

# Recurrent urticaria

Lyn Ventilacion

Susan Leech

## Abstract

Urticaria is characterized by the sudden development of wheals and/or angioedema. It is a common problem. Acute spontaneous urticaria is the most common form of urticaria, affecting up to 1 in 7 British children. About one-third will progress to chronic or recurrent urticaria. This article highlights the value of a good history and reviews the treatment options available for children.

The diagnosis is usually made on clinical grounds, by a thorough history of eliciting factors. Further investigations should be guided by the urticaria subtype and are often unnecessary. Acute spontaneous urticaria is usually secondary to a viral infection  $\pm$  antibiotic use. Viral infections are usually responsible for flare-ups. In older children, chronic spontaneous urticaria may be associated with antibodies to the  $\alpha$  chain of the high-affinity IgE receptor or, less commonly, other autoimmune disease. Dermographism and cold urticaria are the commonest forms of inducible urticaria in childhood.

Symptomatic relief is usually achieved by elimination of triggers and the use of non-sedating antihistamines. Tranexamic acid is useful to control isolated angioedema. Unresponsive cases may improve with the addition of a leukotriene receptor antagonist, anti IgE therapy or systemic immunosuppression (e.g. Ciclosporin A). Short courses of oral steroids are helpful to control acute episodes and severe exacerbations of chronic spontaneous urticaria. Urticaria remits over time. After 3 years, a quarter of children with chronic spontaneous urticaria are disease free and the vast majority are disease free after 7 years.

**Keywords** angioedema; antihistamines; childhood; dermographism; urticaria

## Prevalence

Urticaria is common in childhood. Acute urticaria affects 4.5–15% of British children. The episodes last for less than 6 weeks. It may be spontaneous or occur in response to a viral infection and persist for several days. Chronic urticaria is less common, affecting 0.1–3%. Chronic urticaria is defined as an episode of urticaria and/or angioedema lasting for more than 6 weeks. Children may have episodic urticaria/angioedema lasting for hours or days and recurring over months or years. Of young children presenting to hospital with acute urticaria, 20–30% progress to chronic or recurrent urticaria. There is no gender bias.

Recent studies in children have provided information about the causes, eliciting factors and pathomechanisms. However, the

distinction between acute and recurrent urticaria remains unclear and there are fundamental differences in populations studied (e.g. primary care, hospital based, selected from specialist clinics). In 2013, an international consortium updated the guidelines for the definition, classification, diagnosis and management of urticaria. This review uses this classification and applies it to childhood urticaria.

## Definition

Urticaria is a manifestation of a heterogeneous group of diseases which share a common skin reaction, namely the sudden development of wheals and/or angioedema.

- A wheal consists of:
  - A central swelling of variable size, usually surrounded by reflex erythema
  - Associated itching or burning sensation
  - A fleeting nature; the skin usually returns to its normal appearance within 1–24 hours
- Angioedema is characterized by:
  - A sudden pronounced swelling of the lower dermis and subcutis
  - A swelling which is pale rather than pink and may be painful rather than itchy
  - Frequent involvement below the mucous membranes
  - Resolution that is slower than for wheals and can take up to 72 hours.

## Mechanism

The wheal is a result of histamine acting on H1 receptors on endothelial cells. The neurogenic flare and pruritis arise from the action of histamine on sensory nerves. The wheal demonstrates oedema of the upper and mid dermis, with dilatation of the postcapillary venules and lymphatics of the upper dermis. In angioedema, the changes occur in the lower dermis and subcutis. Skin affected by wheals usually exhibits upregulation of endothelial adhesion molecules and a mixed perivascular inflammatory infiltrate of neutrophils, eosinophils, macrophages and T-cells. Mast cell numbers may be increased and urticaria involves dermal mast cell degranulation and histamine release. These changes are not specific, nor of diagnostic value.

When angioedema occurs in the absence of wheals (non-histaminergic angioedema), the mechanism usually involves overproduction of kinin. In children, C1 esterase inhibitor deficiency of hereditary angioedema should be considered. Other causes include stress, infection and drugs (classically angiotensin converting enzyme inhibitors). The management of this condition is not covered here.

