REVIEW ARTICLE

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Chronic Urticaria

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Chronic urticaria is defined as wheals (hives), angioedema (swelling), or both that have been continuously or intermittently present for at least 6 weeks,[1,2] in contrast to acute urticaria, which is an episode of less than 6 weeks duration. Patients with chronic urticaria are commonly seen by allergy immunology and dermatology specialists, but primary care providers are frequently the initial resource for patients seeking evaluation, treatment, and reassurance.

Prevalence and Disease Burden

An estimated 500,000 persons in the United States have chronic urticaria, with a prevalence of 0.23%. The disorder may occur at any age, but most affected patients are women, and patients of both sexes tend to be over 40 years of age.[3] The disorder has substantial effects on daily life. The seemingly random occurrence of episodes, intense pruritus that disrupts sleep, and restriction in physical and emotional functioning have been shown to impair quality of life.[4,5] The effect of these disturbances has been appreciated to a greater extent in recent years than previously as a result of the validation and use of patient-reported outcome measures designed for this and related disorders.[4] A higher rate of coexisting psychiatric conditions has been reported among patients with chronic urticaria than in the general population or in association with other chronic conditions.[5] The degree of impairment in the quality of life for patients with chronic urticaria is similar to that reported for patients with coronary artery disease who are awaiting coronary-artery bypass grafting.[6]

Classification

Chronic urticaria has been categorized on the basis of consensus criteria and guidelines[2,7-9] as spontaneous urticaria (previously designated as chronic idiopathic urticaria), in which urticaria, angioedema, or both occur in an unprompted fashion, or as inducible urticaria (previously designated as physical urticaria), in which urticaria, angioedema, or both are elicited by factors such as cold, heat, or pressure.

Pathogenesis

Lesions result from degranulation of cutaneous mast cells, which leads to the release of histamine, the major mediator of pruritic wheals and angioedema, as well as the release of cysteinyl leukotrienes, prostaglandins, platelet-activating factor, and other substances. Proinflammatory cytokines and vasoactive factors are also released, which results in vasodilatation and leakage of plasma from the vascular

system in and below the skin. A predominantly lymphocytic infiltrate is found in lesions of acute and chronic urticaria; eosinophils and neutrophils may also be present.[10]

In acute urticaria, a cause such as a drug, food, or infection can usually be identified,[11] whereas in the chronic form, there is usually no identifiable cause. In patients with chronic inducible urticaria, lesions may be provoked by physical stimuli,[12] leading to the release of histamine, with the pruritic wheal flare response that is characteristic of chronic urticaria. The inducible form can occur in isolation or concomitantly with the spontaneous form. The pathogenesis of several inducible chronic urticaria syndromes has not been fully established. For instance, the pathogenesis of aquagenic urticaria has not been elucidated, but a proposed mechanism entails an interaction of water with a component in the stratum corneum or sebum that creates a toxic compound, which, on absorption in the skin, leads to mast-cell activation.[12] Patients with chronic urticaria may have an underlying systemic disorder (e.g., rheumatologic disease, infection, or hematologic cancer), but this is rare; most do not have an identifiable exogenous cause.[1,13]

CLINICAL FEATURES

These disorders are characterized by pruritic wheals with circumferential erythema on any part of the body. Figure 1 shows urticaria on the skin of a Black patient and on the skin of a White patient. Lesions range from a few millimeters to several centimeters in diameter and resolve in less than 24 hours, without residual bruising. In an often-cited series,[14] two thirds of patients had both urticaria and angioedema, with the remaining one third having only one or the other.

