



Chronic Urticaria in Children: an Update on Diagnosis and Treatment

Evelyn A. Wang¹ · Sanny K. Chan^{1,2}

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Abstract

Purpose of Review Both adults and children are frequently affected by symptoms of itchy urticarial lesions that cause considerable distress and impact nearly all their daily activities. A comprehensive history is critical to identify the etiology in patients who have chronic spontaneous urticaria (CSU) (those with symptoms for > 6 weeks) and is more important than extensive laboratory serum tests. Unfortunately, most of the current treatment guidelines have been based on data from adult studies since there is rare data on children. These treatment algorithms have been subsequently used to extrapolate treatments for children.

Recent Findings Current treatment regimens do not achieve complete success in all patients, neither adults nor children. As the pathophysiology of chronic urticaria slowly becomes defined, novel therapies are being tested which target these individual molecular pathways to treat those that continue to experience symptoms.

Summary Future studies are required to establish the natural history, risks/benefits and efficacy of current medications, and biologics used to treat CSU in children.

Keywords Hives · Urticaria · Physical urticaria · Inducible urticaria · Chronic spontaneous urticaria · Angioedema

Introduction

Itchy welts or hives are very common presenting concerns to allergists. The worldwide lifetime prevalence of urticarial lesions that occurs at one time or another is estimated to be above 20% [1]. This affliction can result from many factors and often occurs without warning. It causes considerable concern in patients and significantly impacts their daily activities. It is critically important to establish the correct diagnosis and differentiate between hereditary angioedema, vasculitis, and other underlying conditions so that appropriate therapies can be started. Although practice guidelines exist, these have focused mainly on adults [2, 3•]. There has yet to be a consensus on the treatment and management of urticaria in children.

Clinical Features

Urticaria is characterized by recurrent migrating often pruritic non-bruising skin lesions of wheals (hives), angioedema, or both. Wheals are characterized by central swelling surrounded by blanching erythema, pruritus, and a fleeting nature. The skin returns to its normal appearance within 24 h. Chronic urticaria is urticaria that is present intermittently or continuously in different locations for at least 6 weeks. In this case, a referral to a specialist would be recommended for evaluation and treatment. Chronic urticaria is divided into inducible/physical urticarial and chronic spontaneous urticaria (CSU) or idiopathic urticaria. Angioedema, in contrast, is characterized by sudden swelling (skin colored or erythematous) of the lower dermis and subcutis or mucous membranes [3•]. It can be painful, but is not classically pruritic. The resolution of angioedema is slower than that of hives as it can take up to 72 h and is thought to resolve as the causative bradykinins are metabolized and broken down. Distinguishing urticaria from angioedema is critical in establishing a correct diagnosis so treatment can be started effectively.

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✉ Sanny K. Chan
chans@njhealth.org

¹ Dept. of Pediatrics, Div. of Allergy and Immunology, National Jewish Health, Denver, CO 80206, USA

² Dept. of Biomedical Research, National Jewish Health, Denver, CO 80206, USA

Epidemiology

Chronic urticaria has a significant impact on quality of life. The pain, pruritus, and swelling often lead to lack of sleep and

adversely impact daily life. Chronic urticaria is estimated to be consistently present in 0.5–5% of the general population [2]. Women are affected more than men, almost twice as much. The average duration of CSU is 2–5 years; however, 35–50% of adults have spontaneous remission within the first year [4, 5]. Remission rates in children may be somewhat better, but data in children is scarce [6].

Pathophysiology

Urticaria is thought to be primarily a pathogenic event originating from cutaneous mast cells driving the disease process. Degranulation of mast cells leads to a release of histamine, proteases, and cytokines and generates platelet-activating factors and arachidonic acid metabolites like prostaglandin D₂ and leukotrienes C₄, D₄, and E₄ [7•]. These mediators led to increased vascular permeability and vasodilation that causes the redness and swelling as well as the itching. Specifically, during edema formation of the wheal, mast cell degranulation causes a perivascular mixed infiltrate composed of predominantly CD4⁺ lymphocytes, monocytes, neutrophils, eosinophils, and basophils similar to an allergen-mediated late-phase reaction. The cytokine profile is characterized by increases in interleukin (IL)-4, IL-5, and interferon-gamma, which is suggestive of a mixed type 1 T helper (Th1) and type 2 T helper (Th2) response [8, 9].

