

# British Association of Dermatologists guidelines for the management of people with chronic urticaria 2021\*

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## Conflicts of interest

The following interests were declared over the duration of the guideline development.

C.E.H.G.: honoraria and research investigator – Novartis – specific. M.R.A.-J.: (1) sponsorship to conferences – Allergy Therapeutics, Novartis, Celgene – specific; (2) grant/research support – AbbVie, Emblation, Unilever – nonspecific. A.B.: (1) consultant, AbbVie, Almirall, Eli Lilly, LEO Pharma, Galderma, Novartis, Pierre Fabre, Janssen Pharmaceuticals, UCB – specific. C.F.: sponsorship to attend a conference – Novartis – specific; (2) travel grants from LEO Pharma, Almirall, Novartis – specific; (3) investigator-initiated studies from Janssen and LEO Pharma – nonspecific. T.A.L.: advisory board – Galderma, La Roche-Posay, Novartis – specific. A.M.M.: (1) consultant and advisory board – Novartis – specific; (2) invited speaker – Novartis – specific. G.O.: advisory board – Novartis – specific. R.A.S., F.L., L.C., W.A.C.S., M.H. L.S.E., M.F.M.M. and M.C.E. declare they have no conflicts of interest.

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NICE has renewed accreditation of the process used by the British Association of Dermatologists to produce clinical guidelines. The renewed accreditation is valid until 31 May 2026 and applies to guidance produced using the processes described in the updated guidance for writing a British Association of Dermatologists clinical guideline – the adoption of the GRADE methodology 2016. The original accreditation term began on 12 May 2010. More information on accreditation can be viewed at [www.nice.org.uk/accreditation](http://www.nice.org.uk/accreditation).

## 1. Purpose and scope

The overall objective of the guideline is to provide up-to-date, evidence-based recommendations for the management of urticaria. The document aims to

- offer an appraisal of all relevant literature up to March 2020, focusing on any key developments,
- address important, practical clinical questions relating to the primary guideline objective, and
- provide guideline recommendations and if appropriate research recommendations.

The guideline is presented as a detailed review with highlighted recommendations for practical use in primary, secondary and tertiary care, in addition to an updated patient information leaflet (PIL; available on the BAD Skin Health Information website, <https://www.skinhealthinfo.org.uk/a-z-conditions-treatments>).

### 1.1 Exclusions

Other than providing background information, the guideline does not cover angio-oedema without weals [other than idiopathic, which is now classified as part of chronic spontaneous urticaria (CSU)], hereditary angio-oedema, autoinflammatory syndromes or differential diagnosis. Additionally, the guideline focuses on chronic rather than acute urticaria.

## 2. Methodology

This set of guidelines has been developed using the BAD's recommended methodology.<sup>1</sup> Further information can be found in Appendix J (see Supporting Information) with reference to the AGREE II instrument ([www.agreetrust.org](http://www.agreetrust.org))<sup>2</sup> and GRADE.<sup>3</sup> The recommendations were developed for implementation in the UK National Health Service (NHS).

The Guideline Development Group (GDG), which consisted of eight consultant dermatologists managing adults, children and young people; a consultant immunologist; a consultant psychodermatologist; a drug allergy specialist; two patient representatives and a technical team (consisting of an information scientist, guideline research fellows and a project manager providing methodological and technical support), established a number of clinical questions pertinent to the scope of the guideline and two sets of outcome measures of importance to

patients, ranked according to the GRADE methodology (section 2.1; and Appendix A; see Supporting Information).

A systematic literature search of the PubMed, MEDLINE, Embase and Cochrane databases was conducted to identify key articles on urticaria from January 2007 to March 2020. An additional, targeted literature search for the antihistamines acrivastine and bilastine was also carried out (from January 1980 to March 2020). Subsequently published papers known to the GDG were included. The final literature searches were run ahead of journal submission in 2021 to ensure currency. The search terms and strategies are detailed in Appendix K (see Supporting Information). Additional references relevant to the topic were also isolated from citations in the reviewed literature and the previous version of the guideline.<sup>4</sup> Evidence from the included studies was graded according to the GRADE system (high, moderate, low or very low certainty).

The recommendations are based on evidence drawn from systematic reviews of the literature pertaining to the clinical questions identified, following discussions with the entire GDG and factoring in all four factors that would affect their strength rating according to the GRADE approach (i.e. balance between desirable and undesirable effects, quality of evidence, patient values and preferences, and resource allocation). All GDG members contributed towards drafting and/or reviewing the narratives and information in the guideline and Supporting Information documents. When there was insufficient evidence from the literature, informal consensus was reached based on the experience of medical and patient GDG members.

The summary of findings with forest plots (Appendix B), tables Linking the Evidence To the Recommendations (LETR; Appendix C), GRADE evidence profiles indicating the quality of evidence (Appendix D), summary of included studies (Appendix E), narrative findings for noncomparative studies (Appendix F), PRISMA flow diagram (Appendix G), list of excluded studies (Appendix H) and AMSTAR 2 appraisal of the included systematic reviews (Appendix I) are detailed in the Supporting Information.

The strength of recommendation is expressed by the wording and symbols shown in Table 1.

## 2.1 Clinical questions and outcomes

The GDG established the following clinical questions pertinent to the scope of the guideline.

### Review question 1: investigation

Do tests, such as blood tests and the autologous serum skin test, alter the management of urticaria?

### Review question 2: treatment

What is the clinical effectiveness of any H<sub>1</sub>-antihistamine compared with another for the treatment of urticaria?

### Review question 3: treatment

Would changing from one H<sub>1</sub>-antihistamine to another lead to benefit in the treatment of urticaria?

### Review question 4: treatment

Would adding an H<sub>2</sub>-antihistamine to an H<sub>1</sub>-antihistamine lead to benefit in the treatment of urticaria?

### Review question 5: treatment

What is the effectiveness of leukotriene receptor antagonists in the treatment of urticaria?

### Review question 6: treatment

What are the effectiveness and safety of increasing doses of H<sub>1</sub>-antihistamines?

### Review question 7: treatment

Would adding other therapies to an H<sub>1</sub>-antihistamine lead to benefit in the treatment of urticaria, including sulfasalazine, dapsone, thyroxine, tricyclic antidepressants, hydroxychloroquine, methotrexate, danazol, tranexamic acid, mycophenolate mofetil, intravenous immunoglobulins (IVIg) and anticoagulants?

### Review question 8: treatment

What is the effectiveness of taking systemic corticosteroids for the treatment of urticaria?

**Table 1** Strength of recommendation ratings

| Strength                                                 | Wording                                                                 | Symbol | Definition                                                                                                                                                                                                                                                                                                                          |
|----------------------------------------------------------|-------------------------------------------------------------------------|--------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Strong recommendation for the use of an intervention     | 'Offer' (or similar, e.g. 'use', 'provide', 'take', 'investigate' etc.) | ↑↑     | Benefits of the intervention outweigh the risks; most patients would choose the intervention whilst only a small proportion would not; for clinicians, most of their patients would receive the intervention; for policymakers, it would be a useful performance indicator                                                          |
| Weak recommendation for the use of an intervention       | 'Consider'                                                              | ↑      | Risks and benefits of the intervention are finely balanced; most patients would choose the intervention but many would not; clinicians would need to consider the pros and cons for the patient in the context of the evidence; for policymakers it would be a poor performance indicator where variability in practice is expected |
| No recommendation                                        |                                                                         | ⊖      | Insufficient evidence to support any recommendation                                                                                                                                                                                                                                                                                 |
| Strong recommendation against the use of an intervention | 'Do not offer'                                                          | ↓↓     | Risks of the intervention outweigh the benefits; most patients would not choose the intervention whilst only a small proportion would; for clinicians, most of their patients would not receive the intervention                                                                                                                    |

**Review question 9: treatment**

What is the effectiveness of dietary exclusions or supplements for the treatment of urticaria?

**Review question 10: treatment**

What is the effectiveness of *Helicobacter pylori* eradication for the treatment of urticaria?

**Review question 11: treatment**

What is the effectiveness of avoiding nonsteroidal anti-inflammatory drugs (NSAIDs) for the treatment of urticaria?

**Review question 12: treatment**

What is the effectiveness of ciclosporin for the treatment of urticaria and are there any long-term benefits?

