

Pediatric Urticaria

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KEYWORDS

• Urticaria • Pediatric urticaria • Quality of life • Evidence-based approach

KEY POINTS

- Although acute urticaria is common, chronic urticaria is a rare but troubling disorder, for which a stepwise approach is required toward investigations and treatment.
- Unique and varied associations with autoimmune conditions, such as thyroid and celiac disease, are described in a subset of patients, suggesting an underlying autoimmune predisposition.
- Unlike in adults, there is no good evidence that the presence of autoantibodies translates into a more severe and prolonged disease course, but this has been examined in only a few small studies.
- Whatever the cause, families need reassurance that chronic urticaria is a nonallergic condition, with an excellent overall prognosis.
- Symptoms generally respond well to high-dose antihistamine regimens (up to 4 times the standard licensed dose if required), and airway compromise is not a feature, even when angioedema is pronounced.
- More research, including head-to-head drug trials to establish relative efficacy and safety, is needed to gain a deeper understanding of this poorly understood condition in children.

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INTRODUCTION

Urticaria is a skin condition identified by itchy red wheals that are characteristically transient, with well-defined borders and a central pallor.¹ In up to 50% of cases, sudden swelling of the lower dermis and subcutaneous tissues, known as angioedema, may also occur.¹ Whether urticaria presents with wheals, angioedema, or both, several specific clinical patterns are believed to typify this disease in both children and adults.² However, efficient diagnosis and management are hampered by confusion surrounding the numerous classification systems for urticaria, which has resulted in extensive heterogeneity among studies. Furthermore, most data in this field pertain to adults, with a tiny pediatric evidence base that is often of low quality or tends to extrapolate data from studies focusing on older age groups or other clinical conditions, such as allergic rhinitis. Yet, although urticaria is only rarely life-threatening, its impact on quality of life in children should not be overlooked, with 1 study estimating that the negative impact of urticaria is comparable with other chronic diseases of childhood, such as diabetes and epilepsy.³ A systematic search of online databases, including Medline, was performed to inform this review (search strategy available from the authors on request). This review equips the clinician with an evidence-based approach to all aspects of pediatric urticaria, hinging on an illustrative case and including a summary table of studies ([Table 1](#)) pertaining to disease management in children.

PATHOGENESIS

Mast cell and basophil degranulation is the fundamental event causing wheal formation. In the classic type 1 immediate hypersensitivity reaction, allergen-specific IgE is produced after initial contact with a particular allergen. On subsequent contact, the allergen, bound to specific IgE, then cross-links high-affinity IgE receptors (FcεR1) on the surface of mast cells. This event triggers the mast cells to release histamine and vasoactive mediators, causing vasodilatation, increased blood flow, and enhanced vascular permeability. The resulting erythema, fluid extravasation, and swelling of the superficial dermis together give rise to the urticarial wheal. However, it is also possible for other stimuli such as anti-IgE and anti-FcεR1 IgG antibodies to signal via the high-affinity IgE receptors on mast cells⁴; wheals generated in this way are classified as autoimmune urticaria. Nonimmunologic stimuli such as opiates, neuropeptides, and stem cell factor, as well as physical triggers, may also cause wheals by binding to receptors independent of the FcεR1 altogether.⁵

CLASSIFICATION

There are numerous overlapping and evolving classification systems for urticaria in both children and adults. Acute urticaria by definition lasts up to 6 weeks; chronic urticaria more than 6 weeks, although the validity of this arbitrary cutoff has been questioned.⁶ The term idiopathic was previously widely used in the context of chronic urticaria, until studies indicated that up to half of adult sufferers harbored an autoimmune mechanism. This finding led to reclassification of a large subset of chronic idiopathic urticaria as chronic autoimmune urticaria.⁷ More recently, the term chronic spontaneous urticaria has been proposed as a preferable alternative to chronic idiopathic urticaria; this places greater emphasis on clinical course and less on cause, which is often unknown and thus arguably less informative.² Nevertheless, when urticaria is triggered by specific stimuli, the term inducible or physical urticaria has been used, comprising a heterogeneous group that includes dermographic, aquagenic,

Table 1
Articles pertaining to urticaria management in children (based on a systematic online literature search)

Reference Country	Article Type	Age (y)	No. of Participants	Focus of Article	Urticaria Type	Key Findings/ Recommendations
Augustin & Ehrle, ⁷⁷ 2009 Germany	Observational postmarketing surveillance study	2–101	9246	Safety and efficacy of desloratadine in chronic idiopathic urticaria	Chronic idiopathic	Itching, number of wheals, and size of the largest wheal decreased significantly from baseline with desloratadine therapy ($P<.0001$). Improvements in sleep and daily activities were reported by 67% and 71% of patients, respectively ($P<.0001$). In patients who had previously received therapy with cetirizine, loratadine, or fexofenadine alone, patients rated the onset of efficacy of desloratadine as faster in 55.5%, 54.7% and 57.6% of cases, respectively. Incidence of adverse events was low (0.5% of patients), with no serious adverse events