At the time of presentation, a patient may not have active lesions, but the diagnosis can be based on a history consistent with chronic urticaria, sometimes supplemented by the appearance of lesions in photos that patients have taken with their cell phones. When lesions are present, they are erythematous; circular, polymorphous, or serpiginous; and either isolated or coalescent. Angioedema, which is characterized by a similar pathogenesis but occurs in the deeper dermis and subcutaneous tissues, may also be present and typically affects the face, extremities, or torso.[1,2,8]

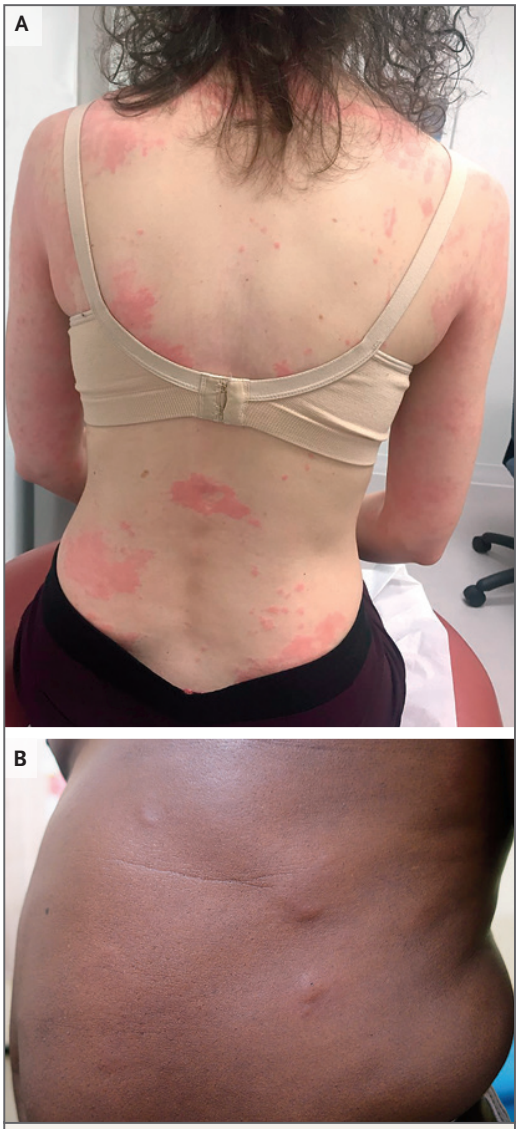

Figure 1. Clinical Images of Urticarial Lesions.
Urticarial lesions are shown on the skin of a White patient (Panel A) and a Black patient (Panel B). The erythematous, raised lesions are discrete or confluent and may vary in appearance on black or brown skin but tend to be less apparent than on white skin because of the similarity in hue with the surrounding skin. Panel B is used with permission from VisualDx.

The initial evaluation usually entails a comprehensive history taking to determine the timing,

Table 1. Chronic Inducible Urticaria Syndromes.

Syndrome	Provoking Factors	Recommended Challenge Procedure	Confirmatory Result	Comments
Aquagenic urticaria	Hot or cold water	Water compress at 35 C applied to skin of upper body for 30 min	Urticaria (perifollicular wheals 1 3 mm in diameter) at challenge site	Very rare, heterogeneous; pathogenesis not well understood
Cholinergic urticaria	Rise in core body temperature (e.g., from hot bath or shower, sweating, exercise, emotion)	Methacholine intradermal challenge (low sensitivity); partial immersion in hot water (42 C)	Appearance of satellite wheal ; provocation of punctate wheals, 1 3 mm in diameter, with or without large flares	Common; may provoke generalized mediator release and serious reaction; selected cases may warrant epinephrine prescription
Dermatographia	Rubbing or scratching	Stroking of skin with firm object (e.g., tongue blade)	Wheal at site of stroking within 1 3 min	Most common chronic inducible urticaria syndrome
Delayed pressure urticaria	Pressure or trauma (e.g., from belt or bra)	7-kg weight hung over shoulder for 10 or 15 min	Area of angioedema 2 12 hr later (peak, 4 6.5 hr)	Tends to be antihistamine-resistant; chronic spontaneous urticaria also present in many cases
Vibratory urticaria	Vibrating device (e.g., drills or musical instrument)	Vortex mixer applied to forearm for 4 min	Area of angioedema sharply demarcated from unaffected skin	Rare; management entails avoidance of provocative stimuli
Cold urticaria	Cold objects, cold wind, lakes or pools	Cold provocation testing (e.g., ice cubes or ice pack) on forearm for 5 min	Urticaria at challenge site during rewarming	Risk of generalized reaction with aquatic sports or cold-weather activities; selected cases may warrant epinephrine prescription
Solar urticaria	Sunlight	Phototesting with specific wavelengths of ultraviolet (A or B) or visible light	Urticaria at challenge site	Urticaria affects sun-exposed skin; severity is based on intensity or duration of exposure
Exercise-induced urticaria	Exertional activity	Exercise (treadmill) challenge	Symptoms (e.g., pruritus, urticaria, angioedema) reflecting systemic mediator release	Injectable epinephrine prescription indicated; exertional activity should be undertaken with a cell phone and a buddy