Although the exact mechanism of mast cell activation is still under debate, there are two subsets of mast cells which are activated through IgE dependent stimulation in urticarial reactions: MC_T (tryptase-positive, chymase-negative; located predominately in lung alveoli and small intestinal mucosa) and MC_{TC} (tryptase-positive, chymase-positive; located in the skin, small intestine submucosa, and in the tonsils). IgE binds to a high-affinity IgE receptor (Fc epsilon RI, FcεRI) which cross-links and leads to intracellular signaling cascades that result in mast cell activation and mediator release [7•]. Additionally, the G protein coupled receptor Mas-related gene X2 (MrgX2) on human MC_{TC} has been shown to bind basic proteins, including vasoactive intestinal polypeptide (VIP), and is elevated in patients with CSU suggesting another possible activation pathway [10].

There is increasing evidence that basophils are also involved in urticaria. They can synthesize IL-4, IL-13, IL-31, and other cytokines in response to activation of their surface IgE receptors. Even though the exact cause remains unknown, basopenia is noted in patients with active CSU perhaps because basophils are being actively recruited from the blood to become activated in the skin [11]. Also, basopenia worsens with increasing urticarial activity scores, and basopenia resolves with disease resolution [12].

The significance of eosinophils in chronic urticaria is also unclear at this moment. Compared with healthy controls, eosinophils are significantly increased in skin biopsy specimens

from both lesional and nonlesional sites [8]. Of note, mast cells, basophils, and eosinophils have no known role in the etiology of hereditary angioedema (which does not usually present with urticaria), though activated endothelial cells may play a role in both diseases.

Inducible Urticaria

Inducible urticaria is a specific type of chronic urticaria. It is readily diagnosed based on a clear history. Classic confirmatory tests have been defined to illicit lesions from cold, heat, cholinergic, dermatographism, solar, vibratory, and aquagenic-induced urticaria (Table 1). These lesions are usually transitory, lasting only up to a couple of hours and do not have cellular infiltration. Interestingly, delayed pressure urticarial lesions are the exception which can last nearly 24 h and has cellular infiltrates.

Diagnostic Procedures

A detailed history includes questions involving time of onset, shape, size, frequency, associated angioedema, associated symptoms, induction by physical agents, correlation with exercise, foods, drugs (most commonly non-steroidal anti-inflammatory), infections, stress, travel, hobbies, and occupation is critical for urticaria. A detailed history will identify the need for skin testing if a specific trigger such as food or drug is suspected. Dermatographism should be evaluated in each case.

General screening labs are not recommended for acute urticaria and angioedema that resolves without treatment. For CSU, a differential blood count, erythrocyte sedimentation rate (ESR), and/or C-reactive protein (CRP) are recommended (Table 2) based on data from a systematic review of 29 studies with over 6400 patients [26••]. Often, liver enzymes, thyroid labs, and tryptase levels are obtained.

Routine screenings for malignancies, autoimmune, endocrine, infectious, and thyroid abnormalities for the diagnosis of underlying causes of urticaria is no longer advised unless indicated by history, but this still remains controversial [3••].

Autologous serum skin and basophil activation tests (an assay for autoantibodies against the high-affinity IgE receptor on cutaneous mast cells) are not recommended as they are non-specific and the data remains conflicting. Recurrent angioedema without hives should be evaluated for hereditary angioedema, while patients with painful wheals and bruising without angioedema should be evaluated for urticarial vasculitis. Autoimmune disorders should be investigated if urticarial lesions occur with fevers, suggesting an underlying fever syndrome (e.g., familial Mediterranean fever, Hyper-IgD syndrome, tumor necrosis receptor-associated periodic fever

Table 1 Characteristics of inducible urticaria types with associated diagnostic criteria

