Investigation, Diagnosis and Management of Chronic Urticaria in Childhood

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Key Amendments

Date	Amendment	Approved by
February 2019	Addition of appendix 5. Link to Omalizumab	Paediatric QI
19th November 2020	Document extended for 1 year	Dr J West/Paediatric QIM
26th March 2021	Approved with no amendments	Paediatric QIM

Introduction

The target patients for this guideline are children and young people up to 16 years of age with chronic urticaria.

Urticaria can be described as migratory, well circumscribed, erythematous, pruritic plaques on the skin which may be accompanied by angio-oedema. Urticaria can be classified into *acute urticaria*, that lasting less than six weeks, and *chronic urticaria,* that lasting more than six weeks (30% cases overall). The traditional definition of chronic urticaria is *daily urticaria or angio-oedema lasting longer than six weeks*. An extended definition might be *episodic acute intermittent urticaria / angio-oedema lasting hours or days and recurring over a period of months or years.*

The incidence of urticaria in children is around 8 per 1000 person years. Prevalence of chronic urticaria has been reported between 1 and 5 per 1000 population[i,ii,iii]

Urticaria alone 40-70%
Urticaria with angiodema 50-80%
Angio-oedema alone 10%

Omalizumab for Allergic Asthma

See Omalizumab Therapy in Children and Young People Guideline

Inclusion criteria:

- A positive skin prick or specific IgE test to a perennial aeroallergen (e.g. dust mites, cats, dogs, and mould)
- Serum total IgE concentration between 30-1500 IU/mL (Patients with IgE <76 IU/ml are unlikely to experience benefit. If >12 years and IgE<76 IU/ml or 6-12 years and IgE <200 IU/ml should have positive IgE to perennial aeroallergen)
- Body weight between 20-150kg, although the weight limit may be lower depending on total IgE level (see dosing table)
- Reduced lung function (FEV1 <80% in adolescents >12 years and adults)
- Frequent day-time symptoms *or* nocturnal awakenings *despite* full trial of high-dose inhaled corticosteroids with good compliance and adequate inhaler technique, LABA medications, leukotriene receptor antagonists, theophyllines and oral corticosteroids and smoking cessation if appropriate

- Multiple documented severe exacerbations
- Continuous or frequent oral prednisolone courses (>4 courses per year)
- Smoking cessation measures if appropriate

The primary benefits to patients who respond to therapy are reduced disease exacerbations requiring fewer unplanned medical visits and fewer hospitalisations with resulting improvement in quality of life. Lung function may also improve, while some patients are able to reduce or discontinue systemic corticosteroids. Approximately 1 in 5 eligible patients fail to respond to a 16 week trial of therapy

Typical clinical signs

Urticaria	• Red, raised, itchy rash resulting from vasodilatation, increased blood flow and increased vascular permeability. • Weal size of a few mm to hand-sized, single or multiple • Affects the superficial skin layers (papillary dermis) • Usually arise spontaneously, peak at 8-12 hours and resolve by 24 hours
Angio-oedema	• Tissue swelling resulting from local increase in vascular permeability affecting the sub-mucosa, deeper reticular dermis and subcutaneous tissue. • Swellings can be painful rather than itchy • May affect skin (most commonly face, hands & feet), oropharynx, GI tract and genitalia, and may persist for days

Approach to the patient

A detailed history and examination usually establishes the diagnosis and aetiology. Physical factors e.g. pressure and cold, are the most commonly diagnosable trigger factors[iv] for chonic urticaria, with other trigger factors accounting for <1%. There is little published evidence for food, preservatives, dyes or additives as a cause. 30% of chonic urticaria has an auto-immune aetiology. 4% have positive anti-thyroid antibodies (but are usually euthyroid).

Always ask about triggers as it will help you diagnose the type of chronic urticaria.

Description	Type	Examples of triggers
Idiopathic urticaria		Stress, infections
Physical urticaria	Dermatographism	Minor trauma 5% of population to minor degree
	Cholinergic	Exercise, emotion Associated with atopy in 50% AKA "heat bumps"
	Delayed pressure	Jogging, sitting, tight clothing
	Cold	Swimming, cold wind
	Exercise	Sport/PE
	Aquagenic	Water contact, hot or cold
	Solar	Sunshine
	Vibratory	Drills, power tools
Drug-induced urticaria		Aspirin, NSAIDs, statins
Contact urticaria	IgE-mediated allergic	Latex, food, animals
Angio-oedema without weals	Idiopathic	Stress, infections
	C1 inhibitor deficiency#	Stress, infections, trauma
	Paraproteinaemia	Stress, infections, trauma
	Drugs	NSAIDs, statins, ACE inhibitors
Vasculitis*	Urticarial vasculitis*	Infections, drugs, autoimmune disease
Rare syndromes	CAPS Schnitzler's Syndrome	Cold

[1] Kozel, M.M., Bossuyt, P.M., Mekkes,and Bos, J.D. (2003) Laboratory tests and identified diagnoses in patients with physical and chronic urticaria and angioedema: a systematic review. *Journal of the American Academy of Dermatology* **48**(3), 409-416.