**Review question 13: treatment**

What is the effectiveness of omalizumab for the treatment of urticaria?

**Review question 14: treatment**

Is the response to treatment for inducible urticarias (e.g. symptomatic dermographism, delayed pressure urticaria, cold urticaria, cholinergic urticaria, vibratory angio-oedema, localized heat urticaria) the same as for CSU?

**Review question 15: treatment**

Do any other specific interventions work for inducible urticarias, such as antibiotics in cold urticaria, sulfasalazine in delayed pressure urticaria, phototherapy in dermographism, plasmapheresis in solar urticaria and anticholinergics in cholinergic urticaria?

**Review question 16: treatment**

Which H<sub>1</sub>-antihistamines can be used in pregnancy?

**Review question 17: treatment**

Which H<sub>1</sub>-antihistamines can be used during breastfeeding?

**Review question 18: treatment**

What are the key differences in the diagnosis and management of paediatric compared with adult urticaria (if there are any)?

**Review question 19: treatment**

What is the clinical effectiveness of miscellaneous monotherapies compared with each other for the treatment of urticaria?

The GDG also established two sets of outcome measures of importance to patients (for treatment and investigation), ranked according to the GRADE methodology,<sup>5</sup> by the patient representatives (for the full review protocol see Appendix A in

the Supporting Information). In the investigation protocol, the outcome is either 'yes' or 'no'. The treatment outcomes (Table 2) use a nine-point scale; outcomes ranked 9, 8 or 7 are critical for decision making; those ranked 6, 5 or 4 are important but not critical for decision making; and those ranked 3, 2 or 1 are the least important for decision making.

### 3. Summary of recommendations

The following recommendations and ratings were agreed upon unanimously by members of the GDG and patient representatives.

For further information on the wording used for recommendations and strength of recommendation ratings see Table 1. The evidence on which the recommendations are based is featured and discussed in Appendices B–E (see Supporting Information). The GDG is aware of the lack of high-quality evidence for many of these recommendations, therefore, strong recommendations with an asterisk (\*) are based on available evidence, as well as informal consensus and specialist experience of medical and patient GDG members. Good practice point (GPP) recommendations are derived from informal consensus.

The recommendations are based on the clinical classification of the disease (section 5.2) and refer to people of all ages. However, note that for people aged < 12 years:

- the recommendations are based on expert opinion as there is very little published evidence
- there are additional notes in section 9.1 and Table 3.

Licensing information, dosages and monitoring requirements for specific drugs are not included. However, of note, apart from H<sub>1</sub>-antihistamines, oral steroids and omalizumab, none of the other treatment options discussed are licensed in the UK for use in urticaria. Except where otherwise stated, we recommend adherence to published guidelines, for example by the manufacturer, the BAD or, in the UK, the British National Formulary ([www.bnf.org](http://www.bnf.org)). In particular, note the licensed dosages for people aged < 14 years (also see Table 3).

The recommendations relate to chronic spontaneous and inducible urticarias. Acute urticaria, angio-oedema without weals (other than idiopathic, which is now classified as part of CSU), hereditary angio-oedema and autoinflammatory diseases are not covered.

For clarity, we have divided the management options into sections (general treatment, first-, second- and third-line options). However, depending on disease severity, disease fluctuation, comorbidities and the national criteria for use of drugs, the order and combinations of treatment may vary and may change during the course of each person's disease.

We note that, since submission of this article for publication, a new international guideline on the management of urticaria has been published.<sup>6</sup> Broadly, the recommendations are similar, except that the international guideline favours omalizumab over ciclosporin for CSU.

**Table 2** Outcome measures and ranking

|                                 |   |
|---------------------------------|---|
| Disease control                 | 9 |
| Decrease in urticarial activity | 9 |
| Adverse effects                 | 9 |
| Quality of life                 | 9 |
| Time to clinical effect         | 7 |
| Relapse                         | 6 |
| When to stop treatment          | 3 |

Table 3 First-line antihistamines for chronic urticaria in children

| Drug                                                              | 1 month<br>to 1 year   | 1–2 years                                                                                            | 2–5 years              | 6–11 years                                        | 12–17 years  |
|-------------------------------------------------------------------|------------------------|------------------------------------------------------------------------------------------------------|------------------------|---------------------------------------------------|--------------|
| <b>Chlorphenamine</b><br>2 mg/5 mL oral solution                  | 1 mg<br>twice<br>a day | x                                                                                                    | x                      | x                                                 | x            |
| <b>Cetirizine</b><br>5 mg/5 mL oral solution<br>10 mg tablets     | x                      | Unlicensed:<br>250 micrograms<br>per kg twice a day<br>(typically doses up to<br>2.5 mg twice a day) | 2.5 mg<br>twice a day  | 5 mg twice a day                                  | 10 mg daily  |
| <b>Desloratadine</b><br>2.5 mg/5 mL oral solution<br>5 mg tablets | x                      | 1.25 mg daily                                                                                        | 1.25 mg daily          | 2.5 mg daily                                      | 5 mg daily   |
| <b>Loratadine</b><br>5 mg/5 mL oral solution<br>10 mg tablets     | x                      | x                                                                                                    | < 31 kg:<br>5 mg daily | < 31 kg:<br>5 mg daily<br>> 31 kg:<br>10 mg daily | 10 mg daily  |
| <b>Fexofenadine</b><br>30 mg/120 mg/180 mg tablets                | x                      | x                                                                                                    | x                      | Unlicensed:<br>30 mg twice daily                  | 180 mg daily |

Table 3 summarizes the antihistamines commonly used in the UK. Chlorphenamine is a sedating antihistamine and thus daytime drowsiness and reduced attention, visual memory and learning are very common. It also causes abnormal sleep at night with delayed and reduced REM sleep. For these reasons, it should be used with caution, particularly over longer periods. It is not recommended for use beyond 1 year when alternative low-sedating antihistamines are available. Cetirizine can cause drowsiness, especially when used above the licensed dose. Hence it is to be used with caution in school-aged children. However, if the child has been started on cetirizine with benefit, then this therapy can be continued. Loratadine and desloratadine may be less effective than cetirizine, but are less likely to cause drowsiness. Like chlorphenamine, they are metabolized in the liver, increasing the risks of drug accumulation and drug interactions. Fexofenadine is licensed for seasonal allergic rhinitis from the age of 6 years, and for urticaria from the age of 12 years. It can be considered for unlicensed use for urticaria from the age of 6 years. For all children with chronic urticaria who have an inadequate response to standard doses, the frequency of administration of nonsedating antihistamines can be increased up to a maximum of four times a day.

### General management for people with all types of chronic urticaria

The most important step is to take a detailed clinical history, with examination supplemented by people's own photographs. In most cases this will provide an accurate clinical diagnosis (section 5.2), which will guide management. Disease pathogenesis may also be important in management (section 5.3).

**R1 (↑)** Only consider baseline investigations if clinically indicated (see section 6.0).

**R2 (GPP)** Consider using appropriate validated scoring systems to assess disease activity and impact, for example Dermatology Life Quality Index (DLQI), weekly Urticaria Activity Score 7 (UAS7), Angioedema Activity Score (AAS) and/or Urticaria Control Test (UCT).

**R3 (GPP)** Provide educational material or a patient information leaflet on urticaria or angio-oedema (<https://www.skinhealthinfo.org.uk/a-z-conditions-treatments>).

**R4 (GPP)** Offer access to support and treatment for anxiety, depression and the psychosocial impact of the disease, where appropriate. The psychological impact can be assessed using, for example, the Hospital Anxiety and Depression Scale (HADS).

**R5 (GPP)** Consider topical antipruritic agents, such as a menthol-containing emollient.

**R6 (GPP)** Advise avoidance of identified triggers or exacerbating factors, such as drugs, and in particular triggers for inducible urticarias.

