Acute and Chronic Urticaria

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Contents

Abstract

Urticaria is a heterogeneous skin disease involving episodic wheals and/or angioedema, which occurs in 10–20% of people at some point in life. Although there are a wide array of etiologies, including infections, medications, allergic reactions, or physical stimuli, most cases remain idiopathic. Many systemic disorders are associated with urticaria, such as various forms of vasculitis, mastocytosis, or rheumatologic illnesses. Diagnosis is largely made by history and exam, at times involving a provocation test to reproduce the lesions if the history suggests inducible (aka physical) urticaria. Treatment with long-acting non-sedating H1-antihistamines is effective in over 50% of cases, but when not, other therapies such as biologics, immunosuppressive agents, or other anti-inflammatory agents may be necessary to control the hives.

Keywords

Hives · Urticaria · Angioedema · Acute · Chronic

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8.1 Introduction and Definition

Urticaria is a heterogeneous skin condition characterized by episodic appearance of wheals and/or angioedema. Wheals are cutaneous swellings of variable size, typically with reflex erythema which is usually very pruritic but could manifest as a burning sensation in some cases. Wheals manifest as a result of extravasation of fluid into epidermal spaces, with return of normal skin appearance in about 1–24 h. Angioedema, in contrast, is defined as rapid and marked extravasation of fluid into deeper dermis tissue spaces. This results in swelling which may be characterized by pain due to stretching nerve fibers, rather than pruritus, with significantly slower resolution, on the order of 1–3 days (Zuberbier et al. 2018; Godse et al. 2018; Kaplan 2002; Bernstein et al. 2014).

Acute urticaria involves episodic hives which last less than 6 weeks, whereas chronic urticaria involves symptoms on most days of the week for more than 6 weeks. The prevalence of urticaria is estimated to affect up to 20% of the general population at some point in life, but the etiology is rarely elucidated (Greaves 1995).

8.2 Epidemiology and Natural History

Acute urticaria is thought to affect approximately 10–20% of people at some point in life, with development of chronic spontaneous urticaria in approximately 1% of the population (Greaves 1995). Although more common in adults, it can also afflict children, but epidemiologic data on this population is lacking. Women seem to be affected about twice as frequently as men, typically starting in the third to fifth decades of life. Urticaria affects up to 1% of the general population in the United States at any particular point in time with similar prevalence described in other countries (Zuberbier et al. 2010; Gaig et al. 2004; Cooper 1991; Champion et al. 1969; Ferrer 2009; Juhlin 1981). Chronic urticaria is often a self-limited disorder, with average disease duration of 2–5 years (Greaves 2000). In patients with no clear etiology or identified underlying cause of urticaria, 30–50% will have spontaneous remission at 1 year. However, it is not uncommon for symptoms to persist for many years (Kulp-Shorten and Callen 1996; Kozel et al. 2001; Kulthanan et al. 2007; Gaig et al. 2004). A study in Spain indicated a prevalence of urticaria of 0.8% in the past year and prevalence of chronic urticaria of 0.6%. In this study, mean age of urticaria was 40 years, with disease duration of 1–5 years in 8.7% of study subjects and more than 5 years in 11.3% of study subjects (Gaig et al. 2004). Angioedema with concomitant hives is present in 40–50% of patients with chronic spontaneous urticaria. About 10% of patients experience angioedema alone without hives, while about 40% of patients exhibit hives alone (Greaves 2000; Kaplan 2002; Grattan 2004; Zuberbier et al. 2018).

8.3 Etiologies, Classification, and Pathophysiology

Diagnosis and classification of urticaria and angioedema are made largely by history (Charlesworth 1996; Beltrani 1996, 2004). Urticaria can be classified into various types and subtypes based on different eliciting stimuli. Most forms of urticaria follow into one of three broad categories: spontaneous urticaria, physical urticaria, or special/uncommon causes of urticaria (Sanchez-Borges et al. 2012; Lang et al. 2013; Zuberbier et al. 2018). Spontaneous urticaria includes acute spontaneous urticaria (episodic spontaneous hives and/or angioedema of less than 6 weeks duration) and chronic spontaneous urticaria (episodic hives and/or angioedema lasting more than 6 weeks duration).

The signs and symptoms of urticaria are mediated by cutaneous mast cells and basophils in the superficial dermis. Upon activation of mast cells and basophils, a variety of mediators are released, including histamine that causes the characteristic pruritus and vasodilation resulting in localized swelling in the epidermis in the case of hives and angioedema when the swelling extends to the deeper dermis/subcutaneous tissue (see Fig. 1) (Ying et al. 2002; Beck et al. 2017).