C1 inhibitor deficiency

May be primary **hereditary angio-oedema (HAE)** or secondary **acquired angio-oedema (AAE)**. HAE may start in childhood from the age of 18 months. Levels of C4 and C1 inhibitor (functional or antigenic) are low. A family history is usually apparent as HAE has an autosomal dominant mode of inheritance.[v]

[1] C1 inhibitor deficiency: consensus document. Clin Exp Immunol. 2005 Mar;139(3):379-94. Gompels MM et al

Vasculitidies and connective tissue disorders

Consider if associated features of

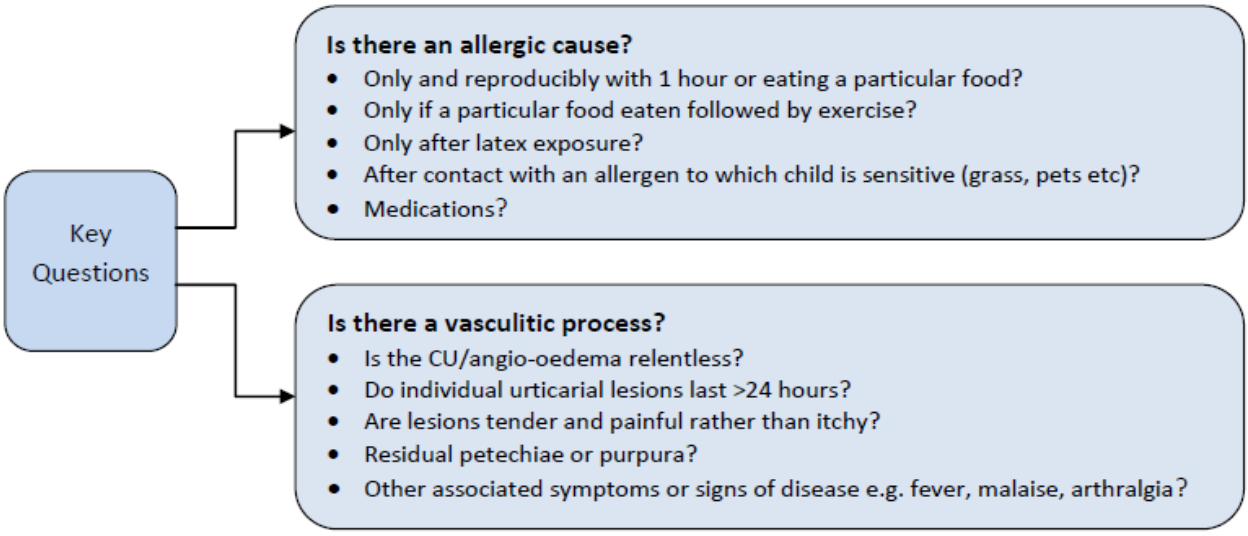
- Fever
- Lesions last >24h
- Residual petichiae or purpura
- Painful lesions
- Arthralgia
- Raised ESR

Biopsy of skin lesion is indicated in suspected urticarial vasculitis, which may demonstrate a leukocytoclastic angiitis, rather than a non-necrotising vasculopathy typical of chronic urticaria.

Diagnosis and Investigations

If the clinical history and examination are typical of chronic idiopathic urticaria, then laboratory investigations are rarely useful. **No investigations are required for the majority of patients mild chronic idiopathic urticaria responding to H1 antihistamines.** Tests should be guided by history, examination and potential aetiology. The history should take into account table 1 and trigger factors regarding potential aetiology/cause. An algorithm-based approach may be helpful (Appendix 1) in some children to minimise unnecessary investigations.

It may be useful to screen non-responders with severe disease initially with **full blood count (FBC)** *[to detect e.g. eosinophilia, or leucopenia in SLE]* and **erythrocyte sedimentation rate (ESR)** *[may be raised in vasculitis]*.



