

BSACI GUIDELINE**BSACI guideline for the management of chronic urticaria and angioedema**R. J. Powell¹, S. C. Leech², S. Till³, P. A. J. Huber⁴, S. M. Nasser⁵ and A. T. Clark⁶

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**Clinical
&
Experimental
Allergy****Summary**

This guidance for the management of patients with chronic urticaria and angioedema has been prepared by the Standards of Care Committee of the British Society for Allergy and Clinical Immunology (BSACI). The guideline is based on evidence as well as on expert opinion and is aimed at both adult physicians and paediatricians practising in allergy. The recommendations are evidence graded. During the development of these guidelines, all BSACI members were included in the consultation process using a Web-based system. Their comments and suggestions were carefully considered by the Standards of Care Committee. Where evidence was lacking, a consensus was reached by the experts on the committee. Included in this management guideline are clinical classification, aetiology, diagnosis, investigations, treatment guidance with special sections on children with urticaria and the use of antihistamines in women who are pregnant or breastfeeding. Finally, we have made recommendations for potential areas of future research.

Keywords adult, allergy, angioedema, antihistamine, anti-IgE, auto-antibody, autoimmune, breastfeeding, BSACI, child, epidemiology, guideline, hypothyroidism, IgE, management, paraprotein, pregnancy, pregnancy, Urticaria

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Introduction

This guidance for the management of patients with chronic urticaria/angioedema is intended for use by physicians treating allergic conditions. It should be recognized that patients referred to an allergy clinic often have a different pattern of presentation (e.g. intermittent acute) from those referred elsewhere and both the patient and referring practitioners often wish to determine whether allergy is involved.

Evidence for the recommendations was collected by electronic literature searches of MEDLINE and EMBASE using these primary key words: urticaria, angioedema, angioneurotic oedema, allergy, allergic, antihistamines, auto-antibody, autoimmune, hypothyroidism, IgE, paraprotein, pregnancy, breastfeeding, child, epidemiology, management, psychology. In addition, hand searches were performed and the Cochrane library and NHS evidence were also searched. Each article was reviewed for suitability by the first and second author of this guideline. The recommendations were evidence graded at the time of preparation of these guidelines

(Appendix Tables B1 and B2). During the development of these guidelines, all BSACI members were consulted using a Web-based system and their comments and suggestions were carefully considered by the Standards of Care Committee (SOCC). Where evidence was lacking, a consensus was reached among the experts on the committee. Conflict of interests were recorded by the SOCC. None jeopardized unbiased guideline development.

Executive summary and recommendations

(Grades of recommendations are described in Appendix Tables B1 and B2)

- Chronic urticaria/angioedema has traditionally been defined as weals, angioedema or both with daily or almost daily symptoms lasting for more than 6 weeks. In these guidelines, we have also included patients with episodic acute intermittent urticaria/angioedema lasting for hours or days and recurring over months or years.
- Weals and angioedema commonly occur together, but may also occur separately.

- Chronic urticaria affects 2–3% of individuals (lifetime prevalence) and significantly reduces quality of life (QoL).
- There are important differences in aetiology and management in children compared to adults.
- The diagnosis is based primarily on the clinical history. Investigations are determined by the clinical history and presentation, but may not be necessary.
- Management must include the identification and/or exclusion of possible triggers, patient education and a personalized management plan (grade of recommendation = D).
- Food allergy can usually be excluded as a cause of urticaria/angioedema if there is no temporal relationship to a particular food trigger, by either ingestion or contact. Food additives rarely cause chronic urticaria and angioedema.
- Certain drugs can cause or aggravate chronic urticaria and/or angioedema, and hence, a detailed drug history is mandatory.
- Autoimmune urticaria/angioedema in older children and adults is reported to account for up to 50% of chronic urticaria and may be associated with other autoimmune conditions such as thyroiditis.
- Autoimmune and some inducible weals can be more resistant to treatment and follow a protracted course.
- The commonest type of angioedema without weals is histaminergic.
- Angioedema without weals is a cardinal feature of hereditary angioedema (HAE) and typically involves subcutaneous sites, gut and larynx. In Types I and II HAE, levels of C4 and C1 inhibitor (functional and/or antigenic) are low.
- Angiotensin converting enzyme (ACE) inhibitors can cause angioedema without weals resulting in airway compromise. They should be withdrawn in subjects with a history of angioedema (grade of recommendation = C). ACE inhibitors are contraindicated in individuals with a history of angioedema with or without weals.
- Pharmacological treatment should be started with a standard dose of a non-sedating H1-antihistamine (grade of recommendation = A).
- The treatment regime should be modified according to treatment response and development of side-effects.
- Higher than normal doses of antihistamines may be required to control severe urticaria/angioedema (grade of recommendation = B). Updosing with a single antihistamine is preferable to mixing different antihistamines.
- If an antihistamine is required in pregnancy, the lowest dose of chlorphenamine, cetirizine or loratadine should be used (grade of recommendation = C).
- If an antihistamine is required during breastfeeding, it is recommended that either cetirizine or loratadine are taken at the lowest dose. Whenever possible, chlorphenamine should be avoided during breastfeeding (grade of recommendation = C).

Definition

Chronic urticaria/angioedema (CU) has traditionally been defined as weals, angioedema or both lasting for more than 6 weeks [1, 2]. Acute urticaria is an episode of spontaneous weals lasting for <6 weeks and is not considered further in this guideline. However, we have included patients with episodic urticaria/angioedema lasting for hours or days and recurring over months or years. Although rarely life-threatening, chronic urticaria/angioedema leads to both misery and embarrassment and has a significant impact on an individual's quality of life [3–5]. Regrettably, this troublesome condition is often trivialized. Box 1 lists the terminology pertaining to urticaria referred to in this guideline.

Urticaria ('hives' or 'nettle rash') is characterized by a red (initially with a pale centre), raised, itchy rash resulting from vasodilatation, increased blood flow and increased vascular permeability. Weals can vary in size from a few millimetres to hand-sized lesions which may be single or numerous. The major feature of urticaria is mast cell activation that results in the release of histamine (and other inflammatory mediators); that in turn accounts for the raised, superficial, erythematous weals and accompanying intense pruritus. Angioedema (tissue swelling) is the result of a local increase in vascular permeability, often notable in the face, oropharynx, genitalia and less frequently in the gastrointestinal tract. These swellings can be painful rather than itchy. Weals affect the superficial skin layers (papillary dermis), whereas angioedema can involve the submucosa, the deeper reticular dermis and subcutaneous tissues. Weals and angioedema often coexist, but either can occur separately. Characteristically the weals arise spontaneously and each lesion resolves within 24 h. This contrasts with angioedematous swellings that can persist for a few days.

When functional antibodies are demonstrated, this suggests an autoimmune basis. In the commonest form

Box 1. Terminology dependent on how study population was characterized

Term	Abbreviation	Definition
Chronic urticaria	CU	Encompasses CsU and CaU
Chronic spontaneous urticaria (previously called CiU – chronic idiopathic urticaria)	CsU	Not associated with auto-antibodies
Chronic autoimmune urticaria	CaU	Associated with antibodies to IgE/IgE receptor
Hereditary Angioedema	HAE	Typically associated with C1 inhibitor deficiency

of the disease (chronic spontaneous urticaria – CsU), there appears to be persistent activation of mast cells in the skin, but the precise mechanism of mast cell triggering in CsU is unknown. Functional auto-antibodies against the high-affinity IgE receptor (FcεR1) have been demonstrated in 30–40% of patients with CU suggesting an autoimmune basis (CaU) [6–8].

