with studies suggesting a mean duration of symptoms between 4 and 9 years.[248,249] With secondary acquired cold urticaria, the urticarial lesions are associated with an underlying disorder, such as cryoglobulinemia; infectious diseases, such as syphilis, rubeola, hepatitis, respiratory syncytial virus, and infectious mononucleosis; medications, such as penicillin, oral contraceptives, ACE inhibitors, and griseofulvin; leukocytoclastic vasculitis; and even malignancy.[249-255] It has also been associated with bee sting reactions.[256]

With both primary acquired cold urticaria and secondary acquired cold urticaria, positive provocative cold testing should confirm the diagnosis. However, several acquired cold urticaria variants have been described in which results of provocative cold testing are typically negative. Patients with systemic atypical acquired cold urticaria (ie, systemic acquired cold urticaria, systemic cold urticaria, or generalized cold urticaria) have generalized urticaria, angioedema, or both more commonly on areas of the body that are not exposed to the cold, and provocation of skin lesions might be dependent on a decrease in core body temperature with cold exposure.[257] Patients with cold-dependent dermatographism have dermographic wheals on stroking of cooled skin but not on warm skin.[258] With cold-induced cholinergic urticaria, patients will have punctuate urticaria after exercising in cold environments, although not in warm environments.[259] Patients given a diagnosis of acquired delayed cold urticaria have urticarial lesions 12 to 48 hours after cold exposure, typically on cold-exposed skin and mucosal surfaces.[260] Localized cold reflex urticaria is diagnosed when cold-induced urticaria appears at distant skin locations and not at the site of cold stimulation.[261,262]

Hereditary subtypes of cold urticaria have also been recognized. Patients with familial delayed cold urticaria have urticarial lesions 9 to 18 hours after cold exposure, which then resolve as hyperpigmented skin lesions. Family studies suggest autosomal dominant inheritance.[263] Familial cold autoinflammatory syndromes (FCASs) are considered in the differential diagnosis of cold urticaria syndromes, although the erythematous papules and plaques typically developing 1 to 2 hours after cold exposure seen in these syndromes are neither clinically nor histopathologically consistent with urticaria. The FCAS (previously referred to as familial cold urticaria) is a hereditary periodic fever disorder inherited in an autosomal dominant fashion. It typically presents within the first 6 months of life (even at birth), and the delayed rash provoked by natural cold exposure generally is accompanied by fever, arthralgias, conjunctivitis, leukocytosis, and other systemic symptoms.[264] A genetic defect in the *CIAS1* gene has been described in a majority of cases.[265] Recently, another type of hereditary cold urticaria syndrome has been described because of genomic deletions of *PLCG2*, leading to a gain of phospholipase γ2 function.[266,267] Affected subjects have variable manifestations, including antibody deficiency, susceptibility to infection, and autoimmunity. Like patients with FCASs, these patients have negative ice cube test results but, in contrast, have positive results on skin testing for evaporative cooling by using droplets of ethanol or air-blown water.

Summary Statement 41: The diagnosis of cold urticaria can be confirmed by applying a cold stimulus (eg, an ice cube on the forearm) to the patients' skin and observing a wheal-and-flare reaction during rewarming of the skin. Some forms of cold urticaria might have a negative ice cube test result. (B) The primary treatment for cold urticaria is avoidance of cold exposure, as feasible; however, prescribing pharmacotherapy is also frequently advisable. (C)

Cold provocation testing (ie, cold stimulation testing or cold-contact stimulation testing or the ice cube test) can assist in the diagnosis of acquired cold urticaria, although it might not confirm acquired cold urticaria in up to 20% of patients.[248] Various methods have been described, although the most common method involves applying a 0°C to 4°C stimulus (eg, an ice cube in a plastic bag) to the volar aspect of the subject's forearm for 5 minutes and then removing the stimulus such that the skin rewarms to ambient room temperature. The development of a typical wheal-and-flare reaction during the rewarming process is interpreted as a positive test result.[248] If the test result is negative after 5 minutes, it can be repeated in incremental steps for up to 10 minutes of cold stimulation, followed by removal of the cold stimulus and observation, although a threshold time for cold exposure to exclude cold urticaria has not been definitively established.[268] Any cold stimulus should not be applied repeatedly to the same skin location to avoid skin desensitization.

With a cold stimulation time test, if the cold stimulation test result is positive at 5 minutes, it is then repeated at 1-minute decrements to ascertain the minimum time needed to induce a wheal; if it is negative at 5 minutes, it is repeated at 1-minute increments up to 10 minutes to again determine the minimum time needed to induce a wheal.[245,248] The cold stimulation time test might assist the clinician in confirming the diagnosis and determine the response of cold-induced urticaria to medications. Hand immersion in 10°C water for 5 minutes has also been proposed as a diagnostic test, with hand urticaria/angioedema during

rewarming designated as positive, but thermal damage to the skin and systemic reactions (including tachycardia and hypotension) have been reported with this maneuver, and it is not recommended.[209,231]

With regard to management of acquired cold urticaria, avoidance measures must be emphasized because patients with both atypical acquired cold urticaria (with negative cold provocation test results) and acquired cold urticaria with positive cold provocation test results have experienced hypotension and shock with aquatic sports and other cold-weather activities.[245,248] Patients with cold stimulation time test results of less than 3 minutes might be at particularly high risk for systemic symptoms.[245] Laryngeal symptoms induced by exposure to cold food or drink might also be a risk factor independent of systemic symptoms.[269] Injectable epinephrine can be prescribed for patients judged to be at increased risk of systemic reactions. In addition, for those who participate in aquatic activities, swimming with a friend might be recommended. Pharmacologic management with antihistamines are effective in suppressing cutaneous symptoms but cannot be relied on to suppress systemic symptoms, although 1 case report documents a patient with acquired cold urticaria who successfully underwent hypothermic cardiopulmonary bypass with premedication with H_1- and H_2-antagonists and intravenous corticosteroids.[270] Cyproheptadine, doxepin, and combinations of cyproheptadine with cimetidine and hydroxyzine with cimetidine have published efficacy in suppressing symptoms and, in some cases, improving symptom scores and prolonging cold stimulation time test results.[271-274] Ketotifen, montelukast, and cetirizine with zafirlukast might also have some efficacy in case studies.[275-277]

Corticosteroids have little published efficacy in suppressing primary or secondary acquired cold urticaria symptoms.[278] If pharmacologic management is ineffective, induced tolerance to cold urticaria has been attempted by means of gradual immersion of the extremities in cold water at regular intervals until the urticaria ceases.[279,280] Although tolerance can be achieved, noncompliance is high; cold tolerance is rapidly lost if patients do not follow a daily schedule of cold immersion, putting noncompliant patients at risk for unexpected cold-induced systemic reactions.[278,280] Thus cold tolerance protocols are not routinely recommended. For patients requiring surgery, the general recommendation is to increase operating theatre temperatures and prewarm all fluids and blood products to prevent cold-induced symptoms, although as noted above, there is 1 case report documenting successful premedication.[270,281]

DPUA

Summary Statement 42: Patients with DPUA have swelling (which can 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. (B)

Patients with DPUA have swelling with exposure of the skin to a pressure stimulus but do so with a delay of 0.5 to 24 hours, with a peak at 4 to 6.5 hours.[233,282-285] Lesions are erythematous, deep, and painful and are accompanied by a burning dysesthesia more often than they are pruritic.[282] This condition rarely is seen alone; patients with DPUA also have concomitant, chronic, non–pressure-induced or spontaneous urticaria and angioedema.[284,286]

However, in contrast to the latter, the lesions of patients with DPUA occur in association with provocation. Common provoking factors include working with tools, sitting on a bench or hard surface, hand clapping, standing for prolonged periods, or wearing constricting garments.[233,282-286]

Patients frequently do not suspect DPUA because of the delay in response after the application of pressure or trauma to the skin. DPUA should be considered in all patients with CIU who also have frequent angioedema, particularly if this involves areas commonly exposed to pressure (eg, palms, soles, buttocks, and skin folds), and are poorly responsive to antihistamines.[282,283,285] Patients might describe arthralgias, particularly in joints adjacent to pressure-induced areas of swelling. Systemic symptoms, including malaise, fever, rigors, and lassitude, can be present.[233,282,283,285] An increase in the erythrocyte sedimentation rate has been reported in as many as 71% in one series but in only 17% in another report.[233,287] Skin biopsy specimens from patients with DPUA differ from those of patients with CIU in demonstrating an eosinophil- or neutrophil-predominant infiltrate on histopathology, which resembles a late-phase cutaneous reaction.[282,288,289] DPUA lesions demonstrate upregulation of E-selectin and increase in IL-6, TNF-α, and IL-3 expression.[290-292] However, in contrast to patients with refractory urticaria as a reflection of leukocytoclastic vasculitis, biopsy specimens of DPUA lesions show no evidence of venulitis.[289]

Summary Statement 43: DPUA can be confirmed by a challenge with 15 lbs of weight suspended over a patient's shoulder for 10 or 15 minutes. Development of angioedema in a delayed fashion at the site of pressure is considered a positive challenge result. (C)

The diagnosis of DPUA is suspected based on history, laboratory studies, or both and can be confirmed by using a challenge procedure. A pressure stimulus that entails the application of a firm weight or force to a unit area of skin will elicit a response. However, published challenge protocols to confirm a diagnosis of DPUA vary according to the pressure stimulus used, the duration of its application, and the site at which the stimulus is applied. Positive or negative likelihood ratios for the challenge procedures have not been determined. DPUA can be confirmed by means of challenge with a 15-lb weight suspended across the shoulder for 10 or 15 minutes.[282,285] A deep painful wheal at the challenge site occurring 2 to 12 hours later, with a peak between 4 and 6.5 hours, is a positive response. Some protocols stipulate that patients should ambulate with weights suspended over the shoulder, but whether ambulation is an essential component for the challenge is not clear. The challenge procedure for DPUA should be performed at a time when concomitant CU is well controlled. This procedure is not appropriate for certain patients, including patients with severe cardiopulmonary disease or musculoskeletal conditions, such as cervical or lumbar disc disease. Other challenge procedures for DPUA include use of a calibrated dermographometer or an apparatus with weighted metal rods.[287,293,294] An at-home challenge procedure has also been reported with a plastic grocery bag containing either 3 wine bottles filled with water, a house brick, or groceries, with a towel looped through the handles of the bag and tied over the forearm, a 1.5-cm glass sphere (aka, a marble) inserted under the towel, and instructions to leave the bag suspended for 5 minutes and to perform the challenge 6 hours before outpatient evaluation.[284]

Summary Statement 44: Management of DPUA differs from other types of CU/angioedema and 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. (C)

Patients with DPUA can have substantial impairment in quality of life because management entails extensive modifications in activities and lifestyle, including but not limited to changing hobbies, employment, forms of exercise, and even types of clothing that can be worn.[229,295] Patients should be made aware of the relationship between exposure to pressure or trauma and the potential for subsequent exacerbation of their condition and should modify or discontinue activities as appropriate. Avoidance is a critical element of successful DPUA management.

Antihistamines at conventional doses might be efficacious for the treatment of CU but are frequently ineffective for prevention of angioedema provoked by pressure.[282,283,285] Advancing doses of antihistamines beyond FDA-approved levels might be associated with greater efficacy, as has been shown in a double-blind, placebo-controlled study of cetirizine at a dose of 30 mg/d.[296] A short course of systemic corticosteroids might be required for episodes of angioedema that are ongoing despite advancing antihistamine medications. However, long-term systemic corticosteroid treatment is not generally regarded as favorable from a risk/benefit standpoint.

Dramatic benefit with use of NSAIDs has been reported[283,285]; however, no benefit was observed in a double-blind trial of 25 mg of indomethacin 3 times daily.[283,285] Because administration of COX-1–inhibiting drugs can provoke a flare in patients with aspirin-exacerbated urticaria/angioedema, prescribing aspirin or aspirin-like drugs to patients with DPUA should be approached with caution.[297] A randomized double-blind trial demonstrated benefit with combined treatment with nimesulide (a relatively COX-2–selective NSAID that has not been available in the United States) and ketotifen (not available orally in the United States) equivalent to outcomes observed in patients with DPUA randomized to high-dose prednisone.[298] A number of therapeutic interventions have been reported in uncontrolled reports to have a salutary effect for DPUA, including montelukast, sulfasalazine, chloroquine, dapsone, intravenous gamma globulin, tranexamic acid, and anti–TNF-α.[299-304] Randomized controlled trials in patients with DPUA are required to substantiate the therapeutic utility of these agents.

Dermatographia

Summary Statement 45: Patients with dermatographia (also known as dermatographism, dermographia, and dermographism) promptly have 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. (B)

Patients with dermatographia (ie, dermatographism, dermographia, or factitious urticaria) have rapid onset of a standard wheal-and-flare reaction after pressure or mild trauma to the skin. It is one of the most common forms of physical urticaria and reported to be present in 2% to 5% of the general population. Only a minority of patients have symptoms to a degree that prompt medical attention. It can present in overlap with patients with other physical urticarias.[212,305] One case of familial dermatographism has been reported.[306] Several variants of dermatographia have been proposed, with asymptomatic (or nonpruritic) patients experiencing simple dermatographism, in which pressure on the skin with a firm object provokes the erythematous wheal at 6 to 7 minutes, which fades by 15 to 30 minutes.[307] With symptomatic dermatographism, patients experience urticaria less than 5 minutes after provocation, and the lesions can last for more than 30 minutes.[211] Symptomatic dermatographism can also present with follicular or inflamed and swollen variants.[308,309] Key historical components include the presence of pruritus and the development of linear wheals after scratching the skin or the development of linear wheals after leaning on a solid object or resting on clothes or bed sheets with a firm edge. Patients can experience a cycle of symptomatic pruritus, which then provokes wheals after scratching, further exacerbating pruritus. Symptomatic dermatographism has been reported in association with bacterial, fungal, or scabies infection and after treatment with penicillin or famotidine[310-312]; however, in most cases, symptomatic dermatographism is idiopathic.

The diagnosis of symptomatic dermatographia can be confirmed in the outpatient setting by stroking the skin with a firm object, such as a tongue blade or other instrument with a firm edge. A white line that occurs on the skin as a result of reflex vasoconstriction is rapidly followed by pruritus, erythema, and linear swelling in a typical wheal-and-flare reaction. A dermographometer, which is a device that applies a defined reproducible amount of pressure to the skin and is used in office-based diagnosis of delayed pressure urticaria, can also be used to diagnose dermatographia. The threshold for eliciting a response in patients with simple (ie, nonpruritic) dermatographism is 4900 g/cm^2, whereas in patients with symptomatic dermatographism, the threshold is 3200 to 2600 g/cm^2.[209,307,313] The wheal-and-flare response should develop within 1 to 3 minutes, whereas in patients with delayed pressure urticaria, the response might manifest after several hours.

With regard to treatment, avoidance measures, skin hydration, and antihistamines are generally recommended for symptomatic patients. Skin hydration and use of emollients to decrease skin pruritus are typically recommended, with few controlled studies documenting efficacy. Both first- and second-generation H_1-antagonists, such as hydroxyzine and cetirizine, respectively, have been demonstrated to improve symptom control.[308,314-316] The addition of H_2-antagonists to H_1-antagonists might be beneficial but has not improved symptom control in all studies.[317-319] Improvement in symptoms with UVB light therapy has also been reported.[320]

Exercise-induced urticaria and anaphylaxis

Summary Statement 46: Urticaria provoked by exercise can occur in patients with 2 conditions: cholinergic urticaria or EIAn. (B)

Summary Statement 47: There are 2 groups of patients with EIAn: one group can experience anaphylaxis provoked by exercise, and a second group can experience anaphylaxis with exercise temporally related to ingestion of food or medication. (C)

Urticaria provoked by exercise can present as one of 2 distinct conditions: cholinergic urticaria or EIAn. As noted above, patients with cholinergic urticaria have urticaria in association

with activities that increase core body temperature. In patients with EIAn, urticaria can occur as a manifestation of anaphylaxis.