frequency, and nature of episodes and whether the appearance of lesions is consistent with chronic urticaria. Painful or burning dysesthesia in the region of lesions, particularly when combined with a history of nonblanching lesions persisting for more than 24 hours that leave a residual bruise, suggests the alternative diagnosis of cutaneous vasculitis.[1,2,10]

Identifying and confirming the chronic inducible form of the disorder provide an opportunity to recommend strategies for avoiding or minimizing exposure to provoking factors. The diagnosis can be confirmed by provocative challenge testing (Table 1). The two most common forms of chronic inducible urticaria are dermatographia and cholinergic urticaria. Dermatographia (skin writing) entails local histamine release generated by pressure applied to the skin. This can be elicited by stroking the skin with a firm object such as a tongue blade (Fig. 2). Dermatographia may affect up to 5% of the general population, although few persons have symptoms prompting medical attention. Cholinergic urticaria, induced by active or passive heating of the body, is also common, accounting for approximately 5% of all cases of chronic urticaria and up to 30% of the inducible form.[12]

Urticaria provoked by exercise can occur in patients with cholinergic urticaria or in a separately defined group of patients with exercise-induced urticaria and anaphylaxis. There are two types of exercise-induced urticaria and anaphylaxis: in one type, urticaria and anaphylaxis are