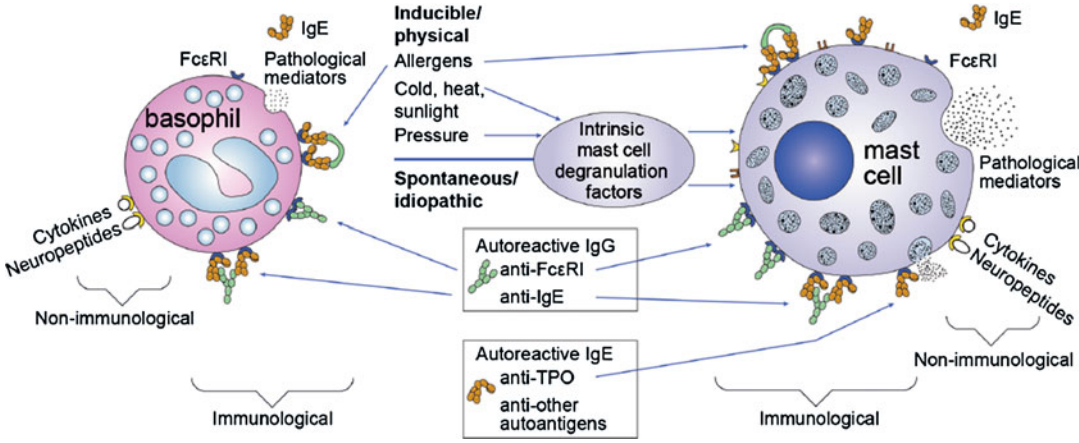

Fig. 1 Pathogenesis of chronic urticaria (CU). CU signs and symptoms develop when skin mast cells or basophils degranulate and release histamine and other pro-inflammatory mediators. In chronic spontaneous urticaria, the degranulation of these cells in some patients is thought to be due to the effects of autoantibodies directed against a subunit of the high-affinity IgE receptor, FcƐRIa, or to IgE itself. Other mechanisms of mast cell or basophil activation that are potentially relevant to chronic spontaneous urticaria involve autoantigens and IgE directed against these autoantigens, as well as complement components, cytokines, and neuropeptides. *TPO* thyroperoxidase (Beck et al. 2017)

There are myriad of potential etiologies for urticaria. There is a greater likelihood of identifying a specific trigger for acute urticaria compared to chronic urticaria. Causes include foods; medications (Fernandez et al. 2017; Kuyucu et al. 2014; Martin-Serrano et al. 2016); envenomation due to insect stings (Matysiak et al. 2013); latex exposure through recreational, occupational, or surgical/dental application (Sussman and Beezhold 1995); and a number of contactants from plant, animal, or occupational exposures (Bourrain 2006).

Infections represent another common cause of urticaria. Viral or bacterial infections, especially in children, are a particularly common cause of urticaria, with reports of as high as 80% of acute urticaria in children being attributed to viral or bacterial infections (Sackesen et al. 2004; Mortureux et al. 1998; Minciullo et al. 2014; Imbalzano et al. 2016; Plumb et al. 2001). In studies where children were evaluated in emergency departments with urticaria in a setting of sick symptoms, viral and bacterial illness were the leading identifiable trigger for urticaria (Mortureux et al. 1998). In one study in which children with sick symptoms, also on beta-lactams, were tested for both viral illness and re-exposed to beta-lactam, roughly 66% were positive for viral illness, while only 4% had recurrence of urticaria with re-exposure to the antibiotic (Mortureux et al. 1998; Caubet et al. 2011). *Mycoplasma pneumoniae* infection in children has been documented to cause acute urticaria that is refractory to antihistamines but responsive to azithromycin (Wu et al. 2009; Shah et al. 2007). Parasitic infections have been well-characterized as a cause of acute, self-limited urticaria in association with peripheral eosinophilia. Examples include *Strongyloides*, *Filaria*, *Echinococcus*, *Trichinella*, and *Toxocara* species (Di Campli et al. 1998).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are an important trigger of urticaria and angioedema. This can occur either by an immediate-type hypersensitivity or by a pharmacologic or pseudoallergic reaction, in which an agent such as ibuprofen or aspirin inhibits cyclooxygenase-1 enzyme resulting in urticaria, presumably due to that individual having an underlying anomaly in arachidonic acid metabolism (Moore-Robinson and Warin 1967; Warin 1960; Champion et al. 1969).

