

Approach to the Patient with Hives



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KEYWORDS

- Chronic spontaneous urticaria • Inducible urticaria • Acute urticaria • Guidelines
- Treatment algorithm • Differential diagnosis

KEY POINTS

- Acute urticaria has been defined as lasting less than 6 weeks whereas chronic spontaneous urticaria persists more than 6 weeks.
- Chronic spontaneous urticaria is more common in women (2:1), typically begins in the third to fifth decades of life, and is a self-limited disorder in most patients, with the average duration of disease 1 to 5 years.
- Initial treatment includes a second-generation H1-receptor antagonist followed by incremental dose advancement up to 4 times the US Food and Drug Administration approved dose and/or adding an H2-antagonist or leukotriene receptor antagonist if therapy is ineffective.
- If hives are persistent then referral to an urticaria specialist is recommended for consideration of alternative therapies including omalizumab or cyclosporine.

INTRODUCTION

Urticaria is a common presenting clinical condition that the internist should be comfortable initially evaluating and treating but recognize that referral to a specialist is appropriate for further management when initial approaches are not effective or well tolerated by the patient. Urticaria episodes are usually of sudden onset, very pruritic, and evanescent meaning lesions come and go over 24 to 48 hours and reappear in different parts of the body. Acute urticaria has been defined as lasting less than 6 weeks whereas chronic spontaneous urticaria (CSU) persists for more than 6 weeks. CSU is more common in women (2:1) and typically begins in the third to fifth decades of life.¹⁻⁴ The economic burden of this condition is significant, with both direct and indirect

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costs (ie, absenteeism defined as missed days from work and presenteeism defined as patients going to work but being less productive), although the absolute health care costs on our health care system are not known. One study from the UK estimated that the annual direct health care costs approximated a mean total cost of €2050 (US\$2664).⁵ This included medication use, outpatient office visits, emergency department/hospital costs, laboratory tests, and indirect costs including loss of earnings because of travel to outpatient visits and absenteeism from work. A more recent European study found that costs seem to vary between countries from approximately €2400 in Italy (approximately US\$2700) to almost €9000 (approximately US\$10,121) in France based on purchasing power parity dollars.⁶ From the patient's perspective, this condition can severely affect daily functioning and quality of life, with impairment comparable to other conditions such as ischemic heart disease and depression, with patients feeling a similar lack of energy, social isolation, and emotional distress.^{7,8}

The 2 cases illustrated here are representative of common clinical presentations of patients with hives and should be reflected upon while reading this article.

CASE PRESENTATION I

A 32-year-old woman presents to the office with a history of sudden onset of hives that began after taking amoxicillin for a sinus infection. The hives began 2 days after completing a 10-day treatment course. The hives were irregularly shaped, polymorphic in size, raised, and extremely pruritic. They involved her face, neck, torso, arms, and upper legs. The hives would come and go over 24 hours and did not leave any scars. She noted some swelling of her lips and felt a constriction in her throat. She initially went to the emergency department, was treated with corticosteroids and antihistamines, and was told to follow up with her primary care physician. She was also given an epinephrine injector and told to avoid penicillin in the future. On presentation to her primary care provider, the hives had returned 1 day off corticosteroids, covered 50% of her body and were very pruritic. She was miserable, and the hives were affecting both her work and sleep. She was unable to tolerate diphenhydramine owing to sedation. Her past medical history is remarkable for chronic rhinitis complicated by 3 to 4 sinus infections a year requiring frequent antibiotics. She has never had trouble taking penicillin or related derivatives. She is otherwise healthy without any known chronic medical problems.

CASE PRESENTATION II

A 62-year-old man with adult-onset diabetes mellitus presents with a history of hives for the past 2 years. The hives are persistent, evanescent, and aggravated by scratching. He is unable to relate the onset of the hives to medications or foods and denies any history of thyroid disease, autoimmune disorders, chronic infections, or malignancies. He has no associated lip, face, or tongue swelling. The hives respond to corticosteroids but he does not like taking them owing to his underlying diabetes. His medical history includes hypertension and hypercholesterolemia. His diabetes is controlled with oral medication and diet. He has dry skin and does not moisturize on a regular basis. He has tried daily antihistamines, which helps with the itch but does not prevent the hives from erupting.