In a recent review of 601 patients with anaphylaxis, EIAn comprised 5% of these cases.[321] Within minutes after onset of exercise, patients with EIAn can experience symptoms associated with release of mediators from mast cells, which can include cutaneous, gastrointestinal, respiratory, and/or cardiovascular symptoms.[321] Such reactions can be life-threatening, and fatalities have been reported.[322,323] An epidemiologic survey of 279 patients with EIAn revealed that jogging was the most frequent exercise precipitating EIAn; however, a variety of activities, including tennis/racquetball, basketball, skiing, dancing, aerobics, and bicycling and even less strenuous activities, such as yard work or walking, have been implicated in provoking EIAn episodes.[324] EIAn in association with natural childbirth has also been reported.[325]

It is important to note that in some patients with cholinergic urticaria, systemic reactions can occur also as a manifestation of aberrant thermoregulatory mechanisms during exercise.[326,327]

Summary Statement 48: Two subgroups of patients with food-dependent EIAn have been described: one group can experience anaphylaxis when exercising in temporal proximity to ingestion of any type of food, and another group can experience anaphylaxis with exercise in conjunction with prior ingestion of a specific food. (C)

Patients with food-dependent EIAn do not have anaphylaxis with ingestion of food without subsequent exercise nor do they have anaphylaxis after exercise without temporally related ingestion of food. The implicated foods in patients with EIAn differ compared with those in patients presenting with IgE-mediated (allergic/anaphylactic) reactions to foods. Food items that have been associated with food-dependent EIAn include but have not been limited to mustard, crustaceans, cephalopods, celery, peaches, egg, wheat, buckwheat, tomato, pistachio, dairy products, lentil, and matsutake mushrooms.[92,323,324,328-338] One case has been described in which the sequence was reversed: anaphylaxis was provoked by food consumption preceded by exercise.[330] Cases of food-dependent EIAn requiring prior consumption of 2 foods related to contamination of pancakes with dust mites or salami with *Penicillium lanoso-caeruleum* have also been reported.[339-341] EIAn can also occur in the postprandial period unrelated to a specific food or beverage.[342] Other factors associated with episodes of EIAn include the phase of the menstrual cycle, use of aspirin or aspirin-like drugs, amount of food ingested, alcohol, season, and climatic conditions, such as ambient temperature and humidity.[324,334,343-345]

EIAn has been associated with mast cell degranulation and increased plasma histamine levels.[346,347] Several additional hypotheses to explain this syndrome have been proposed. In patients with food-dependent EIAn, the physical stimulus of exercise in the postprandial state can enhance the potential for release of histamine and other mediators from mast cells, basophils, or both. A mast cell secretagogue can be elaborated during exercise in the postprandial state in affected subjects. The interaction of specific IgE antibody with food antigen might decrease the mast cell release threshold to the physical stimulus of exercise. With consumption of a food to which IgE-mediated potential exists, exercise can serve to not only influence the degree of mast cell activation but also favor intestinal absorption of a relevant food allergen, such as gliadin-derived proteins from wheat.[326,327]

Summary Statement 49: It is important to distinguish EIAn from cholinergic urticaria. The diagnosis of EIAn can be confirmed by means of exercise challenge in a controlled environment, whereas cholinergic urticaria can be elicited by means of both exercise challenge and passive heating. (C)

Cholinergic urticaria is characterized by the appearance of punctate (1-3 mm) wheals, with circumjacent flares that might coalesce to form large areas of erythema. The urticarial lesions characteristic of EIAn are typically larger than those observed in patients with cholinergic urticaria.[236,347,348]

Exercise challenge might confirm the presence of EIAn; however, this procedure carries risk (for anaphylaxis) and should be done in a setting in which personnel, equipment, and supplies required for anaphylaxis management are present (see Lieberman P, Nicklas RA, Oppenheimer J, Kemp SF, Lang DM, Bernstein D, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. J Allergy Clin Immunol 2010;126:477-522). In patients with food-specific EIAn, clinical relevance of a specific food suspected based on the patient's history can be considered more definitively by demonstration of wheal-and-flare reactions on percutaneous skin testing or detection of increased titers of specific IgE antibodies with *in vitro* testing. Development of urticaria on treadmill exercise challenge can also be provoked in patients with cholinergic urticaria because exercise will increase body temperature; however, as noted above, the morphology of these lesions will likely be different. The presence of cholinergic urticaria is also favored by a history of symptoms provoked by other stimuli that increase core body temperature and by cutaneous reaction to methacholine intradermal challenge or hot-water immersion.[259]

The differential diagnosis of EIAn also includes exercise-induced asthma, cold urticaria (see below), anaphylaxis from Hymenoptera sting, and mastocytosis. Previously unrecognized cardiac conditions, including hypertrophic cardiomyopathy, long QT syndrome, Wolff-Parkinson-White syndrome, arrhythmogenic right ventricular dysplasia, and anomalous origin of the coronary arteries, as well as "commotio cordis," which can cause fatal events during exercise, might also merit consideration.[349-351]

Summary Statement 50: 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. (D)

Patients in whom the diagnosis of food- or drug-dependent EIAn is confirmed should be advised to avoid exercising in proximity to a cofactor, such as a food or drug that can induce episodes of EIAn. The length of time that affected subjects should not exercise after food consumption is controversial. A waiting period of at least 4 hours is generally recommended. Because provocation of EIAn with a latency period after food consumption of 24 hours has been reported, it is prudent to individualize this management recommendation, particularly for patients with postprandial (non–food-specific) EIAn.[329]

Patients with EIAn should exercise with a partner who is aware of their condition, carries a cell phone, and is capable of treating an episode of EIAn if it should occur. Injectable epinephrine should be prescribed and carried by the patient, and medical identification jewelry should be worn. It is recommended that patients avoid exercising on warm humid days, avoid concomitant use of aspirin and aspirin-like drugs, and cease activity with onset

of premonitory symptoms of anaphylaxis, such as flushing, pruritus, or urticaria.[327,343]

Emergency management of an episode of EIAn is similar to the management of other types of anaphylaxis (see the anaphylaxis parameter) and might require administration of epinephrine, intravenous fluids, oxygen, antihistamine, corticosteroid, endotracheal intubation, and other resuscitative measures.

Solar urticaria

Summary Statement 51: Patients with solar urticaria promptly (generally within 1-3 minutes) experience urticaria with exposure of the skin to sunlight. (B)

Patients with solar urticaria experience urticaria on direct exposure of the skin to sunlight. Initial symptoms might include only erythema, pruritus, or a burning sensation on sun exposure, but typical urticarial wheals develop within 1 to 3 minutes. A 1- to 3-hour delay between solar radiation exposure and the appearance of wheals has been reported but is less typical.[352] On physical examination, the urticarial lesions of patients with solar urticaria are indistinguishable from those of patients with other types of urticaria. The key historical finding is that urticaria is limited to sun-exposed skin, although areas of skin that are more commonly exposed to sunlight might be less sensitive than areas of skin that are more commonly covered.[353] However, thin or loose-weave clothing might not sufficiently shield the underlying skin from an urticarial reaction.

The severity and duration of symptoms can vary with the intensity and duration of light exposure. Manifestations of disease typically resolve on removal of affected skin from sun exposure, usually within 30 minutes and almost always within 24 hours. In rare cases the urticaria can persist for more than 24 hours.[354,355] Systemic manifestations of diaphoresis, dyspnea, headache, and loss of consciousness have been described and might be related to extensive body surface exposure to solar radiation.[356,357] Cutaneous reactions that last greater than 24 hours after sun exposure should lead to consideration of other types of photodermatitis, including chronic actinic dermatitis, polymorphic light eruption, drug or chemical photosensitivity, and erythropoietic protoporphyria.

Some studies have suggested a female predominance with solar urticaria.[357-359] It can initially present in pediatric and older adult (age >65 years) patients, with a usual age of onset between 20 and 41 years. The disease can resolve spontaneously, with retrospective studies suggesting there is resolution in 15% to 58% of patients after 5 years of symptoms.[358,359] Patients with solar urticaria can have concomitant photodermatoses, such as polymorphic light eruptions. Patients who have coexisting photodermatoses might have a longer median duration of disease.[359]

Several classification schemes have been proposed based on the wavelength of light that induces lesions, the ability to passively transfer sensitivity to light with serum, or the presence of a sensitizing precursor molecule or chromophore that might be present in patients but not in healthy subjects. Solar urticaria can be triggered by exposure to various wavelengths of light, including UVB (280-320 nm), UVA (320-400 nm), visible light (400-600 nm), and even infrared (>600 nm) radiation (although infrared-triggered urticaria might overlap with local heat urticaria), and diverse chromophores have distinctive absorption and action spectra.

Summary Statement 52: The diagnosis of solar urticaria can be confirmed with phototesting to various wavelengths of light. (B)

The purpose of phototesting is to provoke urticarial lesions similar to those experienced with sun exposure. Reactions are more commonly triggered by UVA or visible wavelengths and less commonly with UVB and infrared radiation.[360] The most commonly used provocative method uses a xenon arc lamp with a monochromator to determine the minimal dose required to provoke an urticarial reaction (minimal urticarial dose [MUD]) at different wavelengths of light. Phototesting is typically performed on normally covered skin, such as the middle and lower back.[361] If a xenon lamp with a monochromator is not available, other light sources, such as a slide projector or liquid crystal display light bulb (for visible light), fluorescent black light (which can test both UVB and UVA wavelengths), fluorescent sunlamp (which can also test UVB and UVA wavelengths), infrared lamp (for infrared wavelengths), and even lasers have been used.[357,361,362] For each wavelength or light source selected, the MUD can be determined by exposing a 1-cm^2 area of skin at a distance of 10 cm from the light source. Alternatively, provocative light exposure can be used to confirm the diagnosis without determining the MUD. Readings are made immediately after light exposure and are typically defined as a visible pruritic erythematous wheal that develops during or shortly after irradiation and usually fades within a few minutes after the light is withdrawn.[361] Even if the initial provocation test result is negative (no response after 1-3 minutes), it can be repeated on the originally affected skin area and, if still negative, should be repeated with direct sunlight before the diagnosis of solar urticaria is excluded.[363,364]

The specific wavelengths necessary to provoke urticarial lesions in individual patients can be variable because the specific action spectra can vary with repeated testing.[365] The potential interaction between different light wavelengths on the affected skin has been proposed to explain this phenomenon, with some patients demonstrating an inhibition spectrum, where exposure of the skin before or concomitantly with the action spectrum will blunt or prevent the development of hives, and others demonstrating an augmentation spectrum, where exposure of the skin before or concomitantly with the action spectrum will intensify the urticarial reaction.[366-368] Typically, longer wavelengths will inhibit the action spectrum of shorter wavelengths, although this is not universally the case.[369] If necessary, the inhibition or augmentation wavelengths can be determined by exposing half of the skin target area to longer or shorter light wavelengths compared with the target action spectrum. After preirradiation, the target wavelength is applied, and the singly and doubly exposed skin are then compared.

Patients are generally managed with avoidance of identified wavelengths of light. Broad-spectrum sunscreens are generally reported to be of limited benefit because most patients are sensitive to wavelengths in the visible range and the majority of sunscreens do not filter visible wavelengths.[361] H$_1$-antihistamines have been reported variably to prevent or ameliorate symptoms with repeated sun exposure.[370-372] Patients have also been desensitized to light by using broadband UVB, narrow-band UVB (NB-UVB), UVA, and visible light therapy.[356,373-375] In addition, skin exposed to natural sunlight on a regular basis might become less reactive than skin routinely covered from the sun.[353] The usual starting dose of light is less than the previously determined MUD, and therapeutic irradiation of increasing dose is administered several times a week, requiring 15 to 20 treatments to obtain

adequate protection. Tolerance generally lasts only a few days unless treatments are continued.[376] Photochemotherapy with 8-methoxypsoralen administered orally before UVA irradiation might lead to a more durable response, although maintenance treatment is also necessary and associated with drug-specific risks, such as burns or skin cancer.[377] Case reports of plasmapheresis, plasmapheresis plus UVA therapy with coadministration of psoralen, cyclosporin A, and intravenous immunoglobulin (IVIG) have also been reported to offer temporary relief.[378-381]

Vibratory angioedema

Summary Statement 53: Patients with vibratory angioedema experience pruritus and swelling with exposure of the skin to a vibratory stimulus. This condition can be familial. (B)

Patients with vibratory angioedema experience localized pruritus, erythema, and edema within 1 to 3 minutes on exposure to a vibratory stimulus, although a delay in symptom onset in one case of 1 to 2 hours has been reported.[382,383] Symptoms typically persist for at least 1 hour, can last up to 8 to 12 hours, and typically have completely resolved within 24 hours.[383-386]

The severity and duration of symptoms might vary with the intensity and duration of the vibratory stimulus and surface area of the body involved. Constitutional symptoms of headache and facial or generalized erythema coincident with the development of vibratory angioedema have been described.[382]

Diverse vibratory stimuli have been identified as provoking angioedema, including riding a motorcycle, working with a jackhammer, mowing the lawn, toweling, massaging, clapping, bowling, using a vibrating hair appliance, showering, walking, jogging, bicycling, or running.[382,384,385,387-389] At-risk occupations include machinists, carpenters, and metal grinders.[383,385] One case report described symptoms coincident with chronic *Torulopsis glabrata* yeast bladder infection, with resolution of symptoms after antifungal therapy.[387]

In the inherited form symptoms manifested in infancy and were provoked by rubbing with towels in the nursery.[382] A pedigree analysis of a Lebanese family including 219 relatives in 6 generations suggested that the familial form can be inherited in an autosomal dominant manner with high penetrance, although the exact genetic defect was not identified.[384] No additional kindreds with hereditary vibratory angioedema have been reported.

Investigations into the pathogenesis of vibratory angioedema have implicated mast cell degranulation and histamine release during symptomatic episodes, although the results of passive transfer experiments have been negative, suggesting a non–IgE-mediated nonimmunologic trigger.[90,382,385,390]

Summary Statement 54: Vibratory angioedema can be confirmed by demonstrating an exaggerated response after exposure of the skin to a vortex mixer. (B)

The initial reports describing the diagnosis of vibratory angioedema described supporting the forearm of the patient under the wrist and elbow so that the skin of the forearm, hand, or finger rested lightly in the rubber cup of a vortex mixer. The mixer was then vibrated at a constant speed for at least 1 minute.[382,390] Angioedema triggered by vibratory provocation was assessed by noting the presence of erythema and edema sharply demarcated from normal skin within 4 minutes of stimulation and persisting for at least an hour; vibratory angioedema was quantified with changes in forearm circumference and finger volume.[382] Skin manifestations of vibration testing in patients with cholinergic

urticaria do not reach the circumferential arm swelling found in patients with vibratory angioedema.[231]

Subsequent studies have been performed with an electronic vibrator mounted on a laboratory stand or a vortex mixer applied to the plane of the patient's forearm skin.[383,386,388] Given the lack of evidence-based studies examining the optimal method of vibratory stimulation, duration of stimulus, and grading of a positive reaction, a vibratory challenge applied with a vortex mixer to the forearm for at least 1 and up to 5 minutes might be an adequate stimulus to provoke vibratory angioedema in affected patients; erythema, pruritus, and angioedema can develop within 30 seconds to 5 minutes. Control subjects can have pruritus and erythema without angioedema, which should resolve in less than 30 minutes.[383,386,388] However, in one report on vibratory provocation, forearm erythema and pruritus faded within 30 minutes of stimulation, recurred at 1 to 2 hours, and peaked at 4 to 6 hours, suggesting that the delayed onset of vibratory angioedema after provocation should still be interpreted as consistent with the diagnosis.[383]

With regard to treatment, patients should avoid identified provocative stimuli. Patients might be able to reduce running-triggered vibratory angioedema by gradually building to a peak level of activity ("warming up") before exercise.[384] Achievement of tolerance to vibration has been reported with progressive exposure to a vibratory stimulus.[386] Antihistamines, such as hydroxyzine, have been reported to provide relief in 1 report, and a single dose of terfenadine could reduce and delay the development of vibratory angioedema in a provocation study.[387,388] However, other reports suggest that some patients experience no relief with H_1-antagonists.[385]

DIFFERENTIAL DIAGNOSIS (TABLE IV)

Summary Statement 55: Cryoglobulinemia is often found in many conditions that result in vasculitis. (D)

Cryoglobulinemia and essential mixed cryoglobulinemia are due to immunoglobulins that precipitate when body temperature decreases. Conditions associated with cryoglobulinemia include cold-induced urticaria, urticarial vasculitis, acral antiphospholipid syndrome, pernio (chilblains), Henoch-Schönlein purpura, Schamberg vasculitis (pigmented purpura), and hepatitis B and C infection. Patients can present with livedo reticularis, acrocyanosis, Raynaud phenomenon, and purpura in cold-exposed areas with occasional necrosis in cryoglobulinemia. In patients with essential mixed cryoglobulinemia, palpable purpura with petechiae of the lower extremities producing a "cayenne pepper" appearance with brawny edema of the lower legs is seen.