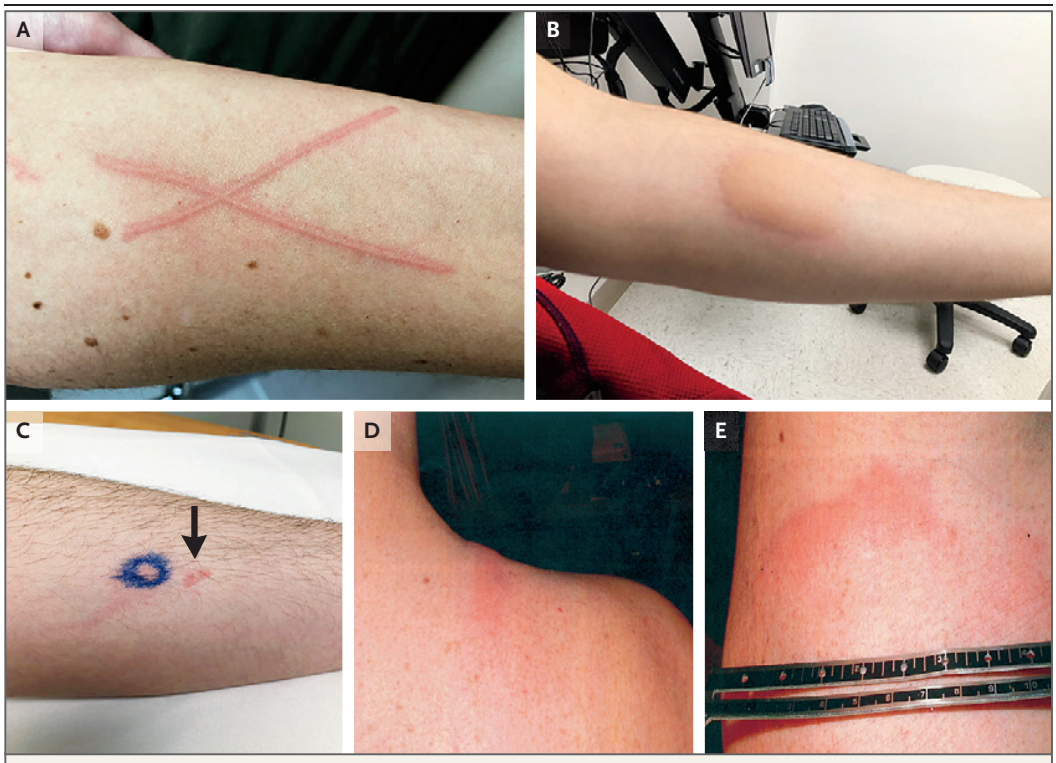

Figure 2. Clinical Images of Positive Diagnostic Challenge Tests.

Positive diagnostic challenge tests are shown for four common chronic inducible urticaria syndromes: dermatographia, characterized by a linear wheal flare reaction elicited with light stroking of the volar surface of the arm with a tongue blade (Panel A); cold urticaria, characterized by raised swelling, which is demarcated from normal skin after application of an ice pack (Panel B); cholinergic urticaria, which has the appearance of a satellite wheal (arrow) after intradermal injection of methacholine (circle) (Panel C); and delayed pressure urticaria, as illustrated by an indurated, swollen area that developed at the site of, and 6 hours after, a pressure stimulus in the patient shown in Panels D and E.

provoked by exercise; in the other type, urticaria and anaphylaxis develop with exercise that coincides with the ingestion of food. The latter has recently been recognized as augmentation factor anaphylaxis, a food allergy syndrome in which a specific food in combination with a second factor (commonly exercise, but also alcohol, opiates, aspirin or other nonsteroidal antiinflammatory drugs [NSAIDs], aeroallergen exposures, and premenstrual or ovulatory phases of the menstrual cycle) can lead to anaphylaxis.[15] In addition, approximately 20 to 30% of patients with chronic urticaria have cutaneous exacerbations provoked by the use of NSAIDs, including aspirin, and the exacerbations may be serious.[16]

ASSOCIATED DISORDERS

Although most cases of chronic urticaria are idiopathic, the disorder has been reported in association with infections (e.g., hepatitis B and C, Epstein Barr virus infection, herpes simplex virus infection, mycoplasma infection, *Helicobacter pylori* infection, and helminthic infestation), rheumatologic diseases (e.g., systemic lupus erythematosus and juvenile rheumatoid arthritis), thyroid disease (hypothyroidism and hyperthyroidism), neoplasms (particularly lymphoreticular cancers and other lymphoproliferative disorders), ovarian tumors, and oral contraceptive use.[1,2,9] Because of the rarity of these associations, routine and extensive laboratory testing

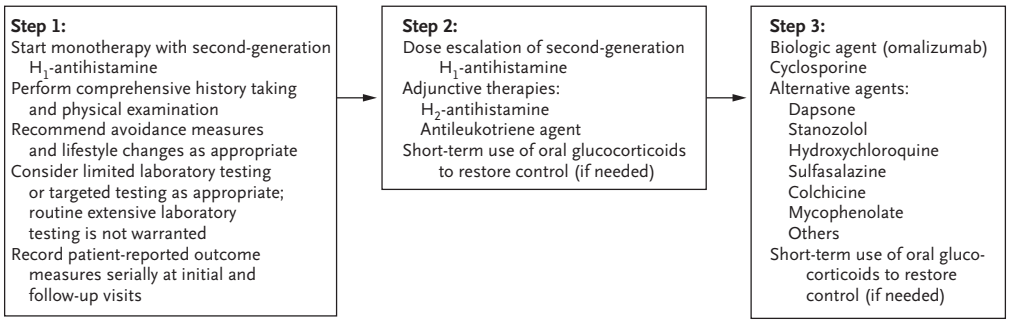

Figure 3. Stepped Care for Patients with Chronic Urticaria.