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Reference Country	Article Type	Age (y)	No. of Participants	Focus of Article	Urticaria Type	Key Findings/ Recommendations
Beno et al, ⁷⁸ 2007 United States	Self-administered cross-sectional survey	n/a	1137 physicians (emergency, pediatric emergency, pediatric)	A survey of emergency department management of acute urticaria in children	Acute	First-generation H ₁ antagonists alone were the most common therapy used on initial presentation of acute urticaria, followed by corticosteroids, H ₂ antagonists, and second- generation H ₁ antagonists (used by only 7.8%, despite their recommendation as first-line therapy). Only 14.2% of physicians overall were familiar with guideline recommendations
Bloom et al, ⁶⁷ 2004 United States	2 parallel RCTs	2–5 6–12	111 120	Safety of desloratadine syrup in children with urticaria or allergic rhinitis	Chronic idiopathic	No serious adverse events; desloratadine syrup is safe for use in children
Boyce, ⁷⁹ 2006 United States	Case report	12	1	Successful treatment of cold urticaria/anaphylaxis with omalizumab (monoclonal IgE antibody)	Cold	This patient with cold urticaria experienced progressively severe symptoms, resistant to antihistamines and antileukotriene therapy. She was atopic and had moderate persistent asthma. A trial of anti-IgE resulted in complete resolution of her urticaria

Doshi & Weinberger, ⁷³ 2009 United States	Retrospective case series	9–16	7	Efficacy and safety of cyclosporine in chronic childhood urticaria, unresponsive to conventional therapies	Chronic idiopathic	All had cessation of symptoms. This occurred after 1–4 wk for 6 of the 7 children and after 8 wk for 1. Whereas some experienced relapses, all were eventually off medications and symptom-free. None experienced adverse effects
Frances et al, ⁸⁰ 2004 Argentina	Case report	Not stated	1	Successful treatment of aquagenic urticaria with hydroxyzine	Aquagenic	Treatment with hydroxyzine (25 mg daily) was successful after a month follow-up in preventing wheals and erythema. However, mild pruritus was still present after contact with water
Giuliodori et al, ⁸¹ 2009 Italy	Case report	12	1	Use of cyclosporine in chronic autoimmune urticaria unresponsive to antihistamines, antileukotrienes, and corticosteroids	Chronic autoimmune	Cyclosporine was started at 4 mg/kg/d for 2 mo, decreasing by 0.3 mg/kg/d every 2 mo for 1 y. Renal function was monitored monthly. This treatment induced and maintained remission by the 14th mo of consecutive therapy

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Reference Country	Article Type	Age (y)	No. of Participants	Focus of Article	Urticaria Type	Key Findings/ Recommendations
Kaplan et al, ⁸² 2005 United States	Multicenter randomized placebo-controlled double-blind study	≥ 12	255	Efficacy and safety of once-daily dosing of fexofenadine hydrochloride (180 mg) on chronic idiopathic urticaria	Chronic	Patients administered with fexofenadine (n = 163) experienced significantly greater improvements in mean number of wheals and pruritus severity scores compared with the placebo group (n = 92) ($P < .001$ for both). There were no significant differences in the frequency of treatment- emergent adverse events between the 2 treatment groups
McGee et al, ⁸³ 2012 United States	Case report	13	1	Review of current treatments for aquagenic urticaria	Aquagenic	Application of topical petrolatum as a protective barrier against water, resulted in complete remission. Other treatments include antihistamines, anticholinergics, and ultraviolet therapy

Saini et al, ⁷⁶ 2011 United States	Phase 2 randomized, placebo-controlled, double-blind, dose-ranging study	12–75	90	Efficacy and safety of omalizumab in patients with chronic idiopathic urticaria who remained symptomatic (urticaria activity score over 7 d >12) despite H ₁ -antihistamine therapy	Chronic	Both the 300-mg omalizumab group (219.9 vs 26.9, $P < .001$) and the 600-mg omalizumab group (214.6 vs 26.9, $P = .047$) showed greater improvement vs the placebo group in urticaria activity scores. Omalizumab was well tolerated, and the incidence of adverse events was similar across treatment groups
Salmun et al, ⁸⁴ 2000 United States	Single-dose bioavailability study	2–5	18	Pharmacokinetics, electrocardiographic effects, and tolerability of loratadine syrup in children with urticaria or allergic rhinitis	Chronic idiopathic	5 mg loratadine syrup provided exposure similar to that seen in adults with 10 mg Loratadine was well tolerated in both single and multiple doses
	Multiple-dose tolerability study (placebo-controlled)		121			Electrocardiographic parameters were not altered with loratadine compared with placebo
Sanada et al, ⁷⁴ 2005 Japan	Case series	4–72	25	Effectiveness of montelukast for antihistamine-resistant urticaria	Chronic idiopathic	Urticaria improved in the 1 pediatric patient aged 4 y