Type I cryoglobulinemia (hypergammaglobulinemia caused by IgM or IgG) is due to hyaline production and/or red cell occlusion of dermal vessels with minimal inflammatory infiltrate. In patients with cryofibrinogen, eosinophilic thrombi of small dermal vessels with necrosis are seen. Periodic acid–Schiff stains cryoprecipitates occluding small dermal vessels. In essential mixed cryoglobulinemia a leukocytoclastic vasculitis with angiocentric inflammation with neutrophils showing fragmentation of nuclei (karyorrhexis), endothelial swelling, fibrinoid necrosis of endothelial cell walls, and if immunofluorescence is performed, deposition of perivascular deposits of IgM and C3 in superficial dermal vessels is seen. Cryoglobulinemia is classified according to the types of immunoglobulins: type I is usually associated with a monoclonal gammopathy (IgM > IgG >> IgA or light chain);

type II (mixed) is an mAb (IgM > IgG) binding to the Fc portion of polyclonal IgG (rheumatoid factor positive); and type III contains polyclonal immunoglobulin (mixed) demonstrating rheumatoid factor properties. Type II and III cryoglobulinemia are usually caused by hepatitis C infection.[391]

Management includes avoidance of cold stimuli, including infusion of cool or cold blood products, and treatment of the underlying cause (eg, monoclonal gammopathy or lymphoreticular malignancy associated with type I and hepatitis C infection with types II and III).[392]

Summary Statement 56: Autoinflammatory syndromes are a group of conditions that involve aberrant activation of mediators of the innate immune response with resultant fever and other symptoms. (C) (Table V)

Autoinflammatory syndromes are a group of relatively rare monogenic disorders of genes regulating innate immune pathways that result in autoinflammatory diseases. The majority of these disorders are associated with different rashes and fevers, which in some cases are periodic and in others recur with unpredictable frequency over months to years without evidence of infection or malignancy. The autoinflammatory syndromes include the following: FCAS; Muckle-Wells syndrome (MWS); neonatal-onset multisystem inflammatory disease (NOMID; also known as chronic infantile neurologic, cutaneous, and articular syndrome); familial Mediterranean fever (FMF); hyper-IgD syndrome with periodic fever (hyper-IgD); TNF receptor–associated fever syndrome (TRAPS); periodic fevers with aphthous stomatitis, pharyngitis, and adenitis (PFAPA); and pyogenic arthritis, pyoderma gangrenosum, and acne syndrome (PAPA).[393] Within the differential diagnosis, Still disease, Reiter syndrome, SLE, rheumatic fever, and other syndromes associated with prolonged fevers should be considered.

FMF presents in patients of Mediterranean heritage, with erysipelas-like lesions on the lower extremities and fever, arthralgias, and serositis (with resultant abdominal pain, pleurisy, and arthritis) but no adenopathy. Attacks are usually self-limited and span 3 days.[394] Patients with FMF show dermal neutrophil-rich infiltrates without vasculitis on skin biopsy.

Hyper-IgD syndrome presents with a polymorphous maculopapular rash and often with severe pain, lymphadenopathy, and fever. Hyper-IgD syndrome presents in childhood in a manner similar in appearance to juvenile rheumatoid arthritis yet with increases in IgD levels (>100 IU/mL). Attacks can be precipitated by viral infections, trauma, or stress. Patients with hyper-IgD syndrome show a similar presentation to those with FMF, with variable degrees of small-vessel vasculitis.

TRAPS presents with fever, abdominal pain, pleurisy, and conjunctivitis with or without periorbital edema but no adenopathy. The rash can entail single or multiple erythematous patches that spread distally. Flare-ups last for at least 5 days. It affects mostly patients of Irish and Scottish descent.[395]

PFAPA syndrome is relatively common and characterized by recurrent pharyngitis, mild aphthous ulcerations, lymphadenopathy, rigors, fatigue, headache, and mild abdominal pain. Fevers recur at 28-day intervals with increases in C-reactive protein levels, sedimentation rate, and leukocytosis. Most patients "outgrow" the febrile episodes.

PAPA presents with joint disease typically in childhood as a result of pyogenic arthritis, with later development of acne and occasionally pyoderma gangrenosum. Patients typically have pauciarticular destructive arthritis with rare cervical involvement.

In patients with PAPA, synovial inflammation (sterile neutrophilic) "switches" to the skin during adolescence, with involvement in boys worse than that in girls.[396]

Pyrinopathies can exhibit autosomal recessive (FMF and hyper-IgD syndrome) or autosomal dominant (TRAPS and PAPA) inheritance patterns. FMF is associated with a mutant pyrin that impairs its function within the inflammasome responsible for IL-1β activation. Apoptosis of inflammatory cells is also impaired in patients with FMF. Mutations in the pyrin/marenostrin gene (FMF), mevalonate kinase (hyper-IgD syndrome), the TNF receptor SF1A (TRAPS), and the CD2BP1 protein localized to genes on the long arm of chromosome 15 (PAPA) have been defined.[397]

FMF responds readily to colchicine, which also decreases the risk of (later) amyloid-associated renal involvement. TRAPS has been treated effectively with etanercept. PAPA has been treated with infliximab, as well as etanercept, with improvement. The response of TRAPS and PAPA to the above therapies implies an influence of TNF-α in the pathogenesis of these debilitating conditions.[398]

Summary Statement 57: Cryopyrin-associated periodic syndromes (also referred to as cryopyrinopathies) are a group of autoinflammatory syndromes that are characterized by abnormalities in the *C1AS1* gene, which encodes for the cryopyrin protein, and are associated with an urticaria-like rash (pseudourticaria). (C) (Table V)

Members of the cryopyrinopathies include MWS, FCAS, and NOMID (also known as chronic infantile neurologic, cutaneous, and articular syndrome). The presentations for each syndrome are different, but the cause is the same: an autosomal dominant mutation in *C1AS1* that encodes for protein cryopyrin (NALP3), a component of the inflammasome that activates IL-1α when the cell perceives danger signals. FCAS is characterized by burning, papular urticaria–like lesions associated with systemic symptoms of arthralgias, myalgias, headache, and signs of fever, chills, and conjunctivitis on exposure to cold. FCAS results in negative "ice-cube challenge" responses. Patients have a family history of cold-induced urticaria-like lesions. Patients with MWS have urticaria-like lesions associated with renal abnormalities (caused by amyloidosis), progressive deafness, and polyarthralgias. The characteristics of patients with NOMID include pseudourticaria within the first 6 weeks of life and signs of bony overgrowth, mental retardation, papilledema, and aseptic meningitis. Patients with NOMID can have bony abnormalities of the knees (deformed and enlarged femora and patellae with tibiae), short stature, and valgus or varus knee deformities. Skin biopsy in patients with NOMID reveals neutrophilic eccrine hidradenitis. Anti–IL-1 therapies, such as anakinra, rilonacept, and canakinumab, have been associated with benefit for treatment of cryopyrin-associated periodic syndromes.[399-401]

Summary Statement 58: Hypocomplementemic or normocomplementemic urticarial vasculitis is associated with decreased or normal complement (C1q, C4, and C3) levels and a biopsy that reveals vasculitis of dermal blood vessels with leukocytoclasis. (C) (Table V)

Summary Statement 59: HUVS 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. (C)

Urticarial vasculitis (UV) is a disorder that typically causes painful and longer-lasting (days) urticarial eruptions with

frequent residual hyperpigmentation. When associated with decreased C4, C3, and C1q levels, it is termed hypocomplementemic urticarial vasculitis. A subset of these patients can be classified as having HUVS. Patients with HUVS must present with urticaria, angioedema, or both for at least 6 months (major criteria) and hypocomplementemia (major criteria) and have 2 of the following minor criteria: venulitis of dermis, arthralgias, mild glomerulonephritis, uveitis or episcleritis, recurrent abdominal pain, and/or a positive C1q precipitin test result. Characteristic of the urticaria associated with UV is a burning sensation and pruritus, with longer duration of the urticaria (each hive can last 3 days). Resolution of the hive might leave hyperpigmentation ("nutmeg" appearance), and on close inspection, the wheals could have a central dark macule suggestive of purpura. However, as discussed previously, many patients with UV can have transient lesions typical of CU. Angioedema can also complicate UV when deeper tissues are involved, often with residual bruising. Other syndromes can be associated with UV, including Schnitzler syndrome, Cogan syndrome (interstitial keratitis and vestibuloauditory dysfunction), MWS, SLE, hepatitis B or C infection, and mixed cryoglobulinemia.

Leukocytoclastic vasculitis with fibrinoid necrosis is seen on biopsy. Injury of the postcapillary venules with extravasation of red blood cells, a perivascular infiltrate of mostly neutrophils, fragmentation of leukocytes with nuclear debris, and fibrin deposition in and around blood vessels are components of the histopathology. This reflects antigen-antibody complex formation, which activates the classical complement cascade and results in mast cell activation with recruitment of neutrophils and destruction of the vasculature in the area involved.[402] Immunofluorescence can reveal deposits of immunoglobulins, complement, and/or fibrin mostly in the dermal-epidermal junction and around blood vessels. If clinical suspicion is consistent with cutaneous vasculitis and the biopsy result is negative, a repeat biopsy would merit consideration. Biopsy for direct immunofluorecence is preferably performed in lesions within 24 hours because loss of immunoglobulin staining in immune deposits in cutaneous vasculitis lesions has been seen starting in less than 48 hours.[403]

In addition to a skin biopsy, laboratory evaluation should include C1q, C4, and C3 measurement. Arthritis with deformities of the fingers and toes (Jaccoud arthropathy) is similar to that seen with rheumatoid arthritis, with the exception that x-rays do not reveal joint destruction in patients with Jaccoud arthropathy. Patients with HUVS and Jaccoud arthropathy have increased risk of aortic and mitral valve pathology and should also have an echocardiogram.[404] Patients with HUVS might have proteinuria with mild renal failure, whereas UV is associated with a wide variety of renal conditions, including crescentic glomerulonephritis, membranoproliferative glomerulonephritis, proliferative glomerulonephritis, and tubulointerstitial nephritis. Spirometry is critical for patients with cough or dyspnea, especially patients who smoke. The development of progressive chronic obstructive pulmonary disease is seen in patients with HUVS, possibly because of enhanced elastase release from neutrophils in those patients who smoke. Because SLE can present with urticaria and hypocomplementemic urticarial vasculitis, anti-nuclear antibody studies, including anti–double-stranded DNA and anti-Ro antibodies can aid in differentiating patients with HUVS from those with SLE.

Antihistamines can be used to manage pruritus but have no substantial effect on the vasculitic process. Chronic administration of oral corticosteroids might be required unless other immunosuppressive therapy is initiated. The dose of prednisone is 0.5 to 1 mg/kg/d for at least 1 week and then tapered slowly.[405] Hydroxychloroquine,[406] colchicine, and dapsone[407] have been used in case reports for management of UV. Pentoxifylline (1200 mg/d) can be beneficial to enhance the effect of dapsone.[408] Patients with hepatitis A, B, or C and UV might benefit from the use of IFN-α used with or without ribavirin.[409] For refractory disease, azathioprine with prednisone (with antecedent testing for thiopurine methyltransferase deficiency) can be used, especially for UV complicating renal disease.[410] Other therapies, such as cyclophosphamide, cyclosporin A, mycophenolate mofetil (MMF), and methotrexate, have been used for severe cases.

Summary Statement 60: Swelling of the area in the medial portion of the upper eyes might be a sign of thyroid orbitopathy and misinterpreted as angioedema. (C) (Table VI)

Patients with autoimmune thyroid disease can present with urticaria but might also present with thyroid orbitopathy, swelling of the area between the upper eyelids and eyebrows, and simulating angioedema of the upper eyelids.

Summary Statement 61: Urticaria-like dermatoses can occur at various stages of pregnancy. (C) (Table VI)

Gestational pemphigoid (pemphigoid gestationis) is a rare condition that affects pregnant women with an abrupt onset of pruritic papular urticaria initially on the trunk (especially about the umbilicus), which becomes generalized. Blistering then occurs. Up to 10% of newborns of affected mothers can present with an eruption. Within the differential diagnosis, urticarial papules, pruritic urticarial papules, and plaques and prurigo of pregnancy can be considered.

Biopsy of a papule reveals subepidermal vesicle formation with a perivascular infiltrate of lymphocytes and eosinophils. Immunofluoresence reveals complement C3 deposition along the dermoepidermal junction, especially along the basement membrane zone. ELISA to BP180NC16A (a hemidesmosomal protein) has 90% sensitivity and similar specificity.[411] Initial treatment includes topical glucocorticoids (class III to class I), with ointments providing the best results. For pemphigoid refractory to topical corticosteroids, treatment with an initial dose of 0.5 mg/kg/d prednisone that is then tapered slowly is beneficial.[412] Flares occur at delivery, and recurrences are seen with menstruation and oral contraceptives (in 25% of women).

Some women can have intense pruritus with a rash that develops past midterm in their pregnancy. Prurigo of pregnancy is characterized by extremely pruritic papules and nodules, usually excoriated and predominantly on the extensor surfaces. The papules can last for weeks to months after delivery. In the differential diagnosis pruritic folliculitis, cholestasis of pregnancy, secondary syphilis, and scabies should be considered. Histopathology is nonspecific with negative immunofluorescence. Treatment is mostly supportive with topical corticosteroids.[413]

Pruritic urticarial papules and plaques of pregnancy begin as pruritic urticarial papules within the abdominal striae (sparing the umbilicus) during the third trimester in primigravid women. The involvement spares the face, hands, and soles and can recur with subsequent pregnancies. There is a higher prevalence of multiple-gestation pregnancy in women with pruritic urticarial papules and plaques of pregnancy.[414] Within the differential, urticaria, prurigo of pregnancy, gestational pemphigoid, viral exanthems, and contact dermatitis can be considered.

The histopathology reveals a tight perivascular infiltrate of lymphocytes and eosinophils, with dermal edema separating collagen fibers. Spongiosis of the epidermis is seen, with parakeratosis and infiltration by eosinophils (less than gestational pemphigoid). Immunofluorescence reveals granular deposition of C3, IgM, or IgA at the dermoepidermal junction in one third of patients. Pruritus usually resolves within 2 weeks postpartum. Treatment entails oral antihistamines to decrease intense pruritus and rarely oral corticosteroids.[414]

Summary Statement 62: Women who present with cyclical urticaria can have autoimmune progesterone-induced dermatitis. (C) (Table VI)

Autoimmune progesterone-induced dermatitis occurs in women of childbearing age. This presents with varying stages of appearance relative to the luteal phase of the menstrual cycle.[415] Autoimmune progesterone-induced dermatitis is usually papular to plaque-like urticaria, angioedema, or both developing 3 to 10 days before menses. Cutaneous eruptions can also present with eczema, EM, bullous lesions, or folliculitis and be part of catamenial anaphylaxis. Within the differential diagnosis, flushing, premenopausal and perimenopausal syndromes, toxic shock syndrome, and catamenial anaphylaxis should be considered.

The diagnosis is made by skin testing with 1 mg/mL aqueous progesterone administered intracutaneously (0.1 ml) with appropriate controls. A positive response is indicated by a greater than 2-mm increase in wheal size compared with that elicited by the negative control. Provocative challenges with progesterone can also be performed if skin test results are negative. Diagnosis of autoimmune progesterone-induced dermatitis is confirmed by prevention of skin eruptions by inhibiting ovulation. Thirty micrograms of ethinyl estradiol and 0.15 mg of levonorgestrel worked for one patient in inhibiting her ovulation.[416] Other treatments include danazol or stanozolol, gonadotropin-releasing hormone/luteinizing hormone–releasing hormone agonists leuprolide acetate, and tamoxifen. Total hysterectomy and bilateral salpingo-oophorectomy has been performed for anaphylaxis unresponsive to the above.[417]

Summary Statement 63: Episodic attacks of angioedema with weight gain are characteristic of the syndrome episodic angioedema with eosinophilia (Gleich syndrome). (C)

Gleich syndrome is a rare condition in which episodic swelling occurs with or without urticaria. The episodes usually last less than 1 week and are associated with a fever and weight gain by as much as 18% of initial body weight. Within the differential diagnosis, acquired angioedema with urticaria can be considered. Pivotal in the diagnosis of this syndrome is the leukocytosis seen on CBC; the majority (up to 88%) are eosinophilic. The increase is limited to the time of the attacks, and no other organ systems are affected, which distinguishes Gleich syndrome from HES. The treatment of Gleich syndrome is oral corticosteroids.[418] Several case reports have documented acute increases in serum IL-5 levels in patients with angioedema caused by Gleich syndrome, which decreases during corticosteroid use.[419]

Summary Statement 64: HES should be considered when the peripheral total eosinophil count exceeds 1500/μL for greater than 6 months in the absence of other causes of peripheral eosinophilia. (C)

Cutaneous lesions are common in patients with HES and might be the first manifestation. Pruritic erythematous macules, plaques, wheals, and nodules are common cutaneous findings. Urticaria and angioedema can occur in patients with all subtypes of HES.[420] In contrast to those with CIU, patients with HES typically have multiorgan involvement. Patients with HES present with fever (12%); fatigue (26%); cough (24%); dyspnea (16%); pruritic papules, plaques, or nodules (12%); angioedema or myalgias (14%); and, rarely, mucosal erosions.[421] Diagnostically, peripheral eosinophilia of greater than 1500 eosinophils/μL (in the absence of parasitic infection) and multiorgan involvement is a requirement for HES.