TERMINOLOGY

The terminology related to urticaria is evolving. Chronic urticaria with no identified cause was referred to as idiopathic chronic urticaria. However, recent international

guidelines endorsed by both the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology advocate using the term CSU with the terms intermittent or persistent to clinically describe this condition. The rationale for not using the term idiopathic is that it does not describe the clinical nature of the urticarial eruption, but rather refers to an unknown pathogenesis, which may or may not be the case when a patient presents to the clinic. Similarly, in discussing physical urticaria, consensus recommendations favor using the term chronic inducible urticaria, because many of the triggers identified to cause physical urticaria are not physical in nature but rather related to the autonomic nervous system such as cholinergic or adrenergic urticaria. It is also recommended to describe chronic urticaria as the presence of wheals, the presence of angioedema, or both because 40% of chronic urticaria presents with wheals alone, 40% with wheals and angioedema, and 20% with angioedema only.⁹ Fig. 1 summarizes the terminology recommended when discussing urticaria with patients or colleagues.²

PATHOGENESIS

There is still a poor understanding of the pathomechanisms related to CSU. Further research is needed to elucidate relevant biologic pathways and biomarkers that would predict responsiveness or unresponsiveness to conventional therapy with H1 antihistamines. It has been demonstrated that autoantibodies to the high-affinity IgE receptors on mast cells and basophils are prevalent in patients with CSU, but the clinical relevance of these antibodies remains unclear. Studies have been inconclusive as to whether certain therapies work better in patients with or without these antibodies.^{10–12} However, with the advent of biologic therapies that target specific immune pathways for treatment of CSU, a better understanding of the relevance of IgE, effector cells such as mast cells, basophils and eosinophils, cytokines, cytokine receptors, and related biologic pathways is being increasingly recognized.

CLINICAL PRESENTATION

Urticaria is described as pruritic eruptions with serpiginous circumscribed borders that are usually raised, erythematous and blanching involving the superficial dermis. Lesions usually vary in size with each individual hive lasting minutes to hours (usually <24 hours). Approximately 20% of individuals experience acute spontaneous urticaria at some point in their life and up to 1% to 3% continue to have chronic spontaneous persistent or intermittent urticaria.¹³ When urticaria occurs acutely, it is often difficult for clinicians to differentiate it from anaphylaxis because patients may report throat

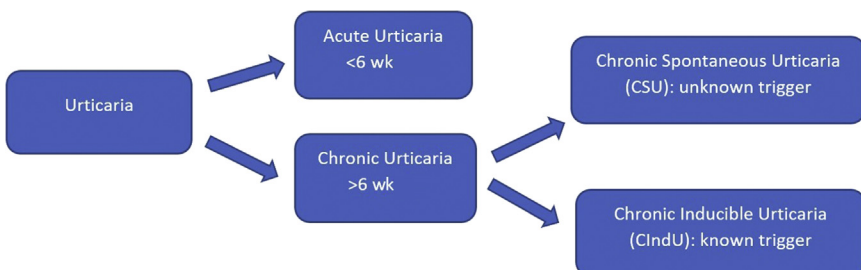


Fig. 1. Classification of urticaria based on the duration and the presence of triggering factors.

tightness and dyspnea. For this reason, in these situations, patients are often treated with oral corticosteroids, H1-antihistamines, and sometimes epinephrine. Furthermore, they may often be told empirically that medications (ie, nonsteroidal anti-inflammatory drugs [NSAIDs], aspirin, antibiotics, etc) or foods are responsible for the episode. Many times, these turn out to be associations versus cause and effect after a more thorough history and appropriate diagnostic testing excludes these suspected agents as triggers. It is important to recognize that complete avoidance of a suspected causative trigger should resolve the hives. If urticaria persists despite strict avoidance, it is possible that hives can persist for a short period of time before completely resolving; however, if they persist for a longer time period it is unlikely that the suspected agent is causative. It is crucial not to reinforce these associations because this further confuses the patient while increasing their anxiety and frustration, and often leads to a long list of erroneous drug and/or food allergies that can confound their general medical care and impact their quality of life. **Table 1** details the clinical approach to a patient who presents with urticaria as portrayed in the 2 case presentations, considering initial presentation, potential triggers, and duration of illness.

