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SPECIAL ARTICLE

BSACI guidelines for the management of chronic urticaria and angio-oedema

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Summary

This guidance for the management of patients with chronic urticaria and angio-oedema has been prepared by the Standards of Care Committee (SOCC) 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 SOCC. Where evidence was lacking a consensus was reached by the experts on the committee. Included in this 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 allergy, angio-oedema, antihistamine, autoantibody, autoimmune, breastfeeding, BSACI, child, guideline, hypo-thyroidism, IgE, paraprotein, pregnancy, urticaria
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Introduction

This guidance for the management of patients with chronic urticaria/angio-oedema 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 want to know whether allergy is involved.

Evidence for the recommendations was collected by electronic literature searches using these primary key words – urticaria, angio-oedema, epidemiology of-, management of-, drugs in chronic urticaria and angio-oedema, antihistamines. Each article was reviewed for suitability by the first and last authors of this guideline. The recommendations were evidence graded at the time of preparation of these guidelines. During the development of these guidelines, all British Society for Allergy and Clinical Immunology (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. Conflicts of interests were recorded by the SOCC. None jeopardized unbiased guideline development.

Executive summary and recommendations

- *Chronic* urticaria/angio-oedema has traditionally been defined as daily or almost daily symptoms lasting for more than 6 weeks. In these guidelines we have also included patients with episodic acute intermittent urticaria/angio-oedema lasting for hours or days and recurring over months or years.
- Urticaria and angio-oedema commonly occur together, but may also occur separately.
- Angio-oedema without urticaria is a cardinal feature of *hereditary angio-oedema* (HAE) and typically involves subcutaneous sites, gut and larynx. In HAE levels of C4 and C1 inhibitor (functional or antigenic) are low.

- *Chronic* urticaria affects 0.5–1% of individuals (lifetime prevalence) and significantly reduces quality of life (QoL).
- *Autoimmune urticaria/angio-oedema* accounts for about 30–50% of chronic urticaria and may be associated with other autoimmune conditions such as thyroiditis [1].
- There are important differences in aetiology and management in *children* compared with 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* can usually be excluded as a cause of urticaria/angio-oedema if there is no temporal relationship to a particular food trigger, either by ingestion or contact. Food additives/preservatives/dyes do not cause chronic urticaria and angio-oedema by an IgE mediated mechanism.
- Certain *drugs* can cause chronic urticaria and/or angio-oedema and hence a detailed drug history is mandatory.
- *Angiotensin converting enzyme (ACE) inhibitors* can cause angio-oedema without urticaria resulting in airway compromise. They should be withdrawn in subjects with a history of angio-oedema (grade of recommendation = C).
- *Autoimmune* and some *physical urticarias* are more resistant to treatment and can follow a protracted course.
- Pharmacological *treatment* should be started with a standard dose of a non-sedating H_1 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/angio-oedema (grade of recommendation = B).
- If an antihistamine is required in *pregnancy*, the lowest dose of chlorphenamine or loratadine should be used (grade of recommendation = C).
- If an antihistamine is required during *breastfeeding* it is recommended that either loratadine or cetirizine are taken at the lowest dose (grade of recommendation = C).

Definition

Chronic urticaria/angio-oedema has traditionally been defined as daily symptoms lasting for more than 6 weeks [1, 2]. In this document we have also included patients with episodic acute intermittent urticaria/angio-oedema lasting for hours or days and recurring over months or years. Although rarely life-threatening, chronic urticaria/angio-oedema causes both misery and embarrassment and has an impact on an individual's QoL comparable with severe coronary artery disease [3, 4]. Regrettably this troublesome condition is often trivialized. In contrast, acute urticaria is a single episode lasting for <6 weeks and is not considered further in this guideline.

Urticaria ('hives' or 'nettle rash') is characterized by a red, 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. Tissue swelling is the result of a local increase in vascular permeability, often notable in the oropharynx, gastrointestinal tract and genitalia. These swellings can be painful rather than itchy. Urticaria affects the superficial skin layers (papillary dermis) whereas angio-oedema involves the submucosa, the deeper reticular dermis and subcutaneous tissue. Urticaria and angio-oedema often co-exist but either can occur separately. Characteristically the lesions of urticaria arise spontaneously, peak between 8 and 12 h and then resolve by 24 h. This contrasts with angio-oedematous swellings that can persist for days.

In the commonest form of the disease [chronic idiopathic urticaria (CIU)] there appears to be persistent activation of mast cells in the skin but the mechanism of mast cell triggering in CIU is unknown. Functional autoantibodies against the high-affinity IgE receptor (FcεR1) have been demonstrated in one third of patients with CIU suggesting an autoimmune basis of disease [5, 6].

Clinical classification

Urticaria may occur alone in about 50% of cases, urticaria with angio-oedema in 40%, and angio-oedema without urticaria in 10% [7, 8]. However a study by Sabroe et al. [9] found a much higher percentage (85%) of patients with urticaria and angio-oedema. Table 1 lists the clinical classification of chronic urticaria/angio-oedema.

Aetiology

Optimal management of chronic and acute intermittent urticaria depends on a thorough understanding of clinical presentation, aetiologies, triggers and aggravating factors. Patients with chronic urticaria are often referred to allergy clinics as cases of possible food allergy – 'to find out what

Table 1. Clinical classification of chronic urticaria/angio-oedema

Description	Type	Examples of triggers
Idiopathic urticaria	Idiopathic	Stress, viral infection
Physical urticaria	Dermatographism	Minor trauma
	Cholinergic	Exercise, emotion
	Delayed pressure	Jogging, sitting, lying, tight clothing
	Cold	Swimming in cold water, cold wind
	Exercise	Physical exertion
	Aquagenic	Contact with hot or cold water
	Solar	Sunshine
	Vibratory	Use of vibrating tools
Drug induced urticaria		Aspirin and other NSAIDs, antidepressants (e.g. citalopram), statins
Contact urticaria	IgE-mediated allergic	Latex, food, animals
Angio-oedema without weals	Idiopathic	Stress, drugs, infection
	C1 inhibitor deficiency (Hereditary Angio-oedema)	Trauma, surgical procedures, stress, infection
	Paraproteinaemia (monoclonal paraprotein binding C1 inhibitor)	Trauma, surgical procedures, stress, infection
	Drugs	ACE inhibitors, oestrogens, anti-psychotic drugs, statins, NSAIDs
Vasculitis	Urticarial vasculitis	Infection, e.g. with hepatitis B/C or streptococcus; drugs e.g. penicillins, allopurinol, quinolones or carbamazepin; autoimmune diseases; paraproteinaemia; malignancy
Rare syndromes	Cryopyrin associated periodic syndrome (CAPS) Schnitzler's syndrome	Cold

ACE, angiotensin converting enzyme; NSAID, non-steroidal anti-inflammatory drug.

they are allergic to'. In the majority of individuals with chronic urticaria, food allergy is not the cause and can usually be excluded on the basis of clinical history. Common triggers for episodes of chronic urticaria are intercurrent viral infections and possibly stress. The aetiological classification of chronic urticaria/angio-oedema is given in Table 2.

Mechanisms

The central effector cell is the dermal/mucosal mast cell, which on degranulation releases vasoactive mediators such as histamine, a major mediator of urticaria and angio-oedema. Membrane-derived mediators such as leukotrienes and prostaglandins are subsequently released, contributing to both the early and late-phase responses with extravasation of fluid into the superficial tissues.

