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

R.A. Sabroe,1 F. Lawlor,2 C.E.H. Grattan,2 M.R. Ardern-Jones,3 A. Bewley,4 L. Campbell,5 C. Flohr,2 T.A. Leslie,6 A.M. Marsland,7 G. Ogg,8 W.A.C.Sewell,9 M. Hashme,10 L.S. Exton,10 M.F. Mohd Mustapa,10 M.C. Ezejimofor10 on behalf of the British Association of Dermatologists’ Clinical Standards Unit\*

1 Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield S10 2JF, U.K.

2 St John’s Institute of Dermatology, Guy’s and St Thomas NHS Foundation Trust, London SE1 9RT, U.K.

3Clinical Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton General Hospital, Southampton SO16 6YD, U.K.

4 Barts Health NHS Trust and Queen Mary University of London Medical School, London E1 1BB, U.K.

5 Patient representative

6 Royal Free London NHS Foundation Trust, Pond St, London NW3 2QG, U.K.

7 University of Manchester & Salford Royal Hospital, Salford M6 8HD, U.K.

8MRC Human Immunology Unit, The MRC Weatherall Institute of Molecular Medicine, University of Oxford, NIHR Oxford Biomedical Research Centre, John Radcliffe Hospital, Oxford OX3 9DS, U.K.

9 University of Lincoln, Lincoln LN6 7TS, U.K.

10 British Association of Dermatologists, Willan House, 4 Fitzroy Square, London W1T 5HQ, U.K.

**Corresponding author:** Ruth A Sabroe, [rsabroe@doctors.org.uk](mailto:rsabroe@doctors.org.uk); [guidelines@bad.org.uk](mailto:guidelines@bad.org.uk)

R.A.S. <https://orcid.org/0000-0002-2642-7067>; M.R.A-J. <https://orcid.org/0000-0003-1466-2016>; A.B. <http://orcid.org/0000-0003-1195-0290>; G.O. <https://orcid.org/0000-0002-3097-045X>; L.S.E <https://orcid.org/0000-0003-0073-1885>; M.F.M.M. <https://orcid.org/0000-0003-4070-0696>; M.C.E. <http://orcid.org/0000-0002-2510-9964>; C.F. <https://orcid.org/0000-0003-4884-6286>

**Produced in 2001 by the British Association of Dermatology**

**Reviewed and updated 2010, 2021**

**Key words**: urticaria, chronic spontaneous urticaria, inducible urticarias, guidelines, management, treatment.

|  |  |
| --- | --- |
| NICE_Accreditation_max | 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). |

**Footnote**:

This is an updated guideline prepared for the British Association of Dermatologists (BAD) Clinical Standards Unit, which includes the Therapy & Guidelines Sub-committee (T&G). Members of the Clinical Standards Unit that have been involved are: NJ Levell (Chair, T&G), SL Chua, P Laws, H Frow, A Bardhan, A Daunton, G Petrof, M Hashme (BAD Information Scientist), LS Exton (BAD Senior Guideline Research Fellow), MC Ezejimofor (BAD Guideline Research Fellow), MF Mohd Mustapa (BAD Director of Clinical Standards).

**1.0 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
* 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), hereditary angio-oedema, auto-inflammatory syndromes or differential diagnosis. Additionally, the guideline focuses on chronic rather than acute urticaria.

**2.0 METHODOLOGY**

This set of guidelines has been developed using the BAD’s recommended methodology1, further information can be found in Appendix J (see Supporting Information) with reference to the Appraisal of Guidelines Research and Evaluation (AGREE II) instrument ([www.agreetrust.org](http://www.agreetrust.org))2 and the Grading of Recommendations Assessment, Development and Evaluation (GRADE).3 Recommendations were developed for implementation in the United Kingdom (U.K.) 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 PubMed, MEDLINE, EMBASE and Cochrane databases was conducted to identify key articles on urticaria from January 2007 up to March 2020 and 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. Search terms and strategies are detailed in Appendix K (see supporting information). Additional references relevant to the topic were also isolated from citations in reviewed literature and the previous version of the guideline. 4 Evidence from included studies was graded according to the GRADE system (high, moderate, low or very low certainty).

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 its 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 (see Appendix B), tables Linking the Evidence To the Recommendations (LETR – see Appendix C), GRADE evidence profiles indicating the quality of evidence (see Appendix D), PRISMA flow diagram (see Appendix G) and list of excluded studies (see Appendix H) are detailed in the supporting information.

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

**Table 1.** Strength of recommendation ratings

|  |  |  |  |
| --- | --- | --- | --- |
| **Strength** | **Wording** | **Symbols** | **Definition** |
| **Strong** recommendation *for* the use of an intervention | “Offer”  *(or similar, e.g. “Use”, “Provide”, “Take”, “Investigate”, etc.)* | **áá** | 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 policy makers, it would be a useful performance indicator. |
| **Weak** recommendation *for* the use of an intervention | “Consider” | **á** | 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 policy makers it would be a poor performance indicator where variability in practice is expected. |
| No recommendation | | **Θ** | Insufficient evidence to support any recommendation. |
| **Strong** recommendation *against* the use of an intervention | “Do not offer” | **ââ** | 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. |

**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 (ASST), alter the management of urticaria?

**Review question 2: treatment**

What is the clinical effectiveness of H1-antihistamines compared with each other for the treatment of urticaria?