	Features/clinical signs	Diagnosis	Pathophysiology
Dermatographic urticaria	Skin wheals occurring at sites of trauma usually from the friction with clothing or scratching [13]	Moderate stroking of the skin with a blunt smooth object and observation for wheals (usually 10 min later) [3]	Histamine degranulation due to a mechano-immunologic trigger [14]
Delayed pressure urticaria/-angioedema	Wheals and/or angioedema develops in 4–6 h at areas of pressure such as tight clothing, backpacks, walking or sitting down [15]	Suspension of 7 kg weight (3 cm width) over shoulder and observation of wheals (usually 6 h later) to approximate a dermatographometer of 100 g/mm ² for 70 s [16]	Proinflammatory cytokines may play a role in mast cell activation [16]
Cholinergic urticaria	Wheals and severe itch in conditions associated with increased core body temperature (exercise and hot showers) [17]	Passive (warm bath in 42 °C to increase body temperature ≥ 1 °C) or active warming (exercise to the point of sweating then continued for 15 min) [18] or alternatively, an intradermal injection of 0.01 mg of methacholine in 0.1 mL saline that induces a localized hive is diagnostic but only about 30% demonstrate positive tests [19]	Possible impaired muscarinic cholinergic receptors [20]
Heat urticaria	Wheals with direct heat contact	Wheals develop 10 min after contact with a heat source for 5 min [21]	Possible heat induced mast cell membrane instability resulting in release of proinflammatory mediators
Solar urticaria	Direct exposure to the sun (wavelengths vary)	Normally covered skin is exposed to UVA (6 J/cm ²), UVB (60 mJ/cm ²), and visible light (projector)	Possible precursor molecules that are photoactivated to become photoallergens [16]
Cold urticaria	Wheals and/or angioedema after exposure to cold object, air or liquid. May evolve to systemic symptoms and anaphylaxis with extensive cold contact like swimming.	Wheals develop after contact with ice cube for 5 min (in a thin plastic bag to distinguish between aquagenic) [22]	Autoimmune. IgE autoantibodies interact with a cold dependent skin antigen [23]
Aquagenic urticaria	Wheals induced by water of different temperature and salinity may cause different reactions.	Apply water drenched compress to upper body at body temperature for 20 min [24]	Unknown
Vibratory angioedema	Presence of skin swellings and itching after exposure to vibration	Vortex vibrator for 10 min (1000 rpm) [25]	Unknown

syndrome (TRAPS), Muckle-Well syndrome, NOMID, Schnitzler syndrome, or cryopyrin-related diseases [3••]).

Treatment

The goal of therapy is to completely eliminate symptoms of wheals and angioedema. Firstly, if any triggering factors are suspected, they should be identified, omitted, and avoided (Table 2). If drugs are suspected (frequently NSAIDs), they should be eliminated and/or substituted by another class. Avoidance of physical triggers of inducible urticaria is encouraged, but hard to achieve. Chronic spontaneous urticaria has been noted to be associated with inflammatory or infectious diseases, such as *Helicobacter pylori* and bacterial infections of the nasopharynx. If this is the case, then appropriate treatment of the infection is indicated [3••]. Similarly, if a patient's history triggered additional screening labs, those underlying conditions should be treated.

In 2014, the Joint Task Force on Practice Parameters (JTFPP) in the USA released treatment guidelines that used a stepwise management plan [2]. While these recommendations used data that included children, they were predominately focused on adult-based studies. Step one is to start with monotherapy of a second generation H1 antihistamine as well as avoidance of triggers. If symptoms persist, the second step is to either increase the second generation H1 antihistamine by fourfold, or add an alternative second generation H1 antihistamine, or add an H2 antihistamine, or add a leukotriene receptor antagonist, or add a first-generation antihistamine to be taken at bedtime. Step three is dose advancement of potent antihistamine (e.g., hydroxyzine or doxepin) as tolerated. Step four is to add alternative agents such as omalizumab, cyclosporine, or other anti-inflammatory agents, immunosuppressants, or biologics [2].