Another trigger of acute urticaria includes the direct activation of mast cells through specific

non-IgE receptors. For example, vancomycin infusion causing "red man syndrome" is a common inpatient cause of urticaria in both children and adults. Human and animal studies of red man syndrome indicate that histamine and other vasoactive mediators are released by direct mast cell activation, with some studies indicating that degree of serum histamine release relating directly to clinical severity of disease (Healy et al. 1990). The mechanism is thought to involve non-immunologic mast cell activation of phospholipase C and phospholipase A2 pathways and may partially occur in an extracellular calcium-dependent manner (Horinouchi et al. 1993; Veien et al. 2000). Often related to the rate of infusion, the phenomenon can be ameliorated by either slowing down the infusion and/or pre-treating with antihistamines (Healy et al. 1990; Renz et al. 1998; Newfield and Roizen 1979; Veien et al. 2000; Wallace et al. 1991). Other triggers of direct mast cell activation include opiates and their derivative products, radiocontrast media, foods high in lectins and/or histamine such as strawberries and tomatoes, or the stinging nettle plant *Urtica dioica*, from which the disorder "urticaria" derives its name (Robledo et al. 2004; Cochran 2005; Plumb et al. 2001; Anderson et al. 2003; Cummings and Olsen 2011; Uslu et al. 2011).

Although rare, there have been several case reports of urticaria triggered by progesterone-containing oral contraceptives or progesterone-containing hormone replacement therapies (Poole and Rosenwasser 2004; Shank et al. 2009; Bernstein et al. 2011).

Several systemic syndromes where urticaria may be a prominent or presenting symptom include urticarial vasculitis, cutaneous small-vessel vasculitis, systemic mastocytosis, systemic lupus erythematosus, rheumatoid arthritis, or other autoimmune disorders (Confino-Cohen et al. 2012).

8.4 Chronic Urticaria

Chronic urticaria (CU) is defined as episodic hives occurring most days of the week for 6 or more weeks. Approximately 40% of patients with CU also experience angioedema (Greaves 2000). In the United States, CU has a prevalence of about 1% in the general population, with similar prevalence reported in other countries (Gaig et al. 2004; Greaves 2000; Lapi et al. 2016). CU affects both children and adults, although it is more common in adults. Women are twice as likely as men to be affected. CU can occur at any time but typically begins in the third to fifth decades of life (Confino-Cohen et al. 2012).

The diagnosis of CU is made clinically based on history and exam (see Table 1). Initial extensive laboratory work-up for CU, unless there are specific clues in the history, is not recommended as studies have demonstrated that empiric blood testing does not impact the management of disease in most cases (Tarbox et al. 2011). However, both the US and international guidelines agree that a routine complete blood count with differential, C-reactive protein and/or erythrocyte sedimentation rate should be obtained at diagnosis. A thyroid-stimulating hormone may also be appropriate in many cases (Jacobson et al. 1980; Jirapongsananuruk et al. 2010). As many as 80–90% of adults and children with CU have no specifically identified trigger and are thus diagnosed with chronic idiopathic urticaria (CIU). Skin biopsy is not routinely recommended for CU, but is indicated to exclude potentially concerning disease processes in the presence of other signs/symptoms, such as urticarial vasculitis. CU is typically a self-limited disease process. Spontaneous remission occurs in 30–50% of patients within 1 year, with an average disease duration of 2–5 years, and only 20% of patients having persistent symptoms beyond 5 years (Kulthanan et al. 2007; Harris et al. 1983). However, patients with a physical/inducible component tend to have a more protracted course (Kozel et al. 2001).

8.5 Antibody-Associated or Autoimmune Urticaria

Autoantibody-associated urticaria involves the presence of autoantibodies such as thyroid autoantibodies or IgE receptor autoantibodies with

Table 1 Guidelines for diagnostic work-up of patients with chronic urticaria (Najib and Sheikh 2009)

History and physical examination
Onset (e.g., timing of symptoms with any change in medication or other exposures)
Frequency, duration, severity, and localization of wheals and itching
Dependence of symptoms on the time of day, day of the week, season, menstrual cycle, or other pattern
Known precipitating factors of urticaria (e.g., physical stimuli, exertion, stress, food, or medications)
Relation of urticaria to occupation and leisure activities
Associated angioedema or systemic manifestations (e.g., headache, joint pain, or gastrointestinal symptoms)
Known allergies, intolerances, infections, systemic illnesses, or other possible causes
Family history of urticaria and atopy
Degree of impairment of quality of life
Response to prior treatment
Physical examination
Laboratory evaluation
Routine evaluation: Testing should be selective. There is an honest difference of opinion concerning the appropriate tests that should routinely be performed for patients with CU in the absence of etiologic considerations raised by a detailed history and careful physical examination.
A majority of members of the Practice Parameters Task Force expressed a consensus for the following routine tests in managing a patient with CU without atypical features
CBC with differential
Erythrocyte sedimentation rate, C-reactive protein level, or both
Liver enzymes
TSH
The utility of performing the above tests routinely for patients with CU has not been established.
Additional evaluation might he warranted based on patients' circumstances and might include but not be limited to the diagnostic tests listed below. A thorough history and meticulous physical examination are essential for determining whether these additional tests are appropriate:
Skin biopsy
Physical challenge tests
Complement system (e.g., C3, C4, and CH_{50})
Stool analysis for ova and parasites
Urinalysis
Hepatitis B and C serologies
Chest radiography, other imaging studies, or both
Antinuclear antibody
Rheumatoid factor, anticitrullinated protein
Cryoglobulin levels
Serologic and/or skin testing for immediate hypersensitivity
Thyroid autoantibodies
Serum protein electrophoresis