**Review question 3: treatment**

Would changing from one H1-antihistamine to another lead to benefit in the treatment of urticaria?

**Review question 4: treatment**

Would adding an H2-antihistamine to an H1- 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 is the effectiveness and safety of increasing doses of H1- antihistamines?

**Review question 7: treatment**

Would adding other therapies to an H1-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?

**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 non-steroidal 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 (symptomatic dermographism, delayed pressure urticaria (DPU), cold urticaria, cholinergic urticaria, vibratory angio-oedema, localized heat urticaria, etc.) the same as for chronic spontaneous urticaria (CSU)?

**Review question 15: treatment**

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

**Review question 16: treatment**

Which H1-antihistamines can be used in pregnancy?

**Review question 17: treatment**

Which H1-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,5 by the patient representatives (see Appendix A for full review protocol; supporting information). In the investigation protocol, the outcome is either ‘Yes’ or ‘No’. The treatment outcomes (see 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. Data on which are extracted from included studies:

**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 |

**3.0 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 section 2. The evidence on which 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.

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 less than 12 years:

* recommendations are based on expert opinion as there is very little published evidence, and
* 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 H1-antihistamines, oral steroids and omalizumab, none of the other treatment options discussed are licensed in the U.K. for use in urticaria. Except where otherwise stated, we recommend adherence to published guidelines, for example by the manufacturer, the BAD or, in the U.K., the British National Formulary (www.bnf.org). In particular, note licensed dosages for people aged less than 14 years (also see table 3).

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

For clarity, we have divided management options into sections (general treatment, first-, second- and third-line options). However, depending on disease severity, disease fluctuation, comorbidities, national criteria for use of drugs, the order and combinations of treatment may vary and 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.6 Broadly, the recommendations are similar, except that the international guideline favours omalizumab over ciclosporin for CSU.

**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 (á)** 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, e.g. dermatology quality of life index (DLQI), weekly urticaria activity score 7 (UAS7), angio-oedema activity score (AAS), and/or urticaria control test (UCT).

**R3 (GPP)** Provide educational material or a patient information leaflet on urticaria/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 anti-pruritic 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 (áá)** Stop angiotensin-converting enzyme inhibitors (ACEi) in people with angio-oedema without weals.

**General management for people with CSU**

**R8 (áá)** Avoid non-steroidal anti-inflammatory drugs (NSAIDs) in people whose CSU appears to be exacerbated by this class of drugs.

**R9 (á)** Consider switching NSAID treatment to a selective cyclooxygenase-2 (COX-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 anti platelet drug is lacking.Refer to National Institute of Clinical Excellence (NICE),7 British Society of Allergy and Clinical Immunology (BSACI)8 or European Academy of Allergy and Clinical Immunology (EAACI) guidance9 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.

**Θ2** There is insufficient evidence to make a recommendation on dietary supplementation.

**R11 (ââ)** Do not offerroutine screening for *Helicobacter pylori*.

**First-line treatment options for people with CSU**

**R12 (áá)** Offer a second-generation H1-antihistamine, using a regular daily licensed dose (see Table 4).

**Table 4.** Examples of first- and second- generation H1-antihistamines

|  |  |  |
| --- | --- | --- |
|  |  | **Licensed oral dose for adultsa (see Table 3 for children)** |
| **First generation** | Chlorphenamine | 4 mg every 4-6 hours, maximum 24 mg per day (elderly maximum 12 mg per day) |
| Cyproheptadine | 4 mg three times per day (maximum 32 mg per day) |
| Hydroxyzine | Initially 10-25 mg nocte, maximum 25 mg three to four times per day (elderly maximum 25 mg twice daily) |
| Promethazine | 10-20 mg two to three times per day |
| **Second generation** | 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 |

a From the British National Formulary

**R13 (ââ)** Do not offer first-generation H1-antihistamines routinely, unless there is no alternative, due to concerns about their short- and long-term effects on the central nervous system.

**R14 (áá)** Offer up-dosing (i.e. increasing the dose above the licenced dose) of a single second-generation H1-antihistamine, by up to four-fold 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 – see supporting information). Attempt step-wise, dose-reduction following complete symptom control. There is no evidence to guide optimum duration of up-dosing or speed of dose reduction.

**R15 (ââ)** Do not up-dose mizolastine (see section 7.2).

**R16 (GPP**) Consider switching from one second-generation H1-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.

**Θ3** There is insufficient evidence to make a recommendation on using two different second-generation H1-antihistamines at the same time.

**R17 (ââ)** Do not up-dose first-generation H1-antihistamines (see **R13**).

**R18 (á)** Consider montelukast, in addition to a second-generation H1-antihistamine,in people whose symptoms are inadequately controlled by standard and increased doses of second-generation H1-antihistamines.

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

**Θ4** There is insufficient evidence to recommend routine addition of H2-antihistamines to second-generation H1-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 (á)** Consider oral prednisolone (e.g. 0.5 mg/kg) for short, infrequent courses of a few days as rescue treatment to control severe exacerbations, in addition to continued use of a second-generation H1-antihistamine.

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

**Second-line treatment options for people with CSU**

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 (ââ)** Do not offer autologous serum or plasma skin tests (ASST/APST) routinely.

**R23 (á)** 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 – see supporting information]).

**R24 (á)** 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 – see supporting information]).

N.B. Total IgE levels (R23) and BHRAs (R24) are only indicative and may not reflect actual clinical responsiveness in all patients.