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Reference Country	Article Type	Age (y)	No. of Participants	Focus of Article	Urticaria Type	Key Findings/ Recommendations
Simons (EPAAC), ⁶⁴ 2001 Canada	RCT	1–2	817	Effect of long-term treatment with cetirizine in prevention of urticaria in children with eczema	Acute	Acute urticaria occurred in 16.2% of placebo-treated children compared with 5.8% of children treated with cetirizine ($P<.001$). The protective effect of cetirizine disappeared when treatment was stopped. Overall, urticaria episodes were most commonly associated with intercurrent infection or with food ingestion or direct skin contact

Simons (EPAAC), ^{65,66} 2007 Canada	RCT	1–2	510	Effect of long-term treatment with levocetirizine on urticaria in young atopic children		27.5% (70/255) of those taking levocetirizine and 41.6% (106/255) of those taking placebo experienced urticaria ($P<.001$). The mean $\pm$ standard error of the mean number of urticaria episodes was 0.71 ± 0.11 in those receiving levocetirizine and $1.71 \pm$ 0.25 in those receiving placebo ($P<.001$). The mean $\pm$ standard error of the mean duration of urticaria episodes was 4.43 ± 1.57 d in those receiving levocetirizine and $5.36 \pm$ 1.27 d in those receiving placebo ($P<.001$). These results strengthen the evidence base for the use of relatively nonsedating, second-generation H_1 - antihistamines in the pediatric population
Visitsunthorn et al, ⁸⁵ 1995 Thailand	Double-blind crossover study with >5 y follow-up	4–9	6	Comparison of effectiveness of cyproheptadine and ketotifen on clinical symptoms of cold urticaria and ice cube scores	Cold	Efficacy of cyproheptadine and ketotifen was not significantly different ($P>.05$). Both showed good results in the treatment of cold urticaria, with mild side effects. During follow-up, 5 cases showed complete recovery

cold, and cholinergic urticaria. Diseases presenting with urticarial eruptions, such as urticarial vasculitis, and systemic conditions such as autoinflammatory diseases (eg, Schnitzler syndrome) or systemic mastocytosis, are not included in the 2006 European Academy of Allergy and Clinical Immunology (EAACI)/GA²LEN/European Dermatology Forum (EDF)/World Allergy Organization (WAO) classification.¹ However, they should be considered as part of the differential diagnosis on encountering a patient with urticarial symptoms in the clinic.

EPIDEMIOLOGY

Urticaria is common, affecting up to 25% of the population during their lifetime. Most of these episodes are acute, and there is a particular paucity of population-based studies in the pediatric setting. One noninterventional birth cohort study reported that 5.4% of 404 6-year-old children had at least 1 episode of urticaria during the previous year.⁸ In line with this finding, Henz and Zuberbier⁹ gave a range of 2.1% to 6.7% for all forms of childhood urticaria. Regarding specific urticaria subtypes, Kaplan⁷ estimated that 0.1% to 3% of children are diagnosed with chronic urticaria. Another study found that 68% of 66 children with urticaria had presented to the emergency department within the previous year, of whom 18% were described as having chronic urticaria.¹⁰ Although there are fewer data available regarding acute childhood urticaria, 1 notable study¹¹ reported no difference in the epidemiologic patterns of acute urticaria between northern and southern Europe, despite marked differences in climate and geography.

CLINICAL FEATURES, COURSE, AND PROGNOSIS

As mentioned earlier, the cardinal feature of urticaria is the repeated occurrence of wheals, accompanied by erythema and itching. These wheals can be round or irregular, of varying size, and located at any skin site. However, their defining characteristic is that they are migratory and transient (lasting <24 hours), resolving with no residual skin lesion. When angioedema coexists, it also resolves within 24 hours and is less consistently associated with itching than the skin wheals. Compared with atopic dermatitis (AD), the pattern of itching may seem different. Whereas children with AD often damage the skin by scratching with their nails, children with urticaria more frequently rub firmly with the palm, hence seldom damaging the skin.