Urticaria and angioedema in adults

Prevalence

The lifetime prevalence for all types of urticaria is 8.8%, but CU only develops in 30–45% of these individuals [8–10].

Clinical classification

Urticaria may occur alone in about 50% of cases, urticaria with angioedema in 40%, and angioedema without weals in 10% [11, 12]. However, a study by Sabroe et al. [13] found a much higher percentage (85%) of patients with urticaria and angioedema. Table 1 lists the clinical classification of chronic urticaria/angioedema.

Aetiology

Optimal management of chronic and acute intermittent urticaria depends on a thorough understanding of clinical presentation, aetiology, triggers and aggravating factors. Patients with chronic urticaria are often referred to allergy clinics as cases of possible food allergy – ‘to find out what they are allergic to’. Rarely is food allergy the cause of chronic urticaria and can typically be excluded on the basis of clinical history. Common triggers/aggravating factors/associations for exacerbations of chronic urticaria are intercurrent viral infections [14] and psychological factors [15]. The aetiological classification of chronic urticaria/angioedema is given in Table 2.

Mechanisms

The central effector cell is the dermal/submucosal mast cell, which on degranulation releases preformed vasoactive mediators such as histamine, a major mediator of urticaria and angioedema. Subsequently cytokines, chemokines and membrane-derived mediators (leukotrienes and prostaglandins) are released, contributing to both the early- and late-phase responses with extravasation of fluid into the superficial tissues.

Table 1. Clinical classification of chronic urticaria/angioedema

Description	Type	Examples of triggers
Spontaneous urticaria	Spontaneous	Stress, infection, drugs (e.g. NSAIDs)
Autoimmune urticaria	Autoimmune	None known
Inducible urticaria	Aquagenic	Contact with hot or cold water
	Cholinergic	Exercise, emotion
	Cold	Swimming in cold water, cold wind
	Delayed pressure	Sitting, lying, tight clothing
	Dermographism	Minor trauma
	Exercise	Physical exertion
	Heat	Hot bath/shower
	Solar	Sunshine
	Vibratory	Use of vibrating tools
	Spontaneous	Stress, infection, drugs (e.g. NSAIDs)
Angioedema without weals	C1 inhibitor deficiency	Trauma, surgical procedures, stress, infection
	C1 inhibitor deficiency related to paraproteinaemia	Trauma, surgical procedures, stress, infection
	Drugs	ACE inhibitors, oestrogens, antipsychotic drugs, statins, NSAIDs
Vasculitis*	Urticarial vasculitis	Infection, e.g. with hepatitis B/C or streptococcus; drugs, e.g. penicillins, allopurinol, quinolones or carbamazepine; autoimmune diseases; paraproteinaemia; malignancy
Rare syndromes*	Cryopyrin-associated periodic syndrome (CAPS)	Cold
	Schnitzler syndrome	

*Vasculitis and rare syndromes are differential diagnoses of chronic urticaria and angioedema.

Table 2. Aetiological classification of chronic urticaria/angioedema

Aetiology	Mechanism	Examples	Investigations
Spontaneous (40–50% cases)	Unknown		Typically negative
Autoimmune	IgG auto-antibody to mast cell IgE receptor or to IgE bound to mast cells	Associated with autoimmune thyroiditis	ANA, thyroid auto-antibodies
Physical stimuli	Direct mast cell mediator release	Exercise, heat, cold, pressure, aquagenic, solar, delayed pressure, vibration, dermographism	Challenge testing with appropriate stimuli, e.g. ice cube, exercise. Cryoglobulins
Drug induced	Reduced kinin metabolism; elevated leukotriene levels	ACE inhibitors (angioedema alone) NSAIDs	Response to avoidance (may be delayed for weeks or months)
Infection	Complement activation due to immune complex formation	Parasites, EBV, hepatitis B and C, viral exanthems	Serology directed by clinical history
Allergic	IgE-mediated allergic contact urticaria	Latex, animals, grass, food	Skin tests, specific IgE to allergen
C1 inhibitor deficiency			
Genetic (i)	Enhanced kinin production	HAE Types I and II	C4, C1 inhibitor
Genetic (ii)	Activation of complement, fibrinolysis and coagulation systems	HAE Type III	C4, C1 inhibitor, Factor XII studies may be useful
Acquired	Binding of C1 inhibitor by paraprotein	Associated with paraproteinaemia	C4, C1 inhibitor, Paraprotein in both blood & urine
Non-IgE-mediated mast cell degranulation	Non-receptor-mediated	Opiates, Adrenocorticotrophic Hormones (ACTH)	Response to avoidance
Vasculitis	Small vessel vasculitis, deposition of immunoglobulin and complement	Urticarial vasculitis	FBC, ESR, renal function, urinalysis, LFT, ASOT, hepatitis B and C serology, immunoglobulin electrophoresis, autoimmune screen including ANA, ANCA, C3, skin biopsy
Food constituent (rare)	Unknown	Salicylates/benzoates	Response to exclusion and subsequent reintroduction

Whereas the mast cell component of urticaria is easily recognized (itching and wealing) and usually responds to antihistamines, swelling in the deeper layers of the skin is more difficult to quantify and additional mechanisms are probably involved. Several inflammatory mediators increase microvascular permeability leading to plasma leakage and oedema formation. Animal experiments have shown that certain mediators, for instance LTB₄ and C5a, cause plasma leakage via neutrophil-dependent pathways in a manner that does not require the neutrophil to traverse the vascular endothelium, i.e. adhesion of neutrophils to the vessel wall is sufficient to initiate plasma leakage [16, 17]. Hence antihistamines are less effective in controlling the angioedema probably due to their inability to affect consequent non-histamine-related tissue oedema.

An examination of lesional skin biopsies from both chronic spontaneous and autoimmune urticaria reveals perivascular infiltrates of CD4⁺ lymphocytes, monocytes and granulocytes (neutrophils, basophils and eosinophils). This contrasts with biopsies from patients with urticarial vasculitis (~1% cases of urticaria) in which there is typically a small vessel vasculitis often

with deposition of immunoglobulin and complement [11]. However, some patients with vasculitis exhibit only subtle changes with endothelial cell swelling, red cell extravasation and possibly leukocytoclasia.

Autoimmune urticaria (CaU). IgG antibodies to the alpha subunit of the IgE receptor on mast cells or less commonly IgG antibodies to IgE have been documented in approximately one-third of individuals with chronic urticaria [7, 18–20]. These antibodies are disease specific with some studies suggesting that this subgroup of patients experiences a more intense and protracted disease course [13]. The mechanism has been reviewed in the EACCI task force position paper [21].

However, sera from subjects with chronic urticaria are also able to degranulate mast cells through mechanisms independent of both IgE and IgG although the precise nature of these histamine-releasing factors remains unknown [22], but *in vitro* studies have suggested activation of the classical complement pathway [23, 24].