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 which 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 [10, 11]. Hence antihistamines are less effective in controlling the angio-oedema probably due to their inability to affect downstream non-histamine related tissue oedema.

An examination of lesional skin biopsies from both CIU and autoimmune urticaria reveals perivascular infiltrates of $CD4^+$ lymphocytes, monocytes and granulocytes (neutrophils, basophils and eosinophils). This contrasts with biopsies from patients with cutaneous vasculitis ($\sim$1% cases of urticaria) in which there is typically a small-vessel vasculitis often with deposition of immunoglobulin and complement [7]. However, some patients exhibit only subtle changes with endothelial cell swelling, red cell extravasation and possibly some leukocytoclasia.

Autoimmune urticaria. IgG antibodies to the α subunit of the IgE receptor on mast cells or less commonly IgG antibodies to IgE bound to mast cells are associated with chronic urticaria in between 40–60% of children [12, 13] and adults [6]. *In vitro* studies have demonstrated that mast cell degranulation by IgG autoantibodies from patients with chronic autoimmune urticaria depends on activation of the classical complement pathway [14, 15].

Table 2. Aetiological classification of chronic urticaria/angio-oedema

Aetiology	Mechanism	Examples*	Investigations
Idiopathic (40–50% cases)	Unknown		Typically negative
Autoimmune	IgG autoantibody to mast cell IgE receptor or to IgE bound to mast cells	Associated with autoimmune thyroiditis	ANA, thyroid auto-antibodies, autologous serum skin test (research only)
Physical stimuli	Direct mast cell mediator release	Exercise, heat, cold, pressure, aquagenic, solar, delayed-pressure, dermatographism	Challenge testing with appropriate stimuli e.g. ice-cube, exercise, etc.; cryoglobulins
Drug induced	Reduced kinin metabolism; elevated leukotriene levels	ACE inhibitors (angio-oedema alone) NSAIDs	Response to avoidance (may be delayed for weeks or months)
Infection	Complement activation from 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	(A) Genetic	(A) Hereditary angio-oedema type 1 and type 2	C4, C1 inhibitor
	(B) Acquired	(B) Associated with paraproteinaemia	
Non-IgE mediated mast cell degranulation	Non-receptor-mediated	Opiates, 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, ANCA, C3, skin biopsy
Lymphoproliferative	Paraproteinaemia	B cell lymphoma	Paraprotein in both blood and urine
Food constituent (rare)	Unknown	Salicylates	Response to exclusion and reintroduction

*Stress may aggravate chronic urticaria from a variety of causes.

FBC, full blood count; ESR, erythrocyte sedimentation rate; ANA, antinuclear antibody; EBV, Epstein-Barr virus; ACTH, adrinocorticotropic hormone; LFT, liver function test; ASOT, anti-streptolysin O test; ANCA, antineutrophil cytoplasmic antibody, NSAID, non-steroidal anti-inflammatory drug.

These antibodies are disease specific with some studies suggesting that this subgroup of patients experiences a more intense and protracted disease course [9]. In about one-fifth of patients chronic urticaria is associated with antithyroid antibodies [16–19] compared with a figure of 6% in the general population [16].

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 antibody and antigen interacting to form immune complexes, e.g. in hepatitis C [20–22] and hepatitis B [23], EBV, other viral and possibly parasitic infections.

Allergic contact urticaria. Urticaria can develop locally after contact with allergens via an IgE-mediated mechanism (latex gloves, egg, dog saliva, etc.) and should be referred to as allergic contact urticaria.

Physical urticarias. Many patients have a physical element to their urticaria with triggering by heat, cold, pressure, vibration, water, ultraviolet light, etc. The physical urticarias are triggered reproducibly after a specific physical stimulus is applied [24]. Weals usually appear immediately and often last for <2 h. A few patients have delayed-pressure urticaria, which as the name implies, comes on slowly after pressure, and lasts several hours or days. The physical urticarias can be more resistant to therapy and follow a protracted course.

Food triggers. Patients or their parents frequently analyse foods, food additives/preservatives/dyes eaten over the previous 24 h or longer in the search for a connection with symptoms. There is no rational basis for this because in genuine food allergy, symptoms usually occur reproducibly within 60 min of exposure to the offending food. Occasionally, exceptions occur for example in some patients wheat allergy is clinically manifested only in association with exercise [25].

Unless there is a relationship to a particular food trigger, either by ingestion, or contact (localized contact urticaria), IgE-mediated food allergy can usually be excluded as a cause of urticaria/angio-oedema particularly if the symptoms come on overnight or are present first thing in the morning. Furthermore, allergic food reactions do not produce an urticarial rash (with or without angio-oedema) lasting several days, nor rashes/swellings

commencing several hours after ingestion of food. Urticaria due to 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. Symptoms of CU are therefore commonly non-allergic with most patients having idiopathic or autoimmune urticaria/angio-oedema.

Stress. Urticaria and angio-oedema can lead to significant stress and the converse is also recognized namely that psychological stress can trigger or aggravate urticaria. A possible mechanism for the latter is through stress-induced release of corticotrophin-releasing hormone (CRH) which is known to be expressed locally in the skin. In chronic urticaria there is up-regulation of the CRH-R1 receptor that mediates CRH-dependent cutaneous mast cell degranulation [26].

Other putative causes. An underlying extraneous cause for chronic urticaria cannot be identified in most patients, but infections may play a causative role in a few cases, and 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. Infection with *Helicobacter pylori* (HP) has been proposed as a possible cause, but the association is unlikely to be causal (particularly in otherwise asymptomatic children where the background prevalence of HP infection is high). Candida colonization of the gut is not a cause of chronic urticaria [27].

Mechanisms specifically related to angio-oedema

Angio-oedema without urticaria. Individuals with *angio-oedema and no urticaria* should specifically have their medications and family history reviewed in order to identify those on ACE inhibitors and those patients with HAE. Non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, and antiepileptics can also induce angio-oedema [28, 29]. Acquired forms of C1 inhibitor deficiency may result from autoantibody binding of C1 inhibitor, or depletion of C1 inhibitor due to C1 activation by paraprotein [30]. Investigations typically show reduced levels of complement C4 and may reveal low levels of C1 inhibitor and the presence of a paraprotein.

Angio-oedema with angiotensin converting enzyme inhibitors. The incidence of ACE inhibitor induced angio-oedema is 0.1–0.2% according to a study collecting available information from 1980 to 1997 [31], but in a more recent study has been found as high as 0.68% [32]. The variation in these estimates may arise because most cases were initially thought to occur in the first week of treatment but it is now appreciated that later onset angio-oedema, sometimes occurring after many years of uneventful drug use, may be more common [31–33]. The mechanism underlying the angio-oedema is likely to be the increased availability of bradykinin; this effect may also aggravate the angio-oedema associated with HAE. Angio-oedema associated with angiotensin receptor blockers has been reported infrequently and hence their use in individuals with ACE inhibitor-related angio-oedema has been questioned but is not contra-indicated [34].