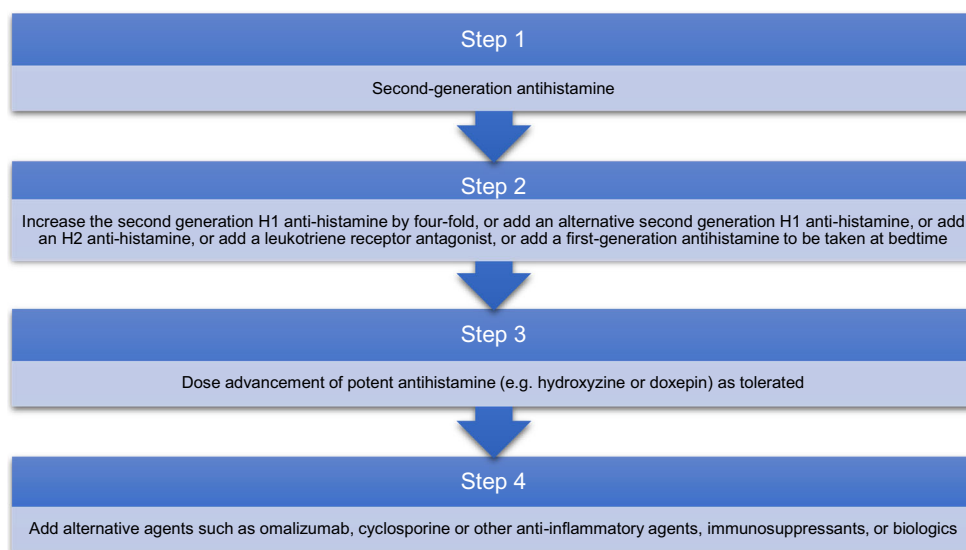
In 2017, the European Academy of Allergology and Clinical Immunology, Global Allergy and Asthma European Network, European Dermatology Forum, and World Allergy Organization guideline was released [3••]. First line is a

Table 2 Chronic urticaria in children and adults may remain refractory to current treatments, but there are new therapies currently undergoing clinical trials

Chronic urticaria	
Criteria > 6 weeks of transient urticarial rash	
Subtypes	Induced
	Spontaneous (CSU)
	Cause unknown
Initial labs for CSU	CBC, ESR and/or CRP
Possible exacerbating factors:	Inconsistent antihistamine use, NSAIDs, alcohol, narcotics, stress (emotional and physical including sleep deprivation and menstruation), and infections
Novel and promising emerging therapies	Ligelizumab, humanized IgG monoclonal antibody that binds to the Cε3 domain of IgE with higher affinity than omalizumab
	GSK2646264 spleen tyrosine kinase (Syk) inhibitors: topical way to inhibit anti-IgE histamine release
	Targeting IL-5 affects the maturation, activation, and recruitment of eosinophils
	Fenebrutinib (GDC-0853), BTK inhibitor, decreases signaling through B–cell receptor
	CRTH2 antagonists (AZD1981): decrease PGD2 expression on eosinophils, basophils, some Th2 cells
	Anti-Siglec-8 (AK002), monoclonal antibodies to siglec-8, targets eosinophils

second-generation antihistamine with up dosing as the second-line treatment (Fig. 1). The guideline suggested omalizumab every 4 weeks for antihistamine refractory patients. Cyclosporine should be reserved for those with omalizumab nonresponsive disease. In general, if no response is obtained after six injections, most practitioners would then consider cyclosporine for that patient [27]. Given its adverse effects include blood pressure and renal function issues, these should be baseline normal and monitored every 4–6 weeks. This guideline also removed leukotriene receptor antagonists, H2 antihistamines, and dapsone due to lack of evidence [3••]. Although followed by most allergists when treating children with CSU, these guidelines have also been based primarily on adult studies. Unfortunately, there still remain extensive gaps in knowledge on the best management strategies in children.

There is limited efficacy data in the different medications used in treatments for children. The 2016 meta-analysis that showed 63.8% of patients with CSU who were not controlled with monotherapy of a second-generation antihistamine responded to a fourfold dose increase of their antihistamine. This meta-analysis did include children that were 12 years old and older, but there was no subset analysis focusing on pediatric patients [28]. Dose escalation in children has therefore been extrapolated without firm evidence. Additionally, different second-generation H2-specific antagonists affect individuals differently. Even at standard doses, cetirizine can lead to somnolence and decreased motivation to complete daily activities in teenagers when compared with loratadine [29]. Many practicing allergists therefore do not routinely use quadruple standard antihistamine doses in children before moving to the next step of treatment.