Vasculitis/immune complex-associated urticaria. Complement activation can mediate or augment histamine

release from mast cells via the anaphylatoxin C5a. This inflammatory pathway is triggered by the interaction between antibody and antigen to form immune complexes for example in hepatitis C [25–27], hepatitis B [28], EBV and possibly parasitic infections.

Inducible urticarias. Patients can have an inducible element to their urticaria with triggering by heat, cold, pressure, vibration, water, ultraviolet light, etc. These urticarias are induced reproducibly after a specific physical stimulus is applied [29]. Weals usually appear immediately and characteristically fade within 1 h. However, delayed pressure urticaria develops more slowly after physical pressure and lasts several hours or days. Inducible urticarias may require higher dose antihistamine therapy and delayed pressure urticaria may remain refractory.

Possible food triggers. Symptoms of chronic urticaria/angioedema are typically non-allergic with most patients having spontaneous or autoimmune urticaria/angioedema. Nevertheless, patients or their parents frequently analyse foods and food additives eaten over the previous 24 h or longer in the search for a connection with the symptoms.

A detailed history usually enables an IgE-mediated food allergy to be excluded as a cause of urticaria/angioedema. Specifically in IgE-mediated food allergy, symptoms typically occur reproducibly within 60 min of exposure to the offending food rather than coming on overnight or being present first thing in the morning. Furthermore, symptoms do not last several days. Also urticaria and angioedema associated with IgE-mediated food allergic reactions seldom occur in isolation, i.e. additional symptoms are usually present such as oropharyngeal itching and discomfort, wheezing, vomiting or abdominal pain. Therefore, unless there is a close temporal relationship to a particular food trigger, by either ingestion or contact, an IgE-mediated food allergy can be excluded.

Exceptions include allergic reactions to allergens, such as omega-5 gliadin in wheat and lipid transfer proteins in plant-derived foods, which may occasionally present as intermittent spontaneous urticaria/exercise-induced anaphylaxis. As exertion is frequently a cofactor for reactions to these allergens, the temporal relation to ingestion may not be immediately obvious.

Allergy to Crustacea may behave similarly, although in practice these allergens are less ubiquitous and a temporal relationship between ingestion and urticarial episodes is usually apparent. Allergy to α GAL in red meat may cause delayed reaction with urticaria, although this is currently believed to be rare in the United Kingdom [30].

Stress. Urticaria and angioedema can lead to significant stress and the converse is also recognized, namely that psychological stress can trigger or aggravate urticaria.

Although psychological stress in isolation is unlikely to be the sole trigger, a high frequency of patients with CsU report a stressful event preceding the onset of CsU [31] and the possibility of a causal influence of emotional distress, especially of stressful life events, on the course of skin diseases has long been postulated [32]. Patients with CsU experience high rates of anxiety, depression and somatoform disorders such as fibromyalgia, with half of subjects with CsU being affected by at least one of these conditions [33, 34]. Psychiatric comorbidity appears to significantly increase QoL impairment [35]. Compared to allergy patients, individuals with CsU had more severe comorbidity and higher levels of life event stress and perceived stress. Furthermore, an association between post-traumatic stress and chronic spontaneous urticaria has also been reported [36]. Psychological therapies could be considered in addition to medical management.

Other putative causes. An underlying extraneous cause for chronic urticaria cannot be identified in many patients, but infections may play a role in certain cases. When present, chronic infections such as dental sepsis, sinusitis, urinary tract infections and cutaneous fungal infections should be treated. However, exhaustive investigations searching for underlying infections are not indicated. Candida colonization does not cause chronic urticaria [37]. There is limited evidence that if *Helicobacter pylori* colonization is present, eradication may result in an improvement in CU; hence, routine screening of *Helicobacter pylori* is not recommended [38, 39].

Mechanisms specifically related to angioedema occurring without weals

Angioedema without weals. Individuals with angioedema without associated weals should specifically have their medication and family history reviewed to identify those on angiotensin converting enzyme (ACE) inhibitors and those patients with hereditary angioedema (HAE). NSAIDs and antibiotics can also induce angioedema [40, 41]. Acquired forms of C1 inhibitor deficiency can result from serum paraproteins that have auto-antibody activity against C1 inhibitor. Immune complex formation by IgG with tumour surface antigens may result in complement consumption. Investigations typically show reduced levels of complement C4 and may reveal low levels of C1 inhibitor.

Angioedema with ACE inhibitors. The incidence of ACE inhibitor-induced angioedema may be as high as 0.68% [42] as most cases were initially thought to occur in the

first weeks of treatment, but it is now appreciated that later onset angioedema, occurring after many years of uneventful drug use, is quite common [42–44]. The mechanism underlying the angioedema is likely to be due to the reduced metabolism of bradykinin; this effect may also aggravate angioedema associated with HAE. Angioedema associated with angiotensin receptor blockers (ARB's) has been occasionally reported and hence their use in individuals with ACE inhibitor-related angioedema has been questioned but is not contra-indicated [45]. The patient usually presents with swelling of the tongue, but the lips, pharynx, larynx and viscera may also be involved. Fatalities are reported [46], and hence, it is mandatory to recommend that the ACE inhibitor is withdrawn. The episodes of angioedema may persist for several months after withdrawal of the ACE inhibitor without undermining the validity of the drug-related diagnosis [45]. Individuals of Afro-Caribbean origin are at increased risk of ACE inhibitor-induced angioedema. As this group of drugs are less effective in such individuals, an alternative choice of antihypertensive is prudent [42, 43, 47]. Antihistamines, corticosteroids and adrenaline have traditionally been used to treat these individuals although their efficacy remains unproven. However, bradykinin antagonists, such as icatibant, may be effective. These drugs are undergoing clinical trials and may prove useful. C1 inhibitor concentrate is not beneficial in patients with acute angioedema associated with ACE inhibitors.

Follow-up studies on individuals with presumed ACE inhibitor-related angioedema show that in the majority symptoms disappear or are drastically reduced after stopping the ACE inhibitor. Individuals who do not improve even after several months of stopping the ACE inhibitor are likely to have an alternative explanation for their angioedema and were coincidentally taking an ACE inhibitor. There are no routine investigations to distinguish responders from non-responders to ACE inhibitor withdrawal. If the ACE inhibitor is responsible but is not withdrawn, the attacks may become more severe and frequent. ACE inhibitors are contraindicated in patients with a history of angioedema and an alternative antihypertensive should be substituted.

Hereditary angioedema (HAE). Angioedema occurs without weals in HAE and typically involves cutaneous sites, gut and larynx. A family history should be sought. HAE can be subdivided into three types. Types I and II are caused by mutations of the SERPING1 gene and are associated with deficient levels of C1 inhibitor or a dysfunctional C1 inhibitor, respectively. Type III is associated with mutations of Factor XII and the levels of C1 inhibitor remain normal or only slightly reduced. These mutations appear to be markers of enhanced kinin production. Type III affects women more frequently

and more severely, probably related to the effect of oestrogen in promoting angioedema [48]. The benefit of progestin contraception rather than an oestrogen–progestin contraception in Type III is reported [49]. Combined oral contraception should be avoided in all women with HAE [50].