Summary Statement 65: Cutaneous mast cell disorders that can present with urticaria-like lesions include UP, mastocytomas, and telangiectasia macularis eruptiva perstans (TMEP). (C) Mast cell activation disorders can also present with urticaria and angioedema but usually have additional systemic symptoms. (C) (Table VII)

Patients with UP present with reddish-brown macules and papules that can urticate when stroked. UP presents mostly in childhood and has a benign course. Mastocytomas are larger clusters of mast cells that urticate and rarely blister when stroked. Patients might not have more aggressive systemic mastocytosis (SM), but if bone pain, a tryptase level of greater than 20 ng/mL, or hepatosplenomegaly is/are present, then a bone marrow biopsy should be performed to exclude SM. Patients with TMEP present with pruritic macules and areas of telangiectasias that might not urticate on stroking (Darier sign), as they do with UP and mastocytomas. Thus it might be difficult to differentiate these patients from those with dermatographism and telangiectasias caused by estrogen effects unless a biopsy specimen of the suspected area is obtained. The histopathology of TMEP reveals increased mast cell numbers in the upper dermis and located about the capillaries, as defined by staining (Giemsa, toluidine blue, or Leder stain).

Separate from cutaneous mastocytosis (see above), SM is defined by major criteria of multifocal dense mast cell infiltrates (>15 mast cells per aggregate) in the bone marrow or extracutaneous organs (ECOs), as detected by using tryptase immunohistochemistry, and 1 minor criterion (serum tryptase >20 ng/mL; atypical mast cells or spindle-shaped cells [>25%] in bone marrow or ECOs; or KIT mutation at codon 816 in ECOs and/or KIT plus mast cells in bone marrow or ECOs coexpressing CD2, CD25, or both) or 3 minor criteria alone. SM is further classified as indolent systemic mastocytosis, systemic mastocytosis with associated clonal hematologic non–mast cell lineage disease, aggressive systemic mastocytosis, mast cell leukemia (MCL; leukemic SM variant), extracutaneous mastocytoma, and mast cell sarcoma.[422] Patients with SM can have UP, which can urticate with rubbing, but spontaneous urticaria is not a feature of SM. Finally, mast cell activation syndromes can present with episodic urticaria or angioedema, typically along with other systemic symptoms, including gastrointestinal, respiratory, or cardiovascular symptoms.[423]

Summary Statement 66: EM can resemble urticaria and might be caused by viral infections (eg, herpes), mycoplasma infection, or medications. (C)

Patients with EM present with a variety of cutaneous eruptions. Initially, urticaria-like lesions can develop before the typical targetoid lesions attributable to EM minor appear. Unlike with urticaria, a central zone of damaged skin (crusted, dusky, and bullous) can appear. All lesions appear within 72 hours and are usually fixed for at least 7 days.[424] Typically, EM minor lasts for no longer than 2 weeks, although immunosuppressants (including prednisone) might provide some relief.[425] When EM progresses to ulcerations of mucosal surfaces, it is classified as EM major (Stevens-Johnson syndrome [SJS]). EM can progress without warning to toxic epidermal necrolysis (TEN). EM differs from

fixed drug eruptions in that the latter usually recur at the same site when a medication is reintroduced.

Biopsy of the affected area reveals vacuolization of the basal cell layer, lymphocytes along the dermoepidermal junction, spongiosis, and exocytosis. Apoptosis of keratinocytes in the stratum malpighii with necrosis is also seen. Large sheets of epidermal necrosis are not seen in patients with EM minor compared with those with EM major or TEN. Levels of soluble Fas ligand, which is secreted by PBMCs, are increased in patients with SJS and TEN but not those with EM minor.[426] A search for the common causes of EM, including herpes and other viral (eg, influenza) infections, drugs (eg, NSAIDs, sulfonamides, allopurinol, and anticonvulsants), atypical bacterial infections, tuberculosis, and fungal infections, is warranted. Drugs that precipitate SJS typically were administered 2 to 6 weeks previously and not immediately before the reaction,[427] although exceptions occur. Patients with recurrent herpetic infections precipitating EM benefit from prophylaxis with 10 mg/kg/d acyclovir for 6 to 12 months.[428] Aggressive corticosteroid therapy early in the course of EM minor might provide some relief. The efficacy of intravenous gammaglobulin at 0.8 g/kg/d for 4 days has been reported in patients with SJS and TEN but not in all studies.[429]

Summary Statement 67: Hepatitis B or C can be associated with urticarial vasculitis and should be considered in the differential diagnosis, particularly for patients whose behaviors predispose to contracting a sexually transmitted disease, who have recently received a blood transfusion, or who have exposure to contaminated needles. (C)

Patients with hepatitis virus infection might have urticaria during their infection. In many instances the urticaria develops acutely during the preicteric phase[16] and resolves before jaundice appears. Patients with chronic infections from hepatitis B or C can have chronic urticarial vasculitis that is difficult to manage.[310] Within the differential diagnosis, urticarial vasculitis, cutaneous small vessel vasculitis, mixed essential cryoglobulinemia, erythema nodosum, EM, polyarteritis nodosa, and Gianotti-Crosti syndrome (even in adults) should be considered.

In evaluating patients with CU, especially those with a vasculitis component (see urticarial vasculitis for histopathology), serology for hepatitis B and C, as well as complement C3, C4, and C1q levels, should be obtained. Patients with systemic autoimmune disease associated with hepatitis C are more likely male and have a higher prevalence of vasculitis, cryoglobulinemia, and neoplasia compared with patients with autoimmune disease who have negative hepatitis C results.[430] The treatment of urticarial vasculitis associated with hepatitis involves treatment of the chronic infection. Depending on the titer of hepatitis B virus DNA and clinical condition (cirrhosis or not), treatment with IFN-α (peginterferon), lamivudine, adefovir, entecavir, or telbivudine can be considered.[431] Immunosuppressant therapy for the management of the urticarial vasculitis component should be limited to severe exacerbations.

The following are included within the differential diagnosis because in most instances the areas involved are excoriated and the characteristics of the eruption might not be clearly evident at the time the patient presents for an evaluation. The patient might describe any pruritic and raised eruption as a "hive," but unlike urticaria, these eruptions and pruritus are refractory to treatment with antihistamines. (Table VIII)

Summary Statement 68: Bullous pemphigoid can present initially with urticaria-like papules or small plaques that can be excoriated by the patient before noticeable blistering occurs. (D) (Table VII)

Patients with bullous pemphigoid often present with pruritic papules and plaques that develop into small tense blisters. Differentiating this from urticaria, bullous mastocytosis, IgA linear dermatitis caused by certain medications, dermatitis herpetiformis, bullous pemphigus vulgaris, and scabies often requires a biopsy with immunofluorescence. The histopathology of perilesional skin of patients with bullous pemphigoid reveals spongiotic dermatitis with subepidermal blister formation. Eosinophils and lymphocytes are dispersed throughout an edematous papillary dermis. Immunofluoresence reveals linear IgG along the epidermal basement zone (roof or epidermal side by using salt split technique). Blistering results from an autoreactive T_H1 response inducing IgG antibodies to BP180 and BP230 target antigens within the dermoepidermal junction.[432] Recently, IgE-specific anti-BP180 autoantibodies have been described and are associated with increased infiltration of eosinophils into the lesions, which is best visualized by using indirect immunofluoresence.[433]

Summary Statement 69: Persistent swelling of the lips without evidence of eczematous dermatitis might be a sign of cheilitis granulomatosa (Melkersson-Rosenthal syndrome). (C)

Melkersson-Rosenthal syndrome (cheilitis granulomatosa) is a chronic condition with persistent swelling of the lips, fissuring of the tongue, and, in some instances, facial nerve paralysis. The differential diagnosis includes contact dermatitis, angioedema, Crohn disease, and sarcoidosis. A biopsy of the lip reveals nonnecrotizing granulomatous inflammation. Treatment includes intralesional injections with extended-release triamcinolone.[434] Clofazimine, 100 to 200 mg/d, alone or in combination with intralesional corticosteroids, has shown efficacy in open studies.[435] Other therapeutic agents reported to be effective include anti-TNF agents, methotrexate, and some antibiotics.[436]

Summary Statement 70: Polymorphous light eruption differs from solar urticaria in that onset usually occurs minutes to hours after sunlight exposure and the eruption lasts for days compared with solar urticaria, which is short-lived between exposures. (D)

Polymorphous light eruption is characterized by pruritic papules and plaques that are clustered in areas of sunlight exposure. The eruptions occur typically in spring and early summer and erupt minutes after sun exposure. The duration of the reaction lasts from days to rarely weeks at 1 site. There is a predilection for sun-exposed areas. Rarely, vesicles can form. Within the differential diagnosis, solar-induced urticaria, photosensitive drug-induced eruptions, SLE, and sunburn should be considered. The pathology reveals superficial and deep dermal perivascular T-lymphocytic infiltrate. Occasionally, bullae are found. Treatment is prevention with sunscreens and protective clothing, although the condition usually resolves with continued sun exposure during the warmer months.[437] Short courses (4-5 days) of oral corticosteroids might shorten the rash and pruritus.[438]

Summary Statement 71: 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. (C)

Recall urticaria is a phenomenon in which patients might have urticaria at sites of previous stings or injections of known allergens when the patient is either challenged or injected with the same allergen. The reactions can occur within hours to days

after the subsequent challenge but repeatedly occur in the same spot as the original reaction. Mast cell concentrations with antigen-specific IgE can be increased in scar tissue of these areas, thus increasing their risk of being noticed by the patient on subsequent challenge. Examples include itching at healed fire ant stings when the patient is tested or during immunotherapy. Reports of recall urticaria have also been reported during immunotherapy[439] and in association with re-exposure to medications.[440]

Summary Statement 72: Patients with Schnitzler syndrome caused by an IgM monoclonal gammopathy present with nonpruritic urticaria (that spares the face), bone pain, and intermittent fever. (D)

Schnitzler syndrome is characterized by nonpruritic urticaria-like wheals that spare the face, intermittent fever, bone pain, and arthralgias.[441] Within the differential diagnosis, FMF and Waldenstrom macroglobulinemia can be considered.

A biopsy reveals a neutrophil-predominant dermal infiltrate without vasculitis. Patients classically have an IgM monoclonal gammopathy and increased sedimentation rate. Other findings associated with IgM multiple myeloma can also be found (increased alkaline phosphatase, anemia, and red blood cell rouleaux) in 15% of patients.

Schnitzler syndrome is refractory to most therapies for CU. Recent reports found anti–IL-1 therapies (anakinra and canakinumab) to be effective.[442,443]

TREATMENT FOR ACUTE URTICARIA AND CHRONIC URTICARIA
Annotations for step-care approach to the treatment of CU and angioedema (Fig 1)

Annotation 1. Monotherapy with second-generation antihistamines

H_1-antagonists are effective in the majority of patients with CU but might not achieve complete control in all patients. Second-generation antihistamines are generally tolerated without remarkable untoward effects.

Annotation 2. Dose advancement of H_1-antihistamine therapy, combining first- and second-generation agents and adding an H_2-antihistamine and/or an antileukotriene agent

Higher doses of second-generation antihistamines can provide greater efficacy when control is not achieved with conventional doses of these agents, either alone or in combination. Efficacy of first-generation antihistamines is similar to that of second-generation antihistamines, but sedation and impairment are greater with first- generation antihistamines, especially with short-term use. A 2- to 4-fold increase in the FDA-approved dose of second-generation antihistamines might be effective for achieving control in some patients.

There are no comparative studies that have examined the relative effectiveness of adding an H_2-antihistamine compared with an antileukotriene drug or an H_1-antihistamine at bedtime. H_2-antagonists have shown benefit in combination with first-generation antihistamines for the treatment of CU. However, the efficacy of H_2-antagonists in patients with CU might be related to pharmacologic interaction and increased blood levels of first-generation antihistamines. Some, but not all, studies have found leukotriene receptor antagonists to have efficacy in patients with CU. Given that these agents are generally well

tolerated, they can be considered in patients with CU, with unsatisfactory responses to antihistamine therapy.

Annotation 3. Therapeutic trial of potent antihistamine (eg, hydroxyzine or doxepin)

Dose advancement of hydroxyzine has been efficacious for patients whose symptoms remain poorly controlled on conventional doses of H_1-antihistamines (with or without H_2-antihistamines). Doxepin, advanced as tolerated, has potent H_1- and H_2-antagonist activity and is also efficacious.

Although the degree of impairment varies among first-generation antihistamines, as a group, they cause significantly greater impairment of cognition and psychomotor function than second-generation antihistamines. For this reason, first-generation antihistamines should be prescribed cautiously in the elderly or patients with occupations (eg, machine operators, airline pilots, or alpine skiers) for which alertness is essential.

Annotation 4. Add an immunosuppressant or biologic agent

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 risk of a given alternative agent is extremely important and needs to be weighed against the patient's current quality of life and any adverse effects from current therapy for their CU.

A number of alternative therapies have been studied for the treatment of CU and merit consideration for refractory patients. Omalizumab and cyclosporine have the greatest published experience documenting efficacy in patients with CU compared with all other alternative agents. Anti-inflammatory agents, including dapsone, sulfasalazine, hydroxychloroquine, and colchicine, can be considered for the treatment of patients with antihistamine-refractory CU. Other immunosuppressants to consider in addition to oral cyclosporine include tacrolimus, mycophenolate, sirolimus, cyclophosphamide, and methotrexate. Other biologic agents, including intravenous (or subcutaneous) gammaglobulin, anti-TNF agents, IL-1 receptor antagonists, and anti–B-cell therapies, have been used in patients with refractory CU.

Nonpharmacologic therapies

Summary Statement 73: NSAIDs, heat, and tight clothing can exacerbate CU in some patients, and avoidance of these factors might be beneficial. (C)

Many patients with CU can have nonspecific triggers that aggravate their urticaria. NSAIDs can exacerbate urticaria in 20% to 30% of patients with CU.[444-446] Avoidance of aspirin and other NSAIDs is recommended for patients with a history of NSAID-induced exacerbation of their CU and might be considered in other patients in whom this history is less clear. Once CU has resolved, patients might tolerate NSAIDs; however, the safety of taking NSAIDs might need to be determined in a physician-supervised setting. If patients require NSAID therapy and do not observe any flares in their CU, avoidance of these agents might not be necessary. Heat is another common trigger for patients with CU, as is tight clothing, with the latter more of a problem for patients with DPUA. Opiates are known to cause non–IgE-mediated reactions and have the potential to exacerbate urticaria in some patients with CU. However, a small study of 25 patients with CU showed very rare reactions to challenges with

codeine.[447] Alcohol has also been reported to be a potential trigger in patients with CU and was found to be a common trigger of CU in a single study from China.[448]

Summary Statement 74: Avoidance of pseudoallergens in the diet is not recommended. (C)

Pseudoallergens have been defined as substances that might induce intolerance reactions and include food additives, vasoactive substances, fruits, vegetables, and spices. Although pseudoallergen-free diets have been recommended,[449,450] the utility of this dietary intervention is unproved and not recommended for management of patients with CU.[185] Although some patients with CU report improvement with a pseudoallergen-free diet, less than 20% of such diet responders reacted to provocation with pseudoallergen challenge.[449]

Topical therapies

Summary Statement 75: Potent topical corticosteroids can improve symptoms from delayed pressure urticaria but have limited utility in the treatment of diffuse CU. (C)

Potent topical corticosteroids have been shown to reduce mast cell numbers and response to stroking the skin in a study of 6 patients with dermographism.[287] Other studies have shown clinical improvement in patients with localized delayed pressure urticaria treated with different preparations of potent topical corticosteroids.[451,452] An open trial in patients with CIU with topical corticosteroids showed only short-term improvement in symptoms.[453] These studies suggest that topical corticosteroids might be beneficial in patients with localized delayed pressure urticaria but have limited utility and long-term efficacy for treating diffuse urticaria.

