JAMA | Review

Chronic Spontaneous Urticaria
A Review

Pavel Kolkhir, MD; Hanna Bonnekoh, MD; Martin Metz, MD; Marcus Maurer, MD

IMPORTANCE Chronic spontaneous urticaria affects approximately 1% of the general population worldwide, including approximately 3 million people in the US, impairs patients' quality of life, and is associated with multiple comorbidities.

OBSERVATIONS Chronic spontaneous urticaria affects patients of any age but is most common in females aged 30 to 50 years. Diagnosis is based on clinical presentation, ie, spontaneously recurring wheals, angioedema, or both. Chronic spontaneous urticaria persists for more than 1 year in most patients (1 or repeated episodes) and may present with comorbidities including chronic inducible urticaria (>10%), autoimmune thyroiditis (approximately 20%), metabolic syndrome (6%-20%), and anxiety (10%-31%) and depression (7%-29%). Known autoimmune endotypes (subtypes of urticaria defined by distinct pathogenesis) of chronic spontaneous urticaria are mediated by mast cell–activating IgE and/or IgG autoantibodies (>50%). Approximately 40% of patients with chronic spontaneous urticaria have a Dermatology Life Quality Index of more than 10, corresponding to a very large or extremely large negative effect on quality of life. Second-generation H_1 antihistamines are first-line treatment; partial or complete response, defined as a reduction in urticaria symptoms of greater than 50%, is observed in approximately 40% of patients. The 2022 international urticaria guideline recommends the monoclonal anti-IgE antibody omalizumab as second-line treatment for antihistamine-refractory chronic spontaneous urticaria. However, at least 30% of patients have an insufficient response to omalizumab, especially those with IgG-mediated autoimmune urticaria. Cyclosporine, used off-label, can improve symptoms in approximately 54% to 73% of patients, especially those with autoimmune chronic spontaneous urticaria and nonresponse to omalizumab, but has adverse effects such as kidney dysfunction and hypertension.

CONCLUSIONS AND RELEVANCE Chronic spontaneous urticaria is an inflammatory skin disease associated with medical and psychiatric comorbidities and impaired quality of life. Second-generation H_1 antihistamines are first-line treatment, omalizumab is second-line treatment, and cyclosporine is third-line treatment for chronic spontaneous urticaria.

JAMA. 2024;332(17):1464-1477. doi:10.1001/jama.2024.15568
Published online September 26, 2024.

Multimedia

CME at jamacmelookup.com

Author Affiliations: Urticaria Center of Reference and Excellence (UCARE), Institute of Allergology, Charité–Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany (Kolkhir, Bonnekoh, Metz, Maurer); Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany (Kolkhir, Bonnekoh, Metz, Maurer).

Corresponding Author: Pavel Kolkhir, MD, Institute of Allergology, Charité–Universitätsmedizin Berlin, Hindenburgdamm 30, 12203 Berlin, Germany (pavel.kolkhir@charite.de).

Section Editor: Kristin Walter, MD, Deputy Editor.

Urticaria is a common skin disease characterized by transient wheals, angioedema, or both.[1] Wheals are itchy, superficial skin swellings, and angioedema is pronounced swelling of the lower dermis and subcutis or mucous membranes. Urticaria can be acute (≤6 weeks) or chronic (lasting >6 weeks and usually several years). Chronic urticaria is classified as inducible if symptoms are elicited reproducibly by specific external triggers such as cold, skin pressure, friction, heat, water, vibration, sweating, exercise, sunlight, ultraviolet light, and skin contact with wheal-inducing agents, such as plant and animal products and metals. Chronic urticaria is classified as spontaneous (previously known as "idiopathic") if symptoms appear without a known specific trigger, and can occur as a single episode or repeated episodes. Chronic inducible urticaria and chronic spontaneous urticaria can be present in the same patient.

Chronic spontaneous urticaria affects approximately 1% of the global population, most commonly females aged 30 to 50 years,[1] and symptoms last for at least 3 years in approximately 66% of patients.[2] Most patients with chronic spontaneous urticaria (57%) develop only wheals; 37% have wheals and angioedema, and 6% have only angioedema.[1,3] In some patients with chronic spontaneous urticaria, disease activity can be exacerbated by stress, nonsteroidal anti-inflammatory drugs (NSAIDs), and infections.

This Review summarizes current evidence on the epidemiology, pathophysiology, diagnosis, and treatment of chronic spontaneous urticaria. Major epidemiologic and burden-of-disease facts for chronic spontaneous urticaria are summarized in **Box 1**.

Methods

A literature search of English-language articles published between January 1, 2014, and May 1, 2024, was conducted using PubMed with the terms (*spontaneous* OR *idiopathic*) AND *urticaria*. We selected

Box 1. Major Epidemiologic and Burden-of-Disease Facts for Chronic Spontaneous Urticaria

- **Progression** from acute urticaria (≤6 weeks of duration) to chronic spontaneous urticaria in most studies is 8% or lower.[1]
- **Prevalence** is about 1% (about 80 million patients worldwide).[4]
- **Incidence** is 0.10 to 2.43 per 1000 person-years.[1]
- **Remission rates** are 17% at 1 year and 45% at 5 years (cumulative average estimate).[2]
- **Sex predominance** is 70% female.[1,5]
- **Typical age at onset** is 30 to 50 years; less than 15% at 19 years or younger vs more than 85% at 20 years or older.[1,6,7,a]
- **Diagnostic criteria** are spontaneously occurring itchy wheals, angioedema, or both occurring for more than 6 weeks.
- **Most common conditions in differential diagnosis** include chronic inducible urticaria, urticarial vasculitis, autoinflammatory syndromes such as Schnitzler syndrome,[b] and hereditary angioedema.
- **Causes/underlying pathogenesis** (endotype) include autoimmune endotype with IgE autoantibodies, IgG autoantibodies, or both (>50%); nonautoimmune endotype (<35%)[8,9]; and, very rarely, infections, cancer, peptic ulcer disease, hypothyroidism, hyperthyroidism, rheumatic diseases, or type 1 hypersensitivity.[1]
- **Triggers** are stress, nonsteroidal anti-inflammatory drugs, and viral infection of respiratory tract.[10]
- **Symptom frequency** is daily or almost daily or an intermittent-recurrent course.[10]
- **Humanistic burden** includes severe impairment of quality of life[11,12,c] and high burden on health care systems and society.
- **Economic burden** is $907 to $2984 in purchasing power parity dollars annually per affected individual, mostly due to therapies.[13]

[a] Studies included patients with chronic urticaria, of whom more than 90% likely had spontaneous urticaria.

[b] Schnitzler syndrome is an autoinflammatory disease characterized by chronic urticarial rash (usually nonpruritic), monoclonal gammopathy and recurrent fever, bone pain, and arthralgia or arthritis.

[c] Comparable with or worse than that in patients with moderate to severe psoriasis, atopic dermatitis, or type 1 diabetes.

recent, relevant, high-quality publications, prioritizing meta-analyses, systematic reviews, and randomized clinical trials when available. Additional articles were identified from reference lists of selected articles. Authors also reviewed the current version of the international urticaria guideline[10] and information available in ClinicalTrials.gov. We prioritized articles published in the past 5 years. Of 2170 articles identified, we included 94, consisting of 27 meta-analyses and/or systematic reviews; 3 randomized clinical trials; 48 epidemiologic, observational, and/or longitudinal studies; 13 narrative reviews; 2 clinical practice guidelines, recommendations, and consensus documents; and 1 basic research study. For trials that reported standardized mean differences (SMDs) between therapies, an absolute difference of ±0.2 approximates a small effect, ±0.4 a moderate effect, and ±0.8 a large effect.

Pathophysiology

Skin mast cells are the major drivers of pathogenesis of chronic spontaneous urticaria. In most patients, 2 underlying mechanisms (endotypes), IgE- and IgG-mediated autoimmunity that can occur in isolation or together (>50%), contribute to the activation and degranulation of skin mast cells (**Figure 1**). In contrast to IgE hypersensitivity to external allergens (eg, pollen) observed in allergic diseases, patients with IgE-mediated autoimmune chronic spontaneous urticaria (also known as autoallergic urticaria) produce IgE antibodies to autoantigens (self-antigens) such as thyroid peroxidase or IL-24. Patients with IgG-mediated autoimmunity (also known as type IIb) have IgG autoantibodies, for example, against IgE or the high-affinity IgE receptor FcεRI on mast cells.[8] Less than 35% of patients with chronic spontaneous urticaria have no autoantibodies.[9,14]

The cross-linking of the IgE receptor FcεRI expressed on skin mast cells by IgE and IgG autoantibodies activates cytoplasmic signaling proteins (eg, Bruton tyrosine kinase). This activation results in the release of vasoactive substances including histamine, the major contributor to urticaria symptoms, and cytokines, leading to activation of sensory nerves, vasodilation, and increased vascular permeability and migration of immune cells such as eosinophils, T lymphocytes, and basophils into the skin.[1,15] Mast cells and other immune cells, epithelial cells, and sensory nerves interact through release of cytokines (mostly Th2 cytokines) such as thymic stromal lymphopoietin, IL-4, IL-13, IL-31, eosinophil proteins, and neuropeptides, and further activation of mast cells through Mas-related G protein–coupled receptor X2 (MRGPRX2).[1] These processes result in the development of urticaria symptoms.