The patient usually presents with swelling of the tongue but may also involve the lips, pharynx, larynx and viscera. Fatalities are reported [35] and hence it is mandatory to recommend that the ACE inhibitor is withdrawn. The episodes of angio-oedema may persist for a few months after withdrawal of the ACE inhibitor without undermining the validity of the drug-related diagnosis [34]. Individuals of Afro-Caribbean origin are at increased risk of ACE inhibitor-induced angio-oedema and as these drugs are less effective in such individuals, an alternative antihypertensive may be prudent [31, 32, 36]. Antihistamines, corticosteroids and adrenaline are often used to treat these individuals although the efficacy of such treatment remains undetermined. C1 inhibitor concentrate is not beneficial in patients with acute angio-oedema associated with ACE inhibitors, although there are anecdotal reports of the benefit of fresh frozen plasma [37, 38].

Follow-up studies of individuals with presumed ACE inhibitor-related angio-oedema show that in 85% 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, probably have idiopathic angio-oedema and are 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 frequent and severe. ACE inhibitors are contra-indicated in subjects with a history of chronic angio-oedema, and alternative drugs should be used.

Hereditary angio-oedema. Angio-oedema occurs without urticaria in HAE and typically involves cutaneous sites, the gut and larynx. A family history should be sought and this condition should be excluded by measurement of C4 and antigenic C1 inhibitor levels (which are low in most cases even between attacks). Functional C1 inhibitor quantitation should be reserved for equivocal cases with a suggestive history but normal levels of antigenic C1 inhibitor. This condition has been reviewed in detail elsewhere [39].

Prognosis

At least 20% of chronic urticaria patients with symptoms severe enough to warrant hospital referral

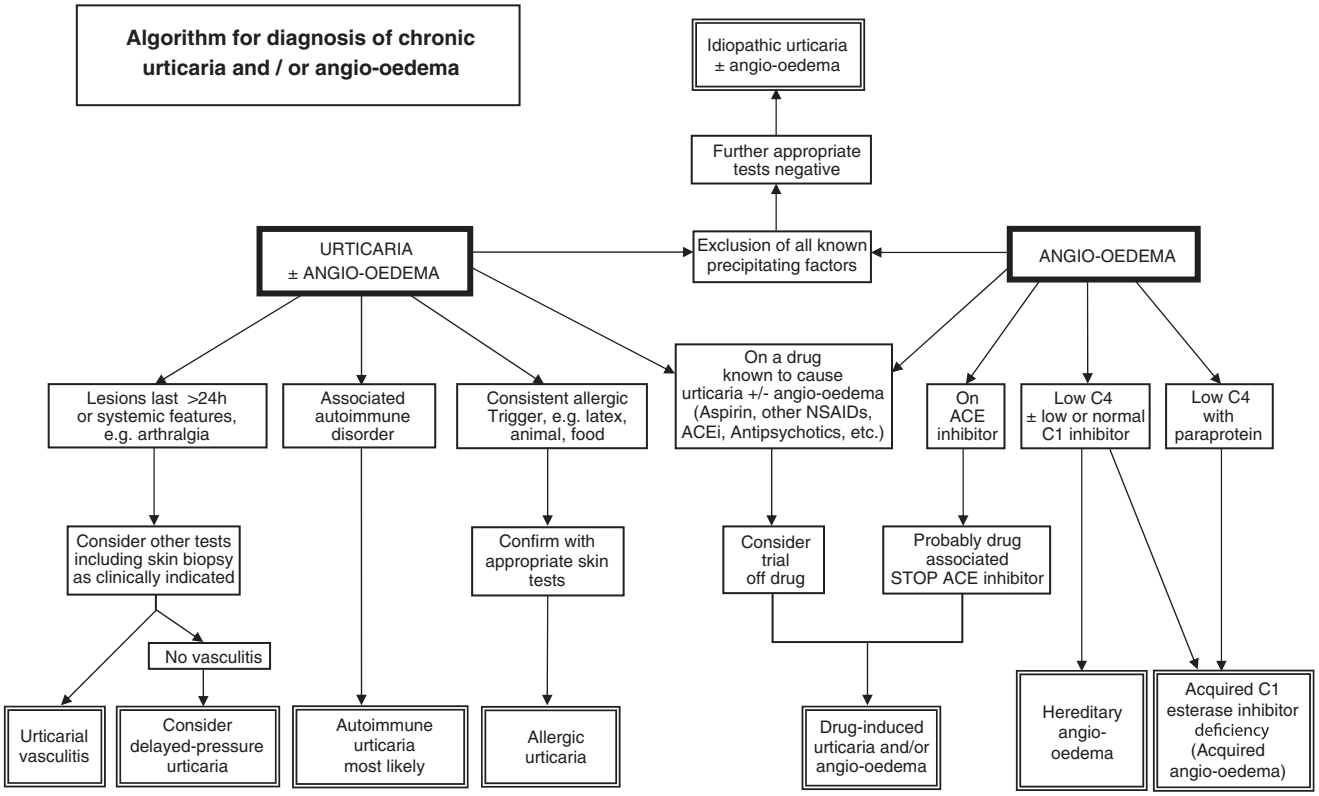

Fig. 1. Algorithm for diagnosis of chronic urticaria and / or angio-oedema.

remain symptomatic 10 years after first presentation [40]. This figure compares closely with a study published a decade earlier [41]. The duration of chronic urticaria correlates with clinical severity, the presence of angio-oedema and positive antithyroid antibodies [42]. A positive autologous serum test is found in patients with more severe symptoms although it is not associated with an overall longer disease duration [6, 9]. The introduction of non-sedating antihistamines does not appear to have influenced the duration of symptoms in the group with persistent disease, however the proportion of patients showing significant relief was 31% in an earlier study [41] compared with 44% in a later study [40] possibly due to increased potency of these newer drugs.

Making the diagnosis

Clinical history and examination

A detailed history of urticaria and angio-oedema is essential. It 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 angio-oedema can be helpful in confirming the nature of the lesions. Detailed drug and family history as well as response to treatment are important. 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 angio-oedema.

Key questions/signs

Text box 1: *Is there an allergic cause?*

- Does it occur only and reproducibly within 60 min (usually within 20 min) of eating a particular food?
- Does it occur only if a particular food has been eaten followed by exercise?
- Does it occur only after exposure to latex?
- Does it occur after contact with an allergen to which the patient is sensitive (cats, contact with horses, rolling on grass, handling a particular food, etc.)
- Could it be caused by any drugs the patient has taken (aspirin/NSAID/ACE-inhibitor in particular)?

Text box 2: *Is there a vasculitic process?*

- Is the urticaria/angio-oedema relentless 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?

Investigations

The diagnosis is based primarily on the clinical history and further investigations may not be required. Investigations which may be used to aid a clinical diagnosis of the underlying aetiology are listed in Table 2 [43].

Skin prick testing. Allergic reactions to foods are rarely the cause of chronic urticaria but patients are often referred to hospital in the belief that foods are responsible. A practical approach is to start by excluding an atopic diathesis by undertaking skin prick tests (SPTs) to a panel of aeroallergens. If negative, this significantly reduces the likelihood of an IgE-mediated allergic reaction to foods and other allergens. Additional skin testing can also be helpful to some of the foods that the patient suspects as the cause of their urticaria. The sight of a negative SPT helps to reassure the patient that allergy is not the cause of their symptoms and may contribute to improved concordance with long-term antihistamines. However, foods may be responsible for the symptoms of acute intermittent urticaria [44], for example wheat followed by exercise can cause urticaria/angio-oedema and even anaphylaxis [45, 46]. In this situation the patient is often atopic and has a positive SPT and/or specific IgE to the implicated food.