**R7 (↑↑)** Stop angiotensin-converting enzyme (ACE) inhibitors in people with angio-oedema without weals.

### General management for people with chronic spontaneous urticaria

**R8 (↑↑)** Avoid NSAIDs in people whose CSU appears to be exacerbated by this class of drugs.

**R9 (↑)** Consider switching NSAID treatment to a selective cyclooxygenase-2 inhibitor, if tolerated and not contraindicated, when there is a history of acute exacerbation of CSU after NSAID intake for inflammation. However, evidence of benefit from switching low-dose aspirin when taken as an antithrombotic to an alternative antiplatelet drug is lacking. Refer to the National Institute for Health and Care Excellence,<sup>7</sup> British Society of Allergy and Clinical Immunology (BSACI)<sup>8</sup> or European Academy of Allergy and Clinical Immunology (EAACI) guidance<sup>9</sup> if reactivity to NSAIDs is suspected.

**R10 (GPP)** Do not advise dietary exclusion routinely. If, from a detailed history, food appears to play a role, investigate appropriately.

**Θ1** There is insufficient evidence to recommend routine screening for vitamin D deficiency.

**Table 4** Examples of first- and second-generation H<sub>1</sub>-antihistamines

|                          | Licensed oral dose for adults <sup>a</sup><br>(see Table 3 for children)                                         |
|--------------------------|------------------------------------------------------------------------------------------------------------------|
| <b>First generation</b>  |                                                                                                                  |
| Chlorphenamine           | 4 mg every 4–6 h, maximum<br>24 mg per day (elderly maximum<br>12 mg per day)                                    |
| Cyproheptadine           | 4 mg three times per day (maximum<br>32 mg per day)                                                              |
| Hydroxyzine              | Initially 10–25 mg at night, maximum<br>25 mg three to four times per day<br>(elderly maximum 25 mg twice daily) |
| Promethazine             | 10–20 mg two to three times per day                                                                              |
| <b>Second generation</b> |                                                                                                                  |
| Acrivastine              | 8 mg three times a day                                                                                           |
| Cetirizine               | 10 mg once daily                                                                                                 |
| Desloratadine            | 5 mg once daily                                                                                                  |
| Fexofenadine             | 180 mg once daily                                                                                                |
| Loratadine               | 10 mg once daily                                                                                                 |
| Levocetirizine           | 5 mg once daily                                                                                                  |
| Mizolastine              | 10 mg once daily                                                                                                 |

<sup>a</sup>From the British National Formulary.

**Ø2** There is insufficient evidence to make a recommendation on dietary supplementation.

**R11** (↓↓) Do not offer routine screening for *Helicobacter pylori*.

#### First-line treatment options for people with chronic spontaneous urticaria

**R12** (↑↑) Offer a second-generation H<sub>1</sub>-antihistamine, using a regular daily licensed dose (Table 4).

**R13** (↓↓) Do not offer first-generation H<sub>1</sub>-antihistamines routinely, unless there is no alternative, due to concerns about their short- and long-term effects on the central nervous system.

**R14** (↑↑) Offer up dosing (i.e. increasing the dose above the licensed dose) of a single second-generation H<sub>1</sub>-antihistamine, by up to fourfold the licensed dose, to people whose symptoms are inadequately controlled by the standard licensed dose, provided it is tolerated and there is no caution or contraindication (see section 7.2 and Appendix C – LETR narratives). Attempt stepwise dose reduction following complete symptom control. There is no evidence to guide the optimum duration of up dosing or speed of dose reduction.

**R15** (↓↓) Do not updose mizolastine (see section 7.2).

**R16** (GPP) Consider switching from one second-generation H<sub>1</sub>-antihistamine to another in people whose symptoms do not respond adequately to, or who do not tolerate, the first drug at standard or increased doses.

**Ø3** There is insufficient evidence to make a recommendation on using two different second-generation H<sub>1</sub>-antihistamines at the same time.

**R17** (↓↓) Do not updose first-generation H<sub>1</sub>-antihistamines (see R13).

**R18** (↑) Consider montelukast, in addition to a second-generation H<sub>1</sub>-antihistamine, in people whose symptoms are inadequately controlled by standard and increased doses of second-generation H<sub>1</sub>-antihistamines.

**R19** (↑↑) Offer\* progression of therapy, through first-line treatment options (see R12–R18) every 2–4 weeks (every 2 weeks in severe treatment-resistant disease).

**Ø4** There is insufficient evidence to recommend routine addition of H<sub>2</sub>-antihistamines to second-generation H<sub>1</sub>-antihistamines for people whose symptoms are inadequately controlled by the latter. However, they may be considered if urticaria is associated with dyspepsia, although dyspepsia should be investigated appropriately. See section 7.4.

**R20** (↑) Consider oral prednisolone (e.g. 0.5 mg kg<sup>-1</sup>) for short, infrequent courses of a few days as rescue treatment to control severe exacerbations, in addition to continued use of a second-generation H<sub>1</sub>-antihistamine.

**R21** (↓↓) Do not offer\* long-term systemic corticosteroids unless there is no other option. Use the lowest effective dose for the shortest possible period.<sup>10</sup>

#### Second-line treatment options for people with chronic spontaneous urticaria

For people with CSU with an inadequate response to first-line treatment, the following additional investigations may be relevant when considering the next treatment options.

**R22** (↓↓) Do not offer autologous serum skin tests (ASSTs) or autologous plasma skin tests (APSTs) routinely.

**R23** (↑) Consider measuring total IgE levels: a high total IgE level may indicate a higher probability of early disease responsiveness to omalizumab, whereas a normal total IgE level may indicate disease responsiveness to ciclosporin (section 6 and Appendix C – LETR narratives).

**R24** (↑) If available, consider a basophil histamine release assay (BHRA), although it is not yet subject to a national quality assurance scheme. A positive BHRA may indicate a higher probability of disease responsiveness to ciclosporin and slower or delayed response to omalizumab, whereas a negative BHRA may indicate a higher probability of disease responsiveness to omalizumab (section 6 and Appendix C – LETR narratives).

Note: total IgE levels (R23) and BHRAs (R24) are only indicative and may not reflect actual clinical responsiveness in all patients.

**R25** (↑↑) Offer omalizumab, in addition to a second-generation H<sub>1</sub>-antihistamine, to people whose symptoms are inadequately controlled by first-line options.

**R26** (↑↑) Offer\* ciclosporin for 3–6 months, in addition to a second-generation H<sub>1</sub>-antihistamine, to people whose symptoms are inadequately controlled by first-line options.

**R27** (↑↑) Avoid long-term use of ciclosporin where possible; if not, use at the lowest effective dose, interrupt treatment

periodically to confirm continued requirement, and consider alternative agents (see R25, R28 and Θ5).

### Third-line treatment options for people with chronic spontaneous urticaria

**R28 (↑)** Consider the following options in people whose symptoms are inadequately controlled by first- and second-line treatment options, or where the latter are contraindicated or inappropriate (in alphabetical order):

- azathioprine
- dapsone
- doxepin (but there are concerns about central nervous system effects, as for first-generation antihistamines)
- hydroxychloroquine (particularly for urticaria occurring with systemic lupus erythematosus)
- IVIg
- methotrexate
- mycophenolate mofetil
- narrowband ultraviolet (UV)B (typically a course of around 30 treatments, repeated after 12 months if necessary, but not for continual treatment)
- oral tacrolimus
- sulfasalazine
- tranexamic acid (only if predominantly angio-oedema).

**Θ5** There is insufficient evidence to recommend the following interventions (in alphabetical order):

- colchicine
- cyclophosphamide
- dipyridamole
- interleukin-1 antagonists (e.g. anakinra)
- plasmapheresis
- psychological interventions (although there is evidence that psychological interventions such as cognitive behavioural therapy, mindfulness and relaxation techniques are beneficial for general psychosocial wellbeing in patients with skin diseases)
- rituximab
- thyroxine
- tumour necrosis factor antagonists
- warfarin.

### **Treatment options for inducible urticarias**

There is much less evidence available than for CSU, but for people with all types of inducible urticaria the following are recommended (based mainly on small case series and anecdotal evidence).

### First-line treatment options for people with all types of inducible urticaria

**R29 (↑↑)** Offer\* a second-generation H<sub>1</sub>-antihistamine, using a regular daily licensed dose (Table 4).

**R30 (↓↓)** Do not offer\* first-generation H<sub>1</sub>-antihistamines routinely, unless there is no alternative, due to concerns about their short- and long-term effects on the central nervous system.