## Diagnosis of urticaria

The diagnosis of urticaria is made on clinical grounds. It is important to obtain a thorough history, including all possible eliciting factors. Questions should be asked regarding:

- Time of onset of disease
- Frequency and duration of wheals
- Shape, size and distribution of wheals
- Associated angioedema
- Associated subjective symptoms of lesion e.g. itch, pain

*Lyn Ventilacion MD MRCPCH is ST8 in the Department of Paediatric Allergy, Kings College Hospital, Denmark Hill, London, UK. Conflicts of interest: none declared.*

*Susan Leech FRCPCH is Clinical Lead for the Paediatric Allergy Service, Department of Paediatric Allergy, Kings College Hospital, Denmark Hill, London, UK. Conflicts of interest: none declared.*

- Precipitating factors including physical agents, exercise, relationship to food,
- Associated viral-type symptoms
- Diurnal variation
- Occurrence in relation to weekends and holidays
- Medication used and efficacy
- Effect on school and daily life
- Family and personal history of urticaria and atopy

Physical examination should include a test for dermatographism, where indicated by the history. Subsequent diagnostic steps depend on the nature of the urticaria subtype. In most cases, further investigations are unnecessary.

### Classification of urticaria subtypes

The classification of urticarial subtypes is based on duration, frequency and causes. (Table 1). Two or more subtypes may co-exist in a single patient.

### Spontaneous urticaria

#### Acute spontaneous urticaria

This is the commonest form of urticaria in children. It is usually generalized. Angioedema affects the eyelids and extremities in 60%. Pruritis is common (90%) and dermatographism less so (21%). Mild fever occurs in 50% of cases. Respiratory symptoms occur in 60% and gastrointestinal symptoms in 21%. Haemorrhagic lesions and arthralgia are more frequent in urticaria caused by infections. This may be misdiagnosed as erythema multiforme or anaphylactoid purpura and be alarming enough to cause hospital admission.

**Investigation of acute spontaneous urticaria:** thorough investigation of acute urticaria reveals a presumptive cause in most children. In younger children, the cause is usually a viral infection, possibly associated with antibiotic therapy. Viral causes include adenovirus, Epstein Barr virus, enterovirus and respiratory syncytial virus. Other infective causes include *Giardia* and *Escherichia coli*. The classic streptococcal cause of urticaria has been debated.

Acute urticaria may be associated with drug ingestion, usually antibiotics or antipyretics. It occurs between the 6th and 10th days of antibiotic therapy, with a drug which may have been used before without problem. Food ingestion, particularly egg, is associated with urticaria in 11%, particularly where the symptoms include angioedema of the lips and atopic dermatitis.

There are no diagnostic tests recommended for children with acute spontaneous urticaria. In routine clinical practice, the cause is usually unidentified.

**Prognosis of acute spontaneous urticaria:** intercurrent viral infections often cause flare-ups of urticaria. Following an acute episode, a quarter of patients will have a recurrence.

#### Chronic spontaneous urticaria

Chronic spontaneous urticaria (CSU) is characterized by daily or almost daily symptoms that persist for more than 6 weeks. It is less common in children than in adults, occurring in 8% of children under 3 years old, following acute urticaria.

Unlike the wheals of most physical urticarias, the wheals of chronic spontaneous urticaria usually last at least 6 hours. They fade without leaving a mark. 50–80% of children have accompanying angioedema. Oropharyngeal oedema is rarely life-threatening. A significant number (35–40%) of children with CSU are atopic, although the symptoms may not be associated with food ingestion (Figure 1).

**Investigation of CSU:** up to 40% of older children with recurrent or chronic urticaria have functionally active autoantibodies against the  $\alpha$ -chain of the high-affinity IgE receptor (FC $\epsilon$ R1) or against IgE, resulting in the promiscuous activation of dermal mast cells. Autoimmune urticaria can be demonstrated using the autologous serum skin test (ASST), where the intradermal injection of autologous serum elicits an immediate wheal and flare response and mast cell degranulation. This is not performed in routine clinical practice.