Susceptibility to chronic spontaneous urticaria may be determined by genetic factors[16] and gut microbiome alterations, including lower levels of short-chain fatty acid–producing bacteria.[17]

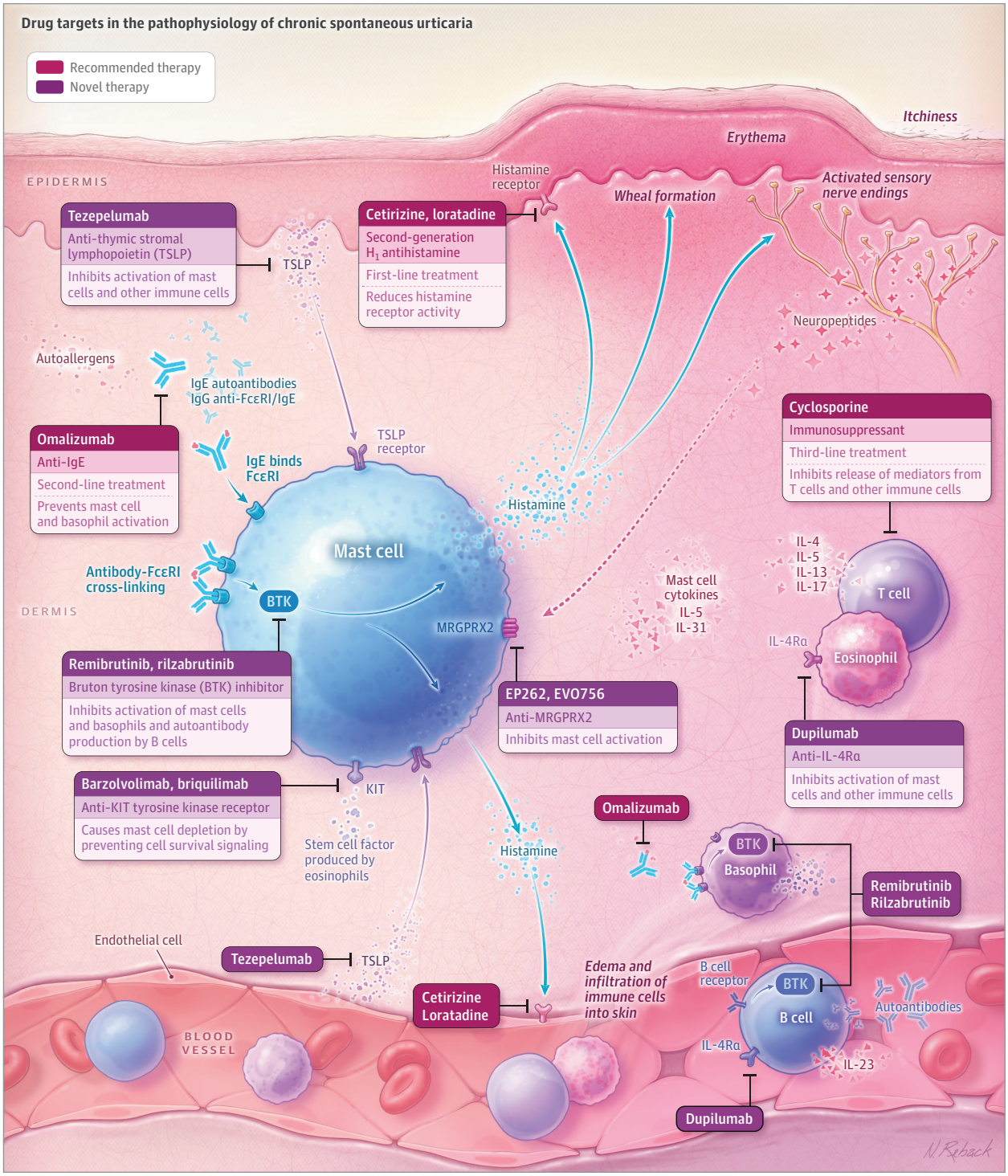
Clinical Presentation

Patients with chronic spontaneous urticaria develop individual wheals, ranging from a few millimeters in diameter to several centimeters in diameter ("giant" urticaria), that typically appear and disappear within a single day, usually within a few hours, whereas angioedema typically lasts for 1 to 3 days (**Figure 2**A-C). Wheals are blanching and can have irregular borders, change shape, and appear anywhere on the body but most commonly occur on the arms, legs, and trunk.[18] Angioedema commonly involves the face, especially the lips and eyelids, but can also affect other body parts. In moderate to severe disease, wheals and/or angioedema occur daily or nearly daily. The clinical manifestations of urticaria are consistent across age, sex, race, and ethnicity groups, with wheals and angioedema appearing in similar anatomical distributions. Among patients with chronic spontaneous urticaria, angioedema affects children less frequently than adults (5%-15% vs 30%-50%), and female predominance may be less common in children with urticaria compared with adults.[19] Detection of erythema associated with wheals can be more difficult in individuals with darker skin tones (Figure 2). In patients with chronic spontaneous urticaria, both wheals and angioedema resolve spontaneously without sequelae.[1,10]

Quality of Life

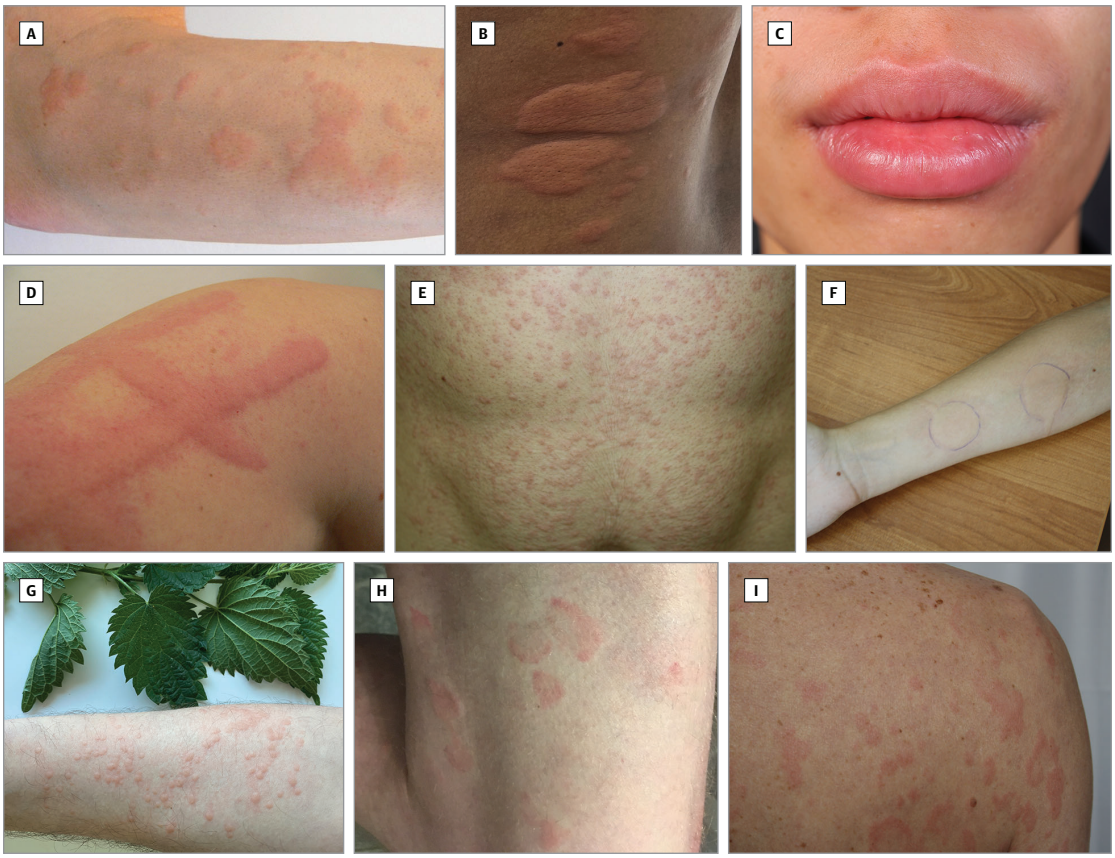
For patients with chronic spontaneous urticaria, severe pruritus and the unpredictable disease course marked by sudden wheals

Figure 1. Pathophysiology of Chronic Spontaneous Urticaria



This figure provides an overview of the main pathogenetic events in chronic spontaneous urticaria and shows current therapies and novel drugs expected to soon be available for routine clinical practice. The pathophysiology of chronic spontaneous urticaria involves activation of skin mast cells on cross-linking of the IgE receptor FcεRI by IgE autoantibodies against autoallergens such as thyroid peroxidase and IL-24 and IgG autoantibodies against FcεRI/IgE (produced by B cells), with subsequent activation of cytoplasmic signaling proteins such as Bruton tyrosine kinase. MRGPRX2 indicates Mas-related G protein–coupled receptor X2.

Figure 2. Clinical Presentation of Chronic Spontaneous Urticaria and Main Differential Diagnoses



Chronic spontaneous urticaria: wheals on less pigmented skin (A), wheals on more pigmented skin (B), and angioedema (C). Chronic inducible urticaria: symptomatic dermographism (elicited by a scratch test) (D), cholinergic urticaria (elicited by exercise) (E), cold urticaria (after provocation test with ice cube) (F), and contact urticaria (wheals after contact with *Urtica dioica* [nettle] leaves) (G). Differential diagnoses of chronic spontaneous urticaria: urticarial vasculitis (bruising, a hallmark of urticarial vasculitis, is seen) (H) and Schnitzler syndrome (I). Images in panels B, C, and D courtesy of Jonny Peter, MD, Kanokvalai Kulthanan, MD, and Melba Muñoz, MD, respectively.