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**R31 (↑↑)** Offer\* up dosing of a single second-generation H<sub>1</sub>-antihistamine by up to fourfold the licensed dose to people whose symptoms are inadequately controlled by the standard licensed dose, provided it is tolerated and there is no caution or contraindication (section 7.2 and Appendix C – LETR narratives). Attempt stepwise dose reduction following complete symptom control. There is no evidence to guide the optimum duration of up dosing or speed of dose reduction.

**R32 (↓↓)** Do not updose mizolastine (see section 7.2).

**R33 (GPP)** Consider switching from one second-generation H<sub>1</sub>-antihistamine to another in people whose symptoms do not respond adequately to, or who do not tolerate, the first drug at the standard or increased dose.

**Θ6** There is insufficient evidence to make a recommendation on using two different second-generation H<sub>1</sub>-antihistamines at the same time.

**R34 (↓↓)** Do not updose first-generation H<sub>1</sub>-antihistamines (see R30).

**Θ7** There is insufficient evidence to recommend routine use of montelukast, although there is some evidence to support its use in some subtypes of inducible urticaria.

### Second-line treatment options for people with all types of inducible urticaria

**R35 (↑)** Consider omalizumab, in addition to a second-generation H<sub>1</sub>-antihistamine, in people whose symptoms are inadequately controlled by first-line options, subject to licensing and funding.

**R36 (GPP)** Offer self-injectable adrenaline, if appropriate, for those at risk of anaphylaxis, for example in association with cold or cholinergic urticaria.

### Third-line treatment options for people with all types of inducible urticaria

Consider the following options, in addition to second-generation H<sub>1</sub>-antihistamines, in people with specific types of inducible urticaria, whose symptoms are inadequately responsive to first- and second-line treatment options, or where the latter are contraindicated or inappropriate.

#### Cholinergic urticaria

**R37 (GPP)** Consider anticholinergic drugs (e.g. oxybutynin), or beta blockers (e.g. propranolol), or danazol, or possibly phototherapy.

#### Cold urticaria

**R38 (GPP)** Consider ciclosporin.

**Θ8** There is insufficient evidence to recommend routine use of antibiotics (e.g. penicillin or tetracyclines).

**R39 (GPP)** Do not offer cold desensitization.

#### Delayed pressure urticaria

**R40 (↑)** Consider dapsone or sulfasalazine.

#### Solar urticaria

**R41 (GPP)** Offer advice about sun avoidance and sun protection.

**R42 (↑)** Consider UV prophylactic phototherapy using the wavelength of light relevant to the individual person, only following photoinvestigation and obtaining advice from a dermatologist at a specialist photodermatology centre.

**Θ9** There is limited evidence to recommend plasmapheresis or IVIg for people with solar urticaria.

#### Symptomatic dermographism

**R43 (↑)** Consider narrowband UVB (typically a course of around 30 treatments, repeated after 12 months, if necessary, but not for continual treatment).

**R44 (GPP)** Consider psoralen plus UVA (similarly, not for continual treatment).

**R45 (GPP)** Consider narrowband UVB for other forms of inducible urticaria.

#### Considerations

**Θ10** There is insufficient evidence to make a recommendation about the safety of use of antihistamines during pregnancy and breastfeeding. However, in active disease and after

counselling the female patient with any type of urticaria, where necessary, consider cetirizine or loratadine (see the individual drug summary of product characteristics<sup>11</sup> for information on safety during pregnancy) and the discussion in Appendix C (LETR narratives).

**R46 (GPP)** Refer to secondary care when:

- there is diagnostic doubt
- the urticaria is not adequately controlled by first-line treatment options
- there are high levels of inflammatory markers
- there are marked or persistent associated systemic symptoms, or if the person is systemically unwell
- the urticaria is having a significant impact on quality of life, such as depression, anxiety, marked psychosocial impact, reduced work/school attendance or sleep disturbance
- the person has angio-oedema without weals, not controlled by first-line treatment options.

#### Future research recommendations

The following list outlines future research recommendations (FRRs).

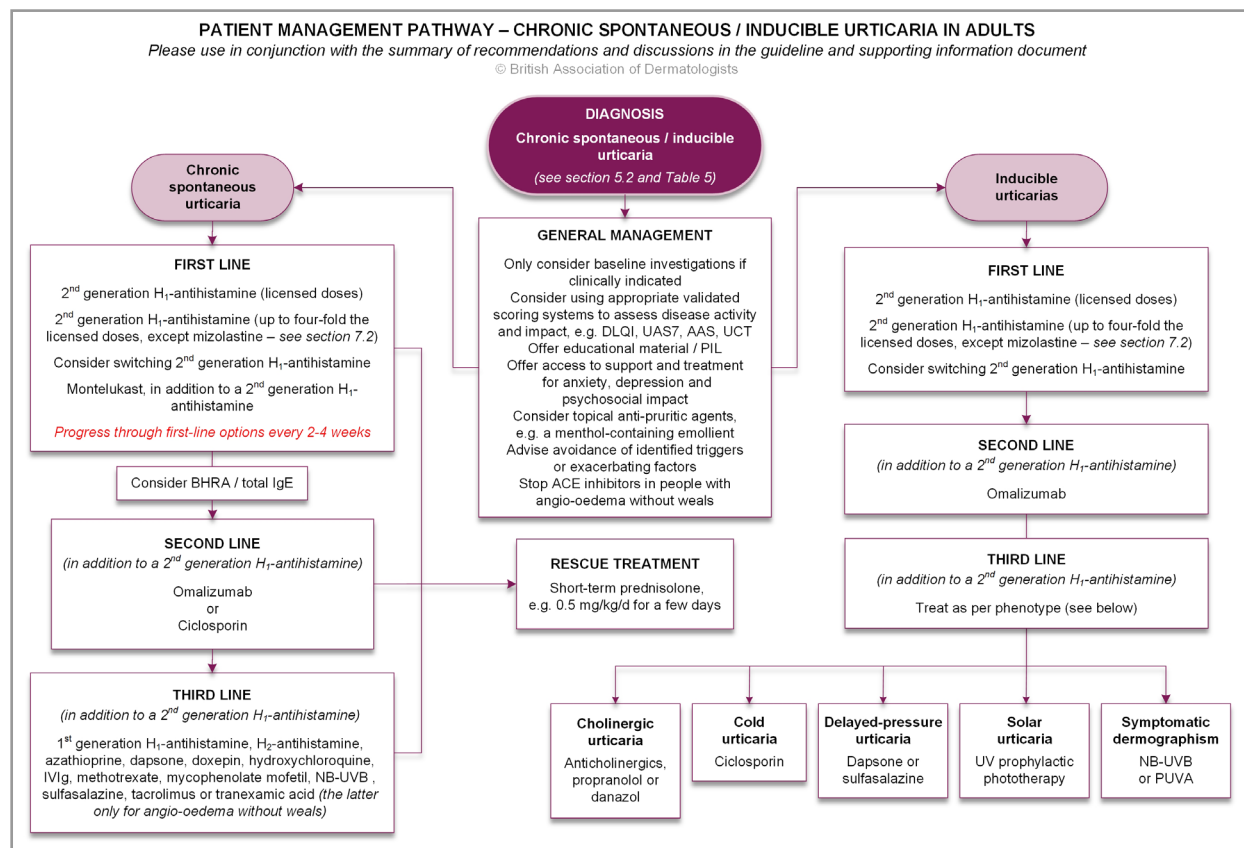


**Figure 1** Patient management pathway for urticaria. For clarity we have divided management options into sections (general treatment, and first-, second- and third-line options). However, depending on disease severity, disease fluctuation, comorbidities and national criteria for use of drugs, the order and combinations of treatment may vary and change during each person's disease. AAS, Angioedema Activity Score; ACE, angiotensin-converting enzyme; BHRA, basophil histamine release assay; DLQI, Dermatology Life Quality Index; IVIg, intravenous immunoglobulin; NB-UVB, narrowband ultraviolet B; PIL, patient information leaflet; PUVA, psoralen plus ultraviolet A; UAS7, Urticaria Activity Score summed over 7 days; UCT, Urticaria Control Test.

**FRR1** Further investigation of the genetic predisposition and/or mechanistic factors that drive the development of all types of urticaria and/or angio-oedema, including the new theory of IgE-mediated 'autoallergy' and characterization of the roles of basophils, eosinophils and lymphocytes.