EVALUATION AND DIAGNOSIS

CSU is a clinical diagnosis based on the episodic and transient appearance of characteristic urticarial lesions with or without angioedema. A detailed history and physical examination are the cornerstones of the initial evaluation with a focus on the signs and symptoms associated with the lesions, duration of individual lesions, and accompanying angioedema. If symptoms and time course are consistent with CSU, then a more detailed clinical history focusing on identifying possible underlying causes and excluding a more serious systemic disease is indicated. Urticarial vasculitis is a rare form of chronic urticaria (0.1% of cases) confirmed by skin biopsy when patients have lesions that persist longer than 48 hours. However, a subsequent biopsy study

Table 1 Clinical approach to a patient presenting with urticaria		
Anaphylaxis	Urticaria	
	Acute (<6 weeks)	Chronic (>6 weeks)
Urticaria and angioedema associated with signs/symptoms in organs other than the skin (pulmonary, cardiac, gastrointestinal)	Identifiable cause like a food or drug allergy ^a Yes: Avoid trigger, treat with antihistamines, refer to allergist	No obvious trigger: CSU Known physical trigger: chronic inducible urticaria Dermatographism Heat urticaria (hot showers, extreme humidity)
Appropriate emergency care and treatment	No: Treat with antihistamines, monitor for resolution	Cold urticaria
Prescribe epinephrine autoinjector and refer to an allergist		Exercise Delayed-pressure urticaria/angioedema (tight clothing or straps) Solar urticaria Cholinergic urticaria Aquagenic urticaria Vibratory angioedema

^a Common causes of acute urticaria include: infection-related (most common cause), medication-related, food-related, and contact-related. The majority of acute episodes do not go on to become a chronic issue.

found that even patients with traditional evanescent hives that dissipate over 24 to 48 hours can have a diagnosis of urticarial vasculitis. This caveat represents another reason to refer a patient refractory to treatment to an urticaria specialist for further evaluation and management. **Box 1** summarizes important components of a comprehensive clinical evaluation.¹⁴

A diagnostic algorithm for differentiating histaminergic and nonhistaminergic urticaria and/or angioedema is summarized in **Fig. 2**.^{2,23}

TESTING

Routine laboratory tests for the evaluation of CSU is not recommended unless the clinical history suggests an underlying allergic etiology (ie, food or drug) or the presence of an underlying systemic disease such as thyroid disease, autoimmune diseases, chronic infections, and rarely malignancies. In general, broad panel serum specific-IgE or skin testing to foods or aeroallergens is not recommended.^{1,23} In patients with a history of allergic rhinitis and testing is required to assess for allergen sensitization, serologic testing is recommended as skin testing can often be difficult to interpret correctly. If there is a concern about food allergy as a contributing cause, it is recommended that these patients be referred to an urticaria specialist for further evaluation before ordering extensive serologic food testing, which can lead to false-positive testing and obfuscate the patient's evaluation and management.

Box 1

Important components of a comprehensive clinical evaluation in a patient presenting with chronic urticarial lesions

Past medical history: recent foreign travel, infections, sexual history, and history of other atopic conditions.

Signs and symptoms of systemic disease: fever, weight loss, arthralgias, arthritis, cold or heat sensitivity, abdominal pain, or bone pain (autoimmune disorders including systemic lupus erythematosus, Sjogren syndrome, chronic urticarial vasculitis, dermatomyositis and polymyositis, and Still disease have been associated with CSU).

