The management of chronic urticaria in primary care for adults and children

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Revision history

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February 2017	Gavin Makin, RDTC	First draft produced at request of PaGDSG	0.1
March 2017	Sarah Jacobs, GMSS	Changes made in response to new version written by: **Dr Marsland, Consultant dermatologist and urticaria specialist, SRFT.** Changes made to dosing information.	0.2
March 2017	Gavin Makin, RDTC	Second draft updated	0.3
April 2017	Sarah Jacobs GMSS	Further amendments and changes in response to comments.	0.4
April 2017	Sarah Jacobs GMSS	Final changes to condense text and improve formatting	0.5
August 2017	Sarah Jacobs GMSS	Add rupatadine to guidance	1.1

Approvals

This document must be approved by the following before distribution:

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PAGDSG	14 September 2017	2.0

Final version available on GMMMMG website.

1. Aim

The aim of this document is to provide the background advice and evidence to support GPs in prescribing off-label / unlicensed doses of antihistamines in the management of urticaria and to reduce unnecessary referrals to secondary / tertiary care.

2. Background

Urticaria is a raised, itchy rash characterised by hives or wheals that come and go, rarely leaving marks.

Individual wheals usually last for less than 24 hours although patients may develop new wheals on a daily basis so the rash might seem constant.

Angioedema is a deeper swelling that may occur by the same mechanisms as the wheals, and the two frequently coexist.

Chronic urticaria is a *skin condition,* characterised by the above, that has lasted for more than six weeks. The activity may fluctuate from day to day but hives, if present, occur almost every day.
Angioedema may occur as frequently as weekly or as infrequently as once or twice per year.

In chronic spontaneous urticaria (CSU), hives and angioedema occur without specific triggers. This has also been referred to as chronic idiopathic urticaria although this term is no longer used.

In chronic inducible urticaria (CIndU), hives only occur following a specific trigger such as stroking of the skin (dermographism), pressure, cold, or raising the core body temperature such as by exercise (cholinergic urticaria). The hives of CIndU are usually shorter lasting (less than an hour).

Some patients have more than one type of chronic urticaria.

Chronic urticaria is a self-limiting skin condition that will eventually disappear. Many patients report resolution of symptoms within 6 months but in some patients treatment may be required to suppress symptoms for many years. There is no cure for chronic urticaria.

Chronic urticaria has a significant impact on quality of life that should not be underestimated. The aim of treatment is to eradicate hives completely. Patients with only partial control of symptoms are often significantly impacted by their disease due to uncertainty about the possibility of flares.

Chronic urticaria is not a life threatening condition. Anaphylaxis may be accompanied by urticarial rashes but this is a different condition.

There are no specific blood tests required in the assessment of patients with chronic urticaria in the absence of other symptoms.

Aggravating Factors

Patients should be reminded that chronic urticaria is a skin condition rather than an allergy.

The variable nature of the condition is such that patients look for triggers, in particular foods. The reality is that whilst alcohol, spices and certain foods may exacerbate symptoms in selected patients, avoidance will not necessarily prevent the rashes of chronic urticaria from occurring.
Often urticarial rash may coincide with meal times. Tolerance of the food on occasions without any rash should enable the clinician to lift dietary restriction. Keeping a food diary can be helpful.

NSAIDs and opioids *may* aggravate some cases of chronic urticaria without being the cause. ACE inhibitors may precipitate angioedema without wheals and should be discontinued in these patients.

3. Treatment

General principles of treatment

- Patients should be reminded that there is no cure but that treatments can be effective in suppressing symptoms
- Only non-sedating antihistamines should be used. Sleep induced by the older, sedating antihistamines is of poor quality, rather like sleep induced by alcohol. Sleep disturbance at night from urticaria is caused by disease activity and if the hives are sufficiently controlled, the patient will not wake with itching. Long term use of sedating antihistamines has also been associated with memory impairment. For these reasons sedating antihistamines are not recommended for chronic urticaria, even at night.
- Continuous daily treatment is more effective than on a rescue basis for flares.
- Patients may require more than the licensed dose of non-sedating antihistamines.
- If patients experience side effects including drowsiness, dosage should be modified or the antihistamine should be changed.
- Prescribing more than one antihistamine at a time is not recommended. It is less effective than increasing the dose of a single antihistamine and may increase the risk of side effects.

Use of off-label doses of antihistamines in the management of urticaria

The first line treatment of urticaria is a daily non-sedating antihistamine at the age appropriate dose in adults and children.

If there is inadequate response to treatment at the licensed dose the treatment options are:

- Switch to an alternative non-sedating antihistamine.
- Double the standard licensed dose of the first choice non-sedating antihistamine. Higher doses of non-sedating antihistamines are generally well tolerated and serious adverse effects are rare.
- Dosing can be increased up to a maximum of four times the licensed dose[1], provided side effects are not experienced. More frequent dosing may give better all-day symptomatic relief.
- International guidelines suggest that increasing the dose of antihistamines also applies to children.

These recommendations are based on expert opinion in separate guidelines from The European Academy of Allergy and Clinical Immunology, the European Dermatology Forum, World Allergy Organization, British Association of Dermatologists and the British Society for Allergy and Clinical Immunology [1, 2, 3, 4, 5].