**FRR2** Better characterization of, and comparisons between, basophil-based assays as predictors of drug responses.

**FRR3** Development of better biomarkers to predict responsiveness to anti-IgE and other therapies.

**FRR4** Utilizing the results from FRR1–3 to address the possibility of personalized therapy and whether new biological targets might offer new therapeutic options.

**FRR5** Randomized controlled trials (RCTs) evaluating the safety and efficacy of up dosing one second-generation H<sub>1</sub>-antihistamine compared with using two different second-generation H<sub>1</sub>-antihistamines at the same time in people with CSU.

**FRR6** RCTs evaluating the safety and efficacy of omalizumab in people with all subtypes of inducible urticaria.

**FRR7** RCTs evaluating the safety and efficacy of other treatment options (as featured in the treatment algorithm) in people with all subtypes of inducible urticaria.

**FRR8** RCTs evaluating the safety and efficacy of emerging treatments for people with all types of urticaria, including the new high-affinity, humanized monoclonal anti-IgE antibody ligelizumab, and potential new treatment options such as tyrosine kinase inhibitors, dupilumab, histamine H<sub>4</sub> receptor antagonists, C5a receptor antagonists and drugs targeting inhibitory mast cell receptors (see section 7.8).

**FRR9** Better characterization of the optimum duration of the various treatment options available to people with all types of urticaria.

**FRR10** Investigations into disease incidence and prevalence, the predictive value of laboratory investigations (such as total IgE levels or basophil-based assays), and the safety and efficacy of the various current and potential future treatment options in children and young people with urticaria and/or angio-oedema of all types.

## 4. Algorithm

The recommendations, discussions in the LETRs (Appendix C) and consensus specialist experience were used to produce management pathways for adults with chronic urticaria – see Figure 1.

## 5. Background

### 5.1 Definition and introduction

Urticaria consists of transient weals, angio-oedema or both. Weals are usually itchy, whereas the swellings of angio-oedema are often not. Depending on the disease subtype, angio-oedema or weals may be painful. Urticaria is usually divided into acute

and chronic forms, becoming chronic when daily or almost daily weals continue for 6 weeks or more, although many attacks of acute urticaria settle much more quickly. Some forms of urticaria may be accompanied by systemic symptoms, such as arthralgia, gastrointestinal disturbance, malaise, lethargy, or wheeze and/or mucosal involvement. Acute urticaria may be a presenting sign of anaphylaxis.

The reported lifetime prevalence rate of urticaria varies from 8% to 24%, with a lifetime prevalence rate of about 1–2% for chronic urticaria.<sup>12–14</sup> The point prevalence of chronic urticaria varies from 0.1% in North America to 1.4% in Asia.<sup>15</sup> The disease is slightly more common in females, except in young children.

People suffer greatly if they have any form of urticaria, and chronic disease may have a significant effect on quality of life.<sup>16,17</sup>

Even though the initial treatment for many types of urticaria is similar, there are some important exceptions. Therefore, accurate clinical categorization, based on a detailed history and examination (section 5.2) and an understanding of disease pathogenesis (section 5.3), are essential to guide investigation and management. Of note, different forms of urticaria commonly occur together.

### 5.2 Clinical classification of urticaria, including diseases presenting with urticaria-like rashes (Table 5)

#### 5.2.1 Spontaneous urticaria

No cause is identified in more than 50% of people with acute urticaria (causes when identified include drugs, infections including COVID-19, and type 1 hypersensitivity reactions) and in many of those with CSU (see section 5.3.2. for pathogenesis of CSU). Weals generally last for up to 24 h, but the swellings of angio-oedema may last for up to 72 h.

#### 5.2.2 Inducible urticarias

These urticarias are usually chronic. Weals are reproducibly induced by the same physical stimulus. Weals usually appear within a few minutes of the stimulus and last for < 2 h, the exception being delayed pressure urticaria, where weals may take 30 min to 12 h to develop, and then last for a few days. The shape and size of the weals may aid diagnosis, for example linear weals in dermographism, or papular weals surrounded by a red flare in cholinergic or aquagenic urticarias. Some inducible urticarias present as a spectrum of symptoms from pruritus, urticaria and angio-oedema to anaphylaxis. Inducible urticarias can be confirmed on provocation testing (see section 6.0). Disease severity may be reduced through the avoidance of triggers, although this can be difficult and disabling. Inducible urticarias tend to be underdiagnosed.

#### 5.2.3 Angio-oedema without weals

Usually no cause is identified. However, it is important not to miss uncommon cases of drug-induced angio-oedema

**Table 5** Clinical classification of urticaria, including diseases presenting with urticaria-like rashes<sup>4</sup>

|                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Spontaneous urticaria</b>                                                                                                                                                                                                                                                                                                                                                                                          |
| <ul style="list-style-type: none"> <li>• Acute</li> <li>• Chronic (6 weeks or more of continuous activity)</li> <li>• Episodic (acute intermittent or recurrent activity)</li> </ul>                                                                                                                                                                                                                                  |
| <b>Inducible urticarias (reproducibly induced by the same physical stimulus)</b>                                                                                                                                                                                                                                                                                                                                      |
| <ul style="list-style-type: none"> <li>• Aquagenic</li> <li>• Cholinergic</li> <li>• Cold contact</li> <li>• Delayed pressure</li> <li>• Exercise-induced anaphylaxis</li> <li>• Heat contact</li> <li>• Solar</li> <li>• Symptomatic dermographism</li> <li>• Vibratory</li> </ul>                                                                                                                                   |
| <b>Angio-oedema without weals</b>                                                                                                                                                                                                                                                                                                                                                                                     |
| <ul style="list-style-type: none"> <li>• Idiopathic (now classified as part of chronic spontaneous urticaria)</li> <li>• Drug induced, e.g. angiotensin-converting enzyme inhibitors</li> <li>• C1 esterase inhibitor deficiency, hereditary or acquired, and hereditary angio-oedema with normal C1 esterase inhibitor</li> </ul>                                                                                    |
| <b>Contact urticaria (contact with allergens or chemicals)</b>                                                                                                                                                                                                                                                                                                                                                        |
| <b>Diseases presenting with urticaria-like rashes</b>                                                                                                                                                                                                                                                                                                                                                                 |
| <ul style="list-style-type: none"> <li>• Urticarial vasculitis (defined by vasculitis on skin biopsy)</li> <li>• Autoinflammatory syndromes</li> <li>• Hereditary, e.g. cryopyrin-associated periodic syndrome (CAPS) (hereditary NLRP3 mutations)</li> <li>• Acquired, e.g. Schnitzler syndrome (paraprotein and chronic urticarial rash), late-onset CAPS (acquired somatic mosaicism in the NLRP3 gene)</li> </ul> |

where the culprit drug must be withdrawn (especially ACE inhibitors, where the angio-oedema may occur soon or many years after drug initiation),<sup>18,19</sup> or rare cases of C1 esterase inhibitor deficiency (see section 6.4). Both may cause life-threatening airway swelling and neither respond to the usual treatment for angio-oedema. Angio-oedema of the gastrointestinal tract is common in C1 esterase inhibitor deficiency.

#### 5.2.4 Contact urticaria

Like inducible urticarias, this is characterized by a weal-and-flare response at the site of contact of a trigger, anaphylaxis may occur, the onset is rapid (within minutes) and reactions usually last for < 2 h. However, the disease is acute, not chronic, and the trigger is not physical but instead may be any of a large variety of substances, for example food, plants, animals, fragrances or preservatives.

#### 5.2.5 Urticarial vasculitis

Weals are usually of prolonged duration, may be painful rather than itchy and sometimes leave residual bruising or postinflammatory change. It can be difficult to differentiate urticarial vasculitis from delayed pressure urticaria. However, in urticarial vasculitis, there are often marked systemic symptoms, there may be joint or renal involvement, an association with other underlying diseases and high inflammatory markers. A skin biopsy is needed to confirm the diagnosis (see section 6.5).<sup>20</sup>

#### 5.2.6 Autoinflammatory syndromes

Autoinflammatory syndromes presenting with urticaria-like rashes include cryopyrin-associated periodic syndrome (CAPS) (usually with onset in childhood, although late-onset acquired disease is recognized) and Schnitzler syndrome (acquired with adult onset). CAPS consists of three overlapping conditions: familial cold autoinflammatory syndrome, Muckle-Wells syndrome and neonatal-onset multisystem inflammatory disorder. These diseases are rare (for pathogenesis see section 5.3.3). They differ in associated organ involvement, but are all usually accompanied by fever, malaise and high levels of inflammatory markers.<sup>21,22</sup>

### 5.3 Pathogenesis and aetiology

#### 5.3.1 Allergic

Some cases of acute or episodic urticaria and some cases of contact urticaria are due to mast cell degranulation caused by allergens crosslinking antigen-specific IgE (type 1 hypersensitivity).