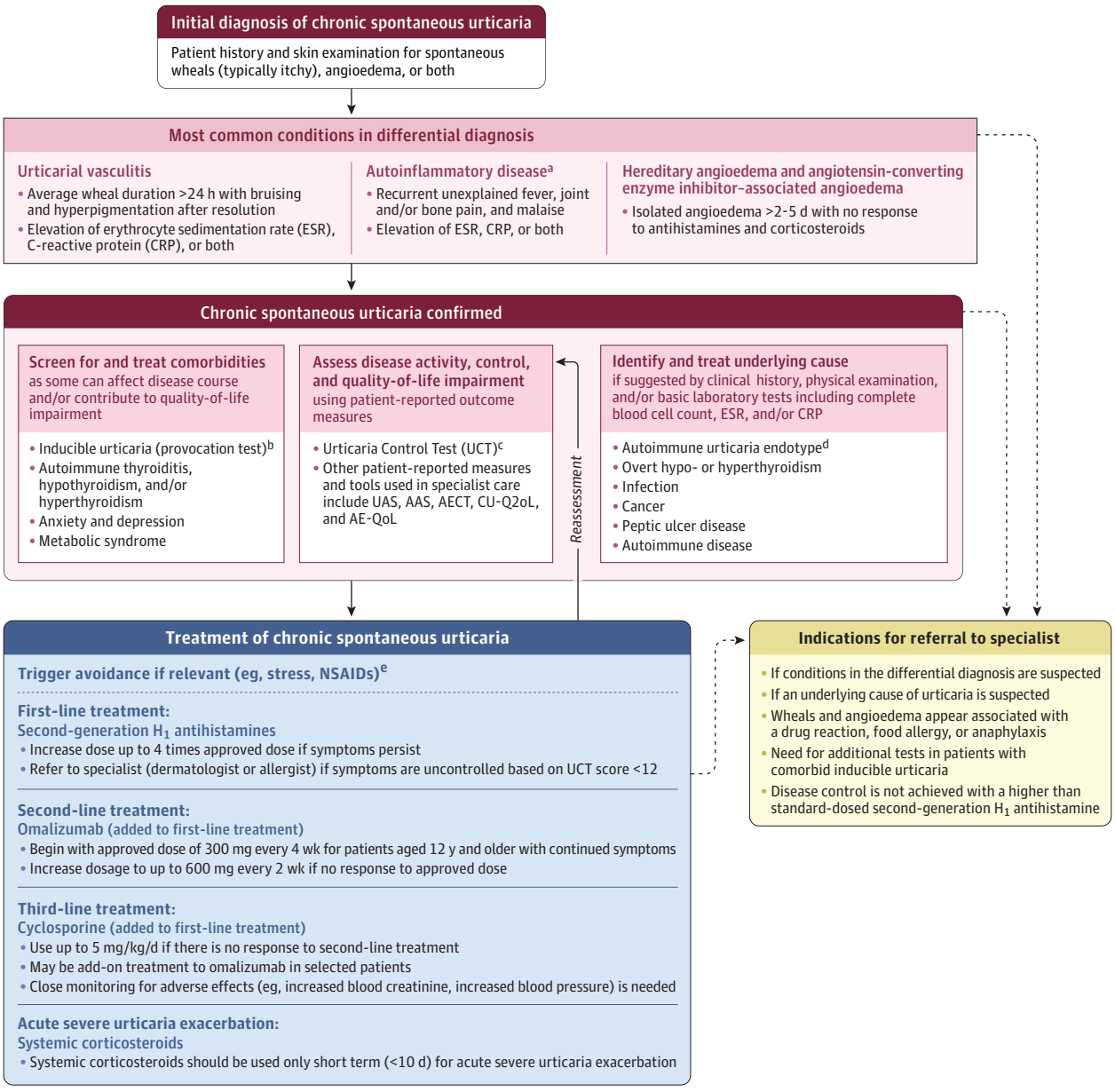
and angioedema are associated with impaired quality of life. Various tools are available to assess quality-of-life impairment in patients with chronic spontaneous urticaria, including the Dermatology Life Quality Index (DLQI) and the Chronic Urticaria–Quality of Life Questionnaire (CU-Q2oL). The DLQI is a 10-item quality-of-life index for patients with dermatological conditions (score range, 0-30; minimum clinically important difference, 3-5), with higher scores indicating more disability on such items as symptoms, activities of daily living, leisure activities, and interpersonal relationships. The CU-Q2oL is a 23-item quality-of-life measure that is specific to patients with chronic urticaria (range, 0-100), with higher scores indicating more disability on such items as pruritus, swelling, effect on life activities, and sleep problems. A very large or extremely large negative effect on a person's life (DLQI >10) is observed in approximately 40% of patients with chronic spontaneous uriticaria, with the CU-Q2oL showing the largest negative effect based on pruritus, sleep, and general appearance.[13] Several features are associated with greater impairment in quality of life among patients with chronic spontaneous urticaria, including concomitant angioedema, mental health disorders such as depression and anxiety, and autoimmune endotype, compared with patients with chronic spontaneous urticaria with wheals but without angioedema (DLQI mean, 9.9 vs 7.3; $P < .001$),[20] without mental health disorders (DLQI mean, 10.7 vs 8.8; $P = .01$),[21] and without autoimmune endotype (DLQI mean, 10.0 vs 6.0; $P = .046$).[9]

Assessment and Diagnosis

The international urticaria guideline recommends the "7C" concept for diagnostic workup of chronic spontaneous urticaria, which includes confirmation of diagnosis and exclusion of differential diagnoses, cause identification, cofactor (trigger) assessments, checking for comorbidities, evaluating consequences, assessing potential biomarkers or predictors of treatment response (components), and monitoring the course of chronic spontaneous urticaria.[10]

The diagnosis of chronic spontaneous urticaria is made clinically based on history and skin examination for spontaneously appearing wheals, angioedema, or both (Figure 2A-C and **Figure 3**). Given the transient nature of wheals and angioedema, clinicians should review patient photographs and documentation of signs and symptoms, if available.[1,10] Initial laboratory measurement of complete blood cell count, erythrocyte sedimentation rate, and/or C-reactive protein and additional testing based on patient history

Figure 3. Overall Approach to Management of Chronic Spontaneous Urticaria



AAS indicates Angioedema Activity Score; AECT, Angioedema Control Test; AE-QoL, Angioedema Quality of Life Questionnaire; CU-Q2oL, Chronic Urticaria Quality of Life Questionnaire; and UAS, Urticaria Activity Score.

[a]Autoinflammatory diseases such as Schnitzler syndrome are a group of rare disorders caused by dysfunction of the innate immune system and are associated with unprovoked episodes of fever and inflammation.

[b]Among patients for whom there is a clinical suspicion of inducible urticarias such as symptomatic dermographism, delayed pressure urticaria, cholinergic urticaria, or cold urticaria, provocation tests include skin scratching with a closed ballpoint pen tip, suspension of a weight over the shoulder, physical exercise, and melting an ice cube in a thin plastic bag on a patient's volar forearm, respectively.

[c]Clinicians may use tools such as the Urticaria Control Test (UCT), a 4-item questionnaire administered to patients that provides objective information about urticaria control (UCT = 16 corresponds to complete disease control/response to treatment; UCT = 12-15 is well-controlled disease/partial response to treatment; and UCT <12 is poor disease control/nonresponse to treatment).

[d]Subtype of urticaria defined by distinct pathogenesis

[e]Certain nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, diclofenac, and ibuprofen, can induce urticaria exacerbation.

can be performed to rule out differential diagnoses such as urticarial vasculitis and hereditary angioedema, underlying conditions associated with chronic spontaneous urticaria, triggers, and comorbidities (Box 2 and Box 3).[10]

Differential Diagnosis

Diseases presenting with wheals and/or angioedema (Figure 2)[1,10] include chronic inducible urticaria, in which wheals are often of shorter duration (≤1 hour). The diagnosis of chronic inducible

Box 2. Questions Commonly Asked About Chronic Spontaneous Urticaria

Which Laboratory Tests Should Be Done for Patients With Chronic Spontaneous Urticaria?

Basic tests include a complete blood cell count with differential and C-reactive protein and/or erythrocyte sedimentation rate, which help to exclude other diagnoses and may identify comorbidities and underlying causes such as autoimmunity, infection, and cancer.

Which Treatments Should Be Implemented in Primary Care Settings?

Primary care clinicians should initiate treatment with a standard dose of a second-generation H_1 antihistamine and increase the dose up to 4 times the standard dose if complete disease control is not achieved, as assessed with the Urticaria Control Test.

When Should Patients Be Referred to a Dermatologist or Allergist?

Patients should be referred to a dermatologist or allergist if they have any of the following symptoms: individual wheals of 24 hours or longer in duration resolving with postinflammatory hyperpigmentation; long-lasting antihistamine-refractory angioedema (>2-5 days) without wheals; or extracutaneous symptoms such as fever, arthralgia, or abdominal pain. Other reasons for referral include need for additional special tests, such as allergy and/or provocation tests or lack of disease control (Urticaria Control Test score <12) with higher than standard-dosed second-generation H_1 antihistamine therapy.[10,22]

Box 3. Comorbidities and Screening Recommendations

Chronic Inducible Urticaria

Provocation testing (the appearance of pruritic wheals within 5-10 minutes after applying specific stimulus) can help confirm the diagnosis. Some simple tools, such as skin scratching with closed ballpoint pen tip, suspension of weight over shoulder, physical exercise, and melting ice cube in thin plastic bag on a patient's volar forearm, can be performed in primary care to diagnose most common forms of inducible urticaria, namely symptomatic dermographism (Figure 2D), delayed pressure urticaria, cholinergic urticaria (Figure 2E), and cold urticaria (Figure 2F), respectively.

Autoimmune Diseases

Patients should be asked about signs and symptoms of autoimmune diseases such as autoimmune thyroid disorders (and their consequences, such as hypothyroidism and hyperthyroidism), vitiligo, and rheumatoid arthritis. In patients with chronic spontaneous urticaria and high titers of antithyroid antibodies, annual reassessment of thyroid function can be considered.

Other Comorbidities

Patients with chronic spontaneous urticaria should be screened for anxiety and depression with specific questionnaires, such as the Hospital Anxiety and Depression Scale (HADS)[23] or the Patient Health Questionnaire (PHQ-9), and should have measurement of metabolic syndrome components along with routine body mass index and blood pressure measurement. Laboratory testing for autoimmune diseases other than thyroiditis and other comorbidities should be performed only if suspected due to patient history, physical examination, and/or results of basic laboratory tests.[24-26]

urticaria is based on history (eg, contact with nettle plants [*Urtica dioica*] causing contact urticaria or cooling of the skin causing cold urticaria) and provocation testing to identify triggers and assess trigger thresholds (Box 3 and Figure 2D-G). Chronic spontaneous urticaria is not associated with anaphylaxis, although anaphylaxis can present with wheals, angioedema, or both.[10] Neutrophilic urticaria with systemic inflammation, Schnitzler syndrome (an autoinflammatory disease characterized by chronic urticarial rash [usually nonpruritic], monoclonal gammopathy, and bone pain [Figure 2I]), and urticarial vasculitis (Figure 2H) are rare conditions associated with antihistamine-resistant wheals (in urticarial vasculitis, wheals are usually of >24 hours' duration and resolving with bruising and/or postinflammatory hyperpigmentation) and are often associated with systemic symptoms such as recurrent fever and arthralgia or arthritis.[27] Hereditary angioedema should be suspected in patients with antihistamine- and corticosteroid-refractory isolated angioedema and a possible family history of angioedema. For patients with angiotensin-converting enzyme inhibitor–induced angioedema, symptom remission usually occurs within a few days (rarely, within weeks or months) after drug withdrawal.[10,28] Laryngeal swelling associated with a fatal outcome, which can occur with angiotensin-converting enzyme inhibitor–induced and hereditary angioedema, has not been reported in patients with chronic spontaneous urticaria.[29]

Underlying Causes

Patients with chronic spontaneous urticaria have been evaluated for different underlying causes, including chronic bacterial infections such as *Helicobacter pylori*,[30] sinusitis and dental infections, connective tissue diseases,[31] peptic ulcer disease,[30] parasites,[32] hepatitis B and hepatitis C infection,[33] cancer,[34] and hypothyroidism,[24] with no clear evidence supporting screening for these conditions in all patients.[35] Similarly, there is limited evidence that treating these conditions leads to improvement in urticaria. The international urticaria guideline advises against intensive and costly testing to identify causes of urticaria.[10] A search for underlying causes should be performed only if presence of a condition, such a parasitic infection, hypothyroidism, cancer, or peptic ulcer disease, is suggested by a patient's clinical history, physical examination, and/or basic urticaria workup. In these cases, treatment of the underlying cause may improve urticaria symptoms.[10]

Factors that suggest autoimmune chronic spontaneous urticaria include female sex, symptoms for more than 5 days per week, angioedema, nocturnal symptoms of itch and wheals, low eosinophil counts ($<0.05 \times 10^9$/L), low basophil counts ($<0.01 \times 10^9$/L), and insufficient response to antihistamines and omalizumab. Additional tests can be helpful to identify autoimmune chronic spontaneous urticaria, such as low total IgE levels (<30-43 IU/mL), high IgG anti–thyroid peroxidase levels (≥34 kU/L),[36] positive in vitro test findings based on the degree of basophil degranulation in response to patients' serum (basophil histamine release assay and/or basophil activation test), and/or detection of autoantibodies by immunoassay.[9,10]