There has been some debate about the proportion of children experiencing wheals, angioedema, or both. A prospective study of 94 Thai children with chronic urticaria reported that 51% had wheals with concomitant angioedema,¹² whereas Volonakis and colleagues¹³ found that most children (78.4%) had wheals alone, 6.6% had angioedema alone, and only 15% had both. This finding was closer to Liu and colleagues'¹⁴ findings in a large series of 1120 children with an initial episode of acute urticaria, of whom just 8.8% had both. This subset appeared to experience a more severe disease course than those with wheals alone.

The prognosis of childhood urticaria has also been a focus of interest, with most studies focusing on chronic urticaria, because acute urticaria is transient and resolves without sequelae in most cases. In Liu and colleagues' report,¹⁴ only 5.4% of children with acute urticaria continued to experience symptoms after 15 days. The prognosis for chronic urticaria is likewise believed to be favorable, with Sahiner and colleagues¹⁵ reporting complete resolution of symptoms in 50% of children at 5-year follow-up. The suggestion that female gender and age younger than 10 years worsened prognosis was not borne out by multivariate analysis. Du Toit's¹⁶ series of 80 children with chronic urticaria found remission in 36% within 3 years, but was no more successful

at identifying predictors of disease course. Khakoo and colleagues¹⁷ retrospective study of 53 children with physical urticaria may indicate a worse prognosis in this subset of patients compared with those with chronic spontaneous urticaria, with a remission rate of only 38.4% within 5 years. Univariate analysis suggested that a history of other allergies and increased frequency of urticaria episodes were associated with a greater risk of nonremission. Unlike in adults, there does not seem to be a difference between chronic idiopathic and autoimmune urticaria with regard to disease severity, medication requirement, or disease remission in children.^{12,18}

CAUSE

Parents are often concerned that allergies, for instance to foods, are to blame for their child's urticaria. However, identifying a cause can prove elusive, and there are widespread inconsistencies in how possible causes are investigated, confirmed, and reported. This situation likely accounts for the wide range (16%–83%) reported in the literature for successful identification of a cause in children with either acute or chronic urticaria.^{13,15,19–24}

Infections

Studies of children with both acute and chronic urticaria have indicated that infection is a major cause. In Liu and colleagues²⁵ retrospective analysis of 953 children presenting to the emergency department with acute urticaria, infections were the leading cause in infants (56.5%), although prevalence of infections decreased as age increased (51.2% in pre-school-aged children, 42.1% in school-aged children, and 17.1% in adolescents). Another study²⁶ delved deeper into possible sources of infection, reporting that of 44 children presenting with acute urticaria associated with clinical infection or a febrile illness, 40 had respiratory tract symptoms and only 4 had gastrointestinal symptoms. Viral screens were suggestive of viral cause in 79.5% patients. However, 47.7% patients had received antibiotics before developing the urticaria, making it difficult to attribute symptoms to infection alone. Potential causality was perhaps better addressed in Konstaninou and colleagues¹¹ epidemiologic study, showing that seasonal variations in respiratory viral infections coincided with variations in acute urticaria.

Bacterial infections have also been implicated in acute childhood urticaria, with Schuller and Elvey's 1980 study suggesting that β -hemolytic streptococci had a role in 13 of 32 cases.²⁷ *Mycoplasma pneumoniae* has been reported in both case series²⁸ and larger observational studies.²⁶ More recently, Sackesen and colleagues²⁹ recommended that urinalysis and cultures should be performed on children presenting with urticaria. These investigators detected urinary tract infection in 6 children with acute urticaria, of 54 participating children with various forms of urticaria. Five of the 6 children were asymptomatic from their urinary tract infection, and none was taking antibiotics at the time of diagnosis. Treatment of the infection resulted in clearance of urticaria.

The contribution of infection to chronic childhood urticaria is less clear. Sackesen and colleagues²⁹ study reported infection in 6 of 17 (35%) participants suffering from this form of the condition, whereas Kilic and colleagues¹⁸ were unable to identify infection as a cause in any of their 40 children with chronic urticaria. Infectious agents reported to cause chronic childhood urticaria range from viruses (Epstein-Barr) to bacteria (staphylococci, streptococci, *Helicobacter pylori*, *Escherichia coli*) and parasites (*Blastocystis hominis*).³⁰ Yet again, Sackesen and colleagues²⁹ highlighted the potential significance of silent infection, documenting *H pylori* in 3 of 17 children, all without

gastrointestinal symptoms. One child had urticaria remission after *H pylori* eradication. Meanwhile, Hameed and colleagues³¹ reported resolution of urticaria symptoms at 1-year follow-up associated with eradication of *Blastocystis hominis*, and a study in Thai children described urticaria remission in 2 of 5 patients treated for parasitic infections.¹² This report seems to be supported by Du Toit and colleagues¹⁶ finding that 2.5% children with chronic urticaria had stool samples positive for parasites, compared with 0% children with AD ($P = .005$). However, such reports predominantly hail from geographic areas in which parasitic infection remains common.