#### 5.3.2 Autoimmune urticaria

Approximately 33% of people with CSU have functional, histamine-releasing IgG autoantibodies. These either directly crosslink high-affinity IgE receptors (FcεRI) or bind IgE.<sup>23</sup>

A new theory is emerging of type 1 autoimmunity or 'autoallergy', in which IgE antibodies are directed at an element of self. Antigens may then crosslink IgE on mast cells or basophils, causing degranulation. It has been observed that there are fast and slow responders to treatment with omalizumab (an anti-IgE antibody). This has led to the proposal that the rapid response may be due to omalizumab rapidly binding free IgE autoantibodies against autoallergens, whilst the slow responses may be due to the slower loss of mast cell (or basophil) membrane-bound IgE and downregulation of FcεRI, thus reducing IgG-mediated activation.<sup>24</sup> The functional importance of IgE 'autoallergic' autoantibodies is under investigation. Thus far, there is some evidence that IgE anti-thyroid peroxidase antibodies and possibly IgE anti-interleukin-24 antibodies may play a role in some patients with CSU.<sup>25,26</sup>

### 5.3.3 Autoinflammatory syndromes

These are characterized by dysregulation of innate immunity. Persistent uncontrolled inflammation occurs in the absence of triggers and is mediated by excessive cytokine production. Most cases of CAPS are due to autosomal dominant or *de novo* mutations in the NLRP3 gene, resulting in increased activity of the NLRP-3 inflammasome and increased secretion of interleukin-1 $\beta$ .<sup>27,28</sup> Late-onset CAPS is now thought to be due to acquired somatic (mosaic) mutations in NLRP3,<sup>29</sup> but these have not been identified in Schnitzler syndrome, even though the clinical presentation is identical.<sup>30</sup> Instead, Schnitzler syndrome is defined by the presence of a monoclonal gammopathy of unknown significance (MGUS), usually IgM, but sometimes IgG.<sup>30</sup>

## 5.4 Associations

Many people with CSU find that nonspecific factors including heat, alcohol, infections and stress exacerbate or trigger their urticaria, but the underlying mechanisms are poorly understood. Drugs may precipitate urticaria by various mechanisms (Table 6).

An urticaria-like rash may also occur as a prodrome of bullous pemphigoid or be a presenting feature of progesterone-induced dermatosis. Urticaria, and particularly urticarial vasculitis, may occur with other diseases, such as systemic lupus erythematosus.

There is an association between CSU and thyroid autoimmunity.<sup>31</sup> There is some evidence that *Helicobacter pylori* infection may be associated with an increased risk of CSU. There is conflicting evidence as to whether eradication of *H. pylori*

alleviates CSU, although identified *H. pylori* infection should, in any case, be treated appropriately (see Appendix C – LETR narratives for question 10). Given the association between chronic urticaria and autoimmunity, including coeliac disease in children<sup>32</sup> and adults,<sup>33,34</sup> clinical suspicion of coexisting autoimmune diseases should remain high, but screening in the absence of associated features is not suggested.

## 6. Appropriate investigations

The most important part of assessment is a thorough clinical history and examination. This will usually lead to accurate clinical classification. In many cases, especially in acute and mild chronic spontaneous or inducible urticarias, responsive to H<sub>1</sub>-antihistamines, there is no need for further investigation.

Urticaria can have a significant effect on people's lives. Therefore, assessments should be made as to the effect the disease is having on the person's quality of life (e.g. using DLQI); anxiety, depression or associated psychological issues (e.g. using the HADS);<sup>35</sup> sleep and attendance at school or work. The activity of the disease should be measured (e.g. using UAS7, AAS or UCT)<sup>36,37</sup> before embarking on second-line treatment options.<sup>38,39</sup>

### 6.1 Acute or episodic spontaneous urticaria

Skin prick tests and/or blood tests for allergen-specific IgE may help to confirm type 1 hypersensitivity as a cause, if suspected. These tests are usually not helpful in chronic urticaria. A full blood count (FBC) and inflammatory markers [C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)] may be helpful in identifying infective causes.

### 6.2 Chronic spontaneous urticaria

A FBC may be useful to identify the minority of cases with an underlying cause. An eosinophilia may suggest a drug-induced rash, pre-bullous pemphigoid urticaria or a parasitic infection. Leucocytosis may be present in infection and sometimes in urticarial vasculitis or autoinflammatory disease, or, conversely, leucopenia may suggest systemic lupus erythematosus.

Inflammatory markers (CRP and ESR) are often normal in CSU, so elevated levels may prompt investigations for urticarial vasculitis, autoinflammatory disease or unrelated causes. Due to the association between CSU and thyroid autoimmunity (section 5.4), testing for thyroid-stimulating hormone (TSH) and thyroid antibodies may be useful.

Thus, performing a small number of tests (FBC, ESR, CRP, TSH and thyroid antibodies) at presentation, may be of benefit in CSU.

In treatment-resistant cases, total IgE levels and tests for IgG histamine-releasing autoantibodies (if available) may help to inform the choice between the second-line treatment agents omalizumab (or in the future perhaps new treatments such as

**Table 6** Pathogenesis and aetiology of urticaria<sup>4</sup>

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Idiopathic</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>Immunological</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Adaptive immune system                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <ul style="list-style-type: none"> <li>• Allergic (mediated by IgE – abnormal response to external antigen)</li> <li>• Autoimmune (mediated by IgG, or possibly IgE 'autoallergy') – (abnormal response to self-antigen)</li> <li>• Immune complex (urticarial vasculitis, or acute urticaria due to blood products)</li> </ul>                                                                                                                                             |
| Innate immune system                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <ul style="list-style-type: none"> <li>• Autoinflammatory (mediated by cytokines)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Other</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <ul style="list-style-type: none"> <li>• Kallikrein–kinin system mediated (acquired or hereditary C1 esterase inhibitor deficiency or hereditary angio-oedema with normal C1 esterase inhibitor)</li> <li>• Direct mast-cell-releasing agents (e.g. opiates, radiocontrast media)</li> <li>• Leukotriene formation (e.g. aspirin, nonsteroidal anti-inflammatory drugs)</li> <li>• Inhibition of kinin breakdown (e.g. angiotensin-converting enzyme inhibitors)</li> </ul> |

the monoclonal anti-IgE antibody ligelizumab) and ciclosporin (see R23 and R24).<sup>40–42</sup> Functional tests may also be useful in understanding disease pathogenesis and in providing an explanation to the person with urticaria.

Total IgE assays are widely available, low cost and well characterized. The BHRA is the most established test for functional autoantibodies; however, it is complex to perform. Some laboratories may prefer measuring basophil activation by other validated means. No functional test is well characterized or has been subject to national quality assurance schemes. Such tests are not always readily accessible or available. Further research is needed to determine the comparative utility of functional tests in predicting treatment responses in CSU. For more details see Appendix C (LETR narratives).

### 6.3 Inducible urticarias

These should be confirmed by history and appropriate provocation tests.<sup>43</sup>

In cold contact urticaria, cryoglobulins may be measured, although they are rarely present and, if so, are usually associated with infection or haematological disease. If they are measured, scrupulous attention to temperature-controlled sampling, transport and processing is required (blood must be kept at 37°C). If weals follow the cold trigger after a delay of a few hours, are associated with systemic symptoms or start in early childhood, and/or there is a family history, investigations should be undertaken for familial cold autoinflammatory syndrome (section 6.6).

In solar urticaria, antinuclear antibodies and porphyrins should be checked. If the diagnosis is unclear, or if the disease is poorly responsive to treatment, referral to a specialist centre for an opinion and, if appropriate, phototesting may help.