Allergy, ie, IgE-mediated hypersensitivity to external allergens such as food, drugs, and pollen, is a rare cause of chronic

Table 1. Comorbidities of Patients With Chronic Spontaneous Urticaria

Parameters	Mental health disorders	Metabolic syndrome	Autoimmune diseases	Chronic inducible urticaria	Cancer, infection, allergy
Patients with chronic spontaneous urticaria who have comorbidity	8.5%-31.6%[23,38,41,42,a]	5.9%-19.7%[38,43]	10.5%-28%[25,38,44]	>10%[1]	Cancer: about 1%; infection: varies depending on infection type; allergic diseases: 7%-22%[34,45]
Appearance in relation to chronic spontaneous urticaria	In many cases, after diagnosis of chronic spontaneous urticaria[41]	Unknown	In about 80% of patients with autoimmune diseases, autoimmune disease is diagnosed after urticaria[44]	Often at the same time (67.4%)[46]	Unknown
Most common forms	Anxiety (9.6%-30.6%), mood disorders including depression (6.6%-29.4%), sleep-wake disorders including insomnia (36.7%)[23,38,42]	Central obesity (13.9%), dyslipidemia (11.3%), hyperglycemia (5.9%), arterial hypertension (19.7%)[38]	Autoimmune thyroiditis (Hashimoto thyroiditis) in about 20% of patients[25]	Symptomatic dermographism (24.8%), cold urticaria (13.4%), delayed pressure urticaria (7.3%)[1,47]	Solid cancers, *Helicobacter pylori*, allergic rhinitis[45,48]
Pathogenetic or causal relation to chronic spontaneous urticaria	Due to urticaria symptoms and impairment in quality of life (consequence of urticaria)	Low-grade chronic inflammation	In rare cases can also induce urticaria, eg, due to systemic lupus erythematosus	Possible pathogenetic association	Causal association is possible but rare[34,37]
Association with chronic spontaneous urticaria endotype[b]	Any endotype	Any endotype	Autoimmune endotype[25]	Any endotype except IgG-mediated autoimmune endotype[46]	Any endotype
Association with chronic spontaneous urticaria characteristics, response to treatment, and quality of life	Further decrease in quality of life[49]	Probably longer urticaria duration	Possibly longer urticaria duration, more active urticaria, worse response to treatment	Longer duration of urticaria, further decrease in quality of life[46,50]	Urticaria can improve after successful treatment of underlying cause[32]

[a] Pooled prevalence in patients with chronic urticaria.[42]

[b] A subtype of urticaria defined by a distinct pathobiological mechanism: autoimmune endotype is mediated by IgG and/or IgE mast cell–activating autoantibodies, whereas nonautoimmune endotype does not show the presence of these autoantibodies.

spontaneous urticaria. In a prospective study, specific IgE antibodies to allergens were detected in 46.7% of 128 patients with chronic spontaneous urticaria, but only 2 patients (1.5%) had clinically relevant allergy (1 to artemisia pollen and 1 to food), without complete remission of their chronic urticaria after withdrawal of these allergens.[37]

Triggers

Clinicians should ask patients with chronic spontaneous urticaria about potential triggers that exacerbate disease activity. A multicenter observational study of 3698 patients with chronic spontaneous urticaria, the Chronic Urticaria Registry (CURE) reported several triggers of urticaria exacerbation, including stress (13.9%), NSAIDs (6.7%), infection (5.5%; mostly viral infections of the respiratory tract), and, rarely, foods such as milk, fish, nuts, spices, fruits, chocolate, and alcohol.[38] To identify the effect of stress on the disease, questionnaires such as the Social Readjustment Rating Scale[39] can be used and/or patients may be referred to a psychologist. Avoidance of NSAIDs can identify NSAIDs as a trigger. In a cross-sectional, international, questionnaire-based, multicenter study of 79 patients with chronic urticaria, 37% of patients with chronic urticaria experienced disease exacerbation after COVID-19 infection.[40]

Avoidance of triggers such as NSAIDs and stress, if possible, can help reduce disease exacerbations (Figure 3).[10]

Comorbidities

Recommended evaluation for comorbidities in patients with chronic spontaneous urticaria is presented in Box 3.

More than 10% of patients with chronic spontaneous urticaria have 1 or more type of chronic inducible urticaria, most commonly symptomatic dermographism, cold urticaria, cholinergic urticaria, and delayed pressure urticaria. In cholinergic urticaria, wheals and angioedema are triggered by sweating, such as due to physical activity and/or passive warming (eg, sauna or hot bath). Delayed pressure urticaria is characterized by recurrent erythematous and often painful swelling that develops 4 to 6 hours after the skin is exposed to sustained pressure (**Table 1**, Box 3, and Figure 2D-G).[1,47] In an international cross-sectional study of 551 patients with cold urticaria, cold-induced anaphylaxis was rare among individuals with cold urticaria and concomitant chronic spontaneous urticaria (4%) and higher among those with cold urticaria alone (39%).[51]

Approximately 10% to 28% of patients with chronic spontaneous urticaria have at least 1 autoimmune disease, most commonly Hashimoto thyroiditis (about 20%), which is associated with subclinical or overt hypothyroidism.[25,26,38,52] In a meta-analysis of 19 case-control studies including 14 351 patients with chronic urticaria, patients with urticaria had a 5-fold higher risk (pooled odds ratio, 5.18; 95% CI, 3.27-8.22) of developing anti–thyroid peroxidase antibodies than controls.[26] Female patients aged 40 years or older with chronic spontaneous urticaria and a family history of autoimmune disease such as autoimmune thyroiditis have the highest risk of developing 1 or more autoimmune diseases.[25,44] In a retrospective study of 12 778 patients with chronic spontaneous urticaria, approximately 17% had autoimmune diseases, including autoimmune thyroid diseases, rheumatoid arthritis, Sjögren syndrome, celiac disease, type 1 diabetes, and systemic lupus erythematosus; most (80%) developed autoimmune disease within 10 years of an urticaria diagnosis.[44]

In a study of a national database in Taiwan of 154 048 to 177 879 cases of chronic spontaneous urticaria per year from 2009 to 2012,

patients had an increasing prevalence of psychiatric disorders such as depression and anxiety during the first 3 years of their urticaria (years 1, 2, and 3: 7.5%, 9.6%, and 10.9%, respectively).[41] A cross-sectional community-based study of 11 261 patients with chronic urticaria and 67 216 age- and sex-matched controls without urticaria reported increased risk of metabolic syndrome in patients with urticaria relative to controls (15.5% vs 14.2%; odds ratio, 1.12; 95% CI, 1.1-1.2) after adjustment for corticosteroid use, supporting evaluation for risk factors of metabolic syndrome such as obesity and high blood pressure.[43] A systematic review and meta-analysis of 38 studies and more than 5 million participants reported a pooled point prevalence of atopic disorders (atopic dermatitis, asthma, and allergic rhinoconjunctivitis) in patients with chronic spontaneous urticaria comparable with the general population (7%-22%).[45] However, increased risk of atopic diseases was reported by studies that compared patients with chronic urticaria with controls from the same population, although the results were heterogeneous in all analyses.[45]

A cross-sectional analysis of a national health insurance database in Korea with 1 399 078 to 1 431 448 participants per year from 2010 to 2013 reported an increased risk of solid cancer in patients with chronic spontaneous urticaria compared with age- and sex-matched controls without urticaria (4.9% vs 2.6%; odds ratio, 1.37; 95% CI, 1.27-1.48).[48]

Treatment

The goal of treatment is to achieve complete disease control with the absence of signs and symptoms of chronic spontaneous urticaria.[10,67] The international urticaria guideline provides a stepwise algorithm of systemic therapy for chronic spontaneous urticaria including use of second-generation H_1 antihistamines; omalizumab, an anti-IgE monoclonal antibody; and cyclosporine.[10] These medications should be taken daily (antihistamines, cyclosporine) (**Table 2**) or monthly (omalizumab) rather than on demand, sometimes for many years.[10] Clinicians may use tools such as the 4-question Urticaria Control Test (UCT), which is administered to patients and provides objective information about urticaria control. A UCT score of 16 corresponds to complete disease control/response to treatment, 12 to 15 is well-controlled disease/partial response to treatment, and less than 12 is poor disease control/nonresponse to treatment.

Second-Generation H_1 Antihistamines

Second-generation H_1 antihistamines such as cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine, rupatadine, bilastine, and ebastine are first-line treatment for chronic spontaneous urticaria in US Food and Drug Administration (FDA)–approved doses. The antihistamine dose may be increased up to 4 times the maximum approved dose in off-label use if the approved dose is insufficient to control symptoms.[10] Compared with first-generation H_1 antihistamines, second-generation H_1 antihistamines are more potent, have longer duration of action, and cross the blood-brain barrier to a lesser extent, so they are less likely to induce sedation or impair cognitive function and psychomotor performance.[10,68] In a network meta-analysis of 22 randomized clinical trials with 3943 patients with chronic spontaneous urticaria, second-generation H_1 antihistamines were superior to placebo in total symptom score changes from baseline (SMDs from −0.67 to −1.26, suggesting moderate to large effect).[53] In a meta-analysis of 7 cohorts with 5664 patients with chronic spontaneous urticaria, receiving a standard-dose second-generation H_1 antihistamine was associated with a partial or complete response, defined as a greater than 50% reduction in urticaria symptoms, in 38.6% of patients (95% CI, 34.7%-42.7%).[69] In a registry-based study of 2078 patients with chronic spontaneous urticaria, complete disease control, defined as a UCT score of 16, with standard and increased doses of second-generation antihistamines was observed in 8.7% and 4.6% of patients taking standard-dose and high-dose second-generation antihistamines, respectively.[67] In a meta-analysis of 13 randomized clinical trials with 3079 patients with chronic spontaneous urticaria, patients who received high-dose second-generation H_1 antihistamines, compared with those who received standard-dose second-generation H_1 antihistamines, had more somnolence (9% vs 5%; $P = .02$) (Table 2).[54] Referral to a specialist (allergist or dermatologist) should be considered if the UCT score is less than 12 despite use of high-dose second-generation antihistamines for 2 to 4 weeks (Box 2).[10]