About 4% of children with CSU have antithyroid antibodies, although most are euthyroid. It is unclear if this association is causal. The urticaria often does not improve with thyroxine

### Classification of urticaria (presenting with wheals and/or angioedema)

Types	Subtypes	Definition
Spontaneous urticaria	Acute spontaneous urticaria	Spontaneous wheals and/or angioedema <6 weeks
	Chronic spontaneous urticaria	Spontaneous wheals and/or angioedema >6 weeks
Inducible urticaria	Symptomatic dermatographism	Eliciting factor: mechanical shearing forces (wheals arising after 1–5 minutes)
	Cold urticaria	Eliciting factor: cold objects/air/fluids/wind
	Delayed pressure urticaria	Eliciting factor: vertical pressure (wheals arising with a 3–12 hour latency)
	Heat urticaria	Eliciting factor: localized heat
	Solar urticaria	Eliciting factor: UV and/or visible light
	Vibratory angioedema	Eliciting factor: vibratory forces, e.g. pneumatic hammer
	Contact urticaria	Elicitation by contact with urticariogenic substance
	Cholinergic urticaria	Elicitation by increase of body core temperature due to physical exercise, spicy food, hot baths
	Aquagenic urticaria	Eliciting factor: water

Table 1



**Figure 1** Chronic spontaneous urticaria in a 5 year old girl.

replacement. Ongoing thyroid function monitoring is encouraged for children with CSU and thyroid autoimmunity.

Case reports of children with chronic urticaria associated with coeliac disease, type 1 diabetes, juvenile rheumatoid arthritis and familial autoimmune disease have been reported and should be investigated if clinically indicated.

Children presenting with CSU are frequently over-investigated. Investigations should be guided by a detailed clinical history. Causative drugs should be omitted.

- Allergy tests. Chronic urticaria is commonly perceived to be due to an allergic or idiosyncratic reaction to foods or food additives. Families often find it helpful to see a lack of atopy demonstrated by negative skin tests. If the clinical history suggests a candidate allergen, or the child has a history of food allergy or atopic dermatitis, then allergy tests (skin testing or measurement of specific IgE) are warranted. The allergens tested should be guided by the history to avoid false positive results.
- Thyroid function and autoantibodies
- Autoantibodies, including antinuclear antibodies, tissue transglutaminase IgA and/or endomysial antibodies if clinically indicated.
- A number of children will improve on a pseudoallergen free diet and a 3 week trial may be considered in selected patients. This should be supervised by a paediatric dietician and followed by rechallenge.
- For unusual presentations or suspected vasculitis, children should be referred for lesional skin biopsy, particularly if there are any systemic symptoms (fever, arthralgia or arthritis), lesions lasting more than 24 hours or associated with tenderness, petechiae, purpura or skin staining as the lesions fade.

**Prognosis of CSU:** parents need reassurance that this is not a severe disease and remits over time. 3 Years after presentation, a quarter of children are disease free; 96% are asymptomatic after 7 years.

### Inducible urticaria

Pressure and cold are the commonest precipitating factors in children. Different types of inducible urticaria may occur

together. Common combinations include dermatographism and cholinergic urticaria or cholinergic and cold urticaria. Once inducible urticaria has been diagnosed, no further investigations are required. The rate of remission is 11% at 1 year and 38% at 5 years. Atopic children and those with more frequent episodes are less likely to remit.

### Symptomatic dermatographism

Patients experience immediate itching and whealing in response to light pressure or friction or develop itchy wheals at the sites of pressure from clothes. The wheals resolve within 30 minutes, which distinguish them from delayed pressure urticaria. Oropharyngeal whealing rarely occurs. It is less frequent on the face and extremities, but may occur anywhere else. This affects a small number of children (1.3%) with chronic urticaria.

**Diagnosis of dermatographism:** the diagnosis is established by gentle stroking of the skin to elicit an isomorphic whealing response along the line of applied pressure. Alternatively, a spring loaded dermatographometer can be used. Antihistamines should be withdrawn 48 hours before challenge testing. If patients undergo allergy skin tests, they develop a wheal and flare response to the negative control and at each skin test site.

**Prognosis of dermatographism:** the condition runs an average course of 2–3 years before resolving spontaneously.

### Cold urticaria

Children present with redness, swelling and itching on exposed skin within minutes of going outside on a cold day, getting splashed by cold water or swimming in a cold pool. Avoidance of cold leads to resolution of wheals after 30–60 minutes. Angioedema of the lips can occur after eating an ice lolly, in which case the symptoms may mimic food allergy. Angioedema of the tongue and palate is uncommon. Systemic symptoms such as headache, fatigue, faintness and vomiting may occur following widespread exposure, such as swimming in seawater. Fatalities have occurred due to drowning. The onset of cold urticaria may be preceded by a viral infection (Figure 2).