Possible triggers

- Inducible stimuli: exercise, heat, cold, and pressure.
- Newly administered drugs: antibiotics, NSAIDs, and hormonal therapies; NSAIDs worsen symptoms in 25% to 50% of patients with CSU.¹⁵
- Alcohol.
- Emotional stress and trauma: worsening hives often correlate with periods of physical or psychological stress.^{16,17} Whether emotional stress is a cause or the result of hives is still debated however, rarely does treating underlying stress with nonhistaminic therapies resolve hives.¹⁸

Debate about diet: patients often identify foods as possible triggers for their symptoms and make dietary decisions without enough information. The interactions between diet and CSU is not fully understood and current guidelines do not advise dietary modifications to better control CSU owing to poor evidence in the medical literature and difficulty in adherence.¹

- Pseudoallergen-free diet refers to avoidance of food additives like artificial preservatives, aromatic chemicals and dyes in processed foods and certain fruits, vegetables, seafood, spices, and a low histamine diet refers to avoiding foods high in vasoactive substances such as histamine have been advocated for initial treatment of patient by some investigators but the scientific data supporting these interventions is low.^{19–21} Furthermore, while instituting dietary changes seems like a relatively benign recommendation, adhering to unnecessarily restrictive diets can potentially have a negative impact on the patient's quality of life and nutritional status.²²

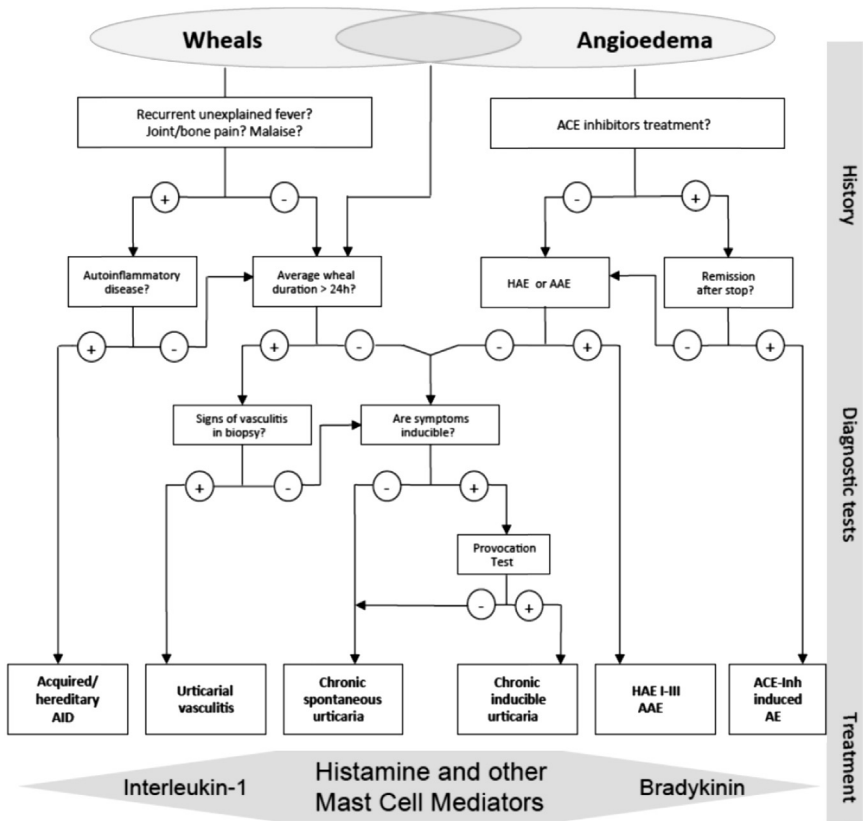


Fig. 2. Diagnostic algorithm for histaminergic and nonhistaminergic urticaria, urticaria and angioedema, or angioedema alone. AAE, acquired angioedema due to C1-inhibitor deficiency; AE, angioedema; ACE-Inh, angiotensin-converting enzyme inhibitor; AID, auto-inflammatory disease; HAE, hereditary angioedema. (Adapted from Zuberbier T, Aberer W, Asero R, et.al. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy 2018;73(7):1400; with permission.)