Omalizumab

Omalizumab is recommended by the international urticaria guideline as add-on therapy for patients with chronic spontaneous urticaria who are aged 12 years or older and whose symptoms persist despite use of high-dose antihistamines.[10,57] In patients with no or insufficient response to the FDA-approved dose of 300 mg every 4 weeks, omalizumab can be increased to up to 600 mg and/or the interval can be shortened to every 2 weeks (off-label).[10,70] In a systematic review and network meta-analysis that included 23 randomized clinical trials and 2480 participants with chronic spontaneous urticaria, omalizumab, 300 mg, was more efficacious than placebo in decreasing urticaria symptoms (SMD, −0.77; 95% CI, −0.91 to −0.63)[56] and improving health-related quality of life (SMD, −0.53; 95% CI, −0.67 to −0.39).[71] In a meta-analysis of 7 randomized trials with 1312 patients, more patients who received omalizumab, 300 mg, had a complete response (Urticaria Activity Score = 0) compared with those who received placebo (36.0% vs 5.6%, respectively; $P < .001$).[72] In a meta-analysis of 45 observational studies with 1158 patients, mean complete and partial response rates were 72.2% and 17.8%, respectively.[58] Omalizumab is considered safe with long-term use,[57,58] with approximately 4.0% of patients having adverse events such as headache, fatigue, and injection site reactions.[58]

Omalizumab can also be used for patients with spontaneous and concomitant inducible urticaria[59,60] and/or IgE-mediated comorbidities (eg, asthma).[73] Chronic spontaneous urticaria that presents with isolated angioedema or with inducible urticaria is rarely autoimmune and is more responsive to omalizumab than chronic spontaneous urticaria with wheals (with or without angioedema) or without inducible urticaria, respectively.[46,74]

For patients with complete response to treatment, antihistamines and omalizumab should be tapered after 3 months and discontinued after 6 to 12 months to determine if remission has occurred.[75] In the event of relapse, antihistamines with or without omalizumab should be restarted.

Approximately one-third to one-fourth of patients with antihistamine-refractory chronic spontaneous urticaria have a partial or no response to omalizumab (Table 2).[58]

Table 2. Current Therapy and Treatments Under Investigation for Patients With Chronic Spontaneous Urticaria[a]

Treatments	Mechanism of action	Dosing	Efficacy	Safety considerations	Additional considerations
First-line treatment					
Second-generation H_1 antihistamines	Bind to histamine receptors, stabilizing their inactive state (inverse agonists)	Standard (approved) or increased up to 4-fold (off-label)[b]	More efficacious than placebo in changes of total symptom score from baseline (SMDs from −0.67 to −1.26; 1 meta-analysis with 22 RCTs; n = 3943)[53c]	Generally safe, but higher somnolence rates at higher doses (9% vs 5%; risk difference, 0.05)[54]	In a prospective, randomized, open-label trial of 109 patients with chronic urticaria, a 4-fold increased dose of the same antihistamine was more effective for complete urticaria control than combination of 4 different antihistamines (40.0% vs 10.7%).[55] There is limited efficacy in autoimmune urticaria.[36]
Second-line treatment					
Omalizumab[d]	Recombinant humanized IgG1 anti-IgE monoclonal antibody	300 mg every 4 weeks (approved) and up to 600 mg every 2 weeks (off-label)	Doses of 300 mg and 600 mg monthly are more efficacious than placebo in decreasing urticaria symptoms (SMDs, −0.77 [95% CI, −0.91 to −0.63] and −0.59 [95% CI, −1.10 to −0.08], respectively; 1 meta-analysis with 23 RCTs; n = 2480).[56]	Safe, including long term[57,58]; mean adverse event rate, 4.0%, most commonly headache, fatigue, and injection site reaction[58]; anaphylaxis is extremely rare	Patients with autoimmune urticaria and low levels of total IgE usually show insufficient response to omalizumab.[36] Omalizumab is similarly effective in chronic inducible urticaria (off-label) vs spontaneous urticaria (odds ratio, −0.83; 95% CI, −0.84 to 2.21; $P > .05$), suggesting that patients with both urticaria forms can benefit.[59,60]
Third-line treatment					
Cyclosporine[d]	Immunosuppressant (off-label)	1 to 5 mg/kg per day; 3 mg/kg per day is a reasonable starting dose for most patients (off-label)[61]	After 4 weeks of cyclosporine treatment, the pooled estimate of mean change in relative weekly Urticaria Activity Score from baseline was −17.89 (95% CI, −21.95 to −13.83) vs −2.3 (95% CI, −3.72 to −0.88) with placebo; response rates at week 4 were 42% vs 0% with placebo and at week 8, 62.5% vs 23.3% with placebo (1 meta-analysis and systematic review of 2 RCTs and 16 real-world studies; n = 909).[61e]	Adverse events were dose dependent and occurred in 6%-57% of patients, including hypertension and abnormal serum creatinine (6.2%-12.8%), as well as gastrointestinal symptoms, headache, hirsutism, infection, and paresthesia (5.7%-46.2%).[61]	Effective in patients with autoimmune urticaria and low levels of total IgE[62]
Only in acute exacerbation of chronic spontaneous urticaria					
Systemic corticosteroids	Immunosuppressants	20-50 mg/d (off-label)[10]	Compared with patients treated with second-generation H_1 antihistamines, add-on systemic corticosteroids improved symptoms by 2.2%-15.0% (absolute difference, 31.5%-98.0% vs 17.5%-95.8%; 1 meta-analysis of 12 RCTs; n = 944).[63f]	Compared with control group, systemic corticosteroids increased adverse events (22.5% vs 9.0%; odds ratio, 2.76; 95% CI, 1.00-7.62), most commonly gastrointestinal, headache, anxiety, fatigue, and sedation.[63]	Short-term use only (<10 days)[10]

(continued)

Table 2. Current Therapy and Treatments Under Investigation for Patients With Chronic Spontaneous Urticaria[a] (continued)

Treatments	Mechanism of action	Dosing	Efficacy	Safety considerations	Additional considerations
Therapies in phase 3 development[g]					
Dupilumab (n = 138)[64]	Fully human IgG4/κ anti-4Rα monoclonal antibody	Loading dose of 400-600 mg, followed by 200-300 mg every 2 weeks based on age and weight	RCT: change in weekly Itch Severity Scale score[h] at week 24 with dupilumab vs placebo: difference, −4.2 (95% CI, −6.6 to −1.8), with rates of complete response (Urticaria Activity Score = 0) of 31.4% vs 13.2% (odds ratio, 2.9; 95% CI, 1.2-7.2) and ≥5-point reduction in weekly Itch Severity Scale score (minimum clinically important difference) of 72.9% vs 42.6% (P = .001)	Similar proportions of patients with any treatment-emergent adverse event with dupilumab vs placebo (57.3% vs 56.6%)	Not superior to omalizumab[64]; patients with urticaria and other diseases, approved indications for dupilumab, can have additional benefit[65i]
Remibrutinib (n = 311)[66]	Small-molecule Bruton tyrosine kinase inhibitor	10 mg, 35 mg, or 100 mg once daily; 10 mg, 25 mg, or 100 mg twice daily	RCT: weekly Urticaria Activity Score change from baseline at week 4: from −14.7 to −20.0 vs −5.4 for placebo; complete response rates (Urticaria Activity Score = 0) for all doses vs placebo at week 12: 26.7%-41.9% vs 14.3%	Mild, moderate, and severe adverse events across all doses in 38.6%, 16.9%, and 2.6% of patients, respectively, most commonly infections and infestations (24%), skin/subcutaneous tissue disorder (16.9%) such as flare of chronic urticaria, and in >5% patients headache, nasopharyngitis, nausea, upper respiratory tract infection, diarrhea, and pyrexia	Rapid onset of action, observed as early as week; effective in patients with and without autoimmune urticaria; may be beneficial in patients with urticaria and other autoimmune diseases; probable disease-modifying properties

Abbreviations: RCT, randomized clinical trial; SMD, standardized mean difference.

[a] According to the latest revision of the international urticaria guideline.[10]

[b] Examples of standard daily doses for an adult patient: cetirizine, 10 mg; fexofenadine, 180 mg; rupatadine, 10 mg; ebastine, 10 mg; examples of increased doses of antihistamines for an adult patient: cetirizine, 10 mg, 2-4 tablets daily, or ebastine, 20 mg, 1-2 tablets daily.

[c] Olopatadine, fexofenadine, bilastine, rupatadine, and levocetirizine.

[d] As add-on to second-generation H_1 antihistamines.

[e] Response rates are from 2 RCTs included in the meta-analysis.

[f] Based on a meta-analysis that included patients with any type of urticaria.

[g] Expected to soon be available for routine clinical practice. In February 2024, Japan was the first country to approve dupilumab for chronic spontaneous urticaria in patients aged 12 years or older whose disease is not adequately controlled with existing therapy.

[h] Among omalizumab-naive patients with chronic spontaneous urticaria inadequately controlled with H_1 antihistamines.

[i] Also approved for patients with atopic dermatitis aged 6 months or older and for patients with asthma, chronic rhinosinusitis with nasal polyposis, prurigo nodularis, and eosinophilic esophagitis.

Cyclosporine

The immunosuppressant cyclosporine is recommended by the international urticaria guideline as an off-label third-line therapy[10] as add-on to antihistamines for patients with severe chronic spontaneous urticaria refractory to the combination of any dose of antihistamines and omalizumab.[10,61] A meta-analysis of 909 patients with chronic spontaneous urticaria treated with cyclosporine reported a higher mean change in Urticaria Activity Score after 4 weeks compared with controls (−17.89 vs −2.3) (Table 2).[61] Overall response rates to low to moderate dose of cyclosporine, defined as less than 2 to 5 mg/kg per day were 54% at 4 weeks, 66% at 48 weeks, and 73% at 12 weeks. Adverse events were dose dependent, occurred in 6% to 57% of patients, and included hypertension, elevated serum creatinine (6.2%-12.8%), abdominal pain, nausea and vomiting, headache, hirsutism, infection, and paresthesia.[61]

In selected patients, cyclosporine may be considered as add-on treatment to omalizumab in patients with chronic spontaneous urticaria who have a partial response to omalizumab.[70] In countries where omalizumab is unavailable, cyclosporine may be safer than long-term use of systemic corticosteroids,[10] with lower relapse rates after discontinuation compared with prednisolone.[76]

Systemic Corticosteroids

There is strong expert-based consensus and recommendation against long-term use of systemic corticosteroids in patients with chronic spontaneous urticaria because of increased risk of adverse effects such as hyperglycemia, hypertension, neuropsychiatric conditions, osteoporosis and osteonecrosis, infections, and weight gain.[77] However, evidence-based recommendations support a short course of corticosteroids (<10 days; doses between 20 and 50 mg/d of prednisone equivalent) for adults with an acute severe exacerbation of chronic spontaneous urticaria.[10,63]