H$_1$-antihistamines

Summary Statement 76: H$_1$-antagonists are effective in the majority of patients with CU but might not achieve complete control in all patients. (C)

Summary Statement 77: Second-generation antihistamines are safe and effective therapies in patients with CU and are considered first-line agents. (A)

Summary Statement 78: Higher doses of second-generation antihistamines might provide more efficacy, but data are limited and conflicting for certain agents. (B)

Summary Statement 79: First-generation antihistamines have proved efficacy in the treatment of CU. Efficacy of first-generation antihistamines is similar to that of second-generation antihistamines, but sedation and impairment are greater with first-generation antihistamines, especially with short-term use. (A) First-generation antihistamines can be considered in patients who do not achieve control of their condition with higher-dose second-generation antihistamines. (D)

Most symptoms of urticaria are primarily mediated by H$_1$-receptors located on nerves and endothelial cells, and therefore H$_1$-antagonists are logical mainstays of therapy for urticaria. Both first- and second-generation antihistamines have been used in the treatment of urticaria. In a study involving 390 patients with urticaria, the majority of whom had CU, 44% of patients reported benefit with H$_1$-antagonists.[454] A cross-sectional survey of 98 patients with CU treated with (mostly first-generation) antihistamines reported that 94% experienced short- or long-term control of pruritus.[455]

A number of double-blind, randomized controlled studies have demonstrated the safety and efficacy of second-generation antihistamines in improving CU symptoms.[456-460] Daily dosing of antihistamines is generally more effective than as-needed dosing for maintaining improvements in quality of life.[461] Relatively few comparative studies have been performed among currently available second-generation antihistamines in the United States for CU.[462-464] Although these studies suggest greater efficacy of certain antihistamines, there are not enough studies to demonstrate clear evidence of superiority of one specific antihistamine in patients with CU. Second-generation antihistamines differ in regard to the FDA's pregnancy category, with cetirizine, levocetirizine, and loratadine having a Category B rating and fexofenadine and desloratadine having a Category C rating.

Many patients with CU might not respond adequately to conventional, FDA-approved doses of second-generation antihistamines. Limited data are available on dosing second-generation antihistamines at higher than conventional doses. Studies evaluating cetirizine in doses ranging from 10 to 30 mg/d showed conflicting results, with one study suggesting benefit from increased dosing[465] and another without demonstrable benefit.[466]

Two large multicenter trials of 439 and 418 patients with CU, respectively, randomized subjects to fexofenadine at doses of 20, 60, 120, or 240 mg twice daily. The 3 higher doses provided better disease control than the lowest dose, but there were no statistically significant differences in effectiveness among the higher doses.[57,326]

A study of 30 patients with acquired cold urticaria evaluated patients in a randomized, placebo-controlled, crossover study comparing 5 mg/d desloratadine with 20 mg/d desloratadine versus placebo by using cold provocation testing and objective outcomes.[58] Although both doses of desloratadine showed efficacy, the 20-mg dose showed greater efficacy than the 5-mg dose.

Finally, a recent study enrolled 80 patients with histories of treatment failure with standard doses of antihistamines in a double-blind randomized trial of levocetirizine or desloratadine.[59] Daily doses were increased weekly from 5 to 10 and then 20 mg at weekly intervals. This study showed that higher doses of either levocetirizine or desloratadine were required for many subjects to become symptom free. Interestingly, there were no reports of increased somnolence with these higher doses compared with placebo in either treatment group, implying that 2- to 4-fold increases in the FDA-approved doses of these agents might be necessary for control of urticaria in some cases and can be tolerated without remarkable untoward effects.

Double-blind, placebo-controlled studies have demonstrated efficacy for first-generation antihistamines in patients with CU, with overall similar efficacy to second-generation antihistamines.[60,457,458] First-generation antihistamines have been recommended as add-on therapy for patients with CU who have had inadequate symptom control with second-generation antihistamines; however, studies to demonstrate the efficacy of this approach are lacking.[185] Sedation and impairment are well documented with first-generation antihistamines. Individual variation exists with respect to the development of sedative effects with first-generation antihistamines. Although the degree of impairment varies among first-generation antihistamines, as a group, they cause significantly greater impairment of cognition and psychomotor function than second-generation antihistamines.[61] Sedating antihistamines are often recommended to be dosed as a single nocturnal dose in an attempt to reduce daytime impairment.[136] Data are lacking regarding whether this approach

reduces daytime somnolence, especially when administered chronically to patients with CU. Studies evaluating use of first-generation antihistamines have shown tolerance to performance impairment after 3 to 5 days of therapy.[78,467,468] First-generation antihistamines differ in regard to the FDA's pregnancy category classification, with diphenhydramine, chlorpheniramine, cyproheptadine, and tripelennamine having a Category B rating and hydroxyzine and doxepin having a Category C rating.

An individualized assessment of the potential for harm compared with the potential for benefit, which incorporates the values and preferences of the patient with CU in the decision-making process, is important for determining whether to proceed with initiation and dose advancement of first-generation antihistamine therapy. In patients whose symptoms are well controlled with H_1-antihistamines, tapering of the dose can be considered. The optimal method for reducing the dose has not been determined. Table IX summarizes the pharmacology of first- and second-generation antihistamines.

H_2-antihistamines

Summary Statement 80: H_2-antihistamines taken in combination with first- and second-generation H_1-antihistamines have been reported to be more efficacious compared with H_1-antihistamines alone for the treatment of CU. (A) However, this added efficacy might be related to pharmacologic interactions and increased blood levels of first-generation antihistamines. (B) Because these agents are well tolerated, the addition of H_2-antagonists can be considered when CU is not optimally controlled with second-generation antihistamine monotherapy. (D)

H_2-receptor antagonists have also been used to treat urticaria in conjunction with H_1-receptor antagonists and are generally well tolerated. Most studies demonstrating efficacy of H_2-antagonists added to H_1-antagonists in patients with CU have been performed with cimetidine.[469-471] Studies evaluating the combination of H_1-antagonists and ranitidine in patients with CU have yielded conflicting results in regard to an additive effect.[472,473] Cimetidine is an inhibitor of a number of cytochrome p450 isoenzymes, including those involved with metabolism of first-generation antihistamines. Plasma concentrations of hydroxyzine are higher in combination with cimetidine than with hydroxyzine alone.[474,475] The increased serum hydroxyzine levels seen with concomitant cimetidine therapy also show enhanced suppression of histamine-induced wheal-and-flare responses.[475] This effect was not seen with cimetidine and cetirizine. This pharmacologic interaction might explain the perceived additional benefit of H_2-antagonists in patients with CU observed in several of these studies. Studies evaluating the combination of H_1-antagonists and ranitidine in patients with CU have yielded conflicting results in regard to an additive effect.[472,473] A recent single-blind comparative trial with famotidine (which does not affect p450 metabolism) in combination with hydroxyzine showed improvement compared with hydroxyzine plus cetirizine but was limited by the small and disproportionate number of evaluable subjects at the end of the study.[323]

Leukotriene modifiers

Summary Statement 81: Leukotriene receptor antagonists have been shown in several, but not all, randomized controlled studies to be efficacious in patients with CU. (A) Leukotriene receptor antagonists are generally well tolerated (A). Leukotriene receptor antagonists can be considered for patients with CU with unsatisfactory responses to second-generation antihistamine monotherapy.

Leukotrienes can have a role in the pathogenesis of some patients with urticaria.

Leukotriene D_4, when injected into the skin, is more potent than histamine in causing a wheal-and-flare response.[476] Sera from patients with autoimmune CU has been shown to induce release of histamine and leukotriene production.[477] Leukotriene modifiers are generally well tolerated. Leukotriene receptor antagonists have shown efficacy in the treatment of CU in single- and double-blind studies, with zafirlukast and montelukast either as single agents or in combination with antihistamines.[4,478-482] However, a double-blind, placebo-controlled crossover trial with zafirlukast in 52 patients with CIU showed no benefit.[483] Most studies showing beneficial effects of leukotriene receptor antagonists have shown improvement within weeks of initiation. Studies comparing the efficacy of leukotriene receptor antagonists with antihistamines have shown mixed results, with some studies showing greater efficacy[478,479] and others showing less efficacy[482] than second-generation antihistamines.

Several factors have been suggested to predict the clinical response to leukotriene modifiers. The pathogenesis of aspirin/NSAID-exacerbated urticaria is linked to systemic overproduction of prostaglandin D_2 and cysteinyl leukotriene production.[484] Initial case reports followed by randomized controlled trials have shown efficacy of montelukast in NSAID-exacerbated patients with CIU, with one study showing efficacy of montelukast being greater than that of cetirizine.[479] Two randomized controlled studies involving 27 and 95 patients with CIU reported ASST result positivity as a predictor of better response to leukotriene modifiers.[4,478] In contrast, an open trial suggested that shorter duration of CU and younger age were more predictive of response to leukotriene modifiers than either a history of NSAID exacerbation or a positive ASST result.[485] Montelukast has also been reported to be beneficial in 3 of 5 patients with urticaria that was induced or aggravated by antihistamines.[486]

Leukotriene modifiers have been reported to have benefit in patients with some physical urticarias. Case reports of leukotriene receptor antagonists either alone or in combination with antihistamines have suggested benefit in patients with cold urticaria.[275,276] In 2 randomized controlled trials leukotriene receptor antagonists in combination with antihistamines were associated with greater efficacy compared with antihistamine monotherapy in patients with DPUA.[487,488]

Antidepressants with H_1- and H_2-antagonist activity

Doxepin. *Summary Statement 82*: Treatment with hydroxyzine or doxepin can be considered in patients whose symptoms remain poorly controlled with dose advancement of second-generation antihistamines and the addition of H_2-antihistamines, first-generation H_1-antihistamines at bedtime, and/or antileukotrienes. (D)

Doxepin is a tricyclic antidepressant with both H_1- and H_2-receptor antagonist properties. It has potent H_1-antagonist activity, with *in vitro* studies showing 775 times more potent antagonism for the H_1-receptor than diphenhydramine.[489] A crossover study in which 25 mg of doxepin 3 times daily was compared with 50 mg of diphenhydramine 3 times daily for the treatment of CIU

found greater efficacy and less sedation with doxepin.[490] Another study comparing doxepin with cyproheptadine and hydroxyzine showed similar efficacy but less adverse effects with doxepin.[273] Because doxepin has a half-life of 13 hours,[491] it can be dosed once a day, and because of its potential for sedation and prominent anticholinergic properties, it is often recommended at bedtime.[492] Doxepin is also associated with numerous drug-drug interactions, which can make its use absolutely or relatively contraindicated.

Other antidepressants (eg, amitriptyline, nortriptyline, and mirtazapine) also possess potent antihistaminic properties, and efficacy for CU has also been described for a number of these agents; however, data are more limited.[493-495]

Dose advancement of hydroxyzine has also been reported to be efficacious for patients whose symptoms remain poorly controlled on conventional doses of H_1-antihistamines (with or without H_2-antihistamines).[185]

Systemic corticosteroids

Summary Statement 83: Systemic corticosteroids are frequently used in 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 symptoms 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. (D)

Systemic corticosteroids are frequently used in patients with CU refractory to antihistamine therapy. No controlled trials have demonstrated the efficacy of systemic corticosteroids in patients with CU. One study evaluated the role of a steroid taper, although not compared with placebo. This study of 40 patients with DPUA compared a combination of nimesulide and ketotifen with a 7-week taper of prednisone and found similar results.[298] Thirty percent of subjects withdrew from the prednisone treatment group because of adverse effects. A prospective study of 17 patients with various types of CU who were taking systemic corticosteroids (3-30 days per month) evaluated the effect of corticosteroid withdrawal and ability to sustain control off corticosteroids[496]; 47% had a short relapse or worsening of their urticaria on withdrawal of corticosteroids. The majority of patients were able to remain off corticosteroids with either complete or partial remission with the addition of H_1-antagonists. There is an honest difference of opinion regarding the utility of oral corticosteroids for management of refractory CU: some recommend daily or alternate-day use at lower doses for refractory patients[185]; others, including international consensus groups, discourage systemic corticosteroids for long-term treatment of CU because dosages necessary to suppress symptoms usually pose a risk for serious adverse effects.[310,450]

Systemic corticosteroids are relatively safe for short-term use but can be associated with transient adverse effects, including weight gain, fluid retention, mood changes, insomnia, hyperglycemia, and, rarely, avascular necrosis. The risk for prolonged hypothalamic-pituitary axis suppression from systemic corticosteroids necessitating a tapering dose varies depending on the dose and duration of corticosteroids. Data suggest tapering is not necessary in patients receiving 40 mg or equivalent doses of prednisone daily for 3 weeks or less.[497] In patients whose symptoms are poorly controlled with significant impairment of quality of life caused by CU, the use of systemic corticosteroids can be considered after careful evaluation of the risks versus benefits. 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. Long-term use (eg, months or years) of systemic corticosteroids should be discouraged unless less toxic alternative agents have been deemed ineffective or are exhausted and risk-benefit analysis favors their use. Risks of long-term systemic corticosteroid use include but are not limited to osteoporosis with increased risk of fracture, avascular necrosis, cataracts, hyperglycemia, adrenal suppression, risk of infection, and thinning of the skin.[498]

Alternative therapies in patients with CU

Summary Statement 84: Patients with CU whose symptoms are not adequately controlled on maximally tolerated antihistamine therapy (eg, doxepin at a dose of 75-125 mg/d) might be considered to have refractory CU. (E)

Summary Statement 85: A number of alternative therapies have been studied for the treatment of CU; these therapies merit consideration for patients with refractory CU. (D)

Although antihistamines are the mainstay of therapy in patients with CU, as many as 50% of these patients might not achieve satisfactory control with antihistamine therapy.[454] Systemic corticosteroids have predictable systemic toxicities that occur frequently in patients on chronic therapy. A number of therapeutic alternatives have been evaluated to treat antihistamine-refractory CU to reduce the need for systemic corticosteroids.[499] The term alternative therapy is used to describe these various agents. Although some of these therapies possess immunosuppressant or immunomodulatory activity, these properties do not apply to all of these therapeutic options, and therefore these terms are not recommended to use to describe alternative therapies as a whole.

Summary Statement 86: 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. (C) These agents are generally well tolerated, might be efficacious in properly selected patients, and can be considered for treatment of patients with antihistamine-refractory CU. (D)

Dapsone. Dapsone produces a variety of effects of potential relevance to both vasculitic and nonvasculitic urticaria. These effects include suppression of prostaglandin and leukotriene activity, interference with release or function of lysosomal enzymes[500] and myeloperoxidase generation of toxic halides,[501] disruption of integrin-mediated neutrophil adhesiveness,[502] inhibition of signals to recruit and activate neutrophils,[503] and scavenging of oxygen free radical intermediates.[504] Many of these activities can affect neutrophil function; however, it is unclear whether dapsone has a preferential response in patients with neutrophil-rich urticaria.

Several case reports and case series have suggested a benefit of dapsone in patients with CIU, idiopathic angioedema, DPUA, and urticarial vasculitis.[407,505-510] A series of 11 patients with antihistamine-unresponsive CU (3 with DPUA) were treated with 35 mg/d dapsone in addition to cetirizine and instructed to withdraw cetirizine when satisfactory control of symptoms was achieved.[507] Nine patients (including the 3 patients with DPUA) had a complete response to the 25-mg dose, with another patient requiring 50 mg of dapsone for complete control. The

majority of patients had a sustained remission of urticaria. Recently, a randomized unblinded study of 65 patients with CIU compared 50 mg/d dapsone and 10 mg/d desloratadine versus 10 mg/d desloratadine alone during 3 months of treatment with an additional 3-month posttreatment observational period.[511] Although the dapsone-treated group had similar reductions in urticaria scores compared with the desloratadine monotherapy group, 9 patients treated with dapsone had complete responses, whereas none of the control subjects did. Additionally, 5 of 9 responders remained urticaria free 3 months after discontinuing dapsone, implying that dapsone might induce remission of CU, as has been suggested in some other reports.[505,507]

Dapsone is usually well tolerated but has predictable side effects, including dose-related anemia. Less common adverse effects include peripheral neuropathy, rash, gastrointestinal complaints, hepatotoxicity, and rarely methemoglobinemia, blood dyscrasias, or the syndrome of drug rash with eosinophilia and systemic symptoms.[512] Before initiation of dapsone therapy, it is recommended to determine the glucose-6-phosphate dehydrogenase (G6PD) level because dapsone should be avoided in G6PD-deficient patients because of the risk of severe hemolysis. Ongoing laboratory monitoring for anemia and hepatotoxicity is recommended.[513]

Sulfasalazine. Sulfasalazine has been associated with a variety of anti-inflammatory effects with potential relevance to urticaria pathogenesis, including decreased prostaglandin D_2 synthesis and histamine release from activated mast cells,[514] attenuation of the respiratory burst of polymorphonuclear leukocytes,[515] and inhibition of proliferation of B lymphocytes.[516] Case reports and case series have suggested efficacy of sulfasalazine in patients with CU and DPUA.[300,517,518] A retrospective observational study of 19 patients with CIU demonstrated significant improvement in 14 of 19 patients, with more modest benefit in 4 additional patients.[199] Therapeutic response occurred within 1 month, and doses of greater than 2 g/d had no additional benefit.