**R25 (áá)** Offer omalizumab, in addition to a second-generation H1-antihistamine, to people whose symptoms are inadequately controlled by first-line options.

**R26 (áá)** Offer\* ciclosporin for 3 to 6 months, in addition to a second-generation H1-antihistamine, to people whose symptoms are inadequately controlled by first-line options.

**R27 (áá)** 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 CSU**

**R28 (á)** 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 CNS effects, as for first-generation antihistamines)
* hydroxychloroquine (particularly for urticaria occurring with systemic lupus erythematosus)
* intravenous immunoglobulins (IVIg)
* methotrexate
* mycophenolate mofetil
* narrowband UVB (typically a course of around 30 treatments, repeated after 12 months, if necessary, but not for continual treatment)
* sulfasalazine
* oral tacrolimus
* 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 (IL-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 (TNF) 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 (áá)** Offer\* a second-generation H1-antihistamine, using a regular daily licensed dose (see Table 4).

**R30 (ââ)** Do not offer\* first-generation H1-antihistamines routinely, unless there is no alternative, due to concerns about their short- and long-term effects on the central nervous system.

**R31 (áá**) Offer\* up-dosing of a single second-generation H1-antihistamine by up to four-fold 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 – see supporting information]). Attempt step-wise, dose-reduction following complete symptom control. There is no evidence to guide optimum duration of up-dosing or speed of dose reduction.

**R32 (ââ)** Do not up-dose mizolastine (see section 7.2).

**R33 (GPP)** Consider switching from one second-generation H1-antihistamine to another in people whose symptoms do not respond adequately to, or who do not tolerate, the first drug at standard or increased dose.

**Θ6** There is insufficient evidence to make a recommendation on using two different second-generation H1-antihistamines at the same time.

**R34 (ââ)** Do not up-dose first-generation H1-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 (á)** Consider omalizumab, in addition to a second-generation H1-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, e.g. 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 H1-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 desensitisation.

***Delayed pressure urticaria***

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

***Solar urticaria***

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

**R42 (á)** Consider UV prophylactic phototherapy using the wavelength of light relevant to the individual person, only following photo-investigation 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 (á)** Consider narrow band UVB (typically a course of around 30 treatments, repeated after 12 months, if necessary, but not for continual treatment).

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

**R45 (GPP)** Consider narrow band 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 with any type of urticaria, where necessary, consider cetirizine or loratadine (see individual drug Summary of Product Characteristics 11 for information on safety during pregnancy) and discussion in Appendix C (LETR narratives) – see supporting information.

**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 inflammatory markers
* there are marked/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).

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

**FRR2** Better characterisation 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** Utilising the results from FRR1-3 to address the possibility of personalised 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 H1-antihistamine compared with using two different second-generation H1-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, humanised monoclonal anti-IgE antibody ligelizumab, and potential new treatment options such as tyrosine kinase inhibitors, dupilumab, histamine H4 receptor antagonists, C5a receptor antagonists and drugs targeting inhibitory mast cells receptors (see section 7.8).

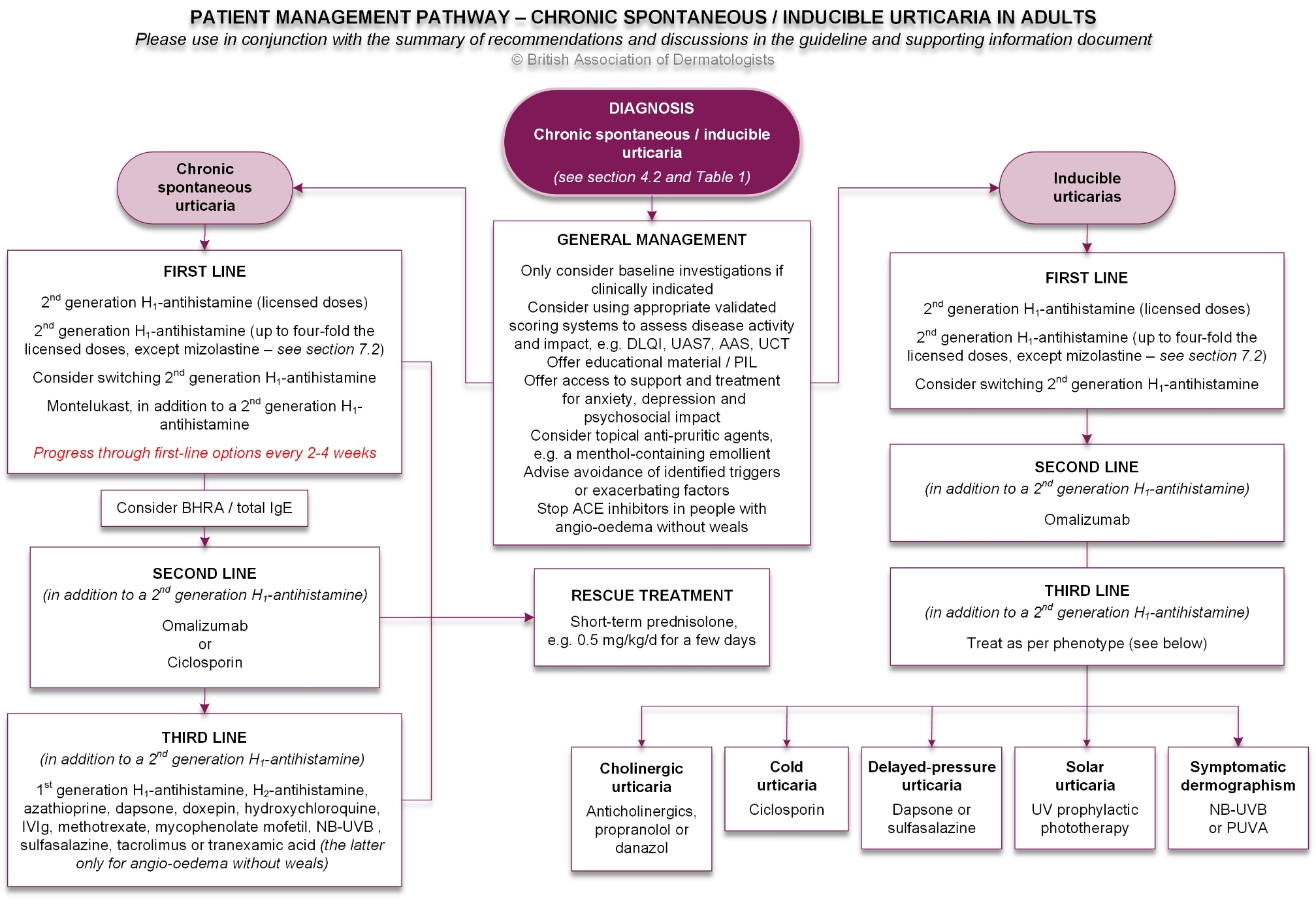
**FRR9** Better characterisation of the optimum duration of the various treatment options available to people with all types of urticaria.