Useful investigations for acute / episodic urticaria

- If history reveals a candidate allergen then **skin prick testing (SPT)** or radioallergosorbent tests (RAST) is indicated.
- Range of allergens tested should be as guided by the history to avoid generation of false positive results
- Negative skin prick testing to show lack of atopy may be reassuring to families
- Cold dermatographism and pressure provocation tests
- Elimination and rechallenge diets

Other tests

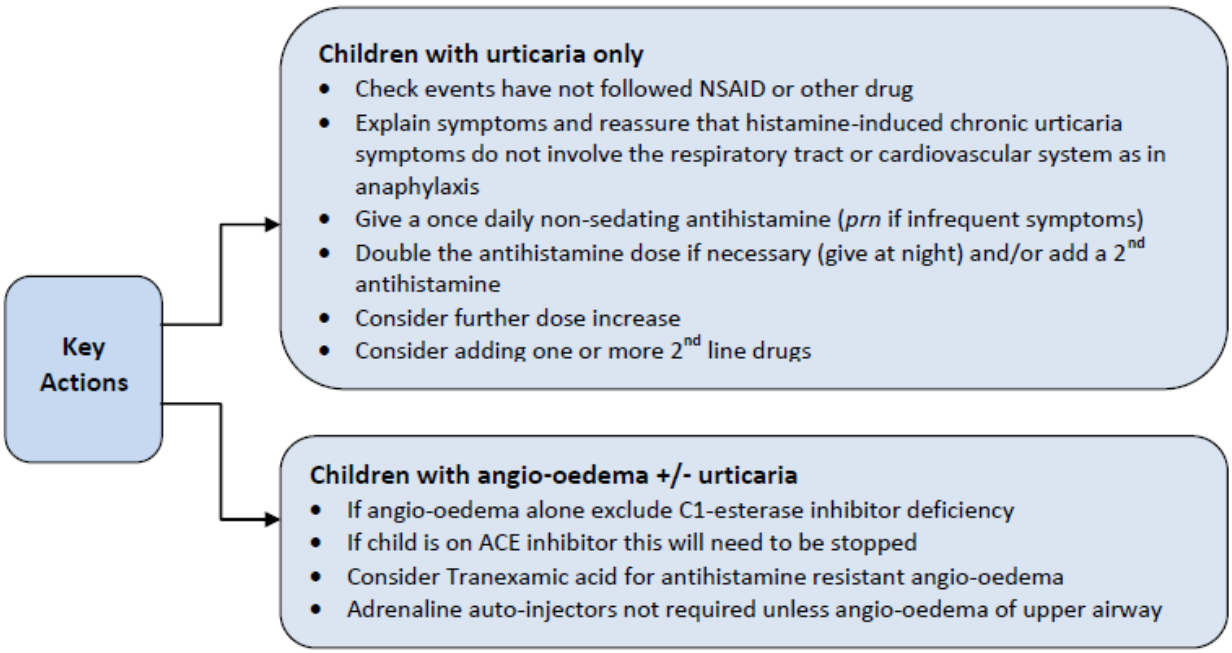
Tests should be as guided by history, examination and potential aetiology (Table 1 and Appendix 1).

May require:

- Urinalysis: for haematuria/proteinuria of an associated renal vasculitis
- FBC: eosinophilia in parasitic infection, drugs; neutrophilia in urticarial vasculitis?
- ESR: for chronic infection, vasculitis
- LFTs (& viral hepatitis screen if elevated transaminases)
- Coeliac screen: case reports of this as a cause of CU
- TFTs and antithyroid antibodies especially if an autoimmune aetiology is likely
- Basophil histamine release assay – gold standard for histamine releasing autoantibodies where available.
- ANA/autoimmune screen if connective tissue disorder suspected
- Skin biopsy if urticarial vasculitis suspected. Needs full vasculitis screen if present (see below)
- Complement **Serum C4** as screening test for hereditary angiooedema / acquired C1 inh deficiency. For angio-oedema only. Can be confirmed with C1 inh assay.
- Cryoproteins: but rarely found in children with cold urticaria
- Infective causes as directed by history