**Diagnosis of cold urticaria:** the diagnosis is confirmed using the ice cube challenge test. An ice cube is sealed in a thin plastic bag and placed on the patient's skin for 10–15 minutes. A positive reaction may not develop until the patient's skin has been allowed to rewarm for a few minutes. In patients with concurrent dermatographism, the challenge test can be modified by immersing the forearm in water at 4 °C for 10 minutes. All antihistamines should be stopped for 48 hours before testing.

**Prognosis of cold urticaria:** most patients improve spontaneously after 1–2 years. Rarely, cold urticaria may be familial.

**Specific treatments for cold urticaria:** in children, most cases are mild and self-limiting and can be managed by avoiding excessive cold exposure (e.g. wearing tracksuits for games, or swimming in warm swimming pools). In very cold weather, children should be excused from having to play outside at school. Children with cold urticaria should never bathe in a swimming pool unsupervised. For persistent symptoms, a daily non-



**Figure 2** Cold contact urticaria in a 6 year old boy.

sedating antihistamine is usually sufficient. Cold tolerance treatment, involving regular exposure of affected skin to deplete histamine stores, may be effective if, for example, the family is going on a skiing holiday.

#### Contact urticaria

This is an immediate local response to contact of the skin with an irritant substance, resulting in transient erythema and, less frequently, oedema. It appears within 1 hour and disappears in a few hours. This is common and rarely severe. It is often seen in children following contact with tomatoes or tomato sauce. Reactions may be brand or product specific.

#### Cholinergic urticaria

A pruritic, papular rash in response to exercise, heat (e.g. a hot bath or shower), emotion or hot food and drink. The rash usually affects the neck, flexor surfaces of the elbows, knees, wrists and inner thighs, but may be generalized. Wheals can become confluent, producing areas of angioedema. The rash may be macular and less easy to see, in which case pruritis is the main complaint. Systemic symptoms, including wheeze, headache and syncope may also occur. If the patient cools down, the rash subsides in 30–60 minutes.

This is uncommon in very young children, but may occur in teenagers. It is more common in atopic children. The rash may be difficult to identify in black or dark brown skin.

**Diagnosis of cholinergic urticaria:** the clinical diagnosis can be confirmed by challenge testing using a warm bath, shower or exercise. The differential diagnoses include heat urticaria and aquagenic urticaria.

**Prognosis of cholinergic urticaria:** the patient may self-limit exposure to precipitating factors, such hot baths or showers or avoid excessive exercise or anxiety. Spontaneous resolution usually occurs in 2–3 years, but may be more persistent.

#### Delayed pressure urticaria

Itchy, tender or painful wheals occur at sites of local pressure (e.g. the palms of the hands after carrying a heavy shopping bag, at the waistband or on the soles of the feet). The wheals take

several hours to develop and last for 24 hours or more. The wheals eventually fade, leaving bruising due to vigorous rubbing or scratching.

Histologically, a perivascular infiltrate occurs in the mid to lower dermis. This is a persistent condition which co-exists alongside chronic spontaneous urticaria and is uncommon in children.

#### Heat urticaria

This rare urticaria appears at the site of direct application of heat. It occurs within minutes and resolves within 2 hours. Provocation testing involves the application of heat from a solid object (e.g. a glass beaker containing warm water at 38–50 °C for 1–5 minutes).

#### Solar urticaria

Redness, itching and whealing which develop within minutes of sun exposure. The symptoms subside in 30–60 minutes if sun is avoided. Systemic symptoms are rare. A photoallergen in the skin is stimulated to degranulate mast cells and release histamine. The action spectrum for whealing ranges from UV-B (290–310 nm) through to visible light. Determination of the action spectrum may be useful in fine-tuning sun protection. Symptoms may persist for several years before subsiding. It is rare in children.

This is a clinical diagnosis based on a history of itching, whealing and redness on exposed skin immediately after sun exposure. The differentials, polymorphic light eruption and cholinergic urticaria in response to solar heat, need to be excluded.