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

concomitant urticaria and is considered a subset of chronic idiopathic urticaria. A large study of nearly 13,000 patients with CU compared to over 10,000 control patients indicated increased prevalence of numerous autoimmune disorders, including thyroid disorders, celiac disease, Sjögren syndrome, systemic lupus erythematosus, dermatomyositis, polymyositis, rheumatoid arthritis, and type 1 diabetes mellitus in CU patients. In particular, in patients with CU, hypothyroidism was diagnosed in 9.8% of subjects (compared to 0.6% of controls) and hyperthyroidism in 2.6% of subjects (compared to 0.5%

of controls) (Confino-Cohen et al. 2012). A study in Korea indicated that individuals with Hashimoto's thyroiditis and Graves' disease had higher rates of CU compared to control subjects (hazard ratio 1.5, 95% confidence interval 1.3–1.7) (Kim et al. 2017).

Thyroid autoantibodies, including thyroid peroxidase antibodies and antimicrosomal antibodies, as well as antinuclear antibodies, are more prevalent in patients with CU compared to the general population (Leznoff et al. 1983). However, the presence of autoantibodies does not necessarily correlate with autoimmune disease. For example, detection of serum thyroid autoantibodies does not necessarily correlate with thyroid dysfunction, and the majority of patients with CU and detectable thyroid autoantibodies have normal thyroid function. Furthermore, treatment with thyroid supplement in these patients has not been demonstrated to control urticaria. Thus, serology to diagnose underlying autoimmune disease in initial evaluation of CU is not warranted in the absence of additional attributes suggestive of concomitant autoimmune disease. The role of autoantibodies in CU is unclear, as it may simply reflect an underlying tendency toward the production of autoantibodies. Interestingly, patients with detectable thyroid autoantibodies who are euthyroid are often poorer responders to standard therapy for CU. The role of IgE antibodies to high-affinity IgE receptors (FcER1 alpha subunit) on mast cells and basophils is also unclear. Autologous serum skin testing and the serologic chronic urticaria index (CUI) assay are not predictive of response to therapy, and therefore, their clinical relevance is still poorly elucidated. Of note, a recent study suggests that patients with FcER1 alpha subunit antibodies refractory to high-dose H1-antihistamines may be slower to respond to omalizumab (Leznoff et al. 1983; Kaplan and Greaves 2009; Kikuchi et al. 2003; Najib et al. 2009; Greiwe and Bernstein 2017).

8.6 Physical or Inducible Urticarias

Physical urticaria, now referred to as inducible urticaria, is a subgroup of chronic urticaria characterized by hives that are reproducibly triggered by physical stimuli, such as scratching of the skin (dermatographism), exposure to cold, physical pressure, exercise, sunlight, heat, and rarely water or vibration (see Table 2). These same physical triggers can also provoke angioedema (Lang et al. 2013; Sanchez-Borges et al. 2012). The term inducible has replaced physical as there are cholinergic and less commonly adrenergic urticaria conditions that are induced by stimuli which provoke the autonomic nervous system such as stress and emotions.

Dermatographism is urticaria that occurs in response to stroking the skin with a firm object, such as a tongue blade or an instrument with a firm edge. Simple dermatographism is present in about 2–5% of the population, while only a minority of people have symptoms to a degree that prompts medical attention (Orfan and Kolski 1993; Kirby et al. 1971). Initially, a white line develops on the skin as a consequence of reflex vasoconstriction. This is followed by development of a linear raised swelling at the challenge site. The response typically occurs within 1–3 min and resolves in about 30 min (Orfan and Kolski 1993; Bernstein et al. 2014; Sanchez-Borges et al. 2012).