Full blood count. A full blood count (FBC) and differential white count are useful and in particular the eosinophil count may be elevated in parasitic infections and in some drug-induced reactions. There may also be an elevated neutrophil count in urticarial vasculitis.

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

Erythrocyte sedimentation rate. An elevated erythrocyte sedimentation rate (ESR) suggests an underlying systemic condition such as chronic infection, vasculitis and paraproteinaemia.

Cryoglobulins. A clotted sample collected and transported to the laboratory at 37 °C can be analysed for cryoglobulins which can be associated with secondary cold urticaria.

Thyroid function and autoantibodies. The presence of thyroid autoantibodies is associated with chronic urticaria in both children and adults with chronic urticaria and suggests a diagnosis of autoimmune urticaria. Patients are often euthyroid but require monitoring over time.

Parasitology. A clear association between parasitaemia and CU has not been established, however, in patients with unexplained eosinophilia and a relevant history of travel abroad, hot stool samples can be sent for cysts, ova and parasites. Serology may be an alternative investigation in some cases.

Challenges. Cold-induced urticaria can usually be diagnosed by placing an ice cube in a sealed plastic bag over the forearm for 20 min (allow skin to re-warm subsequently). Dermatographism is suspected at the time of skin prick testing and confirmed by lightly scratching the skin (<36 g/mm^2) 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 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 [7].

Autologous serum skin test. 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 autoantibodies to the high affinity IgE receptor on the mast cell in chronic urticaria patients [47]. This remains a research tool, is not widely used and has a variable sensitivity of only 70% and specificity of 80% when compared with an *in vitro* basophil-release assay. The ASST is poorly tolerated by younger children due to discomfort experienced by the intradermal injections performed in the absence of topical anaesthetic creams [12]. A positive ASST correlates with

more severe symptoms but is not associated with a prolonged duration of chronic urticaria [6, 9].

Symptom diaries. Symptom diaries are useful as an investigative tool to determine the frequency, duration and severity of the urticarial episodes. Patients should also include possible triggers such as food, drugs and exercise to assess whether there are consistent precipitating factors. Patients who fail to uncover a consistent trigger or an ingested cause after desperately searching with a lengthy diary often find relief when advised to discontinue the search for an external cause.

Complement studies. C1 inhibitor deficiency is not associated with urticaria, hence C1 inhibitor does not need to be measured if urticaria is present. Initial complement investigations in patients with isolated angio-oedema should include C4 and C1 inhibitor while C3 and C4 should be measured in individuals with suspected urticarial vasculitis [42].

Endoscopy. Fibreoptic nasendoscopy undertaken during an attack allows direct visualization of the larynx and may help to exclude angio-oedema where the diagnosis is in doubt. Important differential diagnoses of 'swelling, lump or discomfort in the throat' include globus hystericus, and gastro-oesophageal reflux.

Treatment in adults

Avoidance

If avoidable triggers (Table 1) are identified, the patient should be given clear instructions on avoidance strategies, for example avoiding eating certain foods within 4 h of exercise in food/exercise-induced urticaria/anaphylaxis. Treatment of an associated autoimmune or vasculitic process may help with symptom control for example treatment with thyroxine in autoimmune hypothyroidism. If the patient is taking a drug associated with chronic urticaria or angio-oedema, for example a NSAID or ACE inhibitor, it is prudent for the patient to have a trial for at least several weeks without treatment. Treatment of underlying infections and malignancies may lead to amelioration or resolution of symptoms. Stress management strategies may also help.

Symptom control

In many cases, treatment of CIU is predominantly directed towards symptom control and therefore antihistamines active against the H_1 receptor remain the mainstay of treatment. Second-generation antihistamines that do not cross the blood–brain barrier have been developed to reduce central nervous system adverse effects. Therefore, second-generation antihistamines are more commonly prescribed and are generally well tolerated with minimal sedation: many have a once-daily dosage to improve compliance. Pharmacokinetics indicate 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. Whether higher doses of non-sedating antihistamines are superior to lower doses requires confirmation from randomized clinical trials. However, it is common practice to increase the dose above the normal recommendation when potential benefits are considered to outweigh the risks in patients who do not achieve adequate symptom relief at standard doses [7]. For example in cholinergic urticaria high dose cetirizine (20 mg) was effective compared with placebo and no adverse events were noted [48]. Once symptom control has been accomplished, the length of the proposed treatment course must be established. Empirically 3–6 months regular treatment is advised in most patients. For individuals with a long history at presentation or urticaria with angio-oedema, treatment for 6–12 months is advised with gradual withdrawal over a period of weeks. For patients with infrequent symptoms, treatment may be taken as required, or prophylactically before occasions when symptoms would be most unwelcome, e.g. business presentations. Figure 2 shows a step-up treatment plan for chronic urticaria.

A short course of steroids may be appropriate in severe episodes at any stage (e.g. prednisolone up to 40 mg daily for up to 7 days).

Choice of H_1 antihistamine. All antihistamines are licensed for use in chronic urticaria, but the chronic use of first-generation antihistamines, such as chlorphenamine, should generally be avoided because of sedation and psychomotor retardation. Few comparisons between second-generation antihistamines (H_1 antihistamines) in chronic urticaria have been published and there are individual variations in response to both the therapeutic and adverse effects. 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 [52]. Table 3 lists the antihistamines (H_1 antihistamines) indicated for use in chronic urticaria.

Comparative efficacy of antihistamines. A recent randomized double-blind study of 116 chronic urticaria patients comparing cetirizine (10 mg) with fexofenadine (180 mg) showed that with cetirizine a significantly higher proportion of patients responded with clearance (52%) of symptoms than with fexofenadine (4%) after 1 month of treatment. Similar proportions of patients showed partial

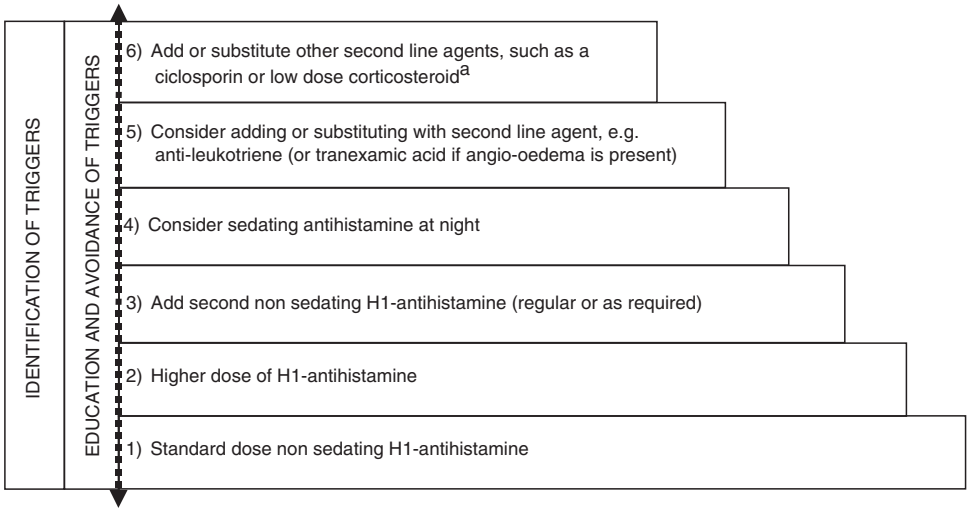

Fig. 2. General management plan for chronic urticaria and angio-oedema*.