Other Treatments

Because signs and symptoms of chronic spontaneous urticaria typically appear at multiple body sites and usually in large numbers, application of topical corticosteroids or topical antihistamines is neither feasible nor recommended. Despite low quality of evidence, treatment with methotrexate, hydroxychloroquine, dapsone, plasmapheresis, and other immunomodulatory therapies may be considered under the guidance of specialists (eg, dermatologists or allergists) for patients with long-lasting, severe, therapy-refractory autoimmune urticaria.[10,56,71,78-80] Despite limited evidence of efficacy, first-generation H_1 antihistamines such as diphenhydramine, tricyclic antidepressants such as doxepin, and H_2 antagonists such as ranitidine are available worldwide, are affordable, and may be prescribed for patients with chronic spontaneous urticaria if first-line treatments are not available.[10] Treatments with conflicting evidence or evidence against their use include sodium cromoglycate (cromolyn sodium), leukotriene receptor antagonists, and tranexamic acid.[10,81]

Special Populations

Some antihistamines, such as cetirizine and loratadine,[82,83] and omalizumab[70] are considered effective and safe in pregnancy, during breastfeeding, and in older adults (Table 2).[84-86] In a systematic review of 85 studies with 1 112 066 patients older than 60 years with chronic urticaria, second-generation H_1 antihistamines were equally or more effective at reducing symptoms in older vs younger adults (45.5%-88.5% vs 31.8%-65.9%, respectively).[86] Children may also have higher response rates to antihistamines than adults (61%-82% vs 46%-75%, respectively).[19]

Novel Therapies

Several targeted therapies are currently being developed for patients with antihistamine-refractory and/or omalizumab-refractory chronic spontaneous urticaria, including Bruton tyrosine kinase inhibitors (eg, remibrutinib, rilzabrutinib), anti-KIT (barzolvolimab, briquilimab), anti–IL-4Rα (dupilumab), anti–thymic stromal lymphopoietin (tezepelumab), and MRGPRX2 antagonists (Table 2).[64,66,87] In a randomized clinical trial of 138 patients with antihistamine-refractory chronic spontaneous urticaria, dupilumab was more efficacious than placebo at 24 weeks, with a 5-point or greater reduction in weekly Itch Severity Scale (minimum clinically important difference) of 72.9% vs 42.6%, respectively (P = .001).[64]

Prognosis

According to most studies, acute urticaria progresses to chronic spontaneous urticaria in less than 8% of cases.[1] Chronic spontaneous urticaria has a mean or median disease duration of approximately 1 to 4 years.[1] Cumulative estimates for spontaneous remission are 17% at 1 year, 45% at 5 years, and 73% at 20 years.[2] Chronic spontaneous urticaria relapses in up to one-third of patients,[1] with recurrence at 5 years in 17.1% of cases.[88] Presence of antithyroid antibodies[6,24,89] and antihistamine refractoriness[90-92] has been associated with a higher risk of progression from acute to chronic spontaneous urticaria, longer urticaria duration, and urticaria recurrence.

Practical Considerations

Extensive investigations to identify a cause of urticaria such as routine allergy testing or serology for infections should be avoided in patients with chronic spontaneous urticaria unless suggested by patients' history and physical examination.[10,93,94] Generalists should advise patients that chronic spontaneous urticaria is not a life-threatening disease, is rarely allergic, often occurs due to autoimmunity, and typically resolves within several years.[22] Patients should be treated until their symptoms resolve[10] and should be referred to a dermatologist or allergist if

- individual wheals persist for longer than 24 hours and resolve with postinflammatory hyperpigmentation, to rule out urticarial vasculitis;
- an underlying cause of urticaria such as autoimmune endotype is suspected;
- patients report long-lasting isolated angioedema (>2-5 days) but do not develop wheals, to rule out bradykinin-mediated angioedema including hereditary angioedema;
- patients experience systemic symptoms such as fever, arthralgia, and abdominal pain in addition to wheals and/or angioedema, to rule out urticarial vasculitis and autoinflammatory conditions such as Schnitzler syndrome;
- wheals and angioedema appear associated with a drug reaction, food allergy, or anaphylaxis;

- there is a need for additional special tests, such as provocation tests in patients with comorbid inducible urticaria; and/or
- disease control is not achieved with a higher than standard-dosed second-generation antihistamine.[10,22]

Limitations

This Review has limitations. First, some relevant studies may have been missed. Second, the quality of included studies was not formally evaluated. Third, novel therapies have been only briefly discussed.

Conclusions

Chronic spontaneous urticaria is an inflammatory skin disease that presents with spontaneously recurring wheals, angioedema, or both, and may be associated with medical and psychiatric comorbidities and decreased quality of life. First-line treatment is use of a second-generation H_1 antihistamine; omalizumab is second-line treatment and cyclosporine is an off-label third-line treatment. Systemic corticosteroids should be used only in the short term (<10 days) to treat acute severe exacerbations of chronic spontaneous urticaria.

ARTICLE INFORMATION

Accepted for Publication: July 17, 2024.

Published Online: September 26, 2024. doi:10.1001/jama.2024.15568

Author Contributions: Drs Kolkhir and Bonnekoh are co–first authors and Drs Metz and Maurer are co–last authors.

Conflict of Interest Disclosures: Dr Kolkhir reported receipt of personal fees from Novartis, ValenzaBio, and Roche. Dr Bonnekoh reported receipt of personal fees from AbbVie, Intercept Pharma, Novartis, Sanofi, and ValenzaBio. Dr Metz reported receipt of honoraria for advising and/or speaking from Amgen, AstraZeneca, Argenx, Celldex, Celltrion, Escient, Jasper, Novartis, Regeneron, Sanofi, Third Harmonic Bio, and Incyte. Dr Maurer reported receipt of personal fees from Allakos, Amgen, AstraZeneca, Lilly, Evommune, GSK, Leo Pharma, Mitsubishi Tanabe Pharma, Noucor, Novartis, Sanofi, Teva, Third Harmonic Bio, and Yuhan and receipt of grants from Celldex and Moxie.

Additional Contributions: We thank Kanokvalai Kulthanan, MD (Urticaria Center of Reference and Excellence [UCARE], Department of Dermatology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand), Melba Muñoz, MD (Institute of Allergology, Charité–Universitätsmedizin Berlin, Berlin, Germany), and Jonny Peter, MD (UCARE, Division of Allergy and Clinical Immunology, Department of Medicine, University of Cape Town, Cape Town, South Africa), for providing clinical photographs for this article.

Additional Information: This publication is in memory of Professor Marcus Maurer, a brilliant person, an outstanding teacher, a remarkable scientist, and a warm-hearted friend.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

REFERENCES

1. Kolkhir P, Giménez-Arnau AM, Kulthanan K, Peter J, Metz M, Maurer M. Urticaria. *Nat Rev Dis Primers*. 2022;8(1):61. doi:10.1038/s41572-022-00389-z

2. Balp MM, Halliday AC, Severin T, et al. Clinical remission of chronic spontaneous urticaria (CSU): a targeted literature review. *Dermatol Ther (Heidelb)*. 2022;12(1):15-27. doi:10.1007/s13555-021-00641-6

3. Weerasubpong P, Jiamton S, Phumariyapong P, Ungprasert P, Kulthanan K. Prevalence of concomitant angioedema in chronic spontaneous urticaria: a systematic review and meta-analysis. *Asian Pac J Allergy Immunol*. 2023;41(1):12-19. doi:10.12932/AP-151222-1515

4. Fricke J, Ávila G, Keller T, et al. Prevalence of chronic urticaria in children and adults across the globe: systematic review with meta-analysis. *Allergy*. 2020;75(2):423-432. doi:10.1111/all.14037

5. Maurer M, Staubach P, Raap U, et al. H1-antihistamine-refractory chronic spontaneous urticaria: it's worse than we thought—first results of the multicenter real-life AWARE study. *Clin Exp Allergy*. 2017;47(5):684-692. doi:10.1111/cea.12900

6. Eun SJ, Lee JY, Kim DY, Yoon HS. Natural course of new-onset urticaria: results of a 10-year follow-up, nationwide, population-based study. *Allergol Int*. 2019;68(1):52-58. doi:10.1016/j.alit.2018.05.011

7. Tayefi M, Bradley M, Neijber A, Fastberg A, Ceynowa D, Eriksson M. Chronic urticaria: a Swedish registry-based cohort study on population, comorbidities and treatment characteristics. *Acta Derm Venereol*. 2022;102:adv00624. doi:10.2340/actadv.v101.737

8. Schoepke N, Asero R, Ellrich A, et al. Biomarkers and clinical characteristics of autoimmune chronic spontaneous urticaria: results of the PURIST study. *Allergy*. 2019;74(12):2427-2436. doi:10.1111/all.13949

9. Xiang YK, Kolkhir P, Scheffel J, et al. Most patients with autoimmune chronic spontaneous urticaria also have autoallergic urticaria, but not vice versa. *J Allergy Clin Immunol Pract*. 2023;11(8):2417-2425. doi:10.1016/j.jaip.2023.02.006

10. Zuberbier T, Abdul Latiff AH, Abuzakouk M, et al. The international EAACI/GA^{2}LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. *Allergy*. 2022;77(3):734-766. doi:10.1111/all.15090

11. Brzoza Z, Nabrdalik K, Moos L, et al. Chronic spontaneous urticaria and type 1 diabetes mellitus—does quality of life impairment always reflect health danger? *J Clin Med*. 2020;9(8):2505. doi:10.3390/jcm9082505

12. Grob JJ, Revuz J, Ortonne JP, Auquier P, Lorette G. Comparative study of the impact of chronic urticaria, psoriasis and atopic dermatitis on the quality of life. *Br J Dermatol*. 2005;152(2):289-295. doi:10.1111/j.1365-2133.2005.06385.x

13. Maurer M, Abuzakouk M, Bérard F, et al. The burden of chronic spontaneous urticaria is substantial: real-world evidence from ASSURE-CSU. *Allergy*. 2017;72(12):2005-2016. doi:10.1111/all.13209

14. Sella JA, Ferriani MPL, Melo JML, et al. Type I and type IIb autoimmune chronic spontaneous urticaria: using common clinical tools for endotyping patients with CSU. *J Allergy Clin Immunol Glob*. 2023;2(4):100159. doi:10.1016/j.jacig.2023.100159

15. Giménez-Arnau AM, DeMontojoye L, Asero R, et al. The pathogenesis of chronic spontaneous urticaria: the role of infiltrating cells. *J Allergy Clin Immunol Pract*. 2021;9(6):2195-2208. doi:10.1016/j.jaip.2021.03.033

16. Losol P, Yoo HS, Park HS. Molecular genetic mechanisms of chronic urticaria. *Allergy Asthma Immunol Res*. 2014;6(1):13-21. doi:10.4168/aair.2014.6.1.13

17. Zhu L, Jian X, Zhou B, et al. Gut microbiota facilitate chronic spontaneous urticaria. *Nat Commun*. 2024;15(1):112. doi:10.1038/s41467-023-44373-x