Cold urticaria involves hives elicited by cold fluids, air, wind, or contact with cold objects. Provocative cold testing, such as an ice cube challenge, can confirm diagnosis of cold urticaria. A common method is to place an ice cube (0 °C to 4 °C) contained in a plastic bag on the forearm for 5 min, followed by observing the challenge site as skin rewarms to room temperature. Development of a wheal or flare response during skin rewarming is a positive test (Wanderer et al. 1986). If, after 5 min, there is no observed reaction, the test may be repeated incrementally up to 10 min. The optimal duration of challenge testing to exclude cold urticaria has not been determined (Wanderer and Hoffman 2004). Notably, a cold stimulus should not be reapplied at a site previously challenged, as this could result in a "false-negative" result due to local desensitization of skin. Variants of acquired cold urticaria have been described in which provocative cold testing is negative. The variants include systemic atypical acquired cold urticaria, cold-dependent dermatographism, cold-induced cholinergic

Table 2 Characteristics of physical or inducible urticarias, including clinical features and diagnostic tests (Lang et al. 2013)

Type	Clinical features	Familial	Angioedema	Diagnostic test	Transfer factor[a]
Aquagenic	More common in women than in men	Yes	No	Application of room-temperature wet compress to upper body for 30 min at 35 °C	No
Cholinergic	Itchy, small 3- to 5-mm monomorphic pale center with surrounding erythema	Yes	Yes	Methacholine intradermal injection, exercise, or hot water immersion	Yes
Cold (primary vs secondary)	Itchy, pale lesions (5% with cyrogiobulins)	Yes	Yes	5- to 10-min ice-cube test	Yes
Delayed pressure	Large painful or itchy lesions	No	Yes	Dermographometer: application of weight or force to a skin area, e.g., 15-lb weight for 15 min	No
Dermatographism	Linear lesions	Yes	No	Light stroking of skin	Yes
Exercise-induced urticaria and anaphylaxis	Hives distinguishable from cholinergic lesions	Yes	Yes	Treadmill exercise challenge; can be performed without or after ingestion of inciting food or other agent	No
Solar	Itchy pale or red swelling	Yes	Yes	Irradiation by solar simulator	Yes
Vibratory	Erythema and edema sharply demarcated from normal skin	Yes	Yes	Vortex mixer for 1–5 min	No

[a]Transfer factor refers to the ability to passively transfer a physical urticaria by intracutaneous injection of serum from a patient with a specific physical urticaria to a naive patient

urticaria, acquired delayed cold urticaria, and localized cold reflex urticaria (Wanderer and Hoffman 2004).

Delayed pressure urticaria and angioedema (DPUA) involves the development of swelling in response to exposure to a pressure stimulus about 30 min to 12 h (peak of 4–6.5 h) after exposure to the stimulus (Ryan et al. 1968; Czarnetzki et al. 1984; Sussman et al. 1982; Dover et al. 1988; Warin 1989). Biopsy of angioedema lesions brought about by a pressure stimulus exhibits an intense inflammatory infiltrate characterized histologically by an infiltrate rich in both eosinophils and neutrophils in the deeper dermis and subcutaneous tissue (Winkelmann et al. 1986; Mekori et al. 1988). Diagnosis of DPUA can be confirmed by application of a pressure stimulus, such as a weight or force, to a specific area of skin, with subsequent development of angioedema at the challenge site after 4–6 h. Various published protocols indicate different pressure stimuli to be used and the challenge duration. Positive and negative values for this challenge procedure have not been determined (Estes and Yung 1981). One example of a recommended challenge involves suspension of a 15 pound weight across the patient's shoulder for 10–15 min (Ryan et al. 1968; Sussman et al. 1982). A painful reaction at the challenge site 2–12 h later (peak swelling at 4–6.5 h) is a positive response. Other approaches include the use of calibrated dermographometer or use of weighted metal rods. The challenge procedure should only be performed if concomitant chronic idiopathic urticaria and angioedema (which may also be present in patients with DPUA) are reasonably well controlled (Estes and Yung 1981; Lawlor et al. 1989; Illig and Kunick 1969).

Exercise-induced urticaria and angioedema are forms of physical urticaria that can be confirmed by an exercise challenge in a controlled setting (Sheffer et al. 1983, 1985). As exercise increases one's risk for anaphylaxis, this challenge should only be performed in a setting with appropriately trained personnel, supplies, and equipment to handle management and treatment of such a possibility. In patients with a specific food (i.e., celery) linked to exercise-induced urticaria and angioedema, the relevance of the specific food suspected by history can be assessed with immediate hypersensitivity skin testing if patients aren't dermatographic or on prophylactic H1-antihistamines or by in vitro serum-specific IgE antibody. If food-associated exercise-induced urticaria and angioedema are still suspected, then a challenge procedure in a supervised setting can be performed with and without food consumption. It is important for the clinician to be mindful that urticaria may also occur during an exercise challenge in patients with cholinergic urticaria as exercise increases body temperature. In this case, the diagnosis of cholinergic urticaria can be confirmed by passive heating and/or intracutaneous injection of methacholine. Furthermore, the morphology of lesions can be used to distinguish these two conditions (Sheffer et al. 1983; Kaplan et al. 1981; Casale et al. 1986)