The information on stepped care is synthesized from recommendations based on the best evidence from clinical guidelines in allergy immunology and dermatology.[1,2,7-9,20] In step 1, the history taking and physical examination are directed toward identifying a possible underlying cause and the presence of one or more chronic inducible urticaria syndromes. Patient-reported outcome measures[4] include the urticaria activity score, angioedema activity score, urticaria control test, angioedema control test, chronic urticaria quality-of-life questionnaire, and angioedema quality-of-life questionnaire. The history taking, physical examination, and patient-reported outcome assessments should also be performed serially at follow-up visits. In step 2, dose escalation of a second-generation H_1-antihistamine, which is associated with greater efficacy but a risk of sedation with all agents except for fexofenadine, should proceed cautiously; dose adjustment may be warranted in patients with coexisting liver or renal insufficiency. Regarding step 3, the effectiveness of omalizumab has been shown in multiple randomized, controlled trials. Cyclosporine has been shown to be efficacious in several randomized, controlled trials, and the efficacy of dapsone, hydroxychloroquine, and stanozolol has also been shown in randomized, controlled trials; however, the desirable and undesirable effects of these agents are closely balanced. The efficacy of other agents (e.g., mycophenolate mofetil, sulfasalazine, and colchicine) has not been shown in randomized, placebo-controlled trials.

has not been encouraged.[1,13,17] For patients with chronic urticaria who have an unremarkable comprehensive medical history and physical examination, routine and extensive laboratory testing is not recommended in the Choosing Wisely guidelines[18] and is not cost-effective.[19] In a retrospective review of 1872 laboratory tests obtained in 356 cases of chronic urticaria, 319 were abnormal; 30 patients (8.4%) underwent repeat and in some cases additional laboratory testing, and some were referred to other specialists.[13] In only one patient, who had an abnormal thyroid-function test, which prompted an increase in thyroid hormone supplementation, was an abnormality uncovered that led to a change in management, with an improved outcome. On the basis of these and other data,[17] laboratory evaluation may be omitted; targeted testing is appropriate if the history or physical examination suggests a specific cause or underlying disease (e.g., a presentation suggesting cutaneous vasculitis, which would lead to a skin biopsy).

Conditions that simulate or are part of the differential diagnosis for chronic urticaria, which occur through different pathophysiological mechanisms, include hereditary angioedema, erythema multiforme, urticaria pigmentosa, autoinflammatory syndromes (e.g., cryopyrin-associated periodic syndromes or Schnitzler s syndrome), Wells s syndrome, the Melkersson Rosenthal syndrome, Gleich s syndrome, and bullous pemphigoid.[1,2,9]

TREATMENT

Most aspects of the management of chronic urticaria are the same for adults and children.[10] Factors that can lower the threshold for breakthrough episodes include alcohol, stress, and opiates; episodes may occur with menses. Behavioral and lifestyle changes to minimize exposures to inciting factors for chronic inducible urticaria are described in Table 1. Since NSAIDs may exacerbate cutaneous episodes, patients with chronic urticaria should be advised to take

acetaminophen instead as an analgesic or antipyretic medication, if one is required. Empirical elimination diets have not been associated with a definite benefit and are not recommended.[1,20]

A stepped-care approach to treatment is shown in Figure 3. Initial treatment consists of second-generation antihistamines, which were developed, in part, to minimize the central and peripheral side effects observed with first-generation antihistamines. The use of second-generation antihistamine monotherapy is supported by evidence from randomized, controlled trials and is endorsed by clinical guidelines.[1,2,7-9,20] To achieve and maintain complete control of chronic urticaria, which is the goal of therapy,[2,8] these medications should be taken on a regular basis rather than as needed, until remission of chronic urticaria occurs. Control of the disorder is achieved at step 1 in less than 50% of patients.[21] Escalation of the dose of second-generation antihistamines, up to four times the dose approved by the Food and Drug Administration (FDA), has been recommended as a next step[1,2,7-9,20] and has been shown to provide satisfactory control while generally causing limited side effects.[22]