Drugs

Drug hypersensitivity is a commonly suspected cause of both acute and chronic urticaria in children, with medication use implicated in up to 29.8% and 17% cases, respectively.^{11,22,23,25,29,32} Antibiotics and nonsteroidal antiinflammatory drugs are the usual culprits. However, both these agents are often prescribed during infections, making it difficult to ascertain true causality.^{22,25} In line with this finding, Caubet and colleagues³³ were able to reproduce an urticarial reaction in only 6.8% of 88 children presenting to the emergency department within 72 hours of ingesting β -lactams. These investigators suggested that viral infections for which β -lactams may have been prescribed were more likely to play a role. To complicate matters further, identification of true drug hypersensitivity can prove elusive, with 2 studies of more than 40 children with a history of drug allergy showing that more than 90% could tolerate the drug after appropriate workup.^{34,35}

Food

Acute urticaria is a cardinal clinical feature of IgE-mediated food hypersensitivity. However, food allergy seems to be an uncommon cause of childhood urticaria, with several studies reporting that it accounts for less than 7% of cases.^{11,23,29} The main foods implicated include egg, milk, soy, peanut, and wheat in infants, and fish, seafood, and nuts in older children. A study of 94 Thai children found that 33 had positive skin prick tests, of whom only 39% had a history to suggest clinical food allergy, and only in these cases was elimination of the implicated food beneficial.¹² Meanwhile, Du Toit and colleagues¹⁶ reported that elimination diets did not seem to affect the natural history of disease and described lower rates of food sensitization among children with chronic urticaria than children with AD. A few studies have attempted to use pseudoallergen-free diets in order to elucidate a role for food additives in pediatric urticaria. Ehlers and colleagues³⁶ recruited 16 German children with chronic urticaria to a 3-week low-pseudoallergen diet, reporting that symptoms in 12 remitted and then reappeared when pseudoallergen-rich foods were reintroduced. Double-blind placebo-controlled food challenges then showed that reactions occurred mainly to coloring agents and preservatives. However, the numbers of children used in such studies are too small for pseudoallergen dietary avoidance to be recommended as a routine part of management.

Autoreactivity

Despite a sea change in the classification of adult urticaria, with the realization that much so-called idiopathic urticaria may be autoimmune, only a few studies have investigated the prevalence of an autoimmune pathogenesis in children. Brunetti and colleagues³⁷ reported that 40% of 52 children had autoantibodies to either the α -chain of the high-affinity IgE receptor or to IgE itself, as seen in adults. These investigators also estimated that the correct identification of the autoimmune subtype by testing for autoreactivity (autologous serum skin test [ASST] and basophil histamine release

assay [BHRA]) would potentially reduce the diagnosis of idiopathic urticaria from 52% to 29%. This finding differed from Du Toit and colleagues¹⁶ study, which identified autoantibodies to the IgE receptor in 47% of 78 children but could not find a correlation between ASST and either histamine-releasing factors or IgE receptor autoantibodies. Nevertheless, Jirapongsansanuruk and colleagues¹² used a positive ASST result to diagnose chronic autoimmune urticaria in 38% of 94 patients, commenting that there were no differences in medication requirement or disease remission between children with negative versus positive ASST results. As mentioned earlier, this finding contrasts strongly with evidence in adults that a positive ASST identifies a subset of urticaria sufferers with higher disease activity and more severely impaired quality of life.³⁸

Physical Triggers

Physical triggers are the most commonly documented cause of chronic urticaria in children, underlying up to 53% of cases²⁹ and often occurring concomitantly with other forms of urticaria. The physical urticarias are referred to by the precipitating factor, with the main types including dermatographic, cholinergic, aquagenic, cold, solar, delayed pressure, vibratory, and exercise-induced. Whereas Sackesen and colleagues²⁹ found that cholinergic and solar triggers were most common, Khakoo and colleagues¹⁷ performed the largest study of physician-diagnosed physical urticaria in children and reported the 3 main subtypes as dermatographic (38%), cholinergic (19%), and mixed (17%). These investigators documented concomitant angioedema in 67% cases. As highlighted earlier, they also found evidence that children with physical urticaria had a longer and more severe disease course than children with other forms of urticaria. That symptom severity should not be underestimated was also highlighted in a study of cold urticaria,³⁹ in which a third of 30 children experienced anaphylactic reactions. These investigators recommended that adrenaline autoinjectors be dispensed to all children with this urticaria subtype. Likewise, a poor chance of disease remission was observed in a historical cohort study of 87 patients with solar urticaria, in which most were still affected at 5-year and 10-year follow-up.⁴⁰

ASSOCIATIONS

Childhood urticaria has been linked to a higher incidence of autoimmune disease and more rarely to underlying malignancy, but these seem to be associations as opposed to being directly causal.