Gastrointestinal complaints, including nausea, vomiting, dyspepsia and anorexia, and headache are the most frequent complications of sulfasalazine therapy.[519] These symptoms typically occur early in therapy and are much more common in patients taking more than 4 g/d (a dose usually not required for treatment of CU). Gradual escalation of dosing over several days might reduce the gastrointestinal effects. Hematologic abnormalities, proteinuria, and hepatotoxicity are uncommon, but laboratory monitoring for these adverse effects is recommended.[520]

Hydroxychloroquine. Hydroxychloroquine is an anti-inflammatory agent that disrupts T-cell receptor cross-linking–dependent calcium signaling[521] and disrupts antigen processing[522] and therefore has potential benefit in patients with CU. Limited data are available on the use of hydroxychloroquine in patients with CU. A case report suggested efficacy in a patient with hypocomplementemic urticarial vasculitis.[406] A randomized, blind, placebo-controlled study of 21 patients with CU demonstrated significant improvement in quality of life but only trends toward improvement in urticaria activity scores or reduction in other medications.[167] The study was underpowered to detect significant differences caused by dropouts.

Hydroxychloroquine is generally well tolerated, with the most worrisome adverse effect being retinopathy. The risk of retinopathy from hydroxychloroquine is exceedingly rare, with less than 20 reported cases in more than 1 million treated patients.[523]

Almost all cases have occurred in patients who have used the drug for more than 5 years. Many cases of toxicity involved dosages greater than 6.5 mg/kg/d. The most recent 2011 American Academy of Ophthalmology recommendations advise a baseline ocular examination within the first year of therapy. Annual screening should begin after 5 years of therapy.[524] High-risk patients should have annual screening without a 5-year delay. High-risk patients are identified as having one of the following factors: hydroxychloroquine dose greater than 400 mg/d (>6.5 mg/kg/d ideal body weight for short subjects), duration of use of greater than 5 years, cumulative dose of greater than 1000 g, elderly age, presence of renal or liver dysfunction, and retinal disease or maculopathy.

Colchicine. Among alternative agents, colchicine has been used relatively frequently to treat CU despite minimal evidence to support its use. Colchicine has some anti-inflammatory activities, particularly as it relates to neutrophils, including suppression of neutrophil leukotriene B_4 generation[525] and expression of adhesion molecules on endothelium and neutrophils[526] that could potentially play a role in patients with CU. A single double-blind, placebo-controlled trial in 13 patients with DPUA did not show a benefit of colchicine.[287] A retrospective chart review followed by a short-term follow-up study found that colchicine was effective and well tolerated for the treatment of urticaria.[527] A recent open study treated patients with CU according to histologic features of their CU, and 8 of 9 colchicine-treated patients with neutrophilic inflammation responded to colchicine.[528] Other case reports suggest efficacy in patients with urticarial vasculitis.[139,529,530] Colchicine is generally well tolerated, with the most frequent adverse effect being diarrhea. High doses can cause bone marrow suppression, and long-term use has rarely been associated with myopathy.[531]

Immunosuppressant agents

Summary Statement 87: Several immunosuppressant agents have been used in patients with antihistamine-refractory CU. Cyclosporine has been studied in several randomized controlled trials. Taken in the context of study limitations, potential harms, and cost, the quality of evidence supporting use of cyclosporine for refractory CUA is low. On the basis of current evidence, this leads to a weak recommendation for use of cyclosporine in patients with CUA refractory to conventional treatment. (A)

Cyclosporine has been studied in several randomized controlled trials. For this reason, cyclosporine was selected for closer examination as to the quality of evidence supporting its administration in patients with refractory CU.

Immunosuppressant agents have been associated with remission of CU in uncontrolled studies. (C) Use of immunosuppressant agents can be considered after analyzing the risks and benefits of therapy and should generally be reserved for more refractory patients, particularly those who require frequent or long-term corticosteroids for control of CU. (D) The quality of evidence supporting use of cyclosporine for refractory CUA is low. (B) The evidence for tacrolimus, mycophenolate, and sirolimus is very low. (C)

Calcineurin inhibitors. Of the pharmacotherapeutic interventions recommended for patients with refractory urticaria/angioedema, cyclosporine has been studied most extensively. There are several published randomized, double-blind, controlled trials investigating the therapeutic utility of cyclosporine for

patients with CUA.[163,164,532,533] For this reason, cyclosporine was selected for closer examination as to the quality of evidence supporting its administration in patients with refractory CUA.

Cyclosporine can exert a salutary effect in patients with CUA through downregulation of T_H1 responses and T cell–dependent antibody generation by B lymphocytes, along with inhibition of the release of histamine and other mediators from mast cells and basophils.[534]

A number of case reports and small case series have described benefit with administration of cyclosporine to patients with CU unresponsive to antihistamines.[166,535,536] However, such studies do not provide high-quality evidence and might be subject to bias.[537,538] Evidence from randomized controlled trials tends to be rated as high quality; however, this initial grading of quality can be decreased based on methodological issues and other factors.[539-541]

The process of using principles of evidence-based medicine to address a clinical issue revolves around a management question formulated using a "PICO" format: a population of patients (P), in this case patients with CUA that is refractory despite treatment with high-dose antihistamines; a therapeutic intervention (I), in this case cyclosporine; the comparator (C), in this case conventional treatment with high-dose H_1-antihistamines (with or without H2-antihistamines); and patient-important outcomes (O), in this case improvement in the course of urticaria/angioedema. A PubMed search was carried out using the terms "urticaria" and "cyclosporine," with "randomized controlled trial" selected as a limit for "type of article," and identified 4 publications.[163,164,532,533] These 4 double-blind, randomized, controlled trials were analyzed using a modified GRADE approach to developing clinical practice guidelines.[537,538] By using the GRADE approach, a sequential series of steps are taken to systematically assess the quality of medical evidence and determine the strength of a recommendation either for or against a particular intervention. Compared with other systems, the GRADE approach clearly separates quality of evidence from strength of recommendations, entails criteria for downgrading and upgrading quality of evidence ratings, and explicitly acknowledges risk- and cost-benefit considerations, as well as patient values and preferences.[537,538] The evidence supporting the use of cyclosporine was evaluated critically by considering improvement in urticaria/angioedema symptoms relative to undesirable effects (harms, burdens, and costs) in the context of specific criteria for judging the quality of evidence.[539] High-quality evidence in which desirable effects outweigh the likelihood of undesirable effects with precise estimates of benefits that outweigh the downsides of treatment can lead to a strong recommendation for use of a particular intervention. Clinical decision making in these circumstances (eg, prescribing a second-generation antihistamine as first-line treatment for a patient with acute urticaria) can be quite straightforward. For interventions that merit weak recommendations, either related to low-quality evidence caused by, for instance, a lack of published randomized controlled trials or uncertainty as to whether the potential for harm exceeds the likelihood of benefit, the clinician is required to consider carefully whether administration of the therapy is favorable from the standpoint of balancing the potential for benefit with the potential for harm/burden and discuss this openly with patients to determine that the treatment decision is consistent with their values and preferences.[537,538]

Acknowledging the challenges involved in carrying out these types of studies, it is important to recognize the methodologic shortcomings that lead to a weak recommendation for the use of cyclosporine. These methodologic issues, which are described in Table X, involve aspects of both internal validity and external validity.

Internal validity. In each of the 4 studies, randomization was performed; however, concealment of allocation was not described. Whether patients, caregivers, collectors of outcomes data, adjudicators of outcome, or data analysts were aware of group allocation was not stated. However, despite this being an important element of a high-quality randomized controlled trial, an observational study reported that authors of randomized controlled trials frequently use concealment of allocation and blinding, despite the failure to note this in the methods section of the published article.[542] This implies that one cannot conclude that concealment, as a bias-reducing procedure, did not occur if this was not specifically described.

More important in assessing the quality of these studies are study-specific findings concerning randomization of subjects for participation. Although 60% of subjects in one study had required prior corticosteroids, 78% of such subjects were assigned to the treatment group, thereby confounding interpretation of study results.[163] In another study patients with severe refractory CIU were enrolled; however, only 2 weeks after randomization to either 10 mg/d cyclosporine or cetirizine, 80% of subjects in the cetirizine group had "daily severe relapses requiring systemic steroid treatment" and were "crossed over" to open cyclosporine treatment.[164] One study randomized subjects to cyclosporine for either 1 or 3 months without a comparator (ie, noncyclosporine) group; for this reason, this study was not included in Table X.[532]

Patients with a positive ASST result were enrolled in 3 of the 4 studies.[163,164,532] In the remaining study the ASST was not performed.[452] In other published studies ASST results have not consistently correlated with *in vitro* assays, and a positive ASST result was observed in patients without CU.[198,543] On the basis of these data, the role of positive ASST results in predicting a salutary effect of cyclosporine is unclear.

Potential for benefit versus potential for harm/burden. The therapeutic benefit of cyclosporine was critically appraised by using 2 studies in which subjects were randomized to cyclosporine or cetirizine. "Refractory" was defined as poor control despite a daily dose of 10 mg[452] or 20 mg[163] of cetirizine.

The primary outcomes from these studies, the urticaria activity and urticaria severity scores, were combined to generate the forest plot shown in Fig 4. Compared with subjects randomized to treatment with cetirizine in these studies, subjects randomized to cyclosporine were 3.57 times more likely to experience benefit in symptoms scores.

As described in Table X, the quality of these studies was downgraded based on indirectness: the study population enrolled did not match our study population of interest. Lack of intent-to-treat analysis[163] was judged to pose a serious risk for bias.

Subjects treated with cyclosporine frequently experienced untoward effects in these 4 studies; however, in most cases these events were not sufficiently severe to require study withdrawal. The criteria for discontinuation of study drug were not clearly articulated and might have been different for each study. Grattan

et al[163] reported that 29 of 30 who received cyclosporine experienced symptoms that were "probably or definitely drug related." Of 16% with adverse events reported by Vena et al,[452] 2 were classified as "serious": gastroenteritis and precordalgia. Combining the data from 2 of the randomized controlled trials, an increase in serum creatinine level was observed in 10% of subjects randomized to cyclosporine.[164,533]

Small randomized trials might not be sufficient for gauging the likelihood of adverse reactions. For this reason, 7 additional clinical studies in which cyclosporine was administered at doses ranging from 2.5 to 6 mg/kg/d using various dose-reduction protocols were examined to gain a more precise estimate of the potential for harm associated with cyclosporine in patients with CUA.[165,166,535,536,544-546] Adverse events reported include renal toxicity (including increased serum creatinine level or hypertension), gastrointestinal symptoms (including abdominal pain, diarrhea, or liver enzyme abnormalities), neurologic symptoms (including headache, tremors, or neuropathy), cold sensitivity, insomnia, hypertrichosis, gingival hyperplasia, paresthesias, and fatigue.[534] Many untoward effects of cyclosporine are dose and/or duration related. Malignancies have rarely been reported with calcineurin inhibitors. A prospective long-term cohort study of 1252 patients with psoriasis treated with cyclosporine and followed for up to 5 years found a higher incidence of dermatologic but no other (ie, nondermatologic) malignancies.[359] Monitoring of blood pressure, renal function, serum drug levels, and other metabolic factors is important in patients treated with calcineurin inhibitors.[534]

External validity. None of these studies described a step-care approach in an attempt to maximize H^1-antihistamine (with or without adjunctive) therapy before administration of cyclosporine. The generalizability of study findings to patients with antihistamine-refractory CUA seen by allergy/immunology specialists is unclear. The comparator treatment in 3 studies was cetirizine at a daily dose of either 10 or 20 mg.[163,164,533] Moreover, the subjects enrolled in these studies were refractory in the sense of having had "poor response to antihistamine therapy" or "persistence of symptoms … despite treatment with cetirizine."[532,533]

For the above reasons, the external validity of these data can be impugned based on subject selection and the lack of exposure to high-dose antihistamine treatment for those randomized to comparator treatment. The latter issue is important because inadequate dose titration of an efficacious comparator treatment can lead to a potentially misleading claim of effectiveness.[539]

Prescribing cyclosporine. Should the presentation of a patient warrant administration of cyclosporine, after careful consideration of the evidence, the potential for benefit relative to harm/burden, and the patient's values and preferences, its administration should proceed with consideration of the following issues.

Of the 4 trials that were critically reviewed, the dose of cyclosporine used was 4 mg/kg in 2 trials, 5 mg/kg tapering to 4 mg/kg in 1 trial, and 5 mg/kg tapering to 4 mg/kg and then 3 mg/kg in 1 trial. For this reason, the data do not permit a recommendation as to a specific dose to prescribe; however, it appears that doses of 4 mg/kg or less would be prudent from a risk/benefit standpoint.

The clinician prescribing cyclosporine should be aware that there are clinically important differences in bioavailability between different cyclosporine preparations; for instance, Neoral (Novartis Pharmaceuticals, East Hanover, NJ) has increased bioavailability in comparison with Sandimmune (Novartis Pharmaceuticals). Different preparations of cyclosporine are not bioequivalent and should not be used interchangeably.

The 2013 average wholesale price of cyclosporine (Neoral) administered at a dose of 5 mg/kg/d for a 70-kg patient is approximately $650 per month.

Summary of cyclosporine data. Randomized controlled trials in patients with refractory urticaria/angioedema are difficult to perform; nevertheless, methodological shortcomings were recognized in each of these randomized, controlled, double-blind studies that examined the role of cyclosporine for patients with CUA. It is unclear whether the likelihood of desirable effects from cyclosporine administration significantly outweighs the risk of undesirable effects, particularly given the lack of appropriate comparator groups used in these studies. Further studies are required to determine the optimal dose and duration of treatment with cyclosporine. Taken in the context of study limitations, potential harms, and cost, the quality of evidence supporting use of cyclosporine for refractory CUA is low. On the basis of current evidence, this leads to a weak recommendation for use of cyclosporine in patients with CUA refractory to conventional treatment. This recommendation implies that further research is very likely to have an important effect on our confidence in the estimate of effect and might change the estimate. Despite the lack of high-quality evidence for efficacy of cyclosporine, there is substantial published observational experience with cyclosporine with varying doses and for long-term use that suggests cyclosporine is efficacious for refractory CU and capable of inducing remission.[547] The weak recommendation does not imply that cyclosporine might not be of benefit in properly selected patients with refractory CUA. Rather, it signifies the need for clinicians 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.[537,538]

Tacrolimus. Tacrolimus is another calcineurin inhibitor that has been evaluated in patients with CU. A pilot observational study of tacrolimus in 12 patients with CIU poorly responsive to antihistamines reported 70% of patients responded to tacrolimus, with 3 patients having resolution of urticaria, including 1 who had not responded to cyclosporine.[118]

Mycophenolate is an immunosuppressant used in transplantation, as well as in a growing number of autoimmune diseases. The active metabolite of MMF is a competitive inhibitor of inosine-5′-monophosphate dehydrogenase and kills activated lymphocytes through the activation of a caspase-independent necrotic signal.[548] In an open-label study of 9 patients with CU with positive ASST results refractory to H_1- and H_2-antagonists, 12 weeks of 1000 mg of MMF twice daily showed significant improvement in symptom scores, reduction in antihistamine use, and steroid-sparing activity.[549] A retrospective case series of more clearly defined patients with refractory CU found mycophenolate to show improvement in 89% of patients; however, 53% of patients reported gastrointestinal side effects.[550] The median dose to achieve complete control was 4000 mg (range, 1000-6000 mg), and the median time for initial improvement

was 4 weeks (range, 1-9 weeks). The most common adverse effects with MMF include gastrointestinal disturbances occurring in up to 20% of patients at doses of 2 g/d.[551] Hematologic side effects, including leukopenia, are less common, usually mild, reversible, and dose related.