*The starting point and the rate of progression between steps depend on clinical severity and response. Short course of corticosteroids (e.g. up to 40 mg/day prednisolone) may be used for severe exacerbations [49, 50], see also 'Corticosteroids'. The treatment should be stepped down once control is achieved. Recent observations on the mechanism of antihistamine action [51] suggest that it is probably sensible to withdraw such therapy gradually, rather than stopping it abruptly.

[a]Low dose daily corticosteroid (5–10 mg/day) or low dose alternative day corticosteroid (15–20 mg alt die) could be considered.

Table 3. Antihistamine (H_1 antihistamines) licensed for CU

Drug	Other comments/side effects	References
Loratadine	Second-generation antihistamine	[53]
Desloratadine	Second-generation antihistamine	[54, 55]
Fexofenadine	Second-generation antihistamine. Effective between 60 and 240 mg	[56]
Cetirizine	Second-generation antihistamine	[57–60]
Levocetirizine	Second-generation antihistamine	[61]
Acrivastine	Second-generation antihistamine. Rapid onset of action, not long lasting, excreted unchanged in urine; non-sedating; 'On demand' therapy	[62]
Hydroxyzine	First-generation antihistamine. Not for long term use; sedating	
Chlorphenamine (formerly known as Chlorpheniramine)	First-generation antihistamine. Not for long term use; injectable; short half life; sedating	
Promethazine	First-generation antihistamine. Not for long term use, injectable; sedating	[63]

improvements (37% and 42%, respectively) [64]. There are no comparisons of loratadine/desloratadine with cetirizine/levocetirizine in chronic urticaria.

Comparative side-effects of antihistamines. Sedation and impaired psychomotor function, although reduced with the second-generation antihistamines, can still occur with these agents. For example the sedative effect of cetirizine was greater than that of fexofenadine in some clinical trials and that of loratadine or fexofenadine in a post-marketing surveillance study [65]. However, a recent study investigating the administration of levocetirizine in 48 healthy subjects compared with placebo showed that memory, attention and tracking were unaffected after acute (1 day) or sub-chronic (4 days) administration [66]. Overall objective tests in RDBPC trials have not shown clinically relevant differences in the central nervous system effects of three second-generation antihistamines: levocetirizine, cetirizine and loratadine [63]. All patients on antihistamines should be warned to avoid excess alcohol and advised that the performance of complex tasks may be affected.

In summary, based on a single study of chronic urticaria, and studies of suppression of *in vivo* histamine-induced weal and flare responses, cetirizine may be more effective than the other antihistamines in chronic urticaria. However, individual patient responses and side-effects to antihistamines vary and hence an endorsement for a particular antihistamine cannot be given. If higher than

Table 4. Second line pharmacotherapy (oral drugs)

Drug (families)	Grade	Specific indication/comments/side effects	References
Leukotriene receptor antagonists (Montelukast, 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	[67–69, 55, 70] Table A1
Ciclosporin	B	Immunosuppresive, i.e. requires monitoring of blood pressure, renal function and serum levels if indicated; significant side-effects	[77] Table A2
Tacrolimus	D	Value in severe, steroid-dependent chronic urticaria needs further randomised controlled studies	[80]
Tranexamic acid	D	Showed reduced frequency of angio-oedema attacks.	[81, 82]
Histamine receptor-2 blockers (Ranitidine)		Not recommended as monotherapy, may be useful in combination with H_1 antihistamines for refractory chronic urticaria; usually better to increase dose of H_1 antihistamines	[83–86]

Grade = Grade of recommendation (see Grade Table A5) [87, 88].
B[1] = Grade only refers to Montelukast, but not to Zafirlukast.

Table 5. Rarely used drugs

Drug (families)	Grade	Specific indication/comments/side effects	Reference
Nifedipine	C	Showed benefits (hive count, hive index, and itch index) in chronic urticaria when added to maximum doses of H_1 and H_2 antihistamines. (DBPC cross-over study)	[89]
Colchicine	D	One patient showed total clearance of urticarial vasculitic rashes and chronic vasculitic ulceration previously unresponsive to steroids in combination with dapsone and hydroxychloroquine	[90]
Sulphasalazine	D	Successful in two patients with refractory delayed-pressure urticaria and angio-oedema. One was steroid-dependent and managed to come off prednisolone	[91, 92]
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	[93, 94]
Methotrexate	D	Beneficial for corticosteroid-dependent chronic idiopathic urticaria (two patients). Efficacy in urticarial vasculitis (one patient)	[95, 96]
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	[97]
Warfarin	C	Improvement in 6/8 patients who were unresponsive to antihistamines	[98]
Thyroxin	D	There is a clear rationale for treating the hypothyroid state with thyroxin, however the use of thyroxin in a euthyroid subject is controversial and not recommended	[18, 99, 100]
Bradykinin β-2 receptor antagonist (Icatibant)		Being assessed presently – received fast track status in the United States for treatment of acute attacks of HAE	
Hydroxychloroquine		Improvement of QoL, but no reduction in urticaria scores or medication requirements	[101]

Grade = Grade of recommendation (see Grade Table A5) [87, 88].
CIU, chronic idiopathic urticaria; HAE, hereditary angio-oedema; QoL, Quality of Life, DBPC, double blind placebo-controlled.

recommended doses of antihistamines are to be considered, incremental up-dosing is advised.

Other oral drug treatments. In cases of chronic urticaria and angio-oedema, resistant to high-dose antihistamines, there is no accepted 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 (LTRAs) may be useful in combination with antihistamines in a subgroup of patients with chronic urticaria and particularly those with adverse responses to aspirin, NSAIDs and in those with delayed-pressure urticaria or possibly chronic autoimmune urticaria [67–69, 74, 102]. See also evidence Table A1.

Ciclosporin. Ciclosporin may be considered in patients with severe unremitting disease uncontrolled by antihistamines [77]. A T cell mediated mechanism has been proposed but ciclosporin also inhibits basophil and mast cell degranulation. See also evidence Table A2.

Tranexamic acid. Tranexamic acid appears to benefit patients with angio-oedema with or without urticaria and

works by inhibiting the conversion of plasminogen to plasmin and consequently the production of bradykinin. The evidence is anecdotal, but common usage recommends consideration in problematic cases.

Corticosteroids. There are no controlled studies on the use of corticosteroids in urticaria and angio-oedema, but their effectiveness is generally accepted (grade of recommendation = D). Rarely a short course of prednisolone may be prescribed for severe exacerbations of chronic urticaria, especially when accompanied by angio-oedema. Corticosteroids may also be considered when the symptoms are not controlled by antihistamines alone or when rapid clinical relief is required. Urticarial vasculitis is more likely to require corticosteroid treatment. Long-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.