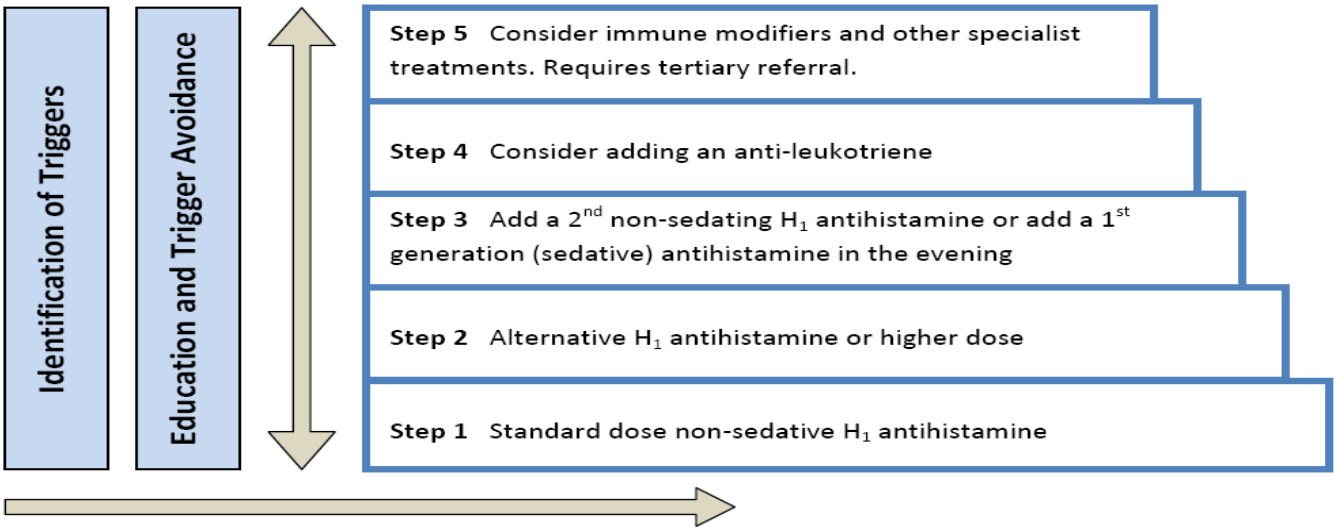
Vasculitis screen should include FBC, U+E, ESR or C-reactive protein, serum albumin, total protein and ANCA.

Management



Management should focus on avoidance of identifiable trigger factors, exclusion of treatable conditions, and then trial of medications in a step-wise fashion:

General measures should include minimizing aggravating factors such as overheating, stress, alcohol and certain drugs (see appendix 3) Symptomatic treatment with cooling antipruritics is often helpful, e.g. Calamine lotion or 1% menthol in aqueous cream.[vi]



First line medication
H1 antihistamines [Grade B]

H1 antihistamines are the mainstay of therapy. A lack of response should lead the clinician to question the diagnosis of chronic urticaria. The first choice medications are the 2nd generation non-sedating H1-antihistamines (see appendix 2 for licensed drugs).

Increasing the dose over the manufacturers' recommended limits may help in non-responders and should be considered where the benefits of doing so outweigh the risks.[vii]

The timing of the doses should be adjusted to anticipate when the urticaria will be worst.

Consider a combination of two different 2nd generation, or a 1st and a 2nd generation antihistamine (see Appendix 2).

Sedative H1 anti-histamines are less commonly used. They may be added to primary therapy with a 2nd generation anti-histamine at night and may help with sleep, but have little if any effect on the urticaria.

Second line medication
H2-Receptor Antagonists (Ranitidine) [Grade C]

An H2-antihistamine may be added to primary H1-antihistamine therapy and may give better control than H1-antihistamine alone.[viii,ix] This indication is off license. The benefit to the urticaria may be marginal but it may also relieve the dyspepsia that often accompanies it.

Leukotriene Receptor Antagonists [Grade C]

Montelukast and zafirlukast are the usual drugs chosen as add on therapy to H1-antihistamines. There is little evidence to support use as a monotherapy. There is some evidence that it may benefit Autologous Serum Skin Test (ASST) positive urticaria more than other patterns.

Corticosteroids [Grade D]

May be used in short courses only if the above are ineffective. Usually poorly effective in physical urticaria. May benefit urticarial vasculitis.

1 mg/kg up to twice a day to max 40 mg/day for 3 days for severe exacerbations. Step down dose once control is achieved.

Long term oral corticosteroids should NOT be used for chronic urticaria except in select cases under regular specialist supervision.

Prognosis

The natural history of chronic urticaria in childhood is disease remission. Resolution rate will depend on the aetiology. In idiopathic urticaria about 50% will resolve within 6 months.[x] In physical urticarias 12% resolve within 12 months and 38% by 3 years.