Sirolimus (rapamycin) was reported to be effective in 2 of 3 patients in a case report.[552] Multiple alternative therapies, including montelukast, dapsone, hydroxychloroquine, colchicine, olsalazine, and MMF, had previously failed. Of note, sirolimus and the related agent everolimus have been implicated in causing isolated angioedema.[553,554]

Biologic agents

Omalizumab. *Summary Statement 88*: In contrast to other alternative agents for refractory CU, the therapeutic utility of omalizumab 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, from an individualized standpoint, a therapeutic trial of omalizumab 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 the patient's values and preferences. (A)

Omalizumab is a recombinant humanized mAb that binds to free IgE and inhibits binding of IgE to FcεRI, the high-affinity IgE receptor. Omalizumab reduces the number of FcεRI receptors on the surfaces of mast cells and basophils.[555] Several case reports and case series have suggested efficacy of omalizumab in a variety of types of CU, including cold urticaria,[556] cholinergic urticaria,[243] solar urticaria,[557] DPUA,[558] urticarial vasculitis,[559] idiopathic urticaria,[557,560,561] and idiopathic angioedema.[562] Failure of omalizumab in patients with physical urticaria/angioedema syndromes has also been reported.[563]

A proof-of-concept study evaluated the efficacy of omalizumab in 12 patients with CUA.[564] This was a single-blind study that included a 4-week placebo phase followed by omalizumab every 2 or 4 weeks for 16 weeks. Seven subjects had complete resolution, 4 had partial improvement, and 1 had no response. A double-blind, placebo-controlled, dose-ranging study was performed in 90 participants with CU who had poorly controlled CU despite treatment with an FDA-approved dose of an H$_1$-antagonist.[565] Subjects received a single dose of 75, 300, or 600 mg of omalizumab or placebo. Both the 300- and 600-mg omalizumab-treated groups showed greater improvement than the placebo group, with an onset of effect within 1 to 2 weeks. Another double-blind, placebo-controlled study evaluated omalizumab versus placebo for 24 weeks in 49 patients with CU and IgE autoantibodies to thyroperoxidase.[566] At the end of the study, the omalizumab group had significantly reduced urticarial activity scores, and 59% were symptom free compared with 14% treated with placebo. A phase III multicenter dose-ranging trial enrolled 323 subjects with moderate-to-severe CUA not responsive to H$_1$-antihistamines to receive 3 subcutaneous injections of omalizumab at 4-week intervals (75 mg, 150 mg, 300 mg, or placebo), followed by a 16-week observation period. The subjects enrolled in this study were refractory to "step 2" combination therapy (H$_1$- and H$_2$-antihistamines with or without antileukotriene agents) and continued combination therapy during study participation. This is in contrast to the inclusion criteria in studies

of cyclosporine described above, for which "indirectness"[567] was cited as a methodological shortcoming; compared with most other randomized controlled trials of patients with refractory CUA, this study offers greater external validity. The primary end point, itch severity score, and other prespecified secondary end points were significantly improved ($P < .001$) in those subjects receiving 150 and 300 mg every 4 weeks compared with placebo after 12 weeks.[568] The frequency of serious adverse events was slightly higher in subjects randomized to 300 mg (6%) compared with 150 mg (1%), 75 mg, (1%) or placebo (3%). The majority of patients had recurrence of urticaria/angioedema after completion of the study.

A recent phase III double-blind, placebo-controlled study of patients with CU unresponsive to high-dose H$_1$-antihistamines with or without concomitant H$_2$-antihistamines and leukotriene-modifying agents investigated the safety of 300 mg of omalizumab compared with placebo.[567] Study participants received injections every 4 weeks for 24 weeks and then were observed over a 16-week period. The overall incidence and severity of adverse events and serious adverse events were similar between omalizumab and placebo recipients. Although the primary outcome was the safety of omalizumab, subjects randomized to monthly injections of 300 mg of omalizumab were statistically significantly more likely to experience benefit in itch severity scores at 12 weeks ($P < .001$) and other outcome measures.[567]

The mechanism of action of omalizumab in patients with CU is not clear but might entail an effect on basophil function, which is abnormal in patients with active CIU.[569] Reports of efficacy have included patients without detectable autoantibodies and low total serum IgE levels.[570] In some studies omalizumab was administered based on the serum IgE level and body weight according to FDA-approved guidelines for patients with moderate-to-severe persistent asthma.[383,386,388] However, more recent studies have found that prescribing omalizumab in this fashion is not necessary because benefit with omalizumab was observed at a dose of either 150 or 300 mg every 4 weeks.[570]

The evidence supporting the therapeutic utility of omalizumab, which includes several large randomized controlled trials, is of higher quality compared with that for other agents (eg, hydroxychloroquine, dapsone, sulfasalazine, IVIG, or anti-TNF). However, omalizumab is more costly than other agents and might be difficult to obtain based on lack of insurance coverage for an agent that is currently FDA approved only for management of moderate-to-severe refractory asthma. Although omalizumab is associated with less potential for harm compared with other therapeutic alternatives (eg, calcineurin inhibitors) for antihistamine-resistant CU, its administration entails the burden of receiving subcutaneous injections on a regular basis in a physician's office because of the risk for anaphylaxis.[571] Although the reported rate of omalizumab-induced anaphylaxis is 0.09% in patients with allergic asthma, it is unknown whether patients with CU have the same risk for anaphylaxis. At this time, additional evidence is required to determine the optimal dose and frequency of administration, treatment duration, and the best approach for stepping down treatment over time to establish a minimal effective dose with omalizumab. There are no validated biomarkers or clinical markers that can predict response to omalizumab; there is a need to identify variables that can predict whether omalizumab will be effective. Other outstanding issues include patient selection and whether the burden of disease

warrants the cost of omalizumab over time. The greater cost of omalizumab might be counterbalanced by lower rates of health service use and indirect medical expenditures because of improved quality of life and fewer flares of CU over time; omalizumab is also associated with less risk for harm compared with other agents. Formal economic models using cost utility (cost per quality year of life gained) and cost-effectiveness (cost per attack prevented) analyses will be helpful in aiding allergy/immunology providers to clarify this issue. Presently, omalizumab should be considered for properly selected patients who have been unresponsive to step 3 care and for whom other immunosuppressive and/or anti-inflammatory agents would be associated with greater potential for harm, have lacked efficacy, and/or have not been well tolerated.

Other biologics. *Summary Statement 89*: Several biologic agents, IVIG, and anti-TNF agents have been reported to be efficacious in patients with refractory CU. (C)

Other biologic therapies have been reported to be helpful in case reports of patients with refractory CU. A patient with DPUA was noted to have a rapid response when treated with the TNF inhibitor etanercept for psoriasis.[304] His response persisted when switched to infliximab because of inadequate control of psoriasis. Numerous case reports have shown efficacy of the IL-1 receptor antagonist anakinra for the autoinflammatory syndrome Schnitzler syndrome.[572-574] Anakinra has also been reported to be beneficial in urticarial vasculitis.[575] Rituximab is an mAb targeted against CD20 transmembrane protein on the surfaces of mature B cells. Individual case reports of the efficacy of rituximab have been reported recently in patients with chronic autoimmune urticaria,[576] idiopathic angioedema,[577] and urticarial vasculitis.[578] In contrast, a case report of a failure of rituximab was reported in a patient with severe steroid-dependent CU who was resistant to numerous other alternative agents.[579] Data are severely limited on these biologic therapies, and with the exception of the treatment of Schnitzler syndrome, they should mainly be considered for patients proved refractory to other alternative agents.

IVIG

IVIG has a variety of immunomodulatory activities that might be important in patients with CU, including modulation of adhesion, complement function, cytokine levels, autoantibodies, and anti-idiotype networks.[580] The earliest report of use of IVIG in patients with CU involved an open-label trial of 10 patients with positive ASST and basophil histamine release test results in whom other therapies, including alternative agents, had failed.[581] Patients were treated with an immunomodulatory dose of 0.4 g/kg/d IVIG for 5 consecutive days. Benefit was noted in 9 of 10 patients, with 3 patients experiencing prolonged remission with 3 years of follow-up. Other case reports have suggested benefit of IVIG with various dosing regimens[582-584]; however, there are other reports of IVIG failures.[409,585] Low-dose IVIG dosed at 0.15 g/kg every 4 weeks resulted in improvement in 26 of 29 patients, including 19 who experienced complete remission.[586] IVIG has also been reported to be beneficial in patients with DPUA,[302] solar urticaria,[381] and urticarial vasculitis.[587] IVIG is relatively safe, with predictable infusion-related adverse reactions, including headache, myalgias, and nausea and, rarely, anaphylactoid reactions, aseptic meningitis, or renal failure.

Methotrexate

Summary Statement 90: Experience with methotrexate in patients with CU is limited (C) to small case reports and case series. (B) Because of the limited evidence and potential for more serious adverse effects, use of methotrexate in patients with CU should be considered only in patients refractory to other anti-inflammatory, immunosuppressant, or other safer alternative agents. (D)

Methotrexate is an anti-inflammatory agent with unclear mechanisms of action that include increasing adenosine levels, inducing apoptosis in activated $CD4^+$ T cells, and decreasing neutrophil chemotaxis.[588] Experience with methotrexate is limited, with a few case reports and a case series.[589-592] The largest case series of methotrexate-treated patients (8 with CIU, 3 with urticarial vasculitis, and 1 with idiopathic angioedema) demonstrated that 12 of 16 responded, 2 with complete response. The effective dose was 10 to 15 mg/wk. Methotrexate has potentially serious adverse effects, including hepatotoxicity and pulmonary fibrosis, and requires extensive laboratory monitoring. Folic acid supplementation has been shown to improve continuation rates of methotrexate by reducing the incidence of liver function test abnormalities[89] and gastrointestinal intolerance.[593] Recommendations for routine liver biopsies in patients receiving methotrexate vary, and a recent study suggests that methotrexate-specific liver lesions are rarely observed in patients with arthritis receiving long-term methotrexate therapy with increased liver enzyme levels.[594]

Phototherapy

Summary Statement 91: Phototherapy might be effective for CIU, as well as some physical urticarias, including solar urticaria. (C) Because of limited availability and frequency of treatment, phototherapy is generally considered in patients refractory to other anti-inflammatory, immunosuppressant, or biologic agents. (D)

Phototherapy includes UVA therapy with coadministration of psoralen or UVB therapy. Phototherapy might decrease histamine release from mast cells.[357] Phototherapy has been reported to be successful in various case reports of solar urticaria.[376,595-597] Case series have reported benefits of phototherapy in patients with other physical urticarias (cold, cholinergic, and dermographism) and CIU.[598,599] A relatively large retrospective study of 94 patients (88 with CIU) treated with NB-UVB demonstrated that 72% of treatment courses produced moderate improvement to clearance of urticaria.[600] Telephone follow-up years later revealed 33% of patients were clear of urticaria, with 45% indicating improvement from NB-UVB therapy. Recently, an open trial of 81 patients with CU receiving levocetirizine with 48 randomized to additional NB-UVB therapy showed improvement in both groups but statistically larger treatment effects in the NB-UVB–treated group.[511] In addition, the NB-UVB–treated group showed much lower scores 3 months later than seen in those treated with levocetirizine alone. Adverse effects of phototherapy include erythema, pruritus, photodegenerative changes, and increased risk for skin cancer.[601]

Miscellaneous alternative agents

Summary Statement 92: Other agents have been used in patients with refractory CU, including but not limited to theophylline, attenuated androgens, anticoagulants, NSAIDs, β-agonists, cyclophosphamide, gold, plasmapheresis, cromolyn, and

nifedipine (C); however, these agents should be reserved for patients with refractory urticaria whose treatment with other anti-inflammatory, immunosuppressant, or biologic agents has failed. (D)

A number of alternative therapies have been described in the treatment of CU, including theophylline,[602,603] attenuated androgens,[242,604-607] anticoagulants,[608-612] NSAIDs,[613,614] β-agonists,[470,615] cyclophosphamide,[168,169,616,617] gold,[618] plasmapheresis,[378,379,619-622] cromolyn,[623,624] and nifedipine,[625-628] and these have been reviewed elsewhere.[499] Some agents (eg, IFN-α) have also been studied in patients with CU with limited to no efficacy.[629,630] Efficacy with stanozolol has been demonstrated in a placebo-controlled randomized study.[607] A small placebo-controlled, double-blind crossover study demonstrated that a CUA subgroup might respond to warfarin.[598] However, based on the potential for harm and burden associated with administration of stanozolol and with warfarin, these agents should be considered only for patients with refractory CU in whom other anti-inflammatory, immunosuppressant, or biologic agents have failed.

Choosing alternative agents for treatment of refractory urticaria

Summary Statement 93: 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 association 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. (D)

There are several factors involved in selecting an alternative agent for refractory CU. First, it should be established that the patient is indeed refractory to antihistamine therapy. Unfortunately, predictive factors for response to the vast majority of alternative agents are lacking. The presence of underlying comorbid factors can also play a role in determining an alternative agent. For example, in a patient with poorly controlled hypertension, a calcineurin inhibitor can have higher risk of exacerbating the hypertension. A patient's tolerability to other medications might also influence drug selection. Baseline laboratories might be required to determine whether any agents are contraindicated, such as dapsone and hydroxychloroquine, in a patient with G6PD deficiency. The frequency of treatment-related visits (eg, phototherapy sessions or visits for parenteral administration) should also be considered because this might be an impediment for certain patients. The cost of alternative agents varies considerably, and their affordability is another important treatment consideration. Rapidity of response to an alternative agent is another factor that influences choice. In patients experiencing significant adverse effects from glucocorticoid toxicity, agents with slow onset of action (eg, hydroxychloroquine) might not be optimal. Finally, the potential risk of a given alternative agent is extremely important and needs to be weighed against the patient's current quality of life and any adverse effects from current therapy for their CU. Although receiving alternative therapies, appropriate laboratory monitoring, if indicated, is important. Suggested laboratory monitoring for select alternative agents is shown in Table XI. Recent guidelines for laboratory monitoring

of many of the rheumatic agents used in the treatment of CU have recently been reviewed.[520]

Therapies for specific conditions associated with CU

Summary Statement 94: 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 CU. (C)

H pylori has been reported in recent years to be associated with CU. Recently, a study of 35 patients with CU (57% were positive for *H pylori*) found an association between heavy bacterial colonization and intense gastric inflammation and the severity of CU.[631] Several studies have evaluated whether eradication of *H pylori* improves urticaria in patients with CU. A recent review of studies of *H pylori* eradication and outcomes on CU revealed 10 studies showing improvement in CU with *H pylori* therapy, and 9 studies showed no improvement.[146] Therefore 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* screening in patients with CU.

Thyroid autoantibodies

Summary Statement 95: Because limited data support the use of thyroid hormone therapy in euthyroid patients with CU and thyroid autoantibodies, prescribing thyroid hormone to euthyroid patients with thyroid autoimmunity remains controversial. (C)

An association of thyroid autoantibodies with CU was described several decades ago.[132,632,633] Several reports have described improvement in the course of CU in patients with elevated thyroid autoantibodies in association with administration of thyroid hormone at doses that suppress the TSH level.[159,634,635] A recent survey of US allergists showed that although the majority were tested for thyroid autoantibodies, only a minority treated euthyroid patients.[636] There is a lack of high-quality evidence demonstrating the efficacy of thyroid hormone supplementation for euthyroid patients with CU and 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, with careful assessment of the potential for benefit and the potential for harm and burden associated with thyroid hormone supplementation, taking patients' values and preferences into consideration and allowing patients to participate actively in the decision-making process.

Herpes infection

Summary Statement 96: Very limited data support the use of antiviral therapies in patients with CU with concomitant herpetic infections or positive viral serologies. (C)

Rare cases of urticaria associated with genital herpes have been reported with successful treatment with acyclovir[637] and valcyclovir.[638] Another case series of 12 patients with CIU, idiopathic angioedema, and hereditary angioedema found that 5 patients responded to acyclovir therapy, with recurrence after discontinuation of acyclovir.[639] None had genital herpes, but they did have increased antibody titers to herpes simplex or EBV.

AUTOIMMUNE PROGESTERONE AND ESTROGEN DERMATITIS

Summary Statement 97: Limited data are available for the use of hormonal therapies in patients with autoimmune progesterone and estrogen dermatitis. (C)

Autoimmune progesterone dermatitis is a rare cyclical disease associated with the luteal phase of the menstrual cycle and a variety of dermatologic manifestations, including urticaria and angioedema[640] and even anaphylaxis.[415,417] The diagnosis can be confirmed through intracutaneous skin testing, although the positive predictive value of this procedure is not optimal.[641] Serologic testing or intramuscular or oral challenge with progesterone might also be used to establish this diagnosis.[417,642,643] Case reports of successful treatment with conjugated estrogen,[642] gonadotropin-releasing hormone agonists,[644] tamoxifen,[645] and bilateral oopherectomy[417] suggest that hormonal manipulation can be efficacious in some cases.

Another even more rare form of hormone sensitivity is estrogen dermatitis, which is associated with premenstrual flares of dermatosis, including urticaria in some cases.[646,647] Patients with urticaria caused by estrogen are given diagnoses based on results of intradermal skin tests to estrogen. Treatment with tamoxifen,[646,647] bilateral oopherectomy,[648] and progestin[649] has been efficacious in some cases.