Prognosis

At least 20% of chronic urticaria patients with symptoms severe enough to warrant hospital referral remain symptomatic 10 years after first presentation and this compares closely with a study published a decade earlier [51, 52]. Increased duration of chronic urticaria correlates with clinical severity, the presence of angioedema and positive antithyroid antibodies [53]. A positive autologous serum test has been correlated with more severe symptoms but not prolonged disease duration [7, 13].

Making the diagnosis

Clinical history and examination. A detailed history of urticaria and angioedema is essential and should fully document the frequency, circumstances of onset, triggers, timing, pattern of recurrence and duration of attacks. The history and examination should also include a description of the nature, site and duration of individual lesions and whether they itch or are painful. Photographs of urticaria and angioedema can be helpful in confirming the nature of the lesions. Detailed drug and family history as well as response to treatment are important. Important points to be considered when taking a clinical history are listed in Boxes 2 and 3. The clinical history often identifies triggers and is essential to direct further investigation. Figure 1 shows an algorithm for the diagnosis of chronic urticaria and/or angioedema.

Box 2. Questions when considering an 'allergic' cause?

- Could it be related to any drugs the patient has taken (ACE inhibitor/aspirin/NSAID)?
- Does it occur only and reproducibly within 60 min (usually within 20 min) of eating a particular food? Exceptions meat and crustaceans (such as prawn).
- Does it occur only if a particular food (e.g. wheat) has been eaten followed by exercise?
- Does it occur after contact with an allergen to which the patient is sensitized (animals, grass, food, latex, etc.)?

Box 3. Is there a vasculitic process?

- Are the episodes of urticaria/angioedema persistent rather than evanescent and self-limiting?
- Do individual lesions last more than 24 h?
- Are the urticarial lesions tender and painful rather than itchy?
- Does the skin show evidence of residual petechial haemorrhage, purpura or bruising?
- Does the patient have any symptoms and signs of underlying disease, e.g. fever, significant malaise, arthralgia, hypertension, and blood or protein in urine?

Investigations

The diagnosis is based primarily on the clinical presentation. The need for investigations to elucidate a possible underlying cause should be guided by the presentation and response to antihistamines (Table 2) [54].

Allergy testing. Patients are often referred to hospital in the belief that foods are responsible for their chronic urticaria. A practical approach could be to exclude an atopic diathesis by skin prick testing (SPT) to a panel of

aeroallergens and suspect foods. The sight of negative SPTs in certain patients helps to reassure the patient that allergy is not the cause of their symptoms and may contribute to improved adherence with long-term antihistamines.

When urticaria symptoms are linked to exertion or exercise, there can be a role for limited specific IgE testing to related food allergens, e.g. omega-5-gliadin or lipid transfer proteins [55]. In certain Mediterranean areas, *Anisakis simplex* hypersensitivity associated with the consumption of raw fish should be considered [56–58].

Full blood count (FBC)—The eosinophil count may be elevated in parasitic infections and in some drug-induced reactions. An elevated neutrophil count can be associated with urticarial vasculitis.

Urinalysis—A screen for haematuria and proteinuria will help to detect the presence of urinary tract infection and renal involvement in vasculitis.

Acute phase response—An elevated ESR and/or CRP suggests an underlying systemic condition such as chronic infection, vasculitis and a high ESR with normal CRP may indicate paraproteinaemia.

Thyroid function and auto-antibodies—The presence of thyroid auto-antibodies is associated with chronic

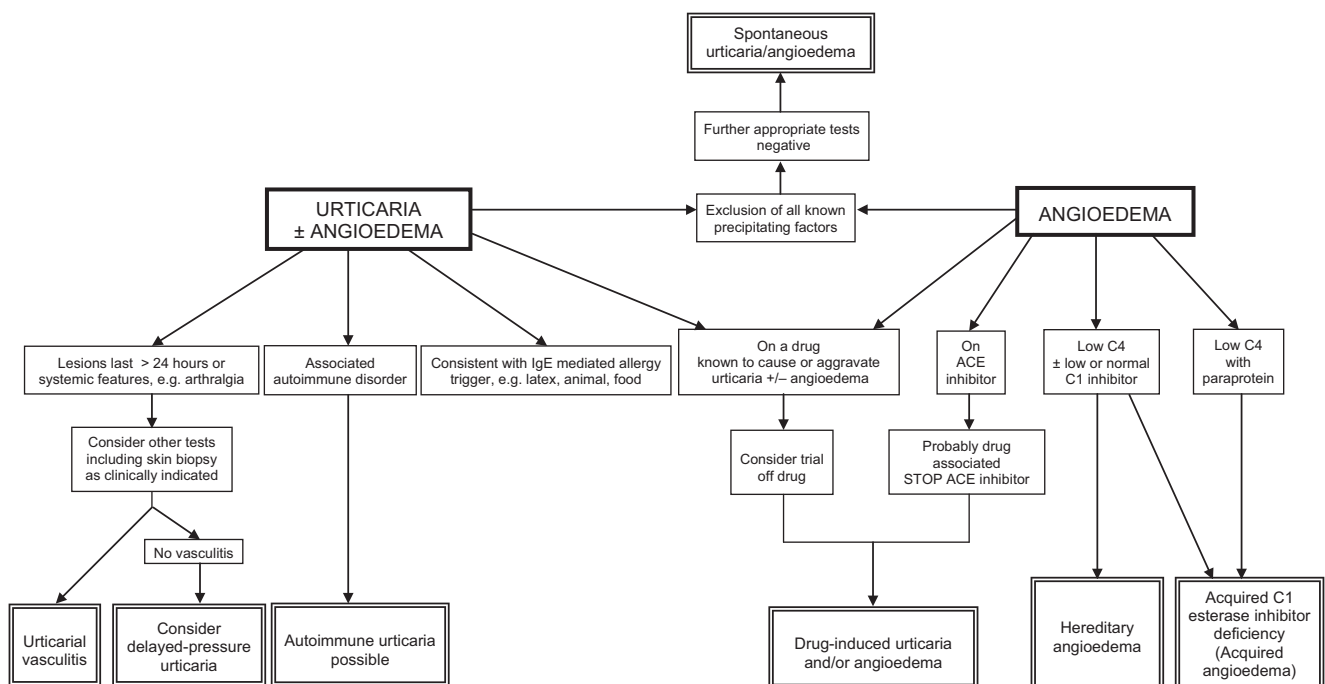


Fig. 1. Algorithm for diagnosis of chronic urticaria and/or angioedema.

urticaria in both children and adults and suggests a diagnosis of autoimmune urticaria. Such patients are often euthyroid but require monitoring over time. Thyroxine treatment is not indicated in euthyroid individuals with CU and thyroid autoimmunity [59]. Approximately 20% of patients with chronic urticaria have antithyroid antibodies [60–62] compared to 6% in the general population [60].

Complement studies—C1 inhibitor deficiency is not associated with urticaria, and hence, if urticaria is present, measurement of C1 inhibitor is not required. Initial complement investigations in patients with angioedema without weals should include C4 and C1 inhibitor. The C4 level will be low in most cases of Types I and II HAE even between attacks. Functional C1 inhibitor quantitation should be reserved for equivocal cases with a suggestive history and low C4 but normal levels of antigenic C1 inhibitor [63]. C3 and C4 should be measured in individuals with suspected urticarial vasculitis [53], and if reduced, measurement of anti-C1q antibodies may be useful.