Autoimmune Diseases

Several autoimmune conditions have been associated with childhood urticaria, including thyroid disease, celiac disease, juvenile rheumatoid arthritis, systemic lupus erythematosus (SLE), and type 1 diabetes.⁴¹ A family history of such disorders may be identified.^{41–43} Kilic and colleagues¹⁸ reported a 14.8% prevalence of thyroid autoimmunity in children with chronic urticaria, whereas Levy and colleagues⁴² reported a prevalence of 4.3%, and a recent case-control study from Taiwan found antithyroid antibodies in 27% of children with chronic urticaria compared with 0% of controls.⁴⁴ Such figures are significantly higher than age-matched healthy children (0.35%–1.6%),^{45–47} although they are generally low compared with the prevalence of thyroid autoimmunity in adults with chronic urticaria (14%–33%).^{48,49} This finding may perhaps be explained by the fact that autoimmunity develops with age and the evolving immune system. Because most patients with thyroid autoimmunity remain clinically euthyroid, thyroid autoantibodies are likely to represent an underlying autoractive predisposition rather than being pathogenic in themselves.

Celiac disease has also been linked with childhood urticaria, with Caminiti and colleagues⁵⁰ case-control study diagnosing celiac disease in 5% of children with chronic urticaria compared with just 0.67% of healthy controls. Children experienced complete remission of their urticaria after 5 to 10 weeks of a gluten-free diet, an observation also documented elsewhere.^{43,51,52} This finding has been taken as long-awaited evidence of dietary-gastrointestinal-cutaneous interplay, which is likely to be a key driver in the pathogenesis of urticaria. Associations with other autoimmune disorders have not been extensively investigated, although a large Brazilian study found urticaria to be a first manifestation of juvenile SLE in 0.7% of patients,⁵³ and there are also numerous case reports in the literature, including one in which a 12-year old boy developed both autoimmune thyroid disease and insulin-dependent diabetes in addition to his urticaria.⁵⁴

Malignancy

Several case reports have suggested an association between childhood urticaria and underlying malignancy. Breda and colleagues⁵⁵ described a 3-month-old infant presenting with recurrent generalized urticaria, subsequently diagnosed with acute myeloid leukemia. Two weeks of combined chemotherapy led to complete remission of both conditions. In another case, a 12-year-old girl experienced urticaria for 3 months before lip fasciculation was observed and she underwent brain computed tomography. This revealed a grade II astrocytoma, which was treated with radiotherapy, resulting in remission of both urticaria and lip fasciculations.⁵⁶ A 17-year-old girl with chronic urticaria was found to have an occult cholangiocarcinoma, with symptoms resolving after a liver transplant.⁵⁷ However, there is a lack of evidence from larger studies investigating a true association between urticaria and malignancy in the pediatric setting.

INVESTIGATIONS

Whatever the uncertainties in this field, it is widely accepted that the history and physical examination are the most important steps toward establishing a diagnosis, identifying possible triggers, and determining the need for further investigations. Although acute urticaria rarely warrants a battery of tests, the usefulness of laboratory investigations in chronic urticaria has been evaluated in a large systematic review including 6462 patients of all ages.⁵⁸ The investigators commented that a detailed history did seem to be most useful, whereas laboratory tests appeared to be useful only when performed because of the history. Similarly, allergy testing should be conducted only in the light of a detailed history, because results can be difficult to interpret, and there is also a high probability of false-positive results. Thomas and colleagues⁵⁹ comment that additional investigations (other than skin prick or specific IgE) in children with chronic urticaria had such a low positive outcome rate (5.2%) that performing them at all may be of questionable value. If autoreactivity is suspected, the ASST or BHRA are sometimes performed, because a positive result suggests an autoimmune component to the disease process (including autoantibodies). However, the uncertainty surrounding the usefulness of ASST and BHRA in children has been outlined above. In addition, the ASST is time consuming and not well tolerated by children. Neither the ASST nor the BHRA is diagnostic of autoimmune urticaria per se, and although used for research purposes, they are not readily available to the practicing clinician. By contrast, if inducible or physical urticaria is suspected, provocation tests such as stroking the skin with a calibrated dermatographometer, applying an ice cube, or exercising the patient may prove useful and practical for diagnosing dermatographic,

cold, and cholinergic urticaria, respectively. A recommended approach has been summarized by the EAACI¹ and the British Society for Allergy and Clinical Immunology (BSACI),⁶⁰ stating that laboratory investigations are rarely useful when history and physical examination indicate a diagnosis of chronic urticaria. Allergy testing may be useful if an allergen is implicated by the history and physical examination, and other specific tests may be considered only if clinically relevant, including urinalysis, a full blood count, inflammatory markers, liver function tests, celiac disease screen, thyroid function and thyroid antibody testing, physical provocation tests, elimination diets, antinuclear antibodies, skin biopsy, C3/4 complement and C1 esterase inhibitor assays, serum cryoproteins, and an infectious disease screen.