Non-oral drug treatments

Intramuscular/aerosolized adrenaline (epinephrine). In the acute management of oedema affecting the upper airway, local use of aerosolized adrenaline (e.g. Primatene Mist on a named patient basis), when available, can be useful, although such use has not been studied in a trial situation. Intramuscular adrenaline is not indicated in chronic urticaria and should only be prescribed for self-administration to patients with a history of angio-oedema affecting the upper airway. In these individuals all possible underlying causes should be investigated and treated appropriately using the step-up treatment schedule (Figs 2 and 3) in an attempt to suppress the oropharyngeal swellings completely. In the small number of patients who continue to experience upper-airway oedema, an emergency self-management protocol should be provided which may include the use of topical and/or i.m. adrenaline.

Intravenous immunoglobulin. Intravenous immunoglobulin (IVIG) has been used in 10 individuals with severe autoimmune chronic urticaria using 400 mg/kg daily for 5 days. Clinical benefit occurred in 9/10 patients with three experiencing long-term benefit [103]. Recent supply problems make the use of IVIG for unlicensed indications problematic.

Dermatological preparations. Cooling antipruritic lotions such as 1% (and empirically up to 4%) menthol in aqueous cream can be soothing [104].

Dietary advice

There is no evidence to support the routine use of low salicylate diets. However, acetyl salicylates may exacerbate urticaria in some patients with chronic urticaria. In those individuals with chronic urticaria aggravated by NSAIDs and who respond to LTRAs, a trial of a low salicylate diet may be considered [68]. Suspected tartrazine-induced urticaria/angio-oedema is rarely reproducible by oral challenge and hence additive-free diets are not justified in patients with CIU [105].

Patient leaflets

Written information sheets are well received by patients and the British Association of Dermatologists' publication on 'Urticaria & Angioedema' [104] is recommended particularly as it reinforces the concept that environmental allergens are usually not the cause of chronic urticaria.

Chronic urticaria in childhood

Epidemiology and clinical presentation

Chronic urticaria is thought to affect 0.1–3% of children in the United Kingdom [7]. Acute urticaria occurs more commonly and affects 4.5–15% of UK children [106]. Acute urticaria differs from chronic urticaria in that a cause is more frequently established, e.g. acute infection or allergen ingestion. The distorted appearance associated with urticaria and/or angio-oedema may significantly impair QoL. It is not uncommon for children to have missed significant periods of school, due to a lay perception that the condition is infectious or allergic and fear that the child is 'unwell'. Approximately 50–80% of children with chronic urticaria also have accompanying angio-oedema [7].

Aetiology and mechanisms

Children presenting with chronic urticaria are frequently over-investigated. A detailed clinical history and physical examination usually establishes the diagnosis and aetiology. In children, physical factors such as pressure or cold exposure are the most commonly diagnosed precipitating factors for chronic urticaria, with other triggers accounting for $<1\%$ [7, 107], Table 1. Thirty percent or more of children with chronic urticaria have an autoimmune aetiology with a positive ASST [13]. About 4% of children with CU have positive antithyroid antibodies, although the majority are euthyroid [108]. In addition to the mechanisms described in 'Aetiology', the following mechanisms may apply to chronic urticaria in children.

Vasculitides and connective tissue disorders. A diagnostic skin biopsy should be considered if features such as fever, painful lesions, arthralgia, raised ESR, lesions lasting 24 h or more or lesions which resolve with residual petechiae or purpura are present. These features are not typical of chronic urticaria and pathological biopsies may

demonstrate a leukocytoclastic angiitis rather than the non-necrotizing vasculopathy typical of chronic urticaria. The commonest cause of acute vasculitic urticaria in children is Henoch–Schonlein purpura which in addition to a leucocytoclastic vasculitis has IgA deposits in vessels.

Thyroid autoimmunity. An association between childhood chronic urticaria and thyroid autoimmunity has been postulated [108, 109]. It is not clear if the association is causal, as the majority of children present with hyper- or hypo-thyroid symptoms either before or some time after the onset of chronic urticaria, and the urticarial symptoms do not always improve with thyroxin replacement therapy. Nonetheless, ongoing thyroid function monitoring is encouraged for children with CU and thyroid autoimmunity [12, 108].

Coeliac disease. There are case reports of an association between chronic urticaria and coeliac disease, which may improve on a gluten-free diet [110, 111].

Prognosis

The natural history of chronic urticaria in childhood is for disease remission. Approximately 25% of children will achieve remission within the first 3 years of presentation [12].

Investigations

If the clinical history and examination are typical of CIU, 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, 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. A detailed clinical history is extremely important for any decisions regarding further investigations.

Skin tests. 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 always be guided by the history in order to avoid the generation of false-positive results.

Additional investigations (if clinically indicated; rationale for tests as detailed in 'Investigations')

- Urinalysis.
- FBC.
- ESR.
- Liver function tests (add viral hepatitis screen if transaminases abnormal).
- Coeliac disease: 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 [112].
- Elimination re-challenge diets: Foods and food additives are unlikely to be the cause of chronic urticaria and are best excluded on clinical history. Although allergy tests (SPTs and specific IgE tests) are useful in diagnosing IgE-mediated allergy, they cannot detect reactions due to food additives and dyes (i.e. non-IgE mediated allergies) and delayed-immunological reactions. Rarely, it may be necessary to undertake carefully planned and dietician-supervised elimination and re-challenge 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 ('Skin biopsy').
- Hereditary or acquired deficiency of C1 inhibitor is not associated with urticaria; therefore, further investigations are only indicated for children presenting with angio-oedema alone.
- Serum cryoproteins are rarely found in children with cold urticaria.
- Investigations aimed at diagnosing current or past viral, bacterial or parasitic infections should be guided by the history, clinical findings and initial screening tests, e.g. eosinophilia.

Treatment

Management plan. As mentioned in 'Avoidance', avoidance of known provoking stimuli should be the primary strategy in any treatment. Figure 3 shows a management plan for chronic urticaria in children.

H_1 antihistamines (grade of recommendation = B; Table A4). Antihistamines are the mainstay of treatment for children with chronic urticaria. A lack of response to high-dose antihistamine therapy should raise the possibility of an alternate diagnosis. The non-sedating second-generation antihistamines have fewer adverse effects and are therefore preferred. Combinations of antihistamines may improve symptom control, e.g. use of two different second-generation antihistamines or alternatively a second-generation antihistamine in the morning and short-term use of a first-generation antihistamine in the evening. Higher than recommended antihistamine doses are frequently required in order to adequately control symptoms. Chronic urticaria