Haematinics and vitamins—If clinically indicated, measurement of serum iron [64] and vitamin B12 [65] levels can be useful.

Immunoglobulins—Individuals, usually older than 40 years with CU and systemic symptoms such as one of the following: malaise, fever, polyarthralgia, lymphadenopathy, leukocytosis, should have serum immunoglobulins and electrophoresis undertaken to search for an IgM paraprotein that may be indicative of Schnitzler syndrome [66]. Cryoglobulins can be associated with secondary cold urticaria (requires a clotted sample collected and transported to the laboratory at 37°C).

Acquired angioedema without urticaria can be associated with a B cell lymphoma and a search for a paraprotein may be indicated.

Parasitology—A clear association between parasitaemia and CU has not been established.

Challenges—Cold-induced urticaria can usually be diagnosed by placing an ice cube in a sealed plastic bag over the forearm for up to 10 min (allow skin to rewarm subsequently). Dermographism is suspected at the time of skin prick testing and confirmed by lightly scratching the skin with weals appearing within 10 min. The water test for aquagenic urticaria may be applied by immersion of a body part into water (at 37°C) or by placing wet towels for a few minutes onto the area of skin most affected. Cholinergic urticaria is triggered by sweating due to heat, emotion or exercise and can be provoked by exercising the patient in a

warm environment although this is not routinely undertaken.

Skin biopsy—A lesional skin biopsy is appropriate when there is an unusual pattern of presentation or in cases of suspected vasculitis. Clinical clues include systemic symptoms (fever and arthralgia or arthritis) and lesions lasting for more than 24 h, or associated with tenderness, petechiae, purpura or skin staining as the lesions fade. Linear bruising suggests excessive scratching [11].

Autologous serum skin test and basophil release assay—These both remain research tools. The autologous serum skin test (ASST) involves intradermal injection of the patient's own serum. A positive weal and flare reaction is considered indicative of circulating auto-antibodies to the high-affinity IgE receptor on the mast cell in CU patients [67]. The ASST is poorly tolerated by younger children due to the discomfort associated with intradermal injections performed in the absence of topical anaesthetic creams [18]. The role of the basophil histamine release assay (BRA) in the clinical management of CU remains unclear. The available assays (BRA and ASST) for autoimmunity in CU do not consistently assist clinicians in their understanding of spontaneous CU pathogenesis [68] and remain research tools.

Nasendoscopy—Nasendoscopy can be considered in an individual with unexplained pharyngeal obstruction, and this can be very useful during an attack allowing direct visualization of the pharynx/larynx to establish or exclude the presence of angioedema of the throat. Important differential diagnoses of 'swelling, lump or discomfort in the throat' include globus, gastro-oesophageal reflux and vocal cord dysfunction.

Treatment in adults

Avoidance strategies. Symptom diaries can be useful as an investigative tool to determine the frequency, duration and severity of the urticarial episodes and disease-specific QoL questionnaires/symptom scores are available [69, 70]. Patients who fail to uncover a consistent trigger are advised to discontinue the search for an external cause.

If avoidable triggers (Table 1) are identified, the patient should be given clear instructions on avoidance strategies, for example avoiding cold or pressure. If the patient is taking a drug associated with chronic urticaria or angioedema, for example a NSAID, it is prudent for the patient to have a trial for at least several weeks without this treatment. ACE inhibitors are contraindicated in angioedema regardless of the presence

or absence of weals. Treatment of underlying infections and malignancies may lead to amelioration or resolution of symptoms. Alcohol can aggravate CU by its effect of vasodilation [71].

Symptom control. In many cases, treatment of CSU is predominantly directed towards symptom control and therefore antihistamines active against the H1 receptor remain the mainstay of treatment. Second-generation antihistamines are commonly prescribed and are generally well tolerated with minimal sedation: many have a once-daily dosage to improve adherence (see Table 4). Pharmacokinetics suggest that to rapidly achieve optimal blood levels and hence rapid relief of symptoms, two tablets of the chosen antihistamine may be taken as the first dose, reverting to a single daily tablet thereafter. Studies of higher dose non-sedating antihistamines demonstrate efficacy with up to 4× the conventional dose using levocetirizine or desloratadine [72]. Once symptom control has been accomplished, daily treatment [73] is advised in most patients for 3–6 months. For individuals with a long history at presentation of urticaria with angioedema, treatment for 6 or even 12 months is advised with gradual withdrawal over a period of weeks. For patients with infrequent symptoms, treatment may be taken as required or even prophylactically (e.g. prior to occasions when symptoms would be most unwelcome, such as business presentations). Figure 2 shows a step-up treatment plan for chronic urticaria. A short course of corticosteroids may be appropriate in severe episodes at any stage (e.g. prednisolone up to 40 mg daily for 7 days) [74].

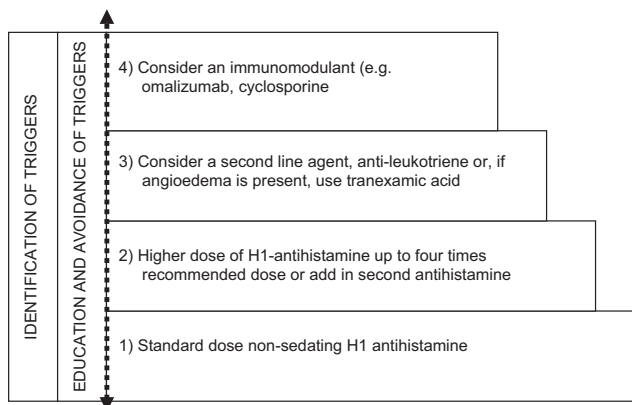


Fig. 2. General management plan for chronic urticaria (Adults and children). The starting point and the rate of progression between steps depend on clinical severity and response. Short course of corticosteroids (e.g. 1 mg/kg prednisolone twice a day, up to 40 mg total per day, for 3 days) may be used for severe exacerbations [74, 146], see also section on rescue medication. The treatment should be stepped down once control is achieved. Observations on the mechanism of antihistamine action [147] suggest that it is probably sensible to withdraw such therapy gradually, rather than stopping it abruptly.

Patient-reported outcomes are available for the evaluation of urticaria patients [75].

Standard treatment. Choice of H1-antihistamine—All antihistamines are licensed for use in chronic urticaria, but the chronic use of first-generation antihistamines, such as chlorphenamine, should be avoided where possible because of sedation and interference with psychomotor performance. Sedation and impaired psychomotor function is reduced with second-generation antihistamines, it but can still occur. Although a sedating antihistamine at night can sometimes be useful, the long half-life of hydroxyzine can cause daytime somnolence [76]. Additional anti-inflammatory effects as suggested by the various antihistamine manufacturers may be relevant to the treatment of chronic urticaria, but the impact on clinical practice has not been quantified [77]. Table 3 lists the antihistamines (H1-antihistamines) indicated for use in chronic urticaria.

The efficacy of the various antihistamines using suppression of the weal and flare response does not correlate with clinical urticarial responses and hence should not be solely used to predict or compare clinical responses in CU [78–80].