**FRR10** Investigations into disease incidence/prevalence, predictive value of laboratory investigations (such as total IgE levels, basophil-based assays), 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.

**4.0 ALGORITHM**

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

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



**5.0 BACKGROUND**

**5.1 Definition/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 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 8-24%, with a lifetime prevalence rate of about 1-2% for chronic urticaria.12-14 The point prevalence of chronic urticaria varies from 0.1% in North America to 1.4% in Asia.15 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.16,17

Even though the initial treatment for many types of urticaria is similar, there are some important exceptions. Therefore, accurate clinical categorisation, 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** (see Table 5)

**Table 5.** Clinical classification of urticaria, including diseases presenting with urticaria-like rashes.4

|  |
| --- |
| **Spontaneous urticaria**   * Acute * Chronic (6 weeks or more of continuous activity) * Episodic (acute intermittent or recurrent activity)   **Inducible urticarias** (reproducibly induced by the same physical stimulus)   * Aquagenic * Cholinergic * Cold contact * Delayed pressure * Exercise-induced anaphylaxis * Heat contact * Solar * Symptomatic dermographism * Vibratory   **Angio-oedema without weals**   * Idiopathic (now classified as part of chronic spontaneous urticaria) * Drug-induced, e.g. ACE inhibitors * C1 esterase inhibitor deficiency, hereditary or acquired, and hereditary angio-oedema with normal C1 esterase inhibitor   **Contact urticaria** (contact with allergens or chemicals)  **Diseases presenting with urticaria-like rashes**   * Urticarial vasculitis (defined by vasculitis on skin biopsy) * Autoinflammatory syndromes * Hereditary, e.g. cryopyrin-associated periodic syndromes (CAPS) (hereditary \*NLRP-3 mutations) * Acquired, e.g. Schnitzler syndrome (paraprotein and chronic urticarial rash), late onset CAPS (acquired somatic mosaicisms in the \*NLRP-3 gene) |

**\*** NLRP-3: Nucleotide-binding oligomerization domain, Leucine rich Repeat and Pyrin domain containing - 3

**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 many of those with chronic urticaria (chronic spontaneous urticaria, CSU) (see section 5.3.2. for pathogenesis of CSU). Weals generally last for up to 24 hours, but the swellings of angio-oedema may last for up to 72 hours.

**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 less than 2 hours, the exception being delayed pressure urticaria where weals may take 30 minutes to 12 hours 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, 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 where the culprit drug must be withdrawn (especially ACE inhibitors, where the angio-oedema may occur soon or many years after drug initiation),18,19 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 characterised 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 less than 2 hours. However, the disease is acute not chronic and the trigger is not physical but instead may be any of a large variety of substances, e.g. food, plants, animals, fragrances, preservatives.

**5.2.5 Urticarial vasculitis**

Weals are usually of prolonged duration, may be painful rather than itchy and sometimes leave residual bruising or post-inflammatory 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).20

**5.2.6 Autoinflammatory syndromes**

Those presenting with urticaria-like rashes include the CAPS (usually with onset in childhood, although late onset acquired disease is recognised) and Schnitzler syndrome (acquired with adult onset). CAPS consist 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 inflammatory markers21,22

**5.3 Pathogenesis/Aetiology**

**Table 6.** Pathogenesis/aetiology of urticaria*.*4

|  |
| --- |
| **Idiopathic**  **Immunological**  Adaptive immune system   * Allergic (mediated by IgE – abnormal response to external antigen) * Autoimmune (mediated by IgG [or possibly IgE “autoallergy”]) – abnormal response to self-antigen) * Immune complex (urticarial vasculitis, or acute urticaria due to blood products)   Innate immune system   * Autoinflammatory (mediated by cytokines)   **Other**   * Kallikrein-kinin system mediated (acquired or hereditary C1 esterase inhibitor deficiency/ hereditary angio-oedema with normal C1 esterase inhibitor * Direct mast cell-releasing agents (e.g. opiates, radiocontrast media) * Leukotriene formation (e.g. aspirin, nonsteroidal anti-inflammatory drugs) * Inhibition of kinin breakdown (e.g. ACE inhibitors) |