MANAGEMENT

Episodes of acute urticaria are normally transient, uncomplicated, and easily managed by single-dose antihistamines in the primary-care setting. Urticaria that arises because of an acute allergic reaction typically settles spontaneously within hours and responds favorably to antihistamines. Urticaria of an infective nature often waxes and wanes over a few days, with a sluggish response to antihistamines. However, it is important to distinguish acute urticaria from urticaria associated with anaphylaxis, which may present with urticaria as its first manifestation. In this scenario, an adrenaline autoinjector should be used immediately, and hospitalization is required if the patient shows respiratory distress or other signs of anaphylaxis such as hypotension or hypotonia.⁶¹ However, the management of chronic urticaria is less clear-cut, and is now discussed in further detail.

Education and Counseling

It is helpful to explain to patients what urticaria is, as well as reassure them that in most cases, there is no serious underlying disease causing symptoms. Fatalities are not described, because parents are often concerned that the risks pertaining to conditions such as peanut allergy also apply here, particularly if angioedema is an associated feature. However, this is not the case, and adrenaline is not indicated in the management of chronic urticaria. It is equally important to reiterate that urticaria is as yet poorly understood and not merely caused by allergies, thus extensive allergy testing and lifestyle restrictions are rarely warranted in the absence of a strongly suggestive history. The BSACI recommends asking patients with refractory disease to keep a symptom diary, recording each episode of urticaria and possible precipitant factors.⁶⁰ If one is identified, then trigger avoidance is key.

Antihistamines

Symptom control is the mainstay of pharmacologic management of urticaria, and antihistamines continue to be widely used in this setting. However, first-generation antihistamines such as chlorphenamine have been shown to have anticholinergic side effects, cause cognitive impairment, and disrupt sleep patterns in children.⁶² These risks have been underlined in the latest GA²LEN position paper,⁶³ and the EAACI/GA²LEN/EDF/WAO now categorically state that non-sedating second-generation antihistamines should be used as first-line therapy, with escalation to up to 4 times the standard dose in refractory cases. However, this recommendation is based on scant high-quality data in the specific context of pediatric urticaria. Simons and colleagues^{64–66} have conducted randomized controlled trials (RCTs) looking at the use of the histamine 1 (H₁) receptor antagonists (H1RA) cetirizine and levocetirizine to reduce frequency of urticaria episodes in infants with AD, whereas Bloom and

colleagues⁶⁷ were able to include children with urticaria in an RCT on desloratadine. However, other RCTs have focused on children with respiratory symptoms and allergic rhinitis.^{68,69} As Marrouche and Grattan² have commented, it is clear that large-scale head-to-head comparison studies are needed to elucidate the risks and benefits of different second-generation antihistamines in the treatment of childhood urticaria. H₂RAs such as ranitidine or cimetidine are occasionally used to treat urticaria, but there is little evidence that they improve symptom control in the adult setting, let alone in children. This finding may be related to reports that although both H₁ and H₂ receptors are involved in the wheal response, H₁ receptors seem primarily responsible for flare and itch.⁷⁰ Accordingly, the BSACI does not recommend H₂RAs as monotherapy, stating that they can be used as a second-line therapy in combination with H₁RAs, although it is usually more effective to increase the H₁RA dose first.⁶⁰ Meanwhile, the EAACI guideline places H₂RAs on the lowest rung of its drug algorithm for chronic urticaria.⁷¹

Other Therapeutic Options

The recent clinical care pathway published by the Royal College of Pediatrics and Child Health recommends cyclosporine and prednisolone as effective second-line treatments.⁷² Cyclosporine was tolerated at a dose of 3 mg/kg/d in 1 retrospective case series of 7 children with chronic urticaria,⁷³ leading to eventual remission of symptoms in all. However, overall experience with this immunomodulating therapy is limited. Corticosteroids can control urticaria symptoms effectively, but prolonged use may be limited by their well-established side effects. Montelukast is licensed for use in children, but its usefulness in childhood urticaria has not been extensively investigated,⁷⁴ although several guidelines recommend their use in conjunction with H₁ antihistamines.^{60,71} Anti-IgE antibody treatment represents another therapeutic avenue that is already well established in adolescents and adults⁷⁵; a 2011 phase II RCT of omalizumab, including children as young as 12 years old, reported significant improvements in urticaria activity scores with active treatment.⁷⁶ Other systemic treatments, sometimes successfully used in adults, should be considered on an individual basis, including methotrexate and mycophenolate mofetil, intravenous immunoglobulin, and induction of tolerance in some inducible urticaria subtypes. However, there is no published evidence for any of these treatment modalities in children.