The absence of head to head comparisons in clinical trials prevents stratification of efficacy. Table 3 lists the antihistamines (H1-antihistamines) indicated for use in chronic urticaria. Individual patient responses and side-effects to antihistamines vary and an endorsement for a particular antihistamine cannot be given. If higher than recommended doses of antihistamines are to be considered, incremental up dosing is advised.

Tranexamic acid—Tranexamic acid appears to benefit patients with angioedema particularly those without weals and inhibits the conversion of plasminogen to plasmin and consequently the production of bradykinin. The evidence is anecdotal, but common usage recommends consideration in problematic cases.

Refractory treatment. In cases of chronic urticaria and angioedema, resistant to high-dose antihistamines, there is no recommended second-line therapy, but the treatment options given in Tables 4 and 5 and Fig. 2 may be considered depending on the presenting clinical symptoms, specific trigger factors and underlying pathology.

Leukotriene receptor antagonists—Leukotriene receptor antagonists may be useful in combination with antihistamines in a subgroup of patients with chronic urticaria, particularly those with adverse responses to aspirin, NSAIDs and in those with delayed pressure urti-

Dose	Licensed dose	Other comments/side-effects	References
Acrivastine	8 mg tds	Second-generation antihistamine Rapid onset of action, not long-lasting, excreted unchanged in urine; non-sedating; 'on-demand' therapy	[97]
Bilastine	20 mg	Second-generation antihistamine	[120]
Cetirizine	10 mg	Second-generation antihistamine	[84, 85, 87, 121]
Chlorphenamine	4 mg qds	First-generation antihistamine Not for long-term use; injectable; short half-life; sedating	
Desloratadine	5 mg	Second-generation antihistamine	[81, 82, 122]
Fexofenadine	120–180 mg	Second-generation antihistamine	[83, 101, 123]
Hydroxyzine	25 mg–100 mg daily	First-generation antihistamine Not for long-term use; sedating	
Levocetirizine	5 mg	Second-generation antihistamine	[71]
Loratadine	10 mg	Second-generation antihistamine	[124, 125]
Mizolastine	10 mg	Second-generation antihistamine	[126]
Promethazine	10–20 mg tds	First-generation antihistamine Not for long-term use, injectable; sedating	T. Dean, personal communication
Rupatadine	10 mg	Second-generation antihistamine	[127]

None of the above second-generation antihistamines has demonstrated superiority over another in licensed doses. The effectiveness of levocetirizine and desloratadine in up to four times the conventional doses has been demonstrated in difficult to treat urticaria [72].

Table 3. Antihistamine (H1-antihistamines) licensed for CU

Table 4. Second-line pharmacotherapy

Drug (families)	Grade	Specific indication/comments/side-effects	Reference
Omalizumab	A	Used for chronic urticaria failed on higher dose antihistamines	[86]
Leukotriene receptor antagonists (montelukast ¹ , zafirlukast)	B ¹	Most effective in combination with antihistamines Autoimmune urticaria; chronic urticaria with positive challenge to food, food additives or aspirin; delayed pressure urticaria	[81–83, 122, 128] Table B3 (Appendix)
Tranexamic acid	D	Showed reduced frequency of angioedema attacks.	[129, 130]
Ciclosporin	B	Immunosuppressive, i.e. requires monitoring of blood pressure, renal function and serum levels if indicated; significant side-effects	[87, 88] Table B4 (Appendix)
Mycophenolate Mofetil	D	Used for chronic urticaria failed on higher dose antihistamines	[89, 131]
Tacrolimus	D	Value in severe, steroid-dependent chronic urticaria needs further randomized controlled studies	[132]

Grade = Grade of recommendation (Table B2) [133, 134]. B¹ = Grade only refers to montelukast, but not to zafirlukast.

caria or CaU [81–85]. See also evidence Table B3 (Appendix).

Anti-IgE therapy—Omalizumab is effective in randomized double-blind placebo-controlled trials in patients with spontaneous and autoimmune CU who have persistent symptoms despite high-dose antihistamines [86]. An EAACI position paper recommends omalizumab when higher dose antihistamines have failed [74]. It requires monthly injections and appears well tolerated.

It is effective in approximately 80% of individuals with persistent/resistant symptoms leading to a rapid improvement. Currently, treatment is recommended for 6 months, but typically relapses occur when treatment is discontinued.

Ciclosporin—Low-dose ciclosporin may also be considered in patients with severe unremitting disease uncontrolled by antihistamines [87, 88]. A T cell-mediated mechanism has been proposed, but ciclosporin also

Table 5. Rarely used drugs

Drug (families)	Grade	Specific indication/comments/side-effects	Reference
Bradykinin B2 receptor antagonist (icatibant)	B	Licensed for acute attacks of HAE	[93, 95]
Dapsone	D	Several single-case reports of successful treatments of urticarial vasculitis in resistant cases Helped one patient with autoimmune thyroiditis to stop oral steroid treatment	[135–137]
Hydroxy-chloroquine	D	Improvement of QoL, but no reduction in urticaria scores or medication requirements	[138]
Methotrexate	D	Beneficial for corticosteroid-dependent chronic spontaneous urticaria (2 patients) Efficacy in urticarial vasculitis (one patient)	[139, 140]
Stanozolol (Danazol)	C	Beneficial effects in patients with refractory CIU (with simultaneous cetirizine dose); Long-term effects unknown; drug currently not licensed, but available on a named-patient basis as winstrol, 4 mg in the United Kingdom. Danazol likely to have similar effects	[141]
Sulfasalazine	D	Successful in 2 patients with refractory delayed pressure urticaria and angioedema. One was steroid-dependent and managed to come off prednisolone	[142–144]
Warfarin	C	Improvement in 6 of 8 patients who were unresponsive to antihistamines	[145]

Grade = Grade of recommendation (Table B2) [133, 134].

inhibits basophil and mast cell degranulation. See also evidence Table B4 (Appendix).

Mycophenolate mofetil—Open-label studies suggest that 1000 mg twice daily is useful; however, its speed of onset is slower than with both, omalizumab and ciclosporin [89].

H2-Antihistamines—A recent review [90] concluded that the evidence for the use of H2-antihistamines in urticaria was weak. The combination of cimetidine with hydroxyzine results in an increased serum level of hydroxyzine confirming the rationale for its co-administration with hydroxyzine in some patients with CU unresponsive to hydroxyzine alone. There is no therapeutic rationale for co-administration of cimetidine with cetirizine in CU [91]. In CU, the combination of ranitidine with terfenadine was superior to terfenadine alone in terms of itch, but there was no significant effect on weals or swellings [92]. There is no strong evidence to support the addition of ranitidine to treatment regimes in CU.

Rescue medication. Corticosteroids—There are no controlled studies on the use of corticosteroids in urticaria and angioedema, but their effectiveness is generally accepted. Rarely, a short course of up to 40 mg prednisolone may be prescribed for severe exacerbations of chronic urticaria, especially when accompanied by angioedema [74]. Corticosteroids may also be considered when the symptoms remain uncontrolled by antihista-

mines alone or when rapid clinical relief is required. Urticarial vasculitis is more likely to require corticosteroid treatment. Longer term corticosteroid usage should be avoided whenever possible but if unavoidable, the lowest dose should be adopted. Topical steroids have no place in the treatment of chronic urticaria.