Skin testing to progesterone preparations can be very challenging. Currently, there is no consensus on the optimal preparation or concentration of progesterone to use for skin testing.[117,415,641,650]

UNPROVED/CONTROVERSIAL THERAPIES

Summary Statement 98: The evidence is weak that pseudoallergen-free diets improve CU. (C) Given the lack of evidence and burden of adhering to these diets, their use in patients with CU is not recommended. (D)

Summary Statement 99: Other unproved therapies for CU that are not recommended include allergen immunotherapy, herbal therapies, vitamins, supplements, and acupuncture. (C)

Although CU is not a manifestation of IgE-mediated food allergy, some have suggested that certain substances in food might exacerbate or even be the cause of CU. This is believed to be due to the presence of "pseudoallergens," which are substances in foods that exacerbate CU. Pseudoallergens include artificial preservatives and dyes in processed foods, as well as naturally occurring histamine or aromatic compounds in certain foods (many fruits, vegetables, seafood, and others). Aromatic compounds in wine, tomatoes, and spices, as well as phenols, such as p-hydroxybenzoic acid, citrus and orange oil, and salicylates, have all been identified as pseudoallergens.[32] The evidence for pseudoallergen-free diets in patients with CU has been evaluated in uncontrolled studies.[449,651] One study concluded that adherence to a low-pseudoallergen diet was helpful because 73% of 64 patients with CU had either cessation or a significant reduction of symptoms within 2 weeks of adopting a pseudoallergen-free diet.[449] However, only 19% of those who improved had symptoms when subsequently challenged with individual pseudoallergens on provocation tests. In contrast to the high rates of response in this study, a subsequent larger study of 140 patients started on a pseudoallergen-free diet found that only 28% had a strong or partial response.[652] The largest study on this topic studied 838 patients with CU, and all underwent a food additive–free diet.[120] Thirty-one percent of subjects noted improvement in CU symptoms, but none had complete remission. Double-blind, placebo-controlled challenges were performed to both additive mixes and individual additives in all subjects with a favorable response to diet, as well as a subset of those with no improvement on the diet. Overall, only 1% to 3% of patients had confirmatory double-blind challenges. The evidence is weak that pseudoallergen-free diets improve CU symptoms, and given the difficulty of adhering to these diets, their widespread use in patients with CU is not recommended.

Other therapies that remain unproved as a therapy in patients with CU include allergen immunotherapy, herbal therapies, vitamins, supplements, homeopathy, and acupuncture.[653-656] Although case reports have suggested efficacy of immunotherapy in seasonal urticaria,[657] allergen immunotherapy is not recommended as a therapy for CU.[456]

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STEP 4
Add an alternative agent
- Omalizumab or cyclosporine
- Other anti-inflammatory agents,immunosuppressants, or biologics

STEP 3
Dose advancement of potent antihistamine (e.g. hydroxyzine or doxepin) as tolerated

STEP 2
One or more of the following:
- Dose advancement of 2nd generation antihistamine used in Step 1
- Add another second generation antihistamine
- Add H_2- antagonist
- Add leukotriene receptor antagonist
- Add 1st generation antihistamine to be taken at bedtime

STEP 1
- Monotherapy with second generation antihistamine
- Avoidance of triggers (e.g., NSAIDs) and relevant physical factors if physical urticaria/angioedema syndrome is present.

- Begin treatment at step appropriate for patient's level of severity and previous treatment history

- At each level of the step-approach, medication(s) should be assessed for patient tolerance and efficacy

- **"Step-down" in treatment is appropriate at any step, once consistent control of urticaria/angioedema is achieved**

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

FIG 2. Diagnosis and management of acute urticaria.

1. Patient presents with history suggestive of chronic urticaria and/or angioedema

2. Does patient have angioedema

YES

3. Consider medications, C1INH syndromes, or conditions that mimic angioedema

NO

4. Is history, review of systems, and physical examination consistent with

NO

5. Consider alternative diagnoses (see Differential Diagnosis Section)

YES

6. Does the history suggest physical urticaria? Is there a physical component to the urticaria and/or

YES

7. Consider appropriate challenge testing for physical urticaria.

NO

8. Does the history or physical examination suggest vasculitis?

YES

9. If skin biopsy diagnostic for vasculitis, manage vasculitis. If biopsy negative go to box 10.

NO

10. Are history, physical examination, and/or basic laboratory tests indicative of an underlying cause?

YES

11. Evaluate and manage specific conditions.

NO

12.
- Management of chronic urticaria/angioedema. (See Figure 1).
- Periodic reassessment for underlying etiology and response to therapy.

FIG 3. Diagnosis and management of CU.

Study or Subgroup	cyclosporine Events	Total	no cyclosporine Events	Total	Weight	Risk Ratio M–H, Fixed, 95% CI
Gratton 2000	8	19	0	10	12.6%	9.35 [0.59, 147.09]
Vena 2006	14	23	4	18	87.4%	2.74 [1.09, 6.90]
Total (95% CI)		42		28	100.0%	3.57 [1.45, 8.81]
Total events	22		4			

Heterogeneity: Chi² = 0.78, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 2.76 (P = 0.006)

FIG 4. Forest plot comparing combined urticaria activity and urticaria severity scores in subjects randomized to cyclosporine versus cetirizine. *M-H,* Mantel-Haenszel.

TABLE I. Causes of acute urticaria, angioedema, or both

Contact urticaria (eg, plant or animal)
Early contact dermatitis (eg, poison ivy or nickel)
Exacerbation of physical urticaria (eg, dermographism or cholinergic urticaria)
Food allergies (IgE mediated)
Adverse reactions to allergen immunotherapy
Adverse medication reactions (eg, opiates, ACE inhibitors, or NSAIDs)
Papular urticaria caused by insect sting/bite (eg, scabies, fleas, or bed bugs)
Infection (eg, parvovirus B19 or EBV)
Food or envenomation/ingested toxin (eg, scombroid)

TABLE II. Guidelines for diagnostic work-up of patients with CU[183]

History and physical examination
- Onset (eg, timing of symptoms with any change in medication or other 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, or other pattern
- Known precipitating factors of urticaria (eg, physical stimuli, exertion, stress, food, or medications)
- Relation of urticaria to occupation and leisure activities
- Associated angioedema or systemic manifestations (eg, headache, joint pain, or gastrointestinal symptoms)
- 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
- Physical examination

Laboratory evaluation

- **Routine evaluation**: Testing should be selective. There is an honest difference of opinion concerning the appropriate tests that should routinely be performed for patients with CU in the absence of etiologic considerations raised by a detailed history and careful physical examination.
- **A majority of members of the Practice Parameters Task Force expressed a consensus for the following routine tests in managing a patient with CU without atypical features**:
  - CBC with differential
  - Erythrocyte sedimentation rate, C-reactive protein level, or both
  - Liver enzymes
  - TSH
  The utility of performing the above tests routinely for patients with CU has not been established.
- **Additional evaluation might be warranted based on patients' circumstances and might include but not be limited to the diagnostic tests listed below. A thorough history and meticulous physical examination are essential for determining whether these additional tests are appropriate:**
  - Skin biopsy
  - Physical challenge tests
  - Complement system (eg, C3, C4, and CH_{50})
  - Stool analysis for ova and parasites
  - Urinalysis
  - Hepatitis B and C serologies
  - Chest radiography, other imaging studies, or both
  - Anti-nuclear antibody
  - Rheumatoid factor, anti-citrullinated protein
  - Cryoglobulin levels
  - Serologic and/or skin testing for immediate hypersensitivity
  - Thyroid autoantibodies
  - Serum protein electrophoresis

More detailed laboratory tests, skin biopsies, or both merit consideration if urticaria is not responding to therapy as anticipated.
Additional laboratory testing might be required before initiation of certain medications, such as G6PD screening before prescribing dapsone.

TABLE III. Challenge procedures for physical urticaria/angioedema syndromes

Syndrome	Challenge procedure	Positive result
Aquagenic	Water compress at 35°C applied to skin of upper body for 30 min	Urticaria at challenge site
Cholinergic	Immersion with hot water (42°C), exercise, or methacholine intradermal challenge	Appearance of "satellite wheal," which is defined as development of pinpoint pruritic wheals with surrounding erythema
Dermatographia	Stroking of skin with tongue blade	Erythematous wheal formation at site of stroking within 1-3 min
Delayed pressure	Fifteen pounds hung over shoulder for 10 or 15 min	Area of angioedema 4-12 h later (peak = 8-9 h)
Vibratory	Vortex mixer applied to forearm for 4 min	Development of angioedema sharply demarcated from normal skin
Cold	Cold provocation testing (eg, ice cube) on forearm for 5 min	Development of urticaria at challenge site during rewarming of skin
Solar	Exposure to specific wavelengths of light	Urticaria at challenge site
Exercise induced	Treadmill challenge	Symptoms reflecting systemic mediator release, such as pruritus, urticaria, and angioedema

TABLE IV. Common and less/uncommon urticaria angioedema or urticaria-like dermatoses

Common	Less common or uncommon
Anaphylaxis	Angiolymphoid hyperplasia with eosinophilia
Atopic dermatitis	Autoimmune progesterone-associated dermatoses
	Autoinflammatory syndromes:
	Familial cold-autoinflammatory syndrome
	Muckle-Wells, NOMID
	Hyper-IgD syndrome, TRAPS, PFAPA, PAPA
	FMF
Autoimmune thyroid disease	Blepharochalasis
Bullous pemphigoid	Cheilitis glandularis
C1-inhibitor deficiencies	Cheilitis granulomatosa
Contact dermatitis	Cryoglobulinemia
Contact urticaria	Drug-related eosinophilia with systemic symptoms
Cutaneous and systemic lupus erythematosus	Episodic angioedema with eosinophilia
Cutaneous mastocytosis	Estrogen-induced angioedema
Dermatitis herpetiformis	Complement factor I deficiency
Erythema multiforme (infection, drug)	HES
Exacerbation of physical urticaria	Schnitzler syndrome/malignancies
Food/insect allergies	SM
Adverse medication reactions	Urticaria-like dermatoses of pregnancy
Angioedema with ACE inhibitors	Gestational pemphigoid
Fixed drug eruptions	PUPPS, prurigo of pregnancy
Parasite/bacterial infections	Well syndrome
Polymorphous light eruption	
Recall urticaria	
Scabies, insect bites	
Urticarial Vasculitis (eg, hepatitis)	
Viral infections	

TABLE V. Causes of autoantibody-associated urticaria, angioedema, or both

Autoantibody to C1q, C1-inhibitor
Autoantibody to IgE or IgE receptor
Cryoglobulinemia
Cutaneous and systemic lupus erythematosus
HUVS
Lymphoreticular malignancy
Still disease

TABLE VI. Endocrine/hormonal/pregnancy-related urticaria and/or angioedema conditions

Autoimmune progesterone-induced dermatitis
Autoimmune thyroid disease
Estrogen-dependent angioedema (type III hereditary angioedema)
Gestational pemphigoid
Pruritic urticarial papules and plaques of pregnancy (PUPPS)

TABLE VII. Other dermatologic diseases presenting with urticaria

Atopic dermatitis
Bullous pemphigoid
Contact dermatitis (type IV hypersensitivity)
Dermatitis herpetiformis
Gestational pemphigoid
Papular urticaria from reduviid bite, fire ant sting

TABLE VIII. Very rare mimickers of urticaria, angioedema, or both

Acute hemorrhagic edema of childhood
Acute idiopathic scrotal edema of childhood
Angiolymphoid hyperplasia with eosinophilia
Blepharochalasis
Cheilitis glandularis
Cryopyrinopathies
Drug-related rash with eosinophilia and systemic symptoms (DRESS)
Factor I deficiency
Gleich syndrome
HES
Kimura disease
Melkersson-Rosenthal syndrome
Romana sign (trypanosomiasis)
Schnitzler syndrome
Schulman syndrome
Still disease
TRAPS
Well syndrome

TABLE IX. Pharmacology of H1-antihistamines[491,658]

H$_1$-antihistamine	Receptor-binding affinity, Ki (nmol/L)	t$_{max}$ (h)	t½ (h)	Onset of action (h)	Duration of action (h)	Common adult doses for urticaria	Conditions that might require dose adjustment
First generation							
Diphenhydramine	NA	1.7	9.2	2	12	25-50 mg 3-4 times daily or at bedtime	Hepatic impairment
Doxepin	NA	2	13	NA	NA	25-50 mg 3 times daily or 50-150 mg at bedtime	Hepatic impairment
Hydroxyzine	NA	2.1	20	2	24	25-50 mg 3-4 times daily or 50-150 mg at bedtime	Hepatic impairment
Second generation							
Cetirizine	47.2	1.0	6.5-10	1	24	10-40 mg/d	Renal and hepatic impairment
Desloratadine	0.87	1-3	27	2	24	5-20 mg/d	Renal and hepatic impairment
Fexofenadine	175	2.6	14.4	2	24	180-540 mg/d	Renal impairment
Levocetirizine	2.0	0.8	7	1	24	5-20 mg/d	Renal and hepatic impairment
Loratadine	138	1.2	7.8	2	24	10-40 mg/d	Hepatic impairment

Data are expressed as means.

NA, Not available; *t½*, half-life; *tmax*, time of maximum concentration.

TABLE X. Critical appraisal of evidence: randomized controlled studies of cyclosporine for treatment of chronic urticaria/angioedema

Study	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CYS + cetirizine	Cetirizine	Effect	Quality
			Quality assessment				No. of patients		Summary of findings	
Vena[533]	RCT	Serious*	None serious	Yes§	None	Yes#	64††	35	62% vs 23% ($P < .05$)*	Low
Grattan[163]	RCT	Serious†	None serious	Yes‖	None	Yes**	20‡‡	10	42% vs 0% ($P < .05$)¶¶	Low
Di Gioacchino[164]	RCT	Very serious‡	None serious	Yes¶		Yes	20§§	20	—	Very low

CYS, Cyclosporine; *RCT*, randomized controlled trial; *UAS*, urticaria activity score.

Primary outcome: improvement in urticaria severity score at 8 weeks: randomized to CYS + cetirizine compared with cetirizine.

*Ninety-nine subjects were randomized, and 38 did not complete the study. Details of blinding or allocation concealment were not described.

†Details of blinding or allocation concealment were not described. Analysis was not by intention to treat.

‡Eighty percent of subjects randomized to cetirizine 10 mg/d were "crossed over" to open treatment with CYS after 2 weeks.

§Refractory was defined as not responsive to 10 mg/d cetirizine when the enrolled population was different from the target population.

‖Subjects were randomized to CYS + cetirizine 20 mg/d or placebo + cetirizine 20 mg/d. An inadequate comparator might lead to overestimation of treatment effect.

¶Subjects were randomized to CYS or cetirizine 10 mg/d. An inadequate comparator might lead to overestimation of treatment effect.

#Adverse events were observed in 69% of subjects randomized to CYS and 46% in those randomized to placebo.

**All subjects had a history of "poor response to antihistamines" and a positive ASST result.

††Cyclosporine dose = 4 mg/kg.

‡‡Cyclosporine dose = 5 mg/kg, tapering to 4 mg/kg, and then tapering to 3 mg/kg.

§§Cyclosporine dose = 5 mg/kg for 8 weeks and 4 mg/kg for 8 weeks.

¶¶Primary outcome: reduction of weekly UAS to less than 25% of baseline.

TABLE XI. Laboratory monitoring of alternative agents for patients with refractory CU

Alternative agent	Baseline laboratory tests	Monitoring on therapy
Montelukast	None	None
Hydroxychloroquine	G6PD, LFT, BUN/Cr	None
Dapsone	G6PD, CBC, LFT	Monthly: CBC, LFT × 6 mo and then periodically
Sulfasalazine	CBC, LFT, BUN/Cr	Monthly: CBC, LFT, BUN/Cr × 3 mo and then every 3 mo
Methotrexate	CBC, LFT, BUN/Cr, CXR	Every 2-4 wk: CBC, LFT, BUN/Cr
Colchicine	LFT, BUN/Cr	None
Cyclosporine	CBC, LFT, BUN/Cr, K, lipids	Every 2-4 wk: BUN/Cr, K, CSA Periodic: lipids, glucose
Tacrolimus	CBC, LFT, BUN/Cr, K, lipids	Same as cyclosporine, except check tacrolimus levels
Mycophenolate	CBC, LFT, BUN/Cr	First month: weekly CBC Then CBC every 2 wk for 2-3 mo and then monthly
Omalizumab	None	None
Immune globulin	BUN/Cr, CBC	Periodic monitoring of BUN/Cr, CBC

BUN, Blood urea nitrogen; *Cr*, creatinine; *CSA*, cyclosporine; *CXR*, chest x-ray; *K*, potassium; *LFT*, liver function test.