18. Maurer M, Ortonne JP, Zuberbier T. Chronic urticaria: an internet survey of health behaviours, symptom patterns and treatment needs in European adult patients. *Br J Dermatol*. 2009;160(3):633-641. doi:10.1111/j.1365-2133.2008.08920.x

19. Saini S, Shams M, Bernstein JA, Maurer M. Urticaria and angioedema across the ages. *J Allergy Clin Immunol Pract*. 2020;8(6):1866-1874. doi:10.1016/j.jaip.2020.03.030

20. Sussman G, Abuzakouk M, Bérard F, et al. Angioedema in chronic spontaneous urticaria is underdiagnosed and has a substantial impact: analyses from ASSURE-CSU. *Allergy*. 2018;73(8):1724-1734. doi:10.1111/all.13430

21. Ghazanfar MN, Sørensen JA, Zhang D, Holgersen NK, Vestergaard C, Thomsen SF. Occurrence and risk factors of mental disorders in patients with chronic urticaria. *World Allergy Organ J*. 2023;16(11):100835. doi:10.1016/j.waojou.2023.100835

22. Ryan D, Tanno LK, Angier E, et al. Clinical review: the suggested management pathway for urticaria in primary care. *Clin Transl Allergy*. 2022;12(10):e12195. doi:10.1002/clt2.12195

23. Tzur Bitan D, Berzin D, Cohen A. The association of chronic spontaneous urticaria (CSU) with anxiety and depression: a nationwide cohort study. *Arch Dermatol Res*. 2021;313(1):33-39. doi:10.1007/s00403-020-02064-3

24. Kolkhir P, Metz M, Altrichter S, Maurer M. Comorbidity of chronic spontaneous urticaria and autoimmune thyroid diseases: a systematic review. *Allergy*. 2017;72(10):1440-1460. doi:10.1111/all.13182

25. Kolkhir P, Altrichter S, Asero R, et al. Autoimmune diseases are linked to type IIb autoimmune chronic spontaneous urticaria. *Allergy Asthma Immunol Res*. 2021;13(4):545-559. doi:10.4168/aair.2021.13.4.545

26. Tienforti D, Di Giulio F, Spagnolo L, et al. Chronic urticaria and thyroid autoimmunity: a meta-analysis of case-control studies. *J Endocrinol Invest*. 2022;45(7):1317-1326. doi:10.1007/s40618-022-01761-2

27. Kolkhir P, Grakhova M, Bonnekoh H, Krause K, Maurer M. Treatment of urticarial vasculitis: a systematic review. *J Allergy Clin Immunol*. 2019; 143(2):458-466. doi:10.1016/j.jaci.2018.09.007

28. Reshef A, Buttgereit T, Betschel SD, et al. Definition, acronyms, nomenclature, and classification of angioedema (DANCE): AAAAI, ACAAI, ACARE, and APAAACI DANCE consensus. *J Allergy Clin Immunol*. Published online April 24, 2024. doi:10.1016/j.jaci.2024.03.024

29. Maurer M, Magerl M. Differences and similarities in the mechanisms and clinical expression of bradykinin-mediated vs mast cell-mediated angioedema. *Clin Rev Allergy Immunol*. 2021;61(1):40-49. doi:10.1007/s12016-021-08841-w

30. Chen CM, Huang WT, Chang LJ, Hsu CC, Hsu YH. Peptic ulcer disease is associated with increased risk of chronic urticaria independent of *Helicobacter pylori* infection: a population-based cohort study. *Am J Clin Dermatol*. 2021;22(1):129-137. doi:10.1007/s40257-020-00561-9

31. Magen E, Mishal J, Schlesinger M. Clinical and laboratory features of chronic idiopathic urticaria in the elderly. *Int J Dermatol*. 2013;52(11):1387-1391. doi:10.1111/ijd.12109

32. Kolkhir P, Balakirski G, Merk HF, Olisova O, Maurer M. Chronic spontaneous urticaria and internal parasites—a systematic review. *Allergy*. 2016;71(3):308-322. doi:10.1111/all.12818

33. Kolkhir P, Pereverzina N, Olisova O, Maurer M. Comorbidity of viral hepatitis and chronic spontaneous urticaria: a systematic review. *Allergy*. 2018;73(10):1946-1953. doi:10.1111/all.13482

34. Gregoriou S, Rigopoulos D, Katsambas A, et al. Etiologic aspects and prognostic factors of patients with chronic urticaria: nonrandomized, prospective, descriptive study. *J Cutan Med Surg*. 2009;13(4): 198-203. doi:10.2310/7750.2008.08035

35. Kozel MMA, Bossuyt PMM, Mekkes JR, Bos JD. Laboratory tests and identified diagnoses in patients with physical and chronic urticaria and angioedema: a systematic review. *J Am Acad Dermatol*. 2003;48(3):409-416. doi:10.1067/mjd.2003.142

36. Kolkhir P, Muñoz M, Asero R, et al. Autoimmune chronic spontaneous urticaria. *J Allergy Clin Immunol*. 2022;149(6):1819-1831. doi:10.1016/j.jaci.2022.04.010

37. Augey F, Gunera-Saad N, Bensaid B, Nosbaum A, Berard F, Nicolas JF. Chronic spontaneous urticaria is not an allergic disease. *Eur J Dermatol*. 2011;21(3):349-353. doi:10.1684/ejd.2011.1285

38. Buttgereit T, Vera C, Aulenbacher F, et al. Patients with chronic spontaneous urticaria who have wheals, angioedema, or both, differ demographically, clinically, and in response to treatment—results from CURE. *J Allergy Clin Immunol Pract*. 2023;11(11):3515-3525. doi:10.1016/j.jaip.2023.08.020

39. Wallace D, Cooper NR, Sel A, Russo R. The Social Readjustment Rating Scale: updated and modernised. *PLoS One*. 2023;18(12):e0295943. doi:10.1371/journal.pone.0295943

40. Kocatürk E, Salman A, Cherrez-Ojeda I, et al. The global impact of the COVID-19 pandemic on the management and course of chronic urticaria. *Allergy*. 2021;76(3):816-830. doi:10.1111/all.14687

41. Chu CY, Cho YT, Jiang JH, Lin EIC, Tang CH. Epidemiology and comorbidities of patients with chronic urticaria in Taiwan: a nationwide population-based study. *J Dermatol Sci*. 2017;88(2): 192-198. doi:10.1016/j.jdermsci.2017.07.006

42. Konstantinou GN, Konstantinou GN. Psychiatric comorbidity in chronic urticaria patients: a systematic review and meta-analysis. *Clin Transl Allergy*. 2019;9:42. doi:10.1186/s13601-019-0278-3

43. Shalom G, Magen E, Babaev M, et al. Chronic urticaria and the metabolic syndrome: a cross-sectional community-based study of 11 261 patients. *J Eur Acad Dermatol Venereol*. 2018;32(2): 276-281. doi:10.1111/jdv.14548

44. Confino-Cohen R, Chodick G, Shalev V, Leshno M, Kimhi O, Goldberg A. Chronic urticaria and autoimmunity: associations found in a large population study. *J Allergy Clin Immunol*. 2012;129 (5):1307-1313. doi:10.1016/j.jaci.2012.01.043

45. Zhang DG, Zahid JA, Ali Z, Thomsen SF. Risk of atopic disorders in patients with chronic urticaria: a systematic review and meta-analysis. *Dermatology*. 2023;239(1):32-44. doi:10.1159/000525870

46. Kovalkova E, Fomina D, Borzova E, et al. Comorbid inducible urticaria is linked to non-autoimmune chronic spontaneous urticaria: CURE insights. *J Allergy Clin Immunol Pract*. 2024;12 (2):482-490. doi:10.1016/j.jaip.2023.11.029

47. Sánchez J, Amaya E, Acevedo A, Celis A, Caraballo D, Cardona R. Prevalence of inducible urticaria in patients with chronic spontaneous urticaria: associated risk factors. *J Allergy Clin Immunol Pract*. 2017;5(2):464-470. doi:10.1016/j.jaip.2016.09.029

48. Kim BR, Yang S, Choi JW, Choi CW, Youn SW. Epidemiology and comorbidities of patients with chronic urticaria in Korea: a nationwide population-based study. *J Dermatol*. 2018;45(1):10-16. doi:10.1111/1346-8138.14075

49. Staubach P, Eckhardt-Henn A, Dechene M, et al. Quality of life in patients with chronic urticaria is differentially impaired and determined by psychiatric comorbidity. *Br J Dermatol*. 2006;154 (2):294-298. doi:10.1111/j.1365-2133.2005.06976.x

50. Maurer M, Giménez-Arnau A, Ensina LF, Chu CY, Jaumont X, Tassinari P. Chronic urticaria treatment patterns and changes in quality of life: AWARE study 2-year results. *World Allergy Organ J*. 2020;13(9):100460. doi:10.1016/j.waojou.2020.100460

51. Bizjak M, Košnik M, Dinevski D, et al. Risk factors for systemic reactions in typical cold urticaria: results from the COLD-CE study. *Allergy*. 2022;77(7):2185-2199. doi:10.1111/all.15194

52. Rubeiz CJ, Asero R, Betschel S, et al. Analysis of questionnaire survey to determine worldwide trends in prescriptions of biologics for the treatment of unresponsive chronic urticaria. *World Allergy Organ J*. 2024;17(1):100858. doi:10.1016/j.waojou.2023.100858

53. Phinyo P, Koompawichit P, Nochaiwong S, Tovanabutra N, Chiewchanvit S, Chuamanochan M. Comparative efficacy and acceptability of licensed dose second-generation antihistamines in chronic spontaneous urticaria: a network meta-analysis. *J Allergy Clin Immunol Pract*. 2021;9(2):956-970. doi:10.1016/j.jaip.2020.08.055

54. Xiao X, Xue P, Shi Y, et al. The efficacy and safety of high-dose nonsedating antihistamines in chronic spontaneous urticaria: a systematic review and meta-analysis of randomized clinical trials. *BMC Pharmacol Toxicol*. 2023;24(1):23. doi:10.1186/s40360-023-00665-y

55. Kim MA, Choi JH, Shin YS, Park HS, Ye YM; KAAACI Work Group on Urticaria/Angioedema/Anaphylaxis. Efficacy of second-line treatments in chronic urticaria refractory to standard dose antihistamines. *Allergy Asthma Immunol Res*. 2023; 15(4):496-511. doi:10.4168/aair.2023.15.4.496

56. Nochaiwong S, Chuamanochan M, Ruengorn C, Awiphan R, Tovanabutra N, Chiewchanvit S. Evaluation of pharmacologic treatments for H_1 antihistamine-refractory chronic spontaneous urticaria: a systematic review and network meta-analysis. *JAMA Dermatol*. 2021;157(11):1316-1327. doi:10.1001/jamadermatol.2021.3237