In aquagenic pruritus, an annual FBC is recommended, as this condition may be associated with polycythaemia rubra vera and other haematological disorders.

### 6.4 Angio-oedema without weals

C1 esterase inhibitor deficiency is characterized by low C4 levels, both between and during attacks.<sup>44</sup> If C4 levels are low, C1 esterase inhibitor level and function should then be checked. In about 85% of cases of hereditary angio-oedema both are reduced (type I), but in the remainder only functional activity is reduced (type II). Reduced C1q levels are characteristic of (but not specific for) acquired C1 esterase inhibitor deficiency. All forms of C1 esterase inhibitor deficiency should be referred to immunology services for further investigation and management, in line with national and international consensus guidelines.

### 6.5 Urticarial vasculitis

A skin biopsy showing a leucocytoclastic vasculitis is required to confirm the diagnosis, but the histological changes are

often subtle. Possible histological features include fragmentation of leucocytes with nuclear debris (leucocytoclasia), endothelial cell swelling or damage, red cell extravasation and rarely fibrin deposition.

Inflammatory markers (CRP, ESR) are often raised. A full vasculitis screen should be checked to investigate for underlying causes, such as connective tissue disease or infection. Low C3 and C4, and positive anti-C1q antibodies may indicate hypocomplementaemic urticarial vasculitis, a more severe disease with a greater potential for associated systemic disease, particularly systemic lupus erythematosus, and internal organ involvement.<sup>20,45</sup>

### 6.6 Autoinflammatory syndromes

Inflammatory markers (CRP and ESR) are usually elevated, as is serum amyloid A, which should be measured. Immunoglobulins and serum protein electrophoresis should be checked to investigate for Schnitzler syndrome in late-onset disease, although a low-level IgM paraprotein can be difficult to detect. Genetic tests should be arranged if CAPS is suspected. In England, patients should be referred to departments approved by NHS England for investigation and treatment.

## 7. Interventions

Largely, these are as listed in the recommendations (section 3.0). However, a few important points are discussed below. Details of the supporting evidence for each recommendation can be found in Appendix C (LETR narratives).

### 7.1 The effectiveness of H<sub>1</sub>-antihistamines compared with each other

No first-generation H<sub>1</sub>-antihistamine was found to stand out as being more effective than others in the Cochrane review.<sup>46</sup> However, the GDG generally considered loratadine and desloratadine to be slightly less effective, a position supported by *in vivo* suppression of weal-and-flare responses by different H<sub>1</sub>-antihistamines.<sup>47,48</sup> See Appendix C, question 2/3 for further information, including a network meta-analysis published in 2021 that graded antihistamines in order of efficacy and acceptability, but acknowledged that this was based on low-quality evidence.<sup>49</sup>

### 7.2 Updosing of H<sub>1</sub>-antihistamines

If licensed doses of H<sub>1</sub>-antihistamines show inadequate response, the GDG agreed that evidence on efficacy supported the updosing of second-generation H<sub>1</sub>-antihistamines for CSU, where tolerated and in the absence of contraindications. Efficacy gains were particularly evident for pruritus and quality of life, but the need for further research was noted.<sup>50</sup> The GDG recommended considering a switch from one second-generation H<sub>1</sub>-antihistamine to another in people with CSU who do not respond adequately to the first drug, or if side-

effects develop. The GDG does not recommend routinely offering combinations of two different second-generation H<sub>1</sub>-antihistamines at the same time to people with CSU, although it was noted that some people may benefit.<sup>51</sup> The safety of giving two H<sub>1</sub>-antihistamines at lower dosages has not been investigated and there is no published evidence on using such combination treatment. The GDG does not recommend up dosing first-generation H<sub>1</sub>-antihistamines in people with CSU.

In general, evidence supported the good safety profile of up to fourfold up dosing of second-generation H<sub>1</sub>-antihistamines, where tolerated, and in the absence of contraindications. However, the following should be considered before proceeding. Firstly, some studies have suggested that a proportion of people may develop increased side-effects, such as sedation, on up dosing second-generation H<sub>1</sub>-antihistamines.<sup>52,53</sup> The possibility of sedation after up dosing second-generation H<sub>1</sub>-antihistamines should be discussed with people with urticaria. Secondly, the summary of product characteristics on [www.medicines.org.uk](http://www.medicines.org.uk) provides specific information on the cautions and contraindications of individual antihistamines and these should be considered before up dosing. These include closed-angle glaucoma, prostatism, interactions with other drugs (e.g. cytochrome P450 modulators, drugs with associated sedation), foods (e.g. grapefruit) and alcohol, renal and liver impairment, epilepsy, elderly people and heart disease. Thirdly, the potential to prolong the electrocardiogram QTc interval should also be considered for all H<sub>1</sub>-antihistamines.<sup>54</sup> For example, among other contraindications, mizolastine is contraindicated in people with known or suspected QT prolongation or with electrolyte imbalance, in particular hypokalaemia or hypomagnesaemia; in clinically significant bradycardia; and where used with medicinal products known to prolong the QT interval, such as class I and III antiarrhythmics. The GDG does not recommend up dosing mizolastine.

The GDG noted that most studies on up dosing have shown significant heterogeneity in terms of study design, doses, specific antihistamines and responses, and recommended that large-scale, high-quality studies be undertaken.

### 7.3 Subsets of urticaria in which montelukast may be of benefit

There is published evidence that montelukast in combination with a second-generation H<sub>1</sub>-antihistamine may be more effective than taking a second-generation H<sub>1</sub>-antihistamine alone for people with CSU.<sup>55</sup> Much less data are available for inducible urticarias, although there is some evidence for efficacy in delayed pressure urticaria,<sup>56</sup> and several members of the GDG try montelukast in people with various inducible urticarias.

There may also be specific circumstances when this combination may be beneficial, such as when urticaria is exacerbated by salicylates, or where angio-oedema is the predominant symptom.<sup>57,58</sup>

Montelukast can be prescribed in primary care without monitoring of blood tests, but a recent Medicines and Healthcare products Regulatory Agency (MHRA) warning reminds

prescribers of the neuropsychiatric side-effects that may occur in a minority of people, particularly in children. People given montelukast should be counselled so as to be vigilant for these symptoms.

### 7.4 H<sub>2</sub>-antihistamines

There is insufficient evidence to recommend routine addition of H<sub>2</sub>-antihistamines to second-generation H<sub>1</sub>-antihistamines for people with chronic urticaria whose symptoms are inadequately controlled by the latter alone.<sup>59</sup> However, some people may benefit, especially if urticaria is associated with dyspepsia. However, dyspepsia should be investigated appropriately. If an H<sub>2</sub>-antihistamine is used, famotidine (at the dose licensed for dyspepsia) is preferable to cimetidine, because the latter has a higher risk of adverse effects and interacts with cytochrome p450 modulators. Indeed, cimetidine interacts with some first-generation H<sub>1</sub>-antihistamines, raising their plasma concentration, which may explain some of the beneficial effects of combination therapy demonstrated many years ago.<sup>60</sup> However, there are very few data on the use of famotidine in urticaria.

It is of note that we no longer recommend ranitidine as it has been withdrawn by the manufacturers due to possible contamination with a known carcinogen.<sup>61</sup>

### 7.5 Oral corticosteroids for inducible urticarias

There are very few published data on the use of systemic corticosteroids in people with inducible urticarias. As for CSU, a short course of oral prednisolone may be considered for severe exacerbations, although it may not be as effective.<sup>62</sup>

### 7.6 Avoidance of triggers in inducible urticarias

Avoidance of triggers may be helpful, especially where disease control is difficult. Avoidance can be disabling. However, where there is a risk of anaphylaxis, people should be warned to avoid particularly dangerous situations. For example, in cold urticaria, swimming in cold water (especially in the sea) or rock climbing could lead to a drop in core temperature or cooling of much of the body surface, resulting in anaphylaxis, potentially with fatal outcome.