#### Aquagenic urticaria

This rare urticaria is evoked only by contact with water, irrespective of its temperature. Sparse, monomorphic, intensely itchy wheals, resembling cholinergic urticaria, develop on the upper trunk, face and neck within minutes of exposure to water. The wheals last less than 2 hours. Challenge testing involves the local application of water at body temperature (e.g. gauze soaked in water at 37 °C) for 20 minutes.

### Assessment of disease activity

#### Quality of life

The distorted appearance and rash of urticaria and angioedema significantly impair quality of life. Children may miss school, due to a perception that the condition is infectious or allergic and the fear that the child is 'unwell'. The CU-Q<sub>2</sub>oL, is a disease specific, validated, questionnaire for assessing quality of life in patients with chronic spontaneous urticaria.

#### Scoring systems

The urticaria activity score, UAS7 (Table 2) is based on the assessment of key urticaria symptoms (wheals and pruritis) and enables an evaluation of the response to treatment. As symptoms change in intensity, this is best evaluated by the patient over the course of a week.

#### Principles of treatment of urticaria

The aim of treatment is to achieve complete symptom relief, as safely as possible. This is achieved by the identification and



**Urticaria activity score (UAS7) for assessing disease activity in chronic urticaria**

Score	Wheals	Pruritis
0	None	None
1	Mild (<20 wheals/24 hours)	Mild (present but not annoying or troublesome)
2	Moderate (20–50 wheals/24 hours)	Moderate (troublesome but does not interfere with normal daily activity or sleep)
3	Intense (>50 wheals/24 hour or large confluent areas of wheals)	Intense (severe pruritis, which is sufficiently troublesome to interfere with normal daily activity or sleep)

Sum of score, 0–6, for each day is summarized over one week (maximum = 42).

From Zuberbier, Allergy 2014.

**Table 2**

elimination of underlying causes and triggers and control of symptoms using medication (Figure 3). In most cases, children should be treated as close to home as possible, usually in primary care or at a local hospital. Referral to a tertiary centre will be needed for cases not responding to second line treatment or with features indicating a complex aetiology.

#### Avoidance of triggers

Avoidance of known provoking stimuli should be the primary strategy. Causative drugs should be stopped. NSAIDs and aspirin should be avoided. Coarse, tight woollen clothes and overheating should be avoided to reduce itching. Symptomatic relief can be obtained from 1% menthol in aqueous cream. Dietary restrictions are only beneficial in children with a positive history of food allergy, confirmed by testing.

#### Non-sedating antihistamines

The mainstay of treatment of urticaria is with oral, non-sedating antihistamines which provide symptomatic relief by reducing the effect of mast cell mediators on the target organs. Second generation antihistamines (e.g. Cetirizine 5–10 mg OD, Loratidine 5

–10 mg OD, Fexofenadine 180 mg OD) have a greater efficacy, longer duration of action and some anti-inflammatory effects. The timing of the dose can be adjusted to suppress the most severe symptoms. Rupatadine 10 mg OD is a combined antihistamine and PAF antagonist, which has a greater efficacy and a product license for children over 12 years of age. First generation antihistamines have pronounced anticholinergic and sedative side effects which last longer than 12 hours, whereas the anti-pruritic effect lasts for only 4–6 hours. They can interfere with rapid eye movement sleep, impact on learning and performance and are not recommended for routine management.

#### Updosing of non-sedating antihistamines

If symptoms persist after 2 weeks, the antihistamine dose can be increased up to 4 times the recommended dose. It is recommended to wait for up to 4 weeks to allow full effectiveness of the antihistamine before considering alternative therapy. It appears to be more effective to stick to a single agent and 4 times a day antihistamine is better than two agents used twice a day in combination. A lack of response to high dose antihistamines should raise the possibility of an alternative diagnosis.