Intramuscular adrenaline—Self-administered intramuscular adrenaline may be indicated in patients with a history of severe angioedema affecting the upper airway or urticaria with significant cardiovascular symptoms. In these individuals, all possible underlying causes should be investigated and treated appropriately using the step-up treatment schedule (Fig. 2) in an attempt to suppress the oropharyngeal swellings completely. Adrenaline is not indicated in non-histaminergic angioedema as seen in HAE and with ACE inhibitors.

Icatibant and C1 inhibitor—The therapeutic benefit of icatibant and C1 inhibitor in acute attacks of HAE is recognized [93, 94]. It has been reported in a case series that icatibant may have efficacy in angioedema induced by ACE inhibitors [95].

Others. Topical preparations—Cooling antipruritic lotions such as 2% menthol in aqueous cream can be soothing [71]. Topical steroids should not be used to treat chronic urticaria.

Dietary advice—Diets low in salicylates and benzoates have been anecdotally adopted in the management of

Box 4. Management of adult patients with weals

- Check that symptomatic episodes have not followed ingestion of a non-steroidal anti-inflammatory drug such as aspirin or ibuprofen.
- Give explanation of the symptoms and reassurance that the histamine-induced chronic urticaria symptoms do not involve the respiratory tract (upper and/or lower) or cardiovascular system – as occurs in anaphylaxis. There are, however, very rare exceptions to this rule.
- Give a once-daily dose of a long acting, non-sedating antihistamine (*prn*, if symptoms are infrequent).
- If necessary, double the dose of antihistamine (usually given at night), and/or add a second antihistamine.
- Consider further increase in dose of antihistamine up to 4× recommended dose.
- Consider adding one or more second-line drugs (see Table 4 and Fig. 2).
- Consider short-term oral corticosteroid rescue treatment.

Box 5. Management plan for patients with angioedema with weals in adults

- In addition to instructions in 'Box 4' above, the following steps should be considered:
- 1 If the patient is taking an ACE inhibitor, this drug should be stopped.
 - 2 Even if the patient is not taking an ACE inhibitor, these drugs should be avoided in the future.
 - 3 Consider addition of tranexamic acid for higher dose antihistamine-resistant angioedema.
 - 4 An adrenaline auto-injector is rarely required and should only be considered if there is a history of significant angioedema affecting the upper airway (rare in angioedema with urticaria). The patient should then be shown how to use the device and provided with a written self-management protocol.
 - 5 Consider short-term oral corticosteroid rescue treatment.

urticaria. However, there is no evidence to support the routine use of low salicylate diets [96]. Individuals with chronic urticaria associated with salicylates may respond to leukotriene receptor antagonists [82]. Suspected tartrazine-induced urticaria/angioedema is rarely reproducible by oral challenge, and hence, additive-free diets are

Box 6. Management plan for patients with angioedema without weals in adults

- 1 Exclude C1 inhibitor deficiency – a normal plasma C4 during an attack, or normal C4, C1 inhibitor, and C1 inhibitor function, between attacks, will typically exclude this.
- 2 If the patient is taking an ACE inhibitor, this drug should be stopped.
- 3 Even if the patient is not taking an ACE inhibitor, these drugs should be avoided in the future.
- 4 Give a once-daily dose of a long acting, non-sedating antihistamine (*prn*, if symptoms are infrequent) and consider higher doses of antihistamines.
- 5 Consider tranexamic acid in antihistamine-resistant angioedema.
- 6 An adrenaline auto-injector and short-term oral corticosteroids are unlikely to be beneficial unless an underlying histaminergic mechanism is considered to be responsible for the angioedema.

not justified in patients with CsU [97]. High-dose supplemental vitamin D₃ has been reported to be beneficial irrespective of a patient's vitamin D status. [98].

Psychological interventions—A recent meta-analysis confirmed the high prevalence of an association between psychological factors and CU [15]. Even if psychological symptoms develop subsequent to CU and play little part in its pathogenesis, the positive correlation between CU and markers of poor psychological wellness indicates that psychotherapeutic treatments and behavioural interventions may prove beneficial.

Patient leaflets—See appendices A1 (Adults) and A2 (children).

Chronic urticaria in childhood**Introduction**

Chronic urticaria is less common in children than it is in adults. Up to 40% of children with chronic urticaria have autoreactive urticaria. There is no difference in medication requirements or remission rates between children who are ASST positive or negative. Cold and pressure urticaria are the most commonly diagnosed induced urticarias in children. These may occur in combination with dermatographism or cholinergic urticaria. Chronic spontaneous urticaria in childhood is rarely a severe disease and usually remits over time. The majority of children will respond to treatment with antihistamines and avoidance of triggers [99].

Acute spontaneous urticaria is not covered in this guideline, although it remains the commonest form of urticaria in childhood. In atopic children, acute urticaria may occur as part of an allergic reaction, e.g. to food. If so, it usually develops within an hour of eating the food and resolves within 24 h. Acute spontaneous urticaria may also occur in response to a viral infection, when it usually persists for longer than 24 h and may last several days.

Epidemiology and clinical presentation

Urticaria (acute, intermittent and chronic) affects around 3.4% of British children. Only a small proportion of these are chronic [100]. Approximately 50–80% of children with chronic urticaria have associated angioedema [11]. Chronic urticaria/angioedema in childhood is usually not life-threatening. Concerns about the physical appearance of weals and angioedema and associated systemic symptoms may combine to impair quality of life. It is not uncommon for children to have missed significant periods of school, due to a lay perception that their appearance is infectious or allergic and fear that the child is 'unwell'.

Aetiology and mechanisms

Investigations are rarely required in children presenting with chronic urticaria. A detailed clinical history and physical examination usually establishes the diagnosis. Most are spontaneous with physical factors such as pressure or cold exposure being the most commonly diagnosed precipitating factors. 31–47% of children with CU have an autoimmune aetiology with a positive ASST [18, 19]. About 4% of children with CU have positive antithyroid antibodies, the majority of these are euthyroid [101] (Table 2).

Vasculitides and connective-tissue disorders. The commonest cause of acute vasculitic urticaria in children is Henoch–Schönlein purpura. This is a clinical diagnosis presenting with a distinctive rash over the extensor surfaces of the legs and buttocks [102]. Rare causes of chronic urticaria should be considered in patients with other systemic symptoms or raised inflammatory markers [103]. A diagnostic lesional skin biopsy could be considered if features such as fever, painful lesions, arthralgia, raised ESR, lesions lasting 24 h or more or lesions that resolve revealing purpura or petechiae.

Thyroid autoimmunity. An association between childhood chronic urticaria and thyroid autoimmunity has been postulated [101, 104]. It is not clear whether the association is causal, as the majority of children present with hyper- or hypothyroid symptoms either before or some time after the onset of chronic urticaria. The urti-

carial symptoms do not always improve with thyroxine replacement therapy. Nonetheless, ongoing thyroid function monitoring is encouraged for children with CU and thyroid autoimmunity [18, 101].

Coeliac disease. There are case reports of an association between chronic urticaria and coeliac disease, which may improve on a gluten-free diet [105, 106].