**5.3.1 Allergic**

Some cases of acute/episodic urticaria and some cases of contact urticaria are due to mast cell degranulation caused by allergens cross-linking 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 cross link high-affinity IgE receptors (FcRI) or bind IgE.23

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 cross link 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 FcRI, thus reducing IgG mediated activation.24 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.25,26

**5.3.3 Autoinflammatory syndromes**

These are characterised 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 *NLRP*-*3* gene, resulting in increased activity of the NLRP-3 inflammasome and increased secretion of interleukin-1β.27,28 Late onset CAPS are now thought to be due to acquired somatic (mosaic) mutations in the *NLR*P-3 gene,29 but these have not been identified in Schnitzler syndrome, even though the clinical presentation is identical.30 Instead, Schnitzler syndrome is defined by the presence of a monoclonal gammopathy of unknown significance (MGUS), usually IgM, but sometimes IgG.30

**5.4 Associations**

Many people with CSU find that non-specific factors including heat, alcohol, infections and stress exacerbate or trigger their urticaria, but 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.31 There is some evidence that *Helicobacter pylori* infection may be associated with an increased risk of CSU. There is conflicting evidence as to whether eradiation of *Helicobacter pylori* alleviates CSU, although identified *Helicobacter pylori* infection should, in any case, be treated appropriately (see Appendix C [LETR narratives for Q10 – see supporting information]). Given the association between chronic urticaria and autoimmunity including coeliac disease in children32 and adults33,34, clinical suspicion of co-existing autoimmune diseases should remain high, but screening in the absence of associated features in not suggested.

**6.0 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 H1-antihistamines, there is no need for further investigation.

Urticaria can have a significant effect on peoples’ lives. Therefore, assessments should be made as to the effect the disease is having on: the person’s quality of life (using, for example, the dermatology quality of life index (DLQI)); anxiety, depression or associated psychological issues (using, for example, the hospital anxiety and depression scale (HADS))35; sleep and attendance at school/work. The activity of the disease should be measured (using, for example, the weekly urticaria activity score 7 (UAS7), the angio-oedema activity score (AAS) or the urticaria control test (UCT)),36,37 before embarking on second line treatment options.38,39

**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. Leukocytosis may be present in infection and sometimes in urticarial vasculitis or autoinflammatory disease, or conversely, leukopenia may suggest systemic lupus erythematosus.

Inflammatory markers (CRP and ESR) are often normal in CSU, so if elevated this 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 the monoclonal anti-IgE antibody ligelizumab) and ciclosporin (see **R23 and R24**).40-42 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 characterised. The basophil histamine release assay (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 characterised or has been subject to national quality assurance schemes. Such tests are not always readily accessible or available. Further research is needed to determine comparative utility of functional tests in predicting treatment responses in CSU. See Appendix C (LETR narratives – see supporting information) for more detail.

**6.3 Inducible urticarias**

These should be confirmed by history and appropriate provocation tests.43

In cold contact urticaria, cryoglobulins may be measured, although are rarely present and, if so, usually are associated with infection or haematological disease. If measured, scrupulous attention to temperature-controlled sampling, transport and processing is required (blood must be kept at 37oC). If weals follow the cold trigger after a delay of a few hours, are associated with systemic symptoms, 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 (ANA) and porphyrins should be checked. If the diagnosis is unclear, or if 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 characterised by low C4 levels, both between and during attacks.44 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 functional activity only 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 leukocytoclastic vasculitis is required to confirm the diagnosis, but the histological changes are often subtle. Possible histological features include fragmentation of leukocytes with nuclear debris (leukocytoclasia), 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, 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.20,45

**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 are suspected. In England, patients should be referred to NHS England approved departments for investigation and treatment.

**7.0 INTERVENTIONS**

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

**7.1 The effectiveness of H1-antihistamines compared with each other.**

No first-generation H1-antihistamine was found to stand out as more effective than others in the Cochrane review.46 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 H1-antihistamines.47,48 See Supporting Information, Section C, Question 2/3, for further information, including a network meta-analysis published in 2021 which graded antihistamines in order of efficacy and acceptability, but acknowledged that this was based on low quality evidence.49

**7.2 Up-dosing of H1-antihistamines**

If licensed doses of H1-antihistamines show inadequate response, the GDG agreed that evidence on efficacy supported the up-dosing of second-generation H1-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.50 The GDG recommended considering a switch from one second-generation H1-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 H1-antihistamines at the same time to people with CSU, although it was noted that some people may benefit.51 The safety of giving two H1-antihistamines at lower dosage has not been investigated and there is no published evidence on using such combination treatment. The GDG does not recommend up-dosing first-generation H1-antihistamines in people with CSU.