#### Short course oral steroids

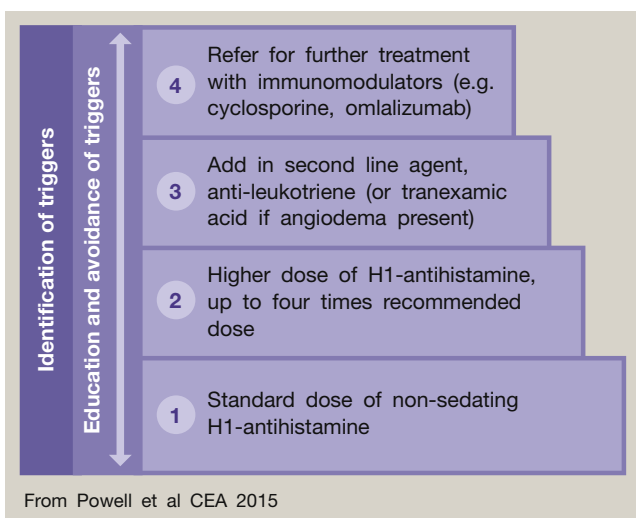
Short courses of oral prednisolone (2 mg/kg/day, maximum 40 mg) are useful, in addition to antihistamines, for acute urticaria and severe exacerbations of chronic urticaria, resulting in decreased itch and faster resolution of the rash. It is also effective in delayed pressure urticaria. They are not recommended for long term control. In some cases of CSU, a pronounced cellular infiltrate is observed, which is refractory to antihistamines, but responds well to a brief burst of corticosteroid.

#### Leukotriene receptor antagonists

Patients not responding to antihistamines alone should be offered a 1–4 week trial of the addition of a leukotriene receptor antagonist (e.g. Montelukast 4–10 mg nocte). Evidence for the effectiveness of leukotriene antagonist monotherapy is poor.

#### Tranexamic acid

Tranexamic acid may benefit some patients with problematic angioedema. A dose of 15–25 mg/kg (maximum 1.5 g) 2–3 times per day is recommended.



**Figure 3** Stepwise management of chronic urticaria.

**Omalizumab**

Omalizumab (anti-IgE) has been shown to be dramatically effective in selected patients. There is increasing evidence that it is safe and effective in children over 7 years of age with chronic urticaria, who are resistant to second line treatment. It involves three to six injections of 150–300 mg administered monthly and should be limited to specialist centres.

**Ciclosporin A**

Ciclosporin has a moderate, direct effect on mast cell mediator release and inhibits basophil histamine release. The addition of Ciclosporin A to a non-sedating antihistamine may be useful for recalcitrant symptoms. It should be limited to difficult cases and administered in specialized centres.

**Follow-up of chronic urticaria**

The severity of urticaria may fluctuate, and spontaneous remission can occur at any time. It is recommended to re-evaluate the necessity for continued or alternative drug treatment every 3–6 months. ◆

**FURTHER READING  
JOURNALS**

- Du Toit G, Prescott R, Lawrence P, et al. Autoantibodies to the high-affinity IgE receptor in children with chronic urticaria. *Ann Allergy Asthma Immunol* 2006; **96**: 341–4.
- Jirapongsananuruk O, Pongpreuksa S, Sangacharoenkit P, Visitsunthorn N, Vichyanond P. Identification of the etiologies of chronic urticaria in children: a prospective study of 94 patients. *Pediatr Allergy Immunol* 2010; **21**: 508–14.
- Khakoo G, Sofianou-Katsoulis A, Perkin MR, Lack G. Clinical features and natural history of physical urticaria in children. *Pediatr Allergy Immunol* 2008; **19**: 363–6.

Maurer M, Rosen K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med* 2013; **368**: 924–35.

Poon M, Reid C. Do steroids help children with acute urticaria? *Arch Dis Child* 2004; **89**: 85–6.

Powell RJ, Leech SC, Till S, et al. BSACI guideline for the management of chronic urticaria and angio-oedema. *Clin Exp Allergy* 2015; **45**: 547–65.

Zuberbier T, Aberer W, Asero R, et al. EAACI/GA2LEN/EDF/WAO Guideline for the definition, diagnosis and management of urticaria: the 2013 revision and update. *Allergy* 2014; **69**: 868–87.

**WEBSITE**

RCPCH care pathways for children with allergies; Urticaria/mastocytosis/angioedema pathway. <http://www.rcpch.ac.uk/allergy>.

**Practice points**

- acute spontaneous urticaria is the most common form of urticaria in childhood. Chronic spontaneous urticaria is less common
- dermatographism and cold urticaria are the most common precipitants of inducible urticaria
- the diagnosis of urticaria is usually made on clinical grounds
- in most cases, investigations are not necessary
- most children respond to treatment with non-sedating antihistamines, the dose of which may need to be increased up to 4 times the conventional dose