### 7.7 Autoinflammatory syndromes

These usually respond very rapidly (usually within 24 h) to agents that inhibit the actions of interleukin-1, such as the interleukin-1 receptor antagonist anakinra. Early treatment may prevent (and possibly reverse) disease complications. A therapeutic trial can be used as a diagnostic tool.<sup>63</sup>

### 7.8 Potential new treatments for chronic spontaneous urticaria

A number of drugs are under investigation and/or in clinical trials for CSU.<sup>64</sup> Biosimilars for omalizumab are being

developed. Ligelizumab, a new anti-IgE monoclonal antibody, may be more efficacious and need less frequent administration than omalizumab. Dupilumab (an anti-interleukin-4 receptor antibody that inhibits the interleukin-4 and interleukin-13 pathways), monoclonal antibodies targeting the interleukin-5 pathway (such as mepolizumab, reslizumab and benralizumab) and Bruton's tyrosine kinase inhibitors are all being investigated for CSU. Other potential therapeutic targets include siglec-8 (an inhibitory receptor on mast cells, basophils and eosinophils), prostaglandin receptors, the  $H_4$  receptor and the C5a receptor.

## 8. Prognosis

Approximately 45% of people with CSU respond to  $H_1$ -antihistamines at licensed doses,<sup>65</sup> and reports estimate that up to two-thirds of the residual may respond to up dosing.<sup>50</sup> About two-thirds of those unresponsive to  $H_1$ -antihistamines respond to omalizumab,<sup>66</sup> and a similar, probably different but overlapping, proportion to ciclosporin, although there is less evidence for the latter.<sup>67</sup> Of note, the response rates given include partial and complete responses, so full disease suppression may not be achieved in many people with CSU with these treatments alone.

Approximately 50% of people with CSU go into remission after 6 months to 5 years (longer if there is angio-oedema), but about 20% still have active disease after 10 years, and 10% after 20 years.<sup>65,68</sup>

In some people, urticaria can be very long lasting, difficult to treat and disabling. This is perhaps particularly so for people with severe inducible urticarias, where there are fewer options and less data to support treatment.

## 9. Considerations

### 9.1 Children and young people

In most aspects, urticaria and angio-oedema are very similar in children and adolescents compared with adults, including treatment approaches. About 75% of children with chronic urticaria have CSU, with most others having inducible urticarias,<sup>69</sup> and both can coexist. However, there are a few important management aspects to consider when seeing children and adolescents.

1. Consider an underlying autoinflammatory disease if a child is systemically unwell and/or has raised inflammatory markers. In England, children who are thought to have autoinflammatory disease should be referred to a rheumatologist with a specialist interest in autoinflammatory syndromes.
2. A parasitic infection may be responsible for chronic urticaria. At-risk children should be screened and, if parasitic infection is present, treated accordingly. Indicators of a potential parasitic infection include eosinophilia, gastrointestinal symptoms and recent foreign travel.

3. The same proportion of children and young people with CSU have a positive BHRA, but there is a lack of evidence that this influences treatment response or disease remission.
4.  $H_1$ -antihistamines currently authorized for use in children aged 2–11 years (Table 3) include cetirizine, levocetirizine, loratadine and rupatadine.<sup>70</sup> When needed, these antihistamines can also be used below age 2 years, despite the licensing age cutoff, given their overall good safety profile. Desloratadine is licensed from age 1 year and chlorphenamine from age 1 month (the latter is licensed in the UK according to the British National Formulary).
5. Second-generation  $H_1$ -antihistamines can be up dosed with care (section 7.2) as for adults, taking into consideration cautions and contraindications, and proportionate to the manufacturers' recommendations for age and weight (Table 3).<sup>71</sup>
6. As for adults, do not offer first-generation  $H_1$ -antihistamines routinely, unless there is no alternative, due to concerns about their short- and long-term effects on the central nervous system.
7. Children may be more likely than adults to have neuropsychiatric side-effects from montelukast, including dysphemia (described as 'stuttering'), nightmares or night terrors, aggression and behavioural changes.
8. Although not licensed in the UK, omalizumab has been successfully used in children below the age of 12 years with CSU and inducible urticarias, typically at the lower dose of 150 mg every 4 weeks and down to age 6 years, but very occasionally at even younger ages.<sup>72</sup> The same applies to ciclosporin (typically 3–4 mg kg<sup>-1</sup> per day).<sup>73–75</sup>
9. As in adults, self-injectable adrenaline should be considered in children with inducible urticarias where there is a risk of anaphylaxis following a significant trigger (those with cold urticaria must not immerse themselves in cold water), especially in children with a history of systemic symptoms.
10. There is very little published evidence for treatment interventions in children under 12 years, or for phototherapy for children of any age, with any subtype of urticaria.

### 9.2 Pregnancy and breastfeeding

There is insufficient evidence to make a recommendation about the safety of using most drugs during pregnancy and breastfeeding. Refer to the manufacturer's summary of product characteristics,<sup>11</sup> or other published guidelines.

However, in active disease and after counselling the person with any type of urticaria, where necessary consider cetirizine or loratadine (see Appendix C – LETR narratives – for available information on antihistamines).

Similarly, to date there is no evidence of harm to the fetus or mother from the use of omalizumab in pregnancy, or whilst breastfeeding, although again the person should be fully informed of the lack of available evidence.

## 10. Recommended audit points

In the last 20 consecutive people with chronic urticaria, is there clear documentation of:

1. The clinical subtype(s) of urticaria.
2. Provision of educational material.
3. Advice on avoidance of triggers.
4. Assessment of disease impact, for example DLQI (at a minimum, prior to commencement of second-line agents).
5. Assessment of disease severity, for example UAS7, AAS or UCT (at a minimum, prior to commencement of second-line agents).
6. Use of a second-generation H<sub>1</sub>-antihistamine at the licensed dosage, as a first-line agent for all types of chronic urticaria.
7. Use of a second-generation H<sub>1</sub>-antihistamine above the manufacturer's recommended dose for all types of urticaria, if a licensed dose fails to adequately control symptoms, unless there are contraindications.
8. The addition of montelukast to a second-generation H<sub>1</sub>-antihistamine, in people with CSU whose symptoms are not adequately responsive to H<sub>1</sub>-antihistamines alone.
9. The addition of omalizumab (or ciclosporin in CSU) to a second-generation H<sub>1</sub>-antihistamine, if symptoms are not adequately controlled by first-line agents.
10. Use of oral corticosteroids limited to short courses, if applicable.
11. Avoidance of first-generation H<sub>1</sub>-antihistamines as first-line treatment.

The audit recommendation of 20 cases per department is to reduce variation in the results due to a single person and allow benchmarking between different units. However, departments unable to achieve this recommendation may choose to audit all cases seen in the preceding 12 months. See Appendix L (Supporting Information) for the set of audit standards, data items and data collection methodology.

## 11. Stakeholder involvement and peer review

The draft document and Supporting Information were made available to the BAD membership, British Dermatological Nursing Group (BDNG), Primary Care Dermatological Society (PCDS), British Society for Allergy & Clinical Immunology (BSACI) and the Royal College of Pathologists' Immunology Specialist Advisory Committee for comments, which were actively considered by the GDG. Following further review, the finalized version was sent for peer review by the Clinical Standards Unit of the BAD, made up of the T&G subcommittee, prior to submission for publication.

## 12. Limitations of the guideline

This document has been prepared on behalf of the BAD and is based on the best data available when the document was prepared. It is recognized that under certain conditions it may be

necessary to deviate from the guidelines and that the results of future studies may require some of the recommendations herein to be changed. Failure to adhere to these guidelines should not necessarily be considered negligent, nor should adherence to these recommendations constitute a defence against a claim of negligence. Limiting the review to English-language references was a pragmatic decision, but the authors recognize this may exclude some important information published in other languages.

## 13. Plans for guideline revision

The proposed revision date for this set of recommendations is scheduled for 2026; where necessary, important interim changes will be updated on the BAD website.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

**Appendix A** Systematic review protocols and clinical questions.

**Appendix B** Forest plots for comparative studies.

**Appendix C** Linking the Evidence To the Recommendations (LETR).

**Appendix D** GRADE evidence tables.

**Appendix E** Summary of included comparative studies.

**Appendix F** Narrative findings for noncomparative studies.

**Appendix G** PRISMA diagram – study selection.

**Appendix H** Papers excluded from quantitative analysis.

**Appendix I** AMSTAR 2 critical appraisal of the included systematic reviews.

**Appendix J** Methodology.

**Appendix K** Search strategy.

**Appendix L** Audit standards, data items and data collection methodology.

**Powerpoint S1** Journal Club Slide Set.

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