Adjunctive therapies, supported in some guidelines with conditional recommendations, include the addition of H_2-antihistamine or antileukotriene medications.[1,8] Systemic glucocorticoids are frequently used when chronic urticaria is poorly controlled. Short-term use may restore control until other therapies can be used to achieve remission, but withdrawal of systemic glucocorticoids may be associated with subsequent relapse.[23] Because of the risk of adverse effects with systemic glucocorticoids,[24] long-term use should generally be avoided.[8,9] When satisfactory control cannot be achieved at step 2, a high dose of a first-generation H_1-antihistamine (e.g., doxepin or hydroxyzine) has been recommended.[1,8] However, these medications, which have not only potent antihistaminic effects but also prominent anticholinergic effects, have been associated with an increased risk of cognitive impairment in older adults.[25] In view of their sedative properties, decisions about prescribing these medications for patients with chronic urticaria should be based on an individualized risk benefit assessment. A prescription for epinephrine is not generally warranted unless a patient with chronic inducible urticaria is at risk for anaphylaxis (Table 1).

Of the therapeutic options available for step 3 in treatment, omalizumab is the only agent that is supported by high-quality evidence, that is approved by the FDA for antihistamine-resistant chronic urticaria, and for which there are strong recommendations in clinical guidelines.[1,2,7-9,20] A systematic review[21] analyzed 10 randomized, controlled trials and found that as add-on treatment, omalizumab at a dose of 300 mg every 4 weeks was associated with clinically meaningful improvements in symptoms and quality of life, with a moderate and a high certainty of evidence, respectively. If after 6 months omalizumab is not effective, evidence favors the use of cyclosporine.[1,2,7-9,20] Alternative agents also merit consideration, particularly if cyclosporine is contraindicated (Table 1). Despite progress in evaluating therapies that are currently available, some patients with chronic urticaria continue to have unmet needs. Clinical trials that are under way are investigating the effectiveness of anti interleukin-4/interleukin-13 (ClinicalTrials.gov number, NCT04180488), anti interleukin-5 (NCT03494881 and NCT04612725), anti thymic stromal lymphopoietin (NCT04833855), and anti Siglec-8 agents (NCT03436797); more potent anti-IgE monoclonal antibodies (NCT03580356); and Bruton s tyrosine kinase inhibitor therapies (NCT05030311).[26]

PROGNOSIS

A prospective study showed that 1 year after the start of treatment, 35% of patients with chronic urticaria were free of symptoms, and 29% had reduced symptoms; remission occurred in almost half (47%) of the patients with chronic spontaneous urticaria but in only 16% of those with chronic inducible urticaria.[27] A prolonged duration of chronic urticaria has been associated with the presence of angioedema, greater disease severity, and autoimmune thyroid disease.[28]

FUTURE DIRECTIONS

In a subset of patients with chronic urticaria, various autoantibodies are present; however, their etiologic, therapeutic, and prognostic value

has not been determined. Emerging data suggest that responsiveness to pharmacotherapeutic agents and the course of illness are related to the presence or absence of one or more of these autoantibodies and inflammatory or clinical markers, as well as the serum IgE level.[29,30] Further studies are required to validate biomarkers that can predict the natural history of chronic urticaria and guide therapy. Although routine and extensive laboratory testing for the purpose of identifying an underlying cause has been discouraged, it is possible that laboratory testing will be recommended in the future to provide information on prognosis, including disease duration and the likelihood of a salutary response to a therapeutic intervention.

CONCLUSIONS

The management of chronic urticaria has evolved on the basis of an enhanced understanding of the pathophysiology of the disorder and the introduction of effective therapeutic agents that are favorable from a risk benefit standpoint. Many patients with chronic urticaria ask about the cause of the disorder. Although health care providers are unable to provide an answer to the question in the overwhelming majority of cases, there is much we can do to improve quality of life by providing patient education and pharmacotherapeutic management based on the best evidence.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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