In general, evidence supported the good safety profile of up to four-fold up-dosing of second-generation H1-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 H1-antihistamines.52,53 The possibility of sedation after up-dosing second-generation H1-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 cautions and contraindications of individual antihistamines and this 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 ECG QTc interval should also be considered for all H1-antihistamines.54 For example, amongst other contraindications, mizolastine is contraindicated in: people with known or suspected QT prolongation or with electrolyte imbalance, in particular hypokalaemia or hypomagnesaemia; clinically significant bradycardia; and use with medicinal products known to prolong the QT interval, such as Class I and III anti-arrhythmics. 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 H1-antihistamine may be more effective than taking a second-generation H1-antihistamine alone for people with CSU.55 Much less data are available for inducible urticarias, although there is some evidence for efficacy in delayed pressure urticaria,56 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.57,58

Montelukast can be prescribed in primary care without monitoring of blood tests, but a recent MHRA warning reminds prescribers of the neuropsychiatric side effects which 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 H2-antihistamines**

There is insufficient evidence to recommend routine addition of H2-antihistamines to second-generation H1-antihistamines for people with chronic urticaria whose symptoms are inadequately controlled by the latter alone.59 However, some people may benefit, especially if urticaria is associated with dyspepsia. However, dyspepsia should be investigated appropriately. If an H2-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 H1-antihistamines, raising their plasma concentration, which may explain some of the beneficial effects of combination therapy demonstrated many years ago.60 However, there are very little 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 the possible contamination with a known carcinogen.61

**7.5 Oral corticosteroids for inducible urticarias**

There are very little 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.62

**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 area, resulting in anaphylaxis, potentially with fatal outcome.

**7.7 Autoinflammatory syndromes**

These usually respond very rapidly (usually within 24 hours) to agents which 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.63

**7.8 Potential new treatments for CSU**

A number of drugs are under investigation and/or in clinical trials for CSU.64 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-IL-4 receptor antibody which inhibits interleukin 4 and 13 pathways), interleukin 5 pathway targeted monoclonal antibodies (such as mepolizumab, reslizumab, 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), prostaglandins receptors, the H4 receptor or the C5a receptor.

**8.0 PROGNOSIS**

Approximately 45% of people with CSU respond to H1-antihistamines at licensed doses,65 and reports estimate that up to two thirds of the residual may respond to up-dosing.50 About two thirds of those unresponsive to H1-antihistamines respond to omalizumab,66 and a similar, probably different but overlapping, proportion to ciclosporin, although there is less evidence for the latter.67 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.65,68

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.

**9.0 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 suffering from inducible urticarias69 and both can co-exist. 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 and at-risk children should be screened and, if present, treated accordingly. Indicators of a potential parasitic infection include eosinophilia, gastrointestinal symptoms or 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. H1-antihistamines currently authorised for use in children aged 2 to 11 years (Table 3) include cetirizine, levocetirizine, loratadine, and rupatadine.70 When needed, these antihistamines can also be used below age 2, despite the licensing age cut off, 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 U.K. according to the British National Formulary).
5. Second generation H1-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/weight (see Table 3).71
6. As for adults, do not offer first-generation H1-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 to have neuropsychiatric side effects from montelukast, including dysphemia (described as “stuttering”), nightmares/night terrors, aggression and behavioural changes.
8. Although not licensed in the U.K., omalizumab has been successfully used in children with CSU and inducible urticarias below the age of 12 years, typically at the lower dose of 150 mg every 4 weeks and down to age 6, but very occasionally at even younger ages.72 The same applies to ciclosporin (typically 3-4 mg/kg/day).73-75
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.

**Table 3. First-line antihistamines for chronic urticaria in children**

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

**Additional information for antihistamine use in children**

* Table 3 summarises the antihistamines commonly used in the UK
* Chlorphenamine is a sedating antihistamine and thus daytime drowsiness, 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 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 metabolised 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 unlicenced 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 non-sedating antihistamines can be increased up to a maximum of four times a day.

**9.2 PREGNANCY AND BREASTFEEDING**

There is insufficient evidence to make a recommendation about the safety of use of most drugs during pregnancy and breast feeding. Refer to manufacturers’ summary of product characteristics,11 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 – see supporting information] for available information on antihistamines).

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

**10.0 RECOMMENDED AUDIT POINTS**

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

1. clinical subtype(s) of urticaria
2. provision of educational material
3. advice on avoidance of triggers
4. assessment of disease impact, e.g. DLQI (at a minimum, prior to commencement of second line agents)
5. assessment of disease severity, e.g. UAS7, AAS, UCT (at a minimum, prior to commencement of second line agents)
6. use of a second-generation H1-antihistamine at licenced dosage, as first line agent for all types of chronic urticaria
7. use of a second-generation H1-antihistamine above the manufacturers’ recommended dose for all types of urticaria, if a licenced dose fails to adequately control symptoms, unless there are contraindications
8. the addition of montelukast to a second-generation H1-antihistamine, in people with CSU whose symptoms are not adequately responsive to H1-antihistamines alone
9. the addition of omalizumab (or ciclosporin in CSU) to a second-generation H1-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 H1-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.

**11.0 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 finalised version was sent for peer-review by the Clinical Standards Unit of the BAD, made up of the Therapy & Guidelines sub-committee (T&G), prior to submission for publication.

**12.0 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 recognised 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 recognise this may exclude some important information published in other languages.