ASSOCIATED CONDITIONS

There are several other clinical conditions, specifically autoimmune conditions, that have been associated with CSU. These disorders make up a small proportion of patients with chronic hives; therefore, screening tests to assess for autoimmune diseases and other rare conditions are not recommended during the initial evaluation unless there are clinical features or suspicions indicative of concurrent disease. A number of studies have associated thyroid autoantibodies, *Helicobacter pylori* infections, and celiac disease with CSU however, the quality of evidence supporting these relationships is weak.^{1,23} Furthermore, clinical studies advocating treatment of these conditions, such as euthyroid patients with thyroid autoantibodies who are treated with thyroid supplementation, is considered highly controversial and not supported by the current medical literature.

TREATMENT

The most recent Joint Task Force (JTF) Practice Parameter for CSU recommends an algorithmic treatment approach detailed in **Box 2**.¹ Initial treatment includes a second-

Box 2**Updated step care approach to the management of chronic urticaria**

Step 1: Monotherapy with second-generation antihistamine, avoidance of triggers (NSAIDs and relevant physical factors if present)

Step 2: Dose advancement of second-generation antihistamine used in step 1^a

Add another second-generation antihistamine

Add an H2 antagonist

Add a leukotriene receptor antagonist (montelukast [Singulair], zafirlukast)

Add a first-generation antihistamine to be taken at bedtime^b

Step 3: Dose advancement of potent antihistamines (eg, hydroxyzine or doxepin) as tolerated.

Failure of steps 1 to 3: patients meet the definition of refractory CSU (not adequately controlled on maximal antihistamine therapy)

Step 4: Add an alternative agent

Biologic (Omalizumab)

Immunosuppressants (eg, cyclosporine)

Other anti-inflammatory agents (eg, hydroxychloroquine, sulfasalazine, colchicine)

Chronic, high-dose systemic corticosteroids should be avoided however short courses for 7 to 10 days are appropriate for severe hives

^a Maximum dose of second-generation antihistamine, up to 4× the recommended US Food and Drug Administration dose.

^b Patients with CSU and dermatographism had a 16 times higher odds of a favorable response to a first- or second-generation H1 antagonist^{11,24}

Adapted from Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. J Allergy Clin Immunol 2014;133(5):1276; with permission.

generation H1-receptor antagonist followed by incremental dose advancements and/or adding an H2-antagonist or leukotriene-modifying agent if therapy is ineffective.

The more recent International Urticaria Guidelines recommend a similar approach to steps 1 and 2 therapies, but do not advocate the use of H2 antagonists or a leukotriene-modifying agent owing to the low level of supporting clinical evidence.²³

Fig. 3 compares the treatment recommendations advocated by the JTF Practice Parameters and the recently updated international chronic urticaria guidelines.

These treatment algorithms differ in many respects largely because the International Guidelines use GRADE methodology for determining evidence-based treatment recommendations, whereas the JTF guidelines used an evidence-based approach coupled with expert consensus to generate recommendations. The major differences between these guidelines, in addition to not advocating H2 antagonists and leukotriene-modifying agent, are that the international guidelines do not advocate first-generation or combination antihistamines, which cause significant sedation and can impact motor and cognitive skills, making it difficult for many patients to tolerate while working or at school. Furthermore, there is no difference between first and second generation antihistamines with respect to the antihistaminergic activity. If first-generation antihistamines such as doxepin and hydroxyzine are used to treat hives, they should be administered at bedtime at the lowest possible dose. Patients should be monitored regularly for side effects and once hives are well-controlled, stepping down on these agents is advisable. Caution should be exercised using these agents in older patients who are more susceptible to their anticholinergic side effects and the risk for cognitive decline. As with any medication, side effects should be discussed with the patient and whether or not to use them should be based on shared decision making that weigh benefits versus risks with patient preference. In addition, step 3