Solar urticaria is provoked by ultraviolet and/or visible light. The diagnosis is confirmed with photo-testing, to stimulate provocation of urticarial lesions with sunlight. Reactions are more often observed with ultraviolet (UVA) or visible wavelengths and less commonly with UVB or infrared wavelengths (Farr 2000). One common provocation test involves using a xenon arc lamp with monochromator to ascertain the minimal urticarial dose at different wavelengths of light. A non-sun-exposed portion of the skin, such as mid and lower back, is ideal for phototesting. Other light sources, such as slide projector light bulb for physical light, fluorescent black light or fluorescent sunlamp for UVA and UVB wavelengths, or infrared lamp for infrared wavelengths can also be used if a xenon lamp with monochromator is unavailable (Roelandts 2003; Alora and Taylor 1998; Uetsu et al. 2000). For each light source or wavelength used, a positive challenge results if a pruritic erythematous wheal develops during or shortly after irradiation and fades within a few minutes after removal of the light stimulus (Roelandts 2003). It is important to distinguish solar urticaria from a polymorphous light eruption. Lesions of polymorphous light eruptions tend to last more than 24 h, in contrast to the short-lived lesions of solar urticaria. Erythropoietic protoporphyria involves lesions that are painful, rather than pruritic, and typically are associated with a positive family history and elevated protoporphyrin levels (Murphy 2003; Fesq et al. 2003).

Cholinergic urticaria is a phenomenon in which an increase in body temperature, either passively or actively, results in sweat release and subsequent provocation of urticaria. The diagnosis can be confirmed by intracutaneous injection of 0.01 mg of methacholine in 0.1 mL of saline with subsequent formation of at least one hive. Unfortunately, this technique has poor sensitivity since as little as 33% of patients with cholinergic urticaria will have a positive methacholine test response and responses that are positive are not always consistently reproducible. Therefore, this test has a poor negative predictive value, and although this test may confirm a diagnosis if positive, it cannot definitively rule out diagnosis if negative (Commens and Greaves 1978). Challenges that increase body temperature, such as hot water immersion or exercise, may have higher sensitivity. For example, partial immersion of a patient in a 42 °C bath, leading to a 0.7 °C body temperature increase, resulting in hives may have a higher sensitivity (Orfan and Kolski 1993). Finally, some patients with cholinergic urticaria may exhibit a wheal and flare response to autologous diluted sweat, suggesting that the sweat of these patients contain factors that lead to histamine release (Fukunaga et al. 2005). It has been reported in such patients that rapid desensitization to autologous sweat has been shown to be as efficacious as therapeutic intervention. However, sweat may be a different entity and not reflective of cholinergic hives (Kozaru et al. 2011).

Vibratory angioedema involves the development of angioedema after exposure to an intense

vibratory stimulus. The diagnosis can be confirmed by an exaggerated reaction to the stimulation of the skin with a vortex mixer. There are currently no standardized recommendations regarding the optimal vibratory stimulus to use, duration of exposure to vibration, or grading of a positive reaction. One generally accepted challenge procedure entails supporting a patient's forearm under the wrist and elbow, so the skin of the forearm, hand, or finger rests in the rubber cup of a vortex mixer. The mixer is vibrated at constant speed for 1–5 min. Subsequent development of erythema and edema that is sharply demarcated from normal skin within 4 min of simulation and persistent for 1 h defines a positive response. If desired, the response can be quantified by measuring the change in the forearm circumference or finger volume (Patterson et al. 1972; Metzger et al. 1976). Delayed onset of erythema and pruritus after vibratory provocation has been reported with peak symptoms occurring 4–6 h after the vibratory stimulus (Keahey et al. 1987).

Aquagenic urticaria is a water-induced etiology with diagnosis confirmed by hives following direct water exposure. One way to confirm the diagnosis is application of a water compress at 35 °C to the upper body skin for 30 min (Baptist and Baldwin 2005). The appearance of punctate 1–3 mm hives at site of application is considered a positive response. This diagnosis should be distinguished from other disorders including aquagenic pruritus, in which water exposure provokes itching but without wheal formation (Greaves et al. 1981); cold urticaria, which is induced by cold rather than water; and cholinergic urticaria, in which punctate lesions manifest in response to heat, rather than water. Notably, cases of concurrent aquagenic urticaria with cold or cholinergic urticaria have been reported (Davis et al. 1981; Mathelier-Fusade et al. 1997).