Prognosis

Parents need reassurance that this is not a severe disease and that it remits over time. A quarter of children with chronic spontaneous urticaria are disease-free 3 years after presentation [18], and 96% are asymptomatic after 7 years. Children with physical urticarias should be advised to avoid triggers and the condition usually regresses spontaneously after 2–3 years.

Investigations

A detailed clinical history is extremely important for any decisions regarding further investigations. If the clinical history and examination are typical of CsU, then further laboratory investigations are rarely useful. Chronic urticaria is commonly perceived by the parents to be due to an allergic or idiosyncratic reaction to foods or food additives, such as food preservatives or food dyes. There is little published evidence to support this. Families often find it helpful to see a lack of atopy demonstrated by negative skin tests.

Skin tests/specific IgE testing. If the clinical history suggests a candidate allergen, then allergy tests (skin testing or specific IgE tests) are warranted. The range of allergens tested should be guided by the history to avoid the need to explain any false-positive results.

Additional investigations if clinically indicated.

- Urinalysis
- Full blood count (FBC)
- Erythrocyte sedimentation rate (ESR)
- Liver function tests (add viral hepatitis screen if transaminases are abnormal)
- Coeliac screen: Tissue transglutaminase IgA antibodies and/or endomysial IgA antibodies – if abnormal or history suggestive, refer for intestinal biopsy. If the patient is on a gluten-free diet or has IgA deficiency, these tests may be misleading
- Thyroid function and antithyroid antibodies
- Cold, dermatographism and pressure provocation tests [107]
- Elimination rechallenge diets: rarely, it may be necessary to undertake carefully planned and dietician-supervised elimination and rechallenge diets

- Antinuclear antibodies should only be measured if a connective-tissue disorder is clinically suspected
- A skin biopsy may be indicated if vasculitis is suspected
- C4 and C1 inhibitor quantitation to detect C1 inhibitor deficiency are only indicated for children, typically teenagers, presenting with angioedema without urticaria to define the presence or absence of C1 inhibitor deficiency [108]
- Tests for current or past viral, bacterial or parasitic infections should be guided by the history, clinical findings and initial screening tests, e.g. eosinophilia

Treatment in children

Management plan. Avoidance of known provoking stimuli should be the primary strategy in any treatment. Drug treatment is described in the management plan in Fig. 2.

H1-antihistamines (grade of recommendation = B)–Non-sedating antihistamines are the mainstay of treatment for children with chronic urticaria. Up to four times the recommended dose may be required to adequately control symptoms. A lack of response to high-dose antihistamine therapy should raise the possibility of an underlying diagnosis such as vasculitis. Chronic urticaria may present as early as the second year of life and this can limit the choice of licensed antihistamine [18, 19]. Cetirizine and desloratadine are licensed for the treatment of chronic urticaria in children from 1 year of age; loratadine and levocetirizine are licensed for the treatment of children of 2 years and older. Acrivastine, bilastine, fexofenadine, mizolastine and rupatadine are licensed for use in children over 12 years. Desloratadine, levocetirizine, loratadine and cetirizine are available in syrup formulations. The metabolism of cetirizine in children is different to that in adults, and hence, this drug should be taken twice daily.

First-generation sedating antihistamines. Children may become accustomed to the sedating effects of first-generation antihistamines; however, the risk of psychomotor impairment remains and this may impact on the child's safety and education. Those licensed for use in childhood include diphenhydramine, hydroxyzine, promethazine and chlorphenamine.

Leukotriene receptor antagonists (grade of recommendation = C)–Evidence for the effectiveness of leukotriene receptor antagonists (LTRAs) as monotherapy is poor. Patients not responding to antihistamines alone should

be offered a 1- to 4-week trial of the addition of a LTRA, e.g. montelukast 4–10 mg nocte.

Corticosteroids (grade of recommendation = D)–Short-term use of oral corticosteroids (3–5 days) may be required to gain control of symptoms. In inducible urticaria unresponsive to first-line therapy, corticosteroids are poorly effective. In patients with delayed pressure urticaria, corticosteroids are more effective [100]. Prolonged use of oral corticosteroids produces unacceptable/severe side-effects.

Tranexamic acid. Tranexamic acid can be effective in the treatment of isolated angioedema [109]. A dose of 15–25 mg/kg (maximum 1.5 g) 2–3 times per day is recommended.

Anti-IgE. There is increasing evidence for the efficacy and safety of Omalizumab in children over 7 years of age with CU, resistant to first-line treatment. Three to six injections of 150–300 mg are administered monthly [86, 110, 111]. The treatment is well tolerated, but should be restricted to specialist centres.

Other treatments. Other therapies such as ciclosporin [100, 101] should be limited to use in difficult cases and only considered in specialist centres.

Chronic urticaria in pregnancy and breastfeeding

Pregnancy. Chronic urticaria often improves in pregnancy, reducing the need for antihistamine treatment, although in some rare cases, urticaria deteriorates. It is best practice to avoid taking drugs in pregnancy. There is no evidence in humans that antihistamines are teratogenic, but in animal studies using high doses of hydroxyzine and loratadine have led to embryotoxicity. The data sheets for cetirizine, desloratadine, hydroxyzine and loratadine all advise avoidance in pregnancy. Hydroxyzine is specifically contraindicated in early pregnancy.

Pregnant women should be informed that no drug can be considered absolutely safe, and the benefits of keeping the mother healthy have to be balanced against the small risk to the foetus. The consequences of inadequately controlled disease should be discussed with the patient and documented in the case notes.

There is considerable clinical experience with cetirizine and loratadine in pregnancy, with no increase in the rate of congenital abnormalities [112–117].

Cetirizine and loratadine have been assigned a category B by the US FDA. Hence, antihistamines should only be used if clearly needed and when the potential benefits outweigh the unknown risks to the foetus.

Breastfeeding. Antihistamines should only be used during lactation when the clinical imperative outweighs the potential harm to the child. The lowest dose should be used for the shortest duration. Significant amounts of antihistamines are excreted in breast milk and, although not known to be harmful, the manufacturers of most antihistamines advise avoidance whilst breastfeeding. Chlorphenamine may cause drowsiness and poor feeding. Both loratadine [118] and cetirizine appear safer with only low levels found in breast milk [119], and therefore, these drugs could be considered if required.

Future research – key areas

- Well-controlled clinical trials in chronic urticaria that does not respond to standard therapy are required. Such studies should have the appropriate statistical power to clarify which drugs should be used, in what dose and for how long. Studies to investigate whether the presence of angioedema affects the prognosis of disease.
- Investigation of the role of exacerbating factors in urticaria and angioedema, e.g. NSAIDs, stress.
- Studies designed to correlate clinical presentation with prognosis and response to treatment, e.g. the use of tranexamic acid in spontaneous (idiopathic) angioedema.
- Studies designed to understand the clinico-pathological association of thyroid autoimmunity and autoimmune urticaria.

- Development of reliable laboratory assays for identification of autoimmune urticaria.
- Systematic review of psychological interventions in CSU.

This *guideline* informs the management of urticaria and angioedema. Adherence to this guideline does not constitute an automatic defence for negligence and conversely non-adherence is not indicative of negligence. It is anticipated that this guideline will be reviewed 5 yearly.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix A1. Patient information sheet - chronic urticaria and angioedema in adults.

Appendix A2. Patient information sheet - chronic urticaria and angioedema in children.