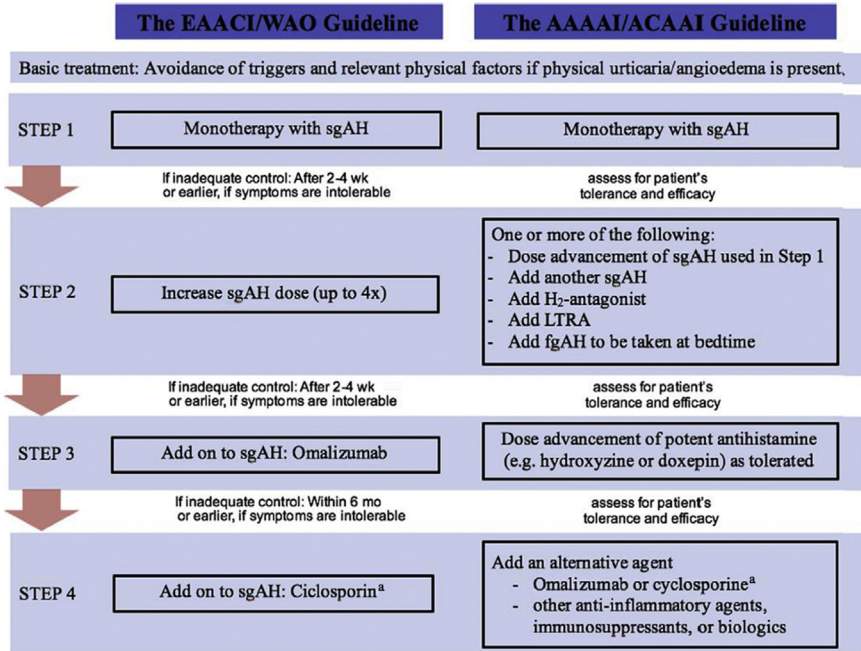


Fig. 3. Comparison of treatment algorithms between the international and American Academy of Allergy Asthma and Immunology (AAAAI)/American College of Allergy, Asthma & Immunology (ACAAI) guidelines. EAACI, European Academy of Allergology and Clinical Immunology; fgAH, first-generation antihistamine; LTRA, leukotriene receptor antagonist; sgAH, second-generation antihistamine; WAO, World Allergy Organization. ^a Different spellings as used in the respective guideline. Additional comments: EAACI/WAO: A short course of corticosteroids may be considered in case of severe exacerbation. AAAAI/ACAAI: Begin treatment at step appropriate for patient's level of severity and treatment history; step-down treatment is appropriate at any step, once consistent control of urticaria/angioedema is achieved. (Adapted from Zuberbier T, Bernstein JA. A Comparison of the United States and International Perspective on Chronic Urticaria Guidelines. *J Allergy Clin Immunol Pract* 2018;6(4):1148; with permission.)

treatment for the international guidelines advocates using omalizumab, an anti-IgE monoclonal antibody, approved for the treatment of CSU. Evidence supporting this treatment as first-line treatment of CSU after high-dose second-generation antihistamines was not available at the time of the publication of the JTF guideline. Finally, step 4 therapy for the international guideline advocates cyclosporin, whereas step 4 for the JTF guideline recommends a choice between omalizumab, cyclosporin, or other anti-inflammatory therapies such as hydroxychloroquine, dapsone, colchicine, or sulfasalazine to name a few.²³ Owing to the low quality of scientific evidence, these therapies have been recommended as alternative therapies by the international guidelines if steps 1 to 4 are not effective.^{2,23} However, for the purpose of this review, discussion of treatment should focus on steps 1 and 2 only, as need for step 3 and 4 therapy should prompt referral to an urticaria allergy or dermatology specialist. It is important for the primary care physician to have a close working relationship with an urticarial specialist because only approximately 45% to 60% of patients achieve an adequate therapeutic response from steps 1 and 2.²⁵

SUMMARY

Urticaria is a frequently encountered problem in the primary care setting in children and adults and therefore a better understanding of terminology and clinical course is important to provide optimal patient care. The evaluation of urticaria in the primary care setting can be complicated because patients present with an assortment of concerns for possible triggers and varied presentations. When obvious causes have been ruled out and symptoms persist despite maximizing step 1 and 2 therapy, referral to an urticaria specialist is indicated. With CSU affecting 1% to 3% of the general population, optimal care that completely controls the hives can significantly reduce the direct and indirect medical costs associated with this condition while improving patient quality of life.

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