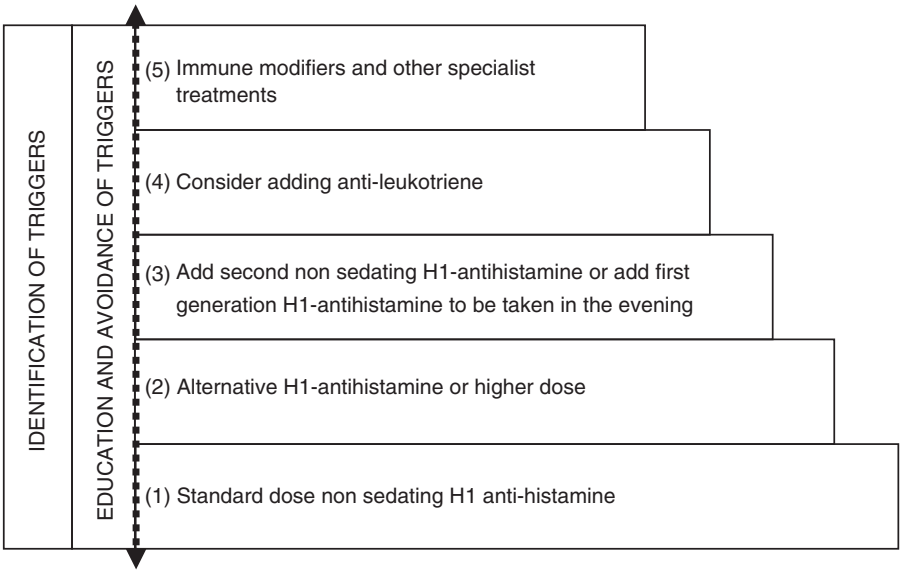

Fig. 3. Management plan for chronic urticaria and angio-oedema in children*.
*The starting point and the rate of progression between steps depend on clinical severity and response. Short course of corticosteroids (e.g. 1 mg/kg prednisolone twice a day, up to 40 mg total per day, for 3 days) may be used for severe exacerbations, see also 'Corticosteroids (level of evidence = 2 − ; Table A4)'. The treatment should be stepped down once control is achieved. Recent observations on the mechanism of antihistamine action [51] suggest that it is probably sensible to withdraw such therapy gradually, rather than stopping it abruptly.

may present as early as the second year of life which limits the choice of licensed antihistamine [12, 13].

Second-generation non-sedating antihistamines. Cetirizine and loratadine are licensed for the treatment of chronic urticaria in children of 2 years and older. Desloratadine can be given to children aged 1 year and older. Fexofenadine and levocetirizine are licensed for use in children over 6 years. There is safety data for the use of cetirizine for younger children aged 1–2 years at a dose of 0.25 mg/kg twice daily [21]. Desloratadine and cetirizine are available in syrup formulations, the latter being sugar free.

First-generation sedating antihistamines. Commonly used first-generation sedating antihistamines, licensed for use in childhood include diphenhydramine, hydroxyzine, promethazine, chlorphenamine, but only chlorphenamine and hydroxyzine are licensed for use in children under 2 years of age. Although children may become accustomed to the sedating effects of first-generation antihistamines, there is a risk of psychomotor impairment which may impact on the child's safety and education. Cyproheptadine has anecdotally been effective for use in children with cold urticaria, but is known to increase appetite.

H_2 receptor antagonists (grade of recommendation = C; Table A4). Only a marginal benefit is gained by the addition of H_2 receptor antagonists (H_2RA) to an H_1-antihistamine, see Table 5.

Leukotriene receptor antagonists (grade of recommendation = C; Table A4). There are a number of case reports which demonstrate that LTRA therapy is superior to placebo in the treatment of children and adults with chronic urticaria. LTRAs should only be used as add-on therapy. Montelukast and zafirlukast are both LTRAs licensed for the prophylaxis of asthma from the age of 6 months and 12 years, respectively. The recommended dose of montelukast in children 6 months to 5 years of age is 4 mg, and can be provided as a granule preparation. From 6 to 14 years of age the recommended dose is 5 mg.

Corticosteroids (grade of recommendation = D; Table A4). Short-term use of oral corticosteroids may be required to gain control if children remain poorly responsive to maximal doses of H_1 antihistamines and a trial of H_2 receptor blockade and LTRAs. In physical urticarias, unresponsive to first-line therapy, corticosteroids are poorly effective. In patients with delayed-pressure urticaria corticosteroids are more effective but prolonged use results in unacceptable side-effects [113].

Additional immune modifiers and experimental therapies (grade of recommendation = D; Table A4). Any other therapies such as plasmapheresis, ciclosporin, sulfasalazine, warfarin and androgens [109, 113] should be limited for use in difficult cases and only considered in specialist centres.

Chronic urticaria in pregnancy and breastfeeding

Pregnancy

It is best practice to avoid taking drugs in pregnancy, as present knowledge is incomplete. None of the currently

licensed antihistamines have been shown to be teratogenic in humans, but high doses of hydroxyzine and loratadine have caused embryotoxicity in animal studies. Therefore the data sheets for cetirizine, desloratadine, hydroxyzine and loratadine all advise avoidance in pregnancy. The pregnant patient should be informed that no drug can be considered absolutely safe but that the small risk has to be balanced against the benefits of keeping the mother healthy in the interest of the foetus. Prescribed drugs must be selected cautiously after the patient has been informed of the potential adverse effects. The possible consequences of inadequately controlled disease should be discussed with the patient and the discussion documented in the case notes. Although chronic urticaria often improves in pregnancy, reducing the need for antihistamine treatment, in some rare cases symptoms of urticaria worsen.

Although there are no controlled studies on the safety of chlorphenamine in human pregnancy there are reports of several thousand exposures to chlorphenamine with no evidence of an increased incidence of congenital abnormality. The Collaborative Perinatal Project reported 3931 women who had taken chlorphenamine during pregnancy of which 1070 had taken chlorphenamine in the first trimester. Although a small number of malformations were reported, there was no consistent pattern. Therefore no evidence for a causal relationship with either a major or minor abnormality could be established when chlorphenamine was taken at any time during pregnancy [114]. In two cohort studies there was no increase in the frequency of congenital abnormalities among more than 275 births in women who took chlorphenamine during the first trimester [115, 116]. There is one report of neonatal respiratory depression following use in the third trimester and although a causal relationship was not established there is a data sheet warning that use of chlorphenamine in the third trimester may result in reactions in neonates.

Using prospectively collected data, no increase in the rate of congenital malformations was found in 1769 pregnant women who had taken loratadine [117]. A further prospective controlled study followed-up 210 women exposed to loratadine of which 78% took loratadine in the first trimester. The rate of congenital malformations was similar for loratadine (2.3%) compared with the control group (3%) with no increase detected in women who had taken loratadine in the first trimester [118].

In a case-controlled study of 39 pregnant women taking cetirizine, there were no excess major or minor congenital malformations compared with the control group. However, there was a trend for more spontaneous abortions with cetirizine although this did not reach statistical significance [119].

As a result, chlorphenamine, loratadine and cetirizine have all been assigned a category B by the US FDA (see Appendix A, Table A3). It is therefore recommended that antihistamines should only be used if clearly needed and when the potential benefits outweigh the unknown risks to the foetus. Using the lowest dose possible chlorphenamine or loratadine are the antihistamines of choice in pregnancy. There is less clinical experience with cetirizine in pregnancy and therefore it should only be considered as a second-line agent.

Breastfeeding

Significant amounts of some antihistamines are excreted in breast milk and although not known to be harmful the manufacturers of cetirizine, cyproheptadine, desloratadine, fexofenadine, hydroxyzine, loratadine and mizolastine all advise avoidance while breastfeeding. Therefore, antihistamines should only be used during lactation when the clinical imperative outweighs the potential harm to the child and the lowest possible dose used for the shortest possible duration. Chlorphenamine has been reported to cause drowsiness and poor feeding. Both loratadine [120] and cetirizine appear much safer with only low levels found in breast milk [121] and therefore either of these drugs can be considered if required.