Do not use off-label higher doses of antihistamines in the following patients:

- Patients with a prolonged QT syndrome. This is because antihistamines as a medicine class have been associated with tachycardia and palpitations in patients with a history of or ongoing cardiovascular disease.
- Patients with impaired hepatic or renal function because there is a theoretical risk of toxicity due to impaired drug clearance.

Additional drug information

- Rupatadine can be tried as a 4th line option in adults following the recommendation of a specialist.
- Desloratadine is available as the active metabolite of loratadine but there is little evidence to confirm additional benefits over loratadine.
- Levocetirizine is the biologically active enantiomer of cetirizine but there is little evidence to confirm additional benefits over cetirizine.
- Acrivastine is not routinely recommended as it has a short half-life and needs to be taken three times a day.
- Mizolastine may cause prolongation of the QT interval and is therefore not normally considered as first line treatment.

4. Dosing of antihistamines

Adults

Drug	Licensed dose in adults	Suggest max off-label dose in adults	GMMMG status	Comments
Cetirizine	10mg od	20mg bd	1st line	Occasional drowsiness when increase dose.
Loratadine	10mg od	20mg bd	2nd line	Rarely causes drowsiness but may be less effective than cetirizine. Use with caution if prolonged QT interval.
Fexofenadine	180mg od	180mg qds	Non-formulary	Use with caution in patients with known prolonged QT interval.
Rupatadine (4th line)	10mg od	20mg bd	Non-formulary	Following specialist recommendation. May cause drowsiness as per cetirizine.

First-line antihistamines for children

Drug	<1 year	1-2 years	2-5 years	6 - 11 years		12 – 17 years
Chlorphenamine 2mg/5ml liquid	1mg bd	**X**	**X**	**X**		**X**
Cetirizine 5mg/ 5ml liquid 10mg tablets	**X**	Off-label dose: 250micrograms / kg bd	2.5mg bd	5mg bd*		10mg od*
Desloratadine 2.5mg/5ml liquid 5mg tablets	**X**	1.25mg od	1.25mg od	2.5mg od		5mg od
Loratadine 5mg/5ml liquid 10mg tablets	**X**	**X**	<31kg 5mg od	<31kg 5mg od	>31kg 10mg od	10mg od
Fexofenadine 30mg / 120mg / 180mg tablets	**X**	**X**	**X**	Unlicensed: 30mg bd		180mg od

Additional information for antihistamine use in children

- Chlorphenamine is a sedating antihistamine and thus causes daytime drowsiness, reduced attention, visual memory and learning plus abnormal sleep at night with delayed and reduced REM sleep. For this reason it should be used in caution, particularly over longer periods.
- *Cetirizine can have cause drowsiness when used multiple times a day and hence is to be used with caution in school age children. However, if the patient has been initiated on cetirizine and finds benefit then this therapy could be continued.
- Loratadine (and desloratadine, which is licensed for younger children) may be less effective than cetirizine but is less likely to cause drowsiness. Like chlorphenamine, it is metabolised in the liver, increasing the risks of drug accumulation and of drug-drug interactions.
- Fexofenadine is licensed for seasonal allergic rhinitis from the age of 6, and for urticaria from the age of 12. It can be considered for unlicensed use for urticaria from the age of 6.
- For all children with chronic urticaria unresponsive to standard doses, frequency of non-sedating antihistamine can be increased up to a *maximum* of four times a day.

5. Criteria for referring patients to secondary care

Refer to a **dermatologist** if:

- Diagnosis is in doubt (there are other skin conditions that may mimic urticaria)
- Patients are not responding to continuous treatment (including increased doses of non-sedating antihistamines) after a prolonged period of time.

Refer to an **allergist/immunologist** only if:

- Rashes only occur following exposure to specific allergens
- Additional features suggestive of anaphylaxis
- Angioedema only and patient not on an ACE-inhibitor

The diagnosis of urticaria is primarily clinical therefore do not routinely refer for allergy testing.

Routine blood tests are **not required** prior to specialist referral and should only be performed to investigate other symptoms e.g. H.pylori investigations for GI symptoms.

The tertiary clinic at Salford Royal FT has broad experience in offering third line treatments for skin disease including ciclosporin, the biologic omalizumab and more obscure treatments such as dapsone. Referral to the clinic ensures that patients with refractory urticaria can be assessed properly for biologics in line with NICE guidance: NICE TA339: Omalizumab for previously treated chronic spontaneous urticaria, June 2015

6. Additional information

A patient information sheet is available from the North West Paediatric Allergy Network on http://allergynorthwest.nhs.uk/resources/allergy-leaflets/chronic-urticaria-and-angioedema/

NICE Clinical Knowledge Summary: NICE CKS: Managing urticaria, May 2016

NICE Evidence Summary: NICE ESUOM31: Chronic urticaria, off-label doses of cetirizine, July 2014

7. References

1. The EAACI/GA2LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. Allergy 2014; DOI: 10.1111/all.12313.
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3. British Society for Allergy and Clinical Immunology. Guideline for the management of chronic urticaria and angioedema accessed December 2015 via:
4. Powell R.J, BSACI guideline for the management of chronic urticaria and angioedema, Clinical and experimental allergy journal. 2015; 45: 547-565.
5. BSACI Primary Care Guideline – Management of chronic urticaria and angioedema.