8.7 Treatment of Acute and Chronic Urticaria

The treatment of acute and chronic urticaria begins with the use of H1 non-sedating antihistamines which can be dosed 1–4 times the Food and Drug Administration (FDA)-approved recommended dose. Treatment begins at a step appropriate for the patient's level of severity and previous treatment history. At each level of the stepwise algorithm, medication(s) should be assessed for patient adherence, tolerance, and efficacy. Once consistent control of urticaria/angioedema is achieved (usually 3–6 months after complete control of hives), a "step-down" approach to treatment can begin (Bernstein et al. 2014; Fine and Bernstein 2016). The US and international guideline treatment algorithms are illustrated and compared regarding similarities and differences in Fig. 2. For the US guidelines, Step 1 involves starting monotherapy with a second-generation non-sedating H1-antihistamine, such as cetirizine, in addition to strict avoidance of suspected or known triggers (such as NSAIDs) and any relevant physical factors if a form of inducible urticaria/angioedema syndrome is present. Step 2 comprises one or more of the following: increasing the dose of the second-generation antihistamine started in Step 1 to 2–4 times the original dose (maximum dose 4× the approved treatment dose), adding another second-generation antihistamine, adding an H2-receptor antagonist medication, adding a leukotriene receptor antagonist, and/or adding a first-generation antihistamine to be taken at bedtime. Recent international guidelines object to using a combination of second-generation antihistamines or a first-generation antihistamine due to the lack of scientific evidence. Concerns about first-generation antihistamines are related to their sedating effects which can affect cognition and motor coordination. Step 3 therapy includes dose advancement to a more potent combination antihistamine (such as doxepin or hydroxyzine) as tolerated. Again, this step is not recommended by the international guidelines due to sedation affecting cognition and mental performance. Finally, Step 4 therapy in the US guidelines, which is Step 3 in the international guidelines, recommends adding an alternative agent, such as cyclosporine, omalizumab, or other anti-inflammatory therapies such as hydroxychloroquine, sulfasalazine, dapsone, or