Box 1 **Illustrative case**

An 8-year-old girl was referred to our children's urticaria service with a 3-month history of near-daily urticaria and asymmetrical facial swelling, particularly of the lips and eyelids (**Figs. 1–3**). She also reported symptoms of grass pollen-induced rhinoconjunctivitis, but otherwise enjoyed excellent health. Her urticarial lesions were reported to make her itchy and uncomfortable, and her facial swelling was causing her embarrassment. She had recently missed many days of school. Her symptoms had persisted despite a daily dose of cetirizine 10 mg. She had once been administered a dose of intramuscular adrenaline when assessed in the emergency department for facial angioedema, and she now carried an adrenaline autoinjector. Clinical examination confirmed her good health; there were no skin changes to suggest urticarial vasculitis, nor were there signs or symptoms suggesting an autoimmune condition or other underlying systemic disease.

This case highlights a classic presentation of spontaneous chronic urticaria in childhood. The patient's investigations and management were discussed, after we had outlined the background of this poorly understood condition.



Fig. 1. Wheals on patient's torso.

MANAGEMENT OF ILLUSTRATIVE CASE

With the patient's history and physical examination complete ([Box 1](#)), we performed several investigations. First, physical stimuli were tested as triggers or exacerbating factors for her urticaria. Standardized techniques for the application of cold, heat, and pressure (using a calibrated dermatographometer) were used, with negative results. The patient's mother had reported that her own irritable bowel syndrome had benefited from a gluten-free diet, so allergy skin prick testing was undertaken to reassure the family that the patient was not food allergic and that wheat (which she tolerated in her diet) was an unlikely cause of her urticaria. Skin prick testing to aeroallergens showed positivity for grass pollen, in keeping with the history of hay fever. However, the patient's urticarial symptoms reportedly came on during the winter pollen-free season, making this an unlikely trigger. Because the child was systemically well, no other investigations were performed.

Based on the skin prick results, the patient's parents were reassured that dietary modification would not be required and that a stepwise approach to treatment was likely to significantly improve symptom control. Her cetirizine dose was increased to



Fig. 2. Wheals on patient's back.



Fig. 3. Angioedema causing facial wheals and lip swelling.

10 mg twice a day (twice the standard dose at this age). It was also explained that chronic urticaria usually remits spontaneously in a matter of years and is unlikely to cause airway compromise, despite frequent and significant facial swelling. The adrenaline autoinjector was therefore withdrawn from her treatment plan.

At 4-week follow-up, the patient's family reported that despite the increased dose of cetirizine, she had not yet achieved an acceptable level of symptom control and was still missing multiple days of school. The decision was then made to use a combined therapy with 2 H1RAs at double the standard dose. Because further improvement was still only moderate at the next clinic visit, montelukast was added, resulting in marginal relief of the spontaneous swelling, but little impact on her wheals.

Frustratingly, after an additional 6 weeks on her new treatment regimen, the patient's symptoms persisted at a level that was unacceptable to both the patient and her family. The use of either oral prednisolone or cyclosporine was then roundly discussed, and the decision made to proceed with cyclosporine, with close monitoring for renal complications. Adequate control was achieved on a daily dose of 3 mg/kg, and the patient remains on this therapy with a plan for gradual weaning once 4 asymptomatic months are achieved.

SUMMARY

This case study of spontaneous chronic urticaria highlights the multiple issues faced by patients, their families, and treating clinicians. Whereas acute urticaria is common, chronic urticaria is a rare but troubling disorder, for which a stepwise approach is required toward investigations and treatment. Unique and varied associations with autoimmune conditions, such as thyroid and celiac disease, are described in a subset of patients, suggesting an underlying autoimmune predisposition. Unlike in adults, there is no good evidence that the presence of autoantibodies translates into a more severe and prolonged disease course, but this has been examined in only a few small studies. Whatever the cause, families need reassurance that chronic urticaria is a nonallergic condition, with an excellent overall prognosis. Symptoms generally respond well to high-dose antihistamine regimens (up to 4 times the standard licensed dose if required), and airway compromise is not a feature, even when angioedema is pronounced. However, this review highlights the paucity of high-quality data pertaining to the presentation, natural history, investigation, and management of

urticaria in the pediatric setting. More research, including head-to-head drug trials to establish relative efficacy and safety, is needed to gain a deeper understanding of this poorly understood condition in children.

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