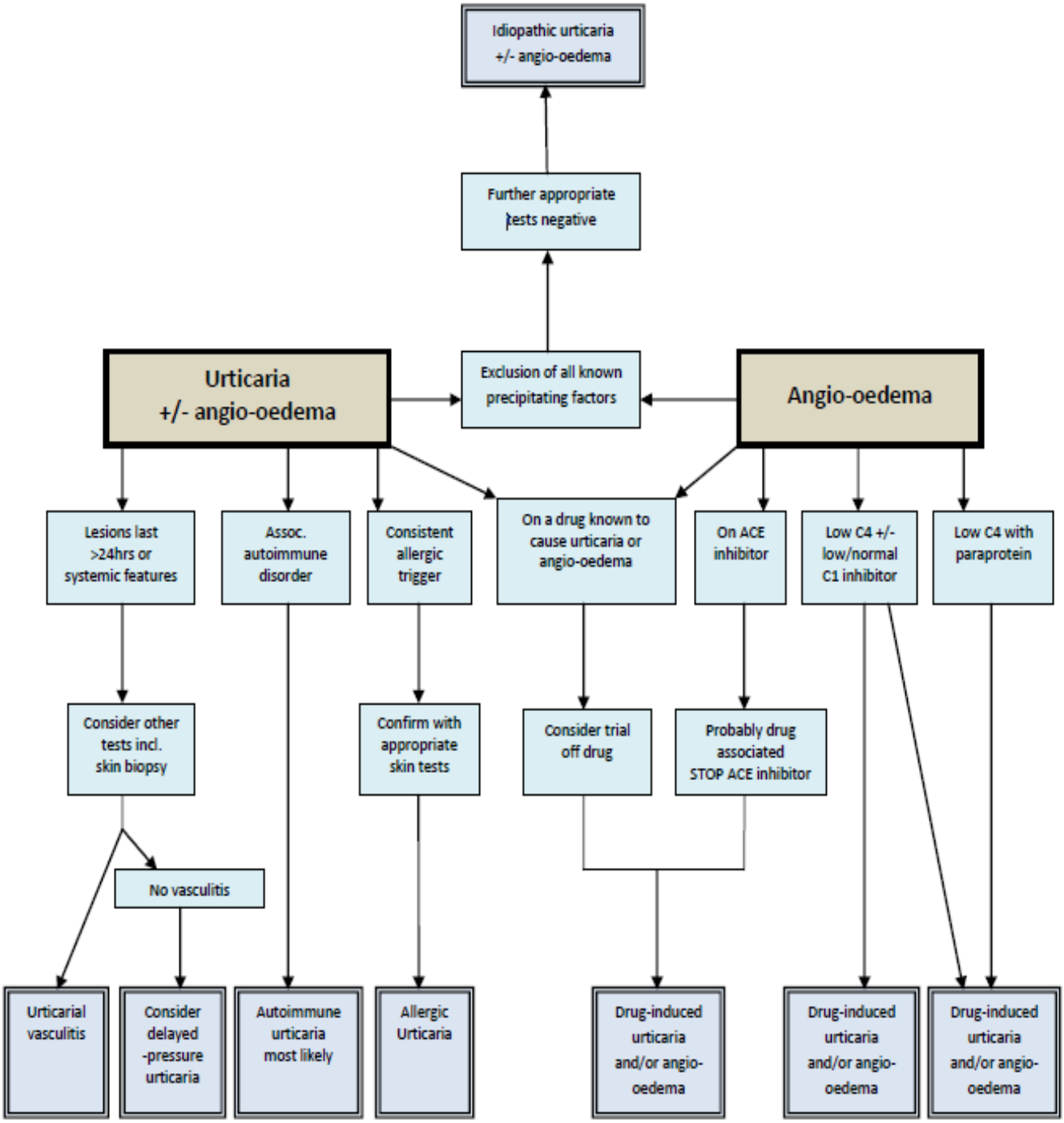
Adult onset chronic urticaria has a poorer prognosis with resolution rates of about 25% in 3 years.[xi]

[1] Schnyder B, Helbling A, Pichler WJ. Int Arch Allergy Immunol. 1999 May;119(1):60-3

[1] C1 inhibitor deficiency: consensus document. Clin Exp Immunol. 2005 Mar;139(3):379-94. Gompels MM et al

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

Start in one of the brown boxes: Urticaria with or without angio-oedema; and angio-oedema.



Appendix 2
Antihistamines

Currently licensed for use in the UK as described [March 2010]. Check appropriate authority for up to date prescribing information.