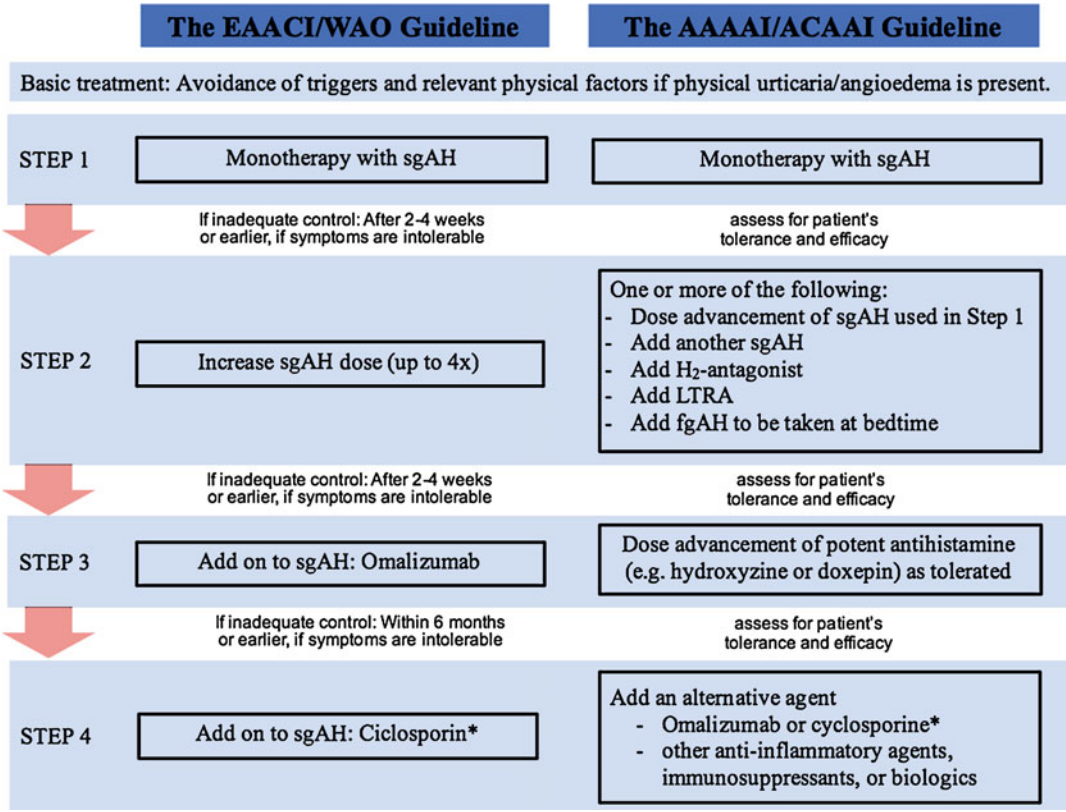

Fig. 2 Comparison of the international and US urticaria guideline treatment algorithms (Zuberbier and Bernstein 2018). *EAACI*, European Academy of Allergy and Clinical Immunology; *fgAH*, first-generation antihistamine; *LTRA*, leukotriene receptor antagonist; *sgAH*, second-generation antihistamine; *WAO*, World Allergy Organization. *Different spellings as used in 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. Used with permission from Zuberbier and Bernstein "*A Comparison of the United States and International Perspective on Chronic Urticaria Guidelines*", *Journal of Allergy and Clinical Immunology in Practice*, 2018 May 18

colchicine. The international guidelines only recommend omalizumab as Step 3 therapy due to the strength of medical evidence supporting this treatment for hives. For the international guidelines, Step 4 involves starting cyclosporine. This treatment is recommended after omalizumab due to a less robust strength of evidence and its toxicity. Oral corticosteroids may be used short term (1–3 weeks maximum) for exacerbations of urticaria or angioedema but are not recommended on a frequent or continuous basis due to short-term and long-term side effects (Zuberbier et al. 2014). A number of therapies recommended by the US guidelines such as montelukast and H2-antihistamines for Step 1 therapy, sedating combination and/or first-generation antihistamines for Step 3 therapy, or anti-inflammatory agents for Step 4 therapy are not recommended by the international guidelines; rather they are relegated to an "alternative treatment" box because of low level of scientific evidence supporting their use (Table 3) (Zuberbier and Bernstein 2018). However, clinicians can use these agents in the proper context for the treatment of their patients unresponsive or incompletely responsive to antihistamines.

Table 3 Alternative treatment options, suggested by the international guideline, that can be considered if treatment according to the recommended algorithm fails or is not possible

Intervention	Substance (class)	Indication
Widely used		
Antidepressant	Doxepin[a]	CSU
Diet	Pseudoallergen-free diet[b]	CSU
H_2-antihistamine	Ranitidine	CSU
Immunosuppressive	Methotrexate Mycophenolate mofetil	CSU ± DPU[c] Antibody associated/autoimmune CSU[d]
Leukotriene receptor antagonist	Montelukast	CSU, DPU
Sulfones	Dapsone Sulfasalazine	CSU ± DPU CSU ± DPU
Infrequently used		
Anabolic steroid	Danazol	Cholinergic urticaria
Anticoagulant	Warfarin	CSU
Antifibrinolytic	Tranexamic acid	CSU with angioedema
Immunomodulator	Intravenous immunoglobulin Plasmapheresis	Antibody associated/autoimmune CSU[d] Antibody associated/autoimmune CSU[d]
Miscellaneous	Autologous blood/serum Hydroxychloroquine[e]	CSU CSU
Phototherapy	Narrow band UVB	Symptomatic dermographism
Psychotherapy	Holistic medicine	CSU
Rarely used		
Anticoagulant	Heparin	CSU
Immunosuppressive	Cyclophosphamide Rituximab	Antibody associated/autoimmune CSU[d] Antibody associated/autoimmune CSU[d]
Miscellaneous	Anakinra Anti-TNF-alpha Camostat mesilate[f] Colchicine Miltefosine Mirtazepine PUVA	DPU CSU ± DPU CSU CSU CSU CSU CSU
Very rarely used		
Immunosuppressive	Tacrolimus	CSU
Miscellaneous	Vitamin D Interferon alpha	CSU CSU

Annotations by authors of the original figure (Zuberbier and Bernstein 2018)

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DPU, delayed pressure urticaria; *PUVA*, psoralen and ultraviolet A; *UVB*, ultraviolet B

[a]Has also H_1- and H_2-antihistaminergic properties

[b]Includes a low histamine diet as the pseudoallergen-free diet is also low in histamine; not widely accepted in the United States

[c]Treatment can be considered especially if chronic spontaneous urticaria and DPU are coexistent in a patient

[d]The international guideline states "autoimmune chronic spontaneous urticaria" only, whereas the US guideline differentiates autoimmune from the presence of antibodies (e.g., FcεR1alpha) that are associated but not cause and effect

[e]More widely used in the United States

[f]Not available in the United States

8.8 Conclusions

Acute and chronic urticaria can be challenging conditions to evaluate and treat. However, if guidelines are followed in an algorithmic manner, the majority of these cases can be treated very successfully which should result in improvement in patient quality of life, decreased morbidity, and reduced health care costs. The clinician should be knowledgeable about the US urticaria guidelines as well as the recent international guidelines and how they agree and differ.

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