**13.0 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.

**SUPPORTING INFORMATION**

Additional supporting information may be found in the online version of this article at the publisher’s website:

Abbreviations

Appendix A: Systematic review protocols and clinical questions

Appendix B: Forest plots for comparative studies

Appendix C: Linking Evidence To Recommendations (LETR)

Appendix D: GRADE evidence tables

Appendix E: Summary of included comparative studies

Appendix F: Narrative findings for non-comparative studies

Appendix G: PRISMA diagram – study selection

Appendix H: Papers excluded from quantitative analysis

Appendix I: A MeaSurement Tool to Assess systematic Reviews (AMSTAR 2)

Appendix J: Methodology

Appendix K: Search strategy

Appendix L: Audit standards, data items and data collection methodology

**ACKNOWLEDGEMENTS**

We are very grateful to Dr Frances Humphreys (formerly South Warwickshire NHS Foundation Trust) who led this guideline updating project initially, both patient representatives including Ms Linda Campbell for their input in formulating the clinical questions, ranking of the outcomes, reviewing the evidence and formulating the recommendations, as well as all those who commented on the draft during the consultation period.

**DECLARATION OF INTERESTS**

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

**MRA-J:** (1) sponsorship to conferences – Allergy Therapeutics, Novartis, Celgene – specific; (2) grant/research support AbbVie, Emblation, Unilever – non-specific; **AB:** (1) consultant, Abbvie, Almirall, Eli Lilly, Leo Pharma, Galderma, Novartis, Pierre Fabry, Janssen Pharmaceuticals, UCB – specific; **CF:** sponsorship to attend conference – Novartis – specific; (2) travel grants from Leo Pharma, Almirall, Novartis – specific; (3) investigator-initiated studies from Janssen and Leo Pharma – non-specific; **CEHG:** honoraria and research investigator – Novartis – specific; **TAL:** advisory board – Galderma, La Roche-Posay, Novartis – specific; **AMM:** (1) consultant & advisory board – Novartis – specific; (2) invited speaker – Novartis – specific; **GO:** advisory board – Novartis – specific. **RAS, FL, FH, LC, WACS, AT, LSE, MFMM** and **MCE** had no interests to declare.

**REFERENCES**

1 Mohd Mustapa MF, Exton LS, Bell HK *et al.* Updated guidance for writing a British Association of Dermatologists clinical guideline: the adoption of the GRADE methodology 2016. *Br J Dermatol* 2017; **176**:44-51.

2 Brouwers MC, Kho ME, Browman GP *et al.* AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ* 2010; **182**:E839-42.

3 GRADEpro GDT. GRADEpro Guideline Development Tool [Software]. In. Canada: McMaster University (developed by Evidence Prime, Inc). 2020.

4 Grattan CE, Humphreys F, British Association of Dermatologists Therapy Guidelines Audit Subcommittee. Guidelines for evaluation and management of urticaria in adults and children. *Br J Dermatol* 2007; **157**:1116-23.

5 Guyatt GH, Oxman AD, Vist GE *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; **336**:924-6.

6 Zuberbier T, Abdul Latiff AH, Abuzakouk M *et al.* The International EAACI/GA(2)LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria. *Allergy* 2021.

7 National Institute for Health and Care Excellence (NICE). NSAIDs - prescribing issues. In, Vol. 2020. London, United Kingdom: NICE. 2019.

8 British Society for Allergy & Clinical Immunology (BSACI). Non-steroidal anti-inflammatory drugs (NSAIDS). In, Vol. 2020. 2020.

9 Kowalski ML, Asero R, Bavbek S *et al.* Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti‐inflammatory drugs. *Allergy* 2013; **68**:1219-32.

10 National Institute for Health and Care Excellence (NICE). NICE Clinical Knowledge Summaries: Corticosteroids - oral. In, Vol. 2020. London, United Kingdom: NICE. 2017.

11 Datapharm LTD. Latest medicine updates. In, Vol. 2020: Datapharm LTD. 2020.

12 Sánchez J, Amaya E, Acevedo A *et al.* Prevalence of inducible urticaria in patients with chronic spontaneous urticaria: associated risk factors. *J Allergy Clin Immunol* 2017; **5**:464-70.

13 Zuberbier T, Balke M, Worm M *et al.* Epidemiology of urticaria: a representative cross‐sectional population survey. *Clin Exp Dermatol* 2010; **35**:869-73.

14 Kim BR, Yang S, Choi JW *et al.* Epidemiology and comorbidities of patients with chronic urticaria in Korea: A nationwide population‐based study. *J Dermatol* 2018; **45**:10-6.

15 Fricke J, Ávila G, Keller T *et al.* Prevalence of chronic urticaria in children and adults across the globe: Systematic review with meta‐analysis. *Allergy* 2019.

16 Maurer M, Abuzakouk M, Bérard F *et al.* The burden of chronic spontaneous urticaria is substantial: Real‐world evidence from ASSURE‐CSU. *Allergy* 2017; **72**:2005-16.

17 Guillet G, Bécherel P-A, Pralong P *et al.* The burden of chronic urticaria: French baseline data from the international real-life AWARE study. *Eur J Dermatol* 2019; **29**:49-54.

18 Bezalel S, Mahlab-Guri K, Asher I *et al.* Angiotensin-converting enzyme inhibitor-induced angioedema. *Am J Med* 2015; **128**:120-5.

19 Stone C, Brown NJ. Angiotensin-converting enzyme inhibitor and other drug-associated angioedema. *Immunology and Allergy Clinics* 2017; **37**:483-95.

20 Mehregan DR, Hall MJ, Gibson LE. Urticarial vasculitis: a histopathologic and clinical review of 72 cases. *J Am Acad Dermatol* 1992; **26**:441-8.