Management plan for urticaria and angio-oedema

When the history suggests non-allergic symptoms

Text box 3: *Management of patients with urticaria only*

- Check that symptomatic episodes have not followed ingestion of a non-steroidal anti-inflammatory drug, such as aspirin
- 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
- Consider adding one or more second line drug (see Table 5 and Fig. 2)

Text box 4: ***Management of patients with angio-oedema (with or without urticaria)***

- In patients with angio-oedema but not urticaria, exclude C1 esterase inhibitor deficiency (normal plasma C4 during an attack, or normal C4, C1 esterase inhibitor, and C1 esterase inhibitor function, between attacks, will exclude this)
- In general, follow paragraph 'A' above, but with the following additional considerations:
- If the patient is taking an ACE inhibitor, this drug should be stopped
- Even if the patient is not taking an ACE inhibitor, these should be avoided in the future
- Consider tranexamic acid for antihistamine resistant angio-oedema
- The prescription of an adrenaline auto-injector is not required when chronic urticaria occurs alone but may be advisable if there is a history of angio-oedema affecting the upper airway. The patient should then be shown how to use the device and provided with a written self-management protocol

Future research – eight key areas

- Epidemiological research to establish the true incidence and prevalence of this chronic disorder across all age groups.
- Well-controlled clinical trials in chronic urticaria with appropriate statistical power to clarify which antihistamines should be used in what dose and for how long when chronic urticaria does not respond to standard therapy.
- Studies to investigate whether the presence of angio-oedema affects the prognosis of disease.
- Investigation of the role of exacerbating factors in urticaria and angio-oedema, e.g. NSAIDs, stress, etc.
- Investigation of the role of second-line agents such as H_2 antihistamines, LTRAs and corticosteroids, etc. in well-designed controlled studies.
- Studies designed to correlate clinical presentation with prognosis and response to treatment, e.g. the use of tranexamic acid in idiopathic angio-oedema.
- Studies designed to understand the clinico-pathological association of thyroid autoimmunity and autoimmune urticaria.
- Development of reliable laboratory assays for identification of autoimmune urticaria.

These *guidelines* inform the management of urticaria and angio-oedema. Adherence to these guidelines does not constitute an automatic defence for negligence and conversely non-adherence is not indicative of negligence. It is anticipated that these guidelines will be reviewed 5 yearly.

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Appendix A

Tables A1–A5.

Table A1. Evidence table for the use of leukotriene receptor antagonists in chronic urticaria

Source	Design and sample	Interventions	Conclusions
Sanada et al. (2005) [71]	Non-randomised uncontrolled $n = 25$ with antihistamine uncontrolled chronic urticaria	Montelukast 10 mg added for at least 1 week	12/25 improved These were younger and had CIU for a shorter duration
White et al. (2005) [72]	RPC, $n = 48$, cross-over design	24 h observation	Fexofenidine showed greater weal and flare suppression and faster onset of action, compared with montelukast
Di Lorenzo et al. (2004) [55]	RDBPC, $n = 160$, four parallel groups	Desloratadine, desloratadine+montelukast, montelukast alone or placebo	Combined treatment no better than desloratadine alone
Nettis et al. (2004) [73]	RDBPC, $n = 81$, three parallel groups	6-weeks treatment Desloratadine alone, desloratadine+montelukast, or placebo	Symptoms and QoL improved with combined treatment more than with desloratadine alone
Bagenstose et al. (2004) [67]	RDBPC, $n = 95$, cetirizine refractory CIU	Zafirlukast+cetirizine vs. placebo+cetirizine 3 weeks treatment	Improvements in urticaria scores with zafirlukast only in subgroup with positive ASST
Nettis et al. (2003) [74]	$n = 20$, with delayed-pressure urticaria, DBPC	Loratadine alone compared to loratadine+montelukast. 15 days treatment	Combined treatment more effective than loratadine alone. 8/10 had complete suppression on pressure challenge
Erbagci (2002) [75]	RSBPC cross-over study $n = 30$, refractory CIU	Cross-over treatments: (i) montelukast+cetirizine *prn*; (ii) placebo+cetirizine *prn* for 6 weeks each	Improvement in urticaria activity scores with combined therapy
Reimers et al. (2002) [70]	RDBPC, $n = 52$, cross-over design	6 weeks active, then 6-weeks placebo treatment	No improvement with zafirlukast compared with placebo
Pacor et al. (2001) [68]	RDBPC, $n = 51$, patients with positive ASA or food additive challenges	Montelukast vs. cetirizine vs. placebo; 4 weeks treatment	More symptom-free days in montelukast group and improved sleep quality
Nettis et al. (2001) [76]	$n = 27$, parallel groups	Montelukast vs. fexofenadine 180 mg; 27 days treatment	Similar improvements in chronic urticaria for both groups. Six/nine patients with a positive ASST on montelukast became negative.

RPC, randomized placebo controlled; CIU, chronic idiopathic urticaria; RDBPC, randomized double blind placebo-controlled; QoL, quality of life; ASST, autologous serum skin test; DBPC, double blind placebo-controlled.

Table A2. Evidence table on the use of ciclosporin in chronic urticaria

Source	Design and sample	Interventions	Conclusions
Baskan et al. (2004) [78]	$n = 20$ open design patients with history of chronic severe idiopathic urticaria and positive ASST	Ciclosporin 4 mg/kg/day for either 4 or 12 weeks	Improvements in urticaria only in first month of treatment
Di Gioacchino et al. (2003) [79]	$n = 40$ RDBPC patients with history of chronic severe idiopathic urticaria and positive ASST	Ciclosporin 5 mg/kg/day for 8 weeks then 4 mg/kg/day for 8 weeks vs. Cetirizine 10 mg daily; follow-up for 9 months	Study unblinded after 2 weeks as 16/20 in cetirizine group developed a severe relapse. All patients placed on ciclosporin. 16/40 in remission at 9 months
Grattan et al. (2000) [77]	$n = 30$ RDBPC patients with history of chronic severe idiopathic urticaria and positive ASST	Ciclosporin 4 mg/kg/day for 4 weeks vs. placebo. All took cetirizine 20 mg daily	8/19 responded to ciclosporin and 0/10 to placebo at 4 weeks 26% of responders still clear at 6 months

Medline/Pubmed search terms for these references: c*closporin and urticaria; c*closporin and angio-oedema

Table A3. Current categories for drug use in pregnancy (US Food & Drug Administration)

Category	Description
A	Adequate, well-controlled studies in pregnant women have not shown an increased risk of foetal abnormalities
B	Animal studies have revealed no evidence of harm to the foetus, however, there are no adequate and well-controlled studies in pregnant women *or* Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the foetus
C	Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women *or* No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women
D	Studies, adequate well-controlled or observational, in pregnant women have demonstrated a risk to the foetus. However, the benefits of therapy may outweigh the potential risk
X	Studies adequate, well-controlled or observational, in animals or pregnant women, have demonstrated positive evidence of foetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant

Table A4. Levels of evidence [88]

Level of evidence	Definition
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1−	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case control or cohort or studies High-quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2−	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

RCT, randonized-controlled trial.

Table A5. Grades of recommendations [87, 88]

Grade of recommendation	Type of evidence
A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; *or* A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; *or* Extrapolated evidence from studies rated as 2+
E	Recommended best practice based on the clinical experience of the guideline development group

RCT, randonized-controlled trial.