2nd Generation non-sedating	Comments	Syrup preparation available?
Cetirizine	Licensed for age 12 months +	Yes
Loratidine	Licensed for age 2rs +	Yes
Levocetirizine	Licensed for age > 6 yrs	Yes
Desloratidine	Licensed for age 12 months +	Yes
Fexofenadine	Licensed for age > 6 yrs	No
Acrivastine	Licensed for age 12 yrs +	No
Mizolastine	Licensed for age	No

1st Generation and sedating	Comments	Syrup preparation available?
Chlorphenamine	Not for long term use Age	Yes
Hydroxizine	Not for long term use Age 6 months +	No
Promethazine	Not for long term use Age 2 yrs +	Yes
Doxepin	A tricyclic antidepressant with antihistamine action. Not for use age < 12yrs. Specialist opinion only.	No

Appendix 3
List of drugs that may aggravate chronic urticaria

Many of these drugs are rarely used in children so are unlikely to be an issue.

Drug	
Opiates	Direct mast cell releasing.
Aspirin	
Non-steroidal anti-inflammatories	
Angiotensin converting enzyme inhibitors	

Appendix 4

Other immune modifiers [Grade D] which may be used in specialist centres only.

Drug	
Ciclosporin	May be effective in some patients with severe urticaria unresponsive to antihistamine. Dose, duration and patient selection have yet to be defined.[xii,xiii]
Methotrexate	Case reports of efficacy only.[xiv]
Tacrolimus	Apparently similar efficacy to ciclosporin but limited evidence.[xv]
Mycophenolate Mofetil	Apparently similar efficacy to ciclosporin but limited evidence.[xvi]

Rarely used drugs

Limited evidence for the following but may be used in specialist centres.

Nifedipine	Studied in adults only
Danazol	Studied in adults only
Warfarin	Studied in adults only
Colchicine	Case report and uncontrolled study in adults
Sulphasalazine	Case reports in adults with steroid dependent chronic urticaria
Dapsone	Case reports of efficacy in vasculitis
Tranexamic acid	Case reports only
Hydroxychloroquine	May improve quality of life scores but little evidence for improvement in other measures.
Cyclophosphamide **Omalizumab** **Etanercept**	Anecdotal reports of success. Limited by cost and availability.[xvii,xviii]
Plasmapheresis **IVIG**	May be effective in severe autoimmune urticaria but limited by cost and availability.[xix,xx]
PUVA / UVB	Results inconsistent. Narrow band UVB is under study and may show some benefit in the future.

Appendix 5 Weekly Urticaria Activity Score

Weekly Urticaria
Activity Score (UAS7)

Complete this questionnaire over 7 consecutive days. Your responses will help your doctor assess how active your chronic idiopathic urticaria (CIU) is. Please circle the score that corresponds to the number of wheals you have and the score that represents the intensity of your pruritus (itching) on a daily basis (see description in chart below). Remember to bring your completed questionnaire to your next visit.

Date	Daily number of wheals	+	Daily intensity of pruritus	=	Daily UAS score*
Example	0 (1) 2 3	+	0 1 (2) 3	=	0 1 2 (3) 4 5 6
Day 1	0 1 2 3	+	0 1 2 3	=	0 1 2 3 4 5 6
Day 2	0 1 2 3	+	0 1 2 3	=	0 1 2 3 4 5 6
Day 3	0 1 2 3	+	0 1 2 3	=	0 1 2 3 4 5 6
Day 4	0 1 2 3	+	0 1 2 3	=	0 1 2 3 4 5 6
Day 5	0 1 2 3	+	0 1 2 3	=	0 1 2 3 4 5 6
Day 6	0 1 2 3	+	0 1 2 3	=	0 1 2 3 4 5 6
Day 7	0 1 2 3	+	0 1 2 3	=	0 1 2 3 4 5 6
					UAS7 score†

Adapted from Zuberbier *et al.*

*The sum of the daily number of wheals and daily intensity of pruritus.
†The sum of the daily UAS scores over 7 consecutive days.

Assessment of disease activity in patients with CIU (UAS scale)

Score	Wheals	Pruritus
0	None	None
1	**Mild** (less than 20 wheals/24 hours)	**Mild** (present but not annoying or troublesome)
2	**Moderate** (20-50 wheals/24 hours)	**Moderate** (troublesome but does not interfere with normal daily activity or sleep)
3	**Intense** (more than 50 wheals/24 hours or large confluent areas of wheals)	**Intense** (severe pruritus, which is sufficiently troublesome to interfere with normal daily activity or sleep)

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