57. Maurer M, Rosén K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med*. 2013;368 (10):924-935. doi:10.1056/NEJMoa1215372

58. Tharp MD, Bernstein JA, Kavati A, et al. Benefits and harms of omalizumab treatment in adolescent and adult patients with chronic idiopathic (spontaneous) urticaria: a meta-analysis of "real-world" evidence. *JAMA Dermatol*. 2019;155 (1):29-38. doi:10.1001/jamadermatol.2018.3447

59. He ZH, Qiu SC, Huang ZW, et al. Comparison between chronic spontaneous urticaria and chronic induced urticaria on the efficacy of omalizumab treatment: a systematic review and meta-analysis. *Dermatol Ther*. 2022;35(12):e15928. doi:10.1111/dth.15928

60. Maurer M, Metz M, Brehler R, et al. Omalizumab treatment in patients with chronic inducible urticaria: a systematic review of published evidence. *J Allergy Clin Immunol*. 2018;141(2):638-649. doi:10.1016/j.jaci.2017.06.032

61. Kulthanan K, Chaweekulrat P, Komoltri C, et al. Cyclosporine for chronic spontaneous urticaria: a meta-analysis and systematic review. *J Allergy Clin Immunol Pract*. 2018;6(2):586-599. doi:10.1016/j.jaip.2017.07.017

62. Santiago L, Ferreira B, Ramos L, Gonçalo M. IgE levels are negatively correlated with clinical response to ciclosporin in chronic spontaneous urticaria. *Br J Dermatol*. 2019;180(1):199-200. doi:10.1111/bjd.17005

63. Chu X, Wang J, Ologundudu L, et al. Efficacy and safety of systemic corticosteroids for urticaria: a systematic review and meta-analysis of randomized clinical trials. *J Allergy Clin Immunol Pract*. 2024;12(7):1879-1889. doi:10.1016/j.jaip.2024.04.016

64. Maurer M, Casale TB, Saini SS, et al. Dupilumab in patients with chronic spontaneous urticaria (LIBERTY-CSU CUPID): two randomized, double-blind, placebo-controlled, phase 3 trials. *J Allergy Clin Immunol*. 2024;154(1):184-194. doi:10.1016/j.jaci.2024.01.028

65. Nettis E, Brussino L, Patella V, et al. Effectiveness and safety of dupilumab in patients with chronic rhinosinusitis with nasal polyps and associated comorbidities: a multicentric

prospective study in real life. *Clin Mol Allergy*. Published online May 19, 2022. doi:10.1186/s12948-022-00171-2

66. Maurer M, Berger W, Giménez-Arnau A, et al. Remibrutinib, a novel BTK inhibitor, demonstrates promising efficacy and safety in chronic spontaneous urticaria. *J Allergy Clin Immunol*. 2022;150(6):1498-1506. doi:10.1016/j.jaci.2022.08.027

67. Kolkhir P, Laires PA, Salameh P, et al. The benefit of complete response to treatment in patients with chronic spontaneous urticaria—CURE results. *J Allergy Clin Immunol Pract*. 2023;11(2):610-620. doi:10.1016/j.jaip.2022.11.016

68. Simons FER, Simons KJ. H_1 antihistamines: current status and future directions. *World Allergy Organ J*. 2008;1(9):145-155. doi:10.1097/WOX.0b013e318186fb3a

69. Guillén-Aguinaga S, Jáuregui Presa I, Aguinaga-Ontoso E, Guillén-Grima F, Ferrer M. Updosing nonsedating antihistamines in patients with chronic spontaneous urticaria: a systematic review and meta-analysis. *Br J Dermatol*. 2016;175(6):1153-1165. doi:10.1111/bjd.14768

70. Türk M, Carneiro-Leão L, Kolkhir P, Bonnekoh H, Buttgereit T, Maurer M. How to treat patients with chronic spontaneous urticaria with omalizumab: questions and answers. *J Allergy Clin Immunol Pract*. 2020;8(1):113-124. doi:10.1016/j.jaip.2019.07.021

71. Nochaiwong S, Chuamanochan M, Ruengorn C, et al. Impact of pharmacological treatments for chronic spontaneous urticaria with an inadequate response to H1-antihistamines on health-related quality of life: a systematic review and network meta-analysis. *J Allergy Clin Immunol Pract*. 2022;10(1):297-308. doi:10.1016/j.jaip.2021.10.022

72. Zhao ZT, Ji CM, Yu WJ, et al. Omalizumab for the treatment of chronic spontaneous urticaria: a meta-analysis of randomized clinical trials. *J Allergy Clin Immunol*. 2016;137(6):1742-1750. doi:10.1016/j.jaci.2015.12.1342

73. Hutyrová B, Bystroň J; Czech Anti-IgE Registry Collaborators. The effect of omalizumab treatment on severe allergic asthma and allergic comorbidities: real-life experience from the Czech Anti-IgE Registry. *Postepy Dermatol Alergol*. 2018;35(5):510-515. doi:10.5114/ada.2018.77243

74. Sabaté-Brescó M, Rodriguez-Garijo N, Azofra J, et al. A comparative study of sex distribution, autoimmunity, blood, and inflammatory parameters in chronic spontaneous urticaria with angioedema and chronic histaminergic angioedema. *J Allergy Clin Immunol Pract*. 2021;9(6):2284-2292. doi:10.1016/j.jaip.2021.03.038

75. Terhorst-Molawi D, Fox L, Siebenhaar F, Metz M, Maurer M. Stepping down treatment in chronic spontaneous urticaria: what we know and what we don't know. *Am J Clin Dermatol*. 2023;24(3):397-404. doi:10.1007/s40257-023-00761-z

76. Loria MP, Dambra PP, D'Oronzio L, et al. Cyclosporin A in patients affected by chronic idiopathic urticaria: a therapeutic alternative. *Immunopharmacol Immunotoxicol*. 2001;23(2):205-213. doi:10.1081/IPH-100103860

77. Ledford D, Broder MS, Antonova E, Omachi TA, Chang E, Luskin A. Corticosteroid-related toxicity in patients with chronic idiopathic urticaria-chronic spontaneous urticaria. *Allergy Asthma Proc*. 2016;37(6):458-465. doi:10.2500/aap.2016.37.3999

78. Patil AD, Bingewar G, Goldust M. Efficacy of methotrexate as add on therapy to H1 antihistamine in difficult to treat chronic urticaria: a systematic review and meta-analysis of randomized clinical trials. *Dermatol Ther*. 2020;33(6):e14077. doi:10.1111/dth.14077

79. Zuberbier T, Peter J, Staubach P, Chularojanamontri L, Kulthanan K. Potential therapeutic approaches for chronic urticaria: beyond H1-antihistamines and biologics. *J Allergy Clin Immunol Pract*. 2023;11(8):2265-2273. doi:10.1016/j.jaip.2023.06.027

80. Bei W, Qian J, Zilu Q, et al. Comparing four immunosuppressive agents for chronic spontaneous urticaria—a network meta-analysis. *Int Immunopharmacol*. 2023;123:110577. doi:10.1016/j.intimp.2023.110577

81. Ribeiro Gonçalves O, Ribeiro VEA, Galvão MTL, et al. Leukotriene receptor antagonists as adjuvant therapy of antihistamines in chronic urticaria: a systematic review and meta-analysis. *Int J Dermatol*. Published online April 22, 2024. doi:10.1111/ijd.17172

82. Weber-Schoendorfer C, Schaefer C. The safety of cetirizine during pregnancy: a prospective observational cohort study. *Reprod Toxicol*. 2008;26(1):19-23. doi:10.1016/j.reprotox.2008.05.053

83. Schwarz EB, Moretti ME, Nayak S, Koren G. Risk of hypospadias in offspring of women using loratadine during pregnancy: a systematic review and meta-analysis. *Drug Saf*. 2008;31(9):775-788. doi:10.2165/00002018-200831090-00006

84. Ventura MT, Cassano N, Romita P, Vestita M, Foti C, Vena GA. Management of chronic spontaneous urticaria in the elderly. *Drugs Aging*. 2015;32(4):271-282. doi:10.1007/s40266-015-0249-x

85. Nettis E, Cegolon L, Di Leo E, Canonica WG, Detoraki A; Italian OCUReL Study Group. Omalizumab in elderly patients with chronic spontaneous urticaria: an Italian real-life experience. *Ann Allergy Asthma Immunol*. 2018;120(3):318-323. doi:10.1016/j.anai.2017.12.007

86. Kulthanan K, Rujitharanawong C, Munprom K, et al. Prevalence, clinical manifestations, treatment, and clinical course of chronic urticaria in elderly: a systematic review. *J Asthma Allergy*. 2022;15:1455-1490. doi:10.2147/JAA.S379912

87. Kolkhir P, Akdis CA, Akdis M, et al. Type 2 chronic inflammatory diseases: targets, therapies and unmet needs. *Nat Rev Drug Discov*. 2023;22(9):743-767. doi:10.1038/s41573-023-00750-1

88. Sánchez J, Álvarez L, Cardona R. Prospective analysis of clinical evolution in chronic urticaria: persistence, remission, recurrence, and pruritus alone. *World Allergy Organ J*. 2022;15(10):100705. doi:10.1016/j.waojou.2022.100705

89. Toubi E, Vadasz Z. Predictive features associated with chronic spontaneous urticaria recurrence. *J Dermatol*. 2021;48(11):1786-1788. doi:10.1111/1346-8138.16119

90. Tanaka T, Hiragun M, Hide M, Hiragun T. Analysis of primary treatment and prognosis of spontaneous urticaria. *Allergol Int*. 2017;66(3):458-462. doi:10.1016/j.alit.2016.12.007

91. Cortellazzo Wiel L, Conversano E, Giangreco M, et al. Natural history and predictors of recovery in children with chronic spontaneous urticaria. *Pediatr Allergy Immunol*. 2021;32(1):201-204. doi:10.1111/pai.13299

92. Kim JK, Har D, Brown LS, Khan DA. Recurrence of chronic urticaria: incidence and associated factors. *J Allergy Clin Immunol Pract*. 2018;6(2):582-585. doi:10.1016/j.jaip.2017.07.012

93. Conlon NP, Abramovitch A, Murray G, et al. Allergy in Irish adults: a survey of referrals and outcomes at a major centre. *Ir J Med Sci*. 2015;184(2):349-352. doi:10.1007/s11845-014-1117-0

94. Kolkhir P, Pogorelov D, Darlenski R, et al; WAO Junior Members Group. Management of chronic spontaneous urticaria: a worldwide perspective. *World Allergy Organ J*. 2018;11(1):14. doi:10.1186/s40413-018-0193-4