Fig. 1 Steps of escalating treatment for CSU

Omalizumab, step four of CSU treatment, is a humanized IgG-anti-IgE injectable antibody that binds to free IgE and prevents it from attaching to the FcεRI on mast cells and basophils. It has been shown to be effective in controlling CSU [7•]. Though the definitive mechanism underlying efficacy in CSU treatment remains unknown, it is currently FDA approved for those 12 years and older at 150 mg or 300 mg every 4 weeks. In a recent study, a complete response rate of 72.2% (95% CI, 66.1%–78.3%; $P < .001$; 45 studies, 1158 patients) with an additional average partial response rate of 17.8% (95% CI, 11.7%–23.9%; $P < .001$; 37 studies, 908 patients) that met or exceeded the benefits identified from prior clinical trials [30••]. There are still questions about titration of omalizumab to match symptoms with longer duration and higher frequency of administration as more effective in more severe cases that may benefit the other ~10% of patients, but more large-scale studies are required to define the optimal dosing regimen for those refractory to conventional doses [31•].

The predictive markers of treatment response remain incompletely elucidated even in adults. Recently, in retrospective multicenter study of 470 CSU adult patients (ages 37–61 years) treated with omalizumab, 300 mg every 4 weeks for 24 weeks, the authors showed that the total serum IgE levels and their change could predict the treatment response [32]. Validation studies of biologic markers of response including IgE and basophil levels should be done in parallel in children as well as adults to define the utility of these labs.

Novel and Emerging Therapies

There are many exciting emerging therapies in chronic spontaneous urticaria that are still in clinical trials pending approval. Even at maximal medical therapy, there are still a significant number of individuals who remain refractory to treatment. These novel therapies will help address those who still need symptomatic relief (Table 2). Ligelizumab is a humanized IgG monoclonal antibody that binds to the Cε3 domain of IgE with higher affinity than omalizumab. A recent phase 2b multicenter dose-finding study as an add-on therapeutic in 382 adult patients suggests improved relief compared with omalizumab, since many still had incomplete symptom control [33]. These promising results have led to ongoing phase 3 global multicenter PEARL 1 and PEARL 2 trials that now also include adolescence (12–17 years old) as well as adults.

Novel spleen tyrosine kinase (Syk) inhibitors have been investigated as a topical way to inhibit anti-IgE histamine release. Syk is involved in the signal transduction in B lymphocytes, mast cells, and macrophages. Stopping the activation of these cells will inhibit cellular release of inflammatory mediators that cause

urticarial lesions. The results of the phase 1 trial have not been published [7•].

Since IL-5 is required for the maturation, activation, and recruitment of eosinophils, it has been a target for CSU. Recent data in a small group of patients suggest this may be another therapy option [34].

Other new targets include intracellular signaling molecules like BTK inhibitors as well as inflammatory cell chemotaxis inhibitors such as CCR2 antagonists, eosinophil targets (including monoclonal antibodies to siglec-8), and other anti-IgE molecules with higher affinity for IgE are being explored either as alternative treatments or as add on therapies [7•].

Conclusions

Current guidelines for chronic urticaria treatment are predominately based on adult studies and subsequently extrapolated onto children. The key factor in the diagnostic workup still relies on a detailed history in both children and adults. Extensive screening labs are not recommended unless symptoms do not resolve with treatment or an underlying disease is indicated by history. If symptoms do not improve with antihistamines, biologics like omalizumab may be beneficial. Unfortunately, there are still patients refractory to current treatments. Promising new emerging therapies are still being tested, including ligelizumab, Syk inhibitors, and anti-IL-5 targets. Urticaria affects many children, and there needs to be studies to close the knowledge gap on traditionally used medications as well as these novel therapies to establish evidence-based therapeutic guidelines for both children and adolescent teens.

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