21 Gusdorf L, Asli B, Barbarot S *et al.* Schnitzler syndrome: validation and applicability of diagnostic criteria in real‐life patients. *Allergy* 2017; **72**:177-82.

22 Kuemmerle-Deschner JB, Ozen S, Tyrrell PN *et al.* Diagnostic criteria for cryopyrin-associated periodic syndrome (CAPS). *Ann Rheum Dis* 2017; **76**:942-7.

23 Niimi N, Francis DM, Kermani F *et al.* Dermal mast cell activation by autoantibodies against the high affinity IgE receptor in chronic urticaria. *J Invest Dermatol* 1996; **106**:1001-6.

24 Kolkhir P, Church MK, Weller K *et al.* Autoimmune chronic spontaneous urticaria: what we know and what we do not know. *J Allergy Clin Immunol* 2017; **139**:1772-81. e1.

25 Sánchez J, Sánchez A, Cardona R. Causal relationship between anti-TPO IgE and chronic urticaria by in vitro and in vivo tests. *Allergy Asthma Immunol Res* 2019; **11**:29-42.

26 Schmetzer O, Lakin E, Topal FA *et al.* IL-24 is a common and specific autoantigen of IgE in patients with chronic spontaneous urticaria. *J Allergy Clin Immunol* 2018; **142**:876-82.

27 Hoffman HM, Mueller JL, Broide DH *et al.* Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle–Wells syndrome. *Nature genetics* 2001; **29**:301-5.

28 Aksentijevich I, Nowak M, Mallah M *et al.* De novo CIAS1 mutations, cytokine activation, and evidence for genetic heterogeneity in patients with neonatal‐onset multisystem inflammatory disease (NOMID): a new member of the expanding family of pyrin‐associated autoinflammatory diseases. *Arthritis & Rheumatism* 2002; **46**:3340-8.

29 Rowczenio DM, Gomes SM, Aróstegui JI *et al.* Late-onset cryopyrin-associated periodic syndromes caused by somatic NLRP3 mosaicism—UK single center experience. *Front Immunol* 2017; **8**:1410.

30 Rowczenio DM, Pathak S, Arostegui JI *et al.* Molecular genetic investigation, clinical features, and response to treatment in 21 patients with Schnitzler syndrome. *Blood* 2018; **131**:974-81.

31 Leznoff A, Sussman GL. Syndrome of idiopathic chronic urticaria and angioedema with thyroid autoimmunity: a study of 90 patients. *J Allergy Clin Immunol* 1989; **84**:66-71.

32 Caminiti L, Passalacqua G, Magazzu G *et al.* Chronic urticaria and associated coeliac disease in children: a case–control study. *Pediatr Allergy Immunol Pulmonol* 2005; **16**:428-32.

33 Confino-Cohen R, Chodick G, Shalev V *et al.* Chronic urticaria and autoimmunity: associations found in a large population study. *J Allergy Clin Immunol* 2012; **129**:1307-13.

34 Lebwohl B, Söderling J, Roelstraete B *et al.* Risk of Skin Disorders in Patients with Celiac Disease: A Population-Based Cohort Study. *J Am Acad Dermatol* 2020.

35 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; **67**:361-70.

36 Weller K, Groffik A, Church MK *et al.* Development and validation of the Urticaria Control Test: a patient-reported outcome instrument for assessing urticaria control. *J Allergy Clin Immunol* 2014; **133**:1365-72. e6.

37 Weller K, Groffik A, Magerl M *et al.* Development, validation, and initial results of the Angioedema Activity Score. *Allergy* 2013; **68**:1185-92.

38 Jáuregui I, Ortiz de Frutos F, Ferrer M *et al.* Assessment of severity and quality of life in chronic urticaria. *J Investig Allergol Clin Immunol* 2014; **24**:80-6.

39 Młynek A, Zalewska‐Janowska A, Martus P *et al.* How to assess disease activity in patients with chronic urticaria? *Allergy* 2008; **63**:777-80.

40 Ertas R, Ozyurt K, Atasoy M *et al.* The clinical response to omalizumab in chronic spontaneous urticaria patients is linked to and predicted by IgE levels and their change. *Allergy* 2018; **73**:705-12.

41 Iqbal K, Bhargava K, Skov PS *et al.* A positive serum basophil histamine release assay is a marker for ciclosporin-responsiveness in patients with chronic spontaneous urticaria. *Clin Transl Allergy* 2012; **2**:19.

42 Maurer M, Giménez-Arnau AM, Sussman G *et al.* Ligelizumab for chronic spontaneous urticaria. *New Engl J Med* 2019; **381**:1321-32.

43 Magerl M, Altrichter S, Borzova E *et al.* The definition, diagnostic testing, and management of chronic inducible urticarias–The EAACI/GA 2 LEN/EDF/UNEV consensus recommendations 2016 update and revision. *Allergy* 2016; **71**:780-802.

44 Gompels M, Lock R, Abinun M *et al.* C1 inhibitor deficiency: consensus document. *Clin Exp Immunol* 2005; **139**:379-94.

45 Sjöwall C, Mandl T, Skattum L *et al.* Epidemiology of hypocomplementaemic urticarial vasculitis (anti-C1q vasculitis). *Rheumatology* 2018; **57**:1400-7.

46 Sharma M, Bennett C, Cohen SN *et al.* H1‐antihistamines for chronic spontaneous urticaria. *Cochrane Database Syst Rev* 2014.

47 Purohit A, Melac M, Pauli G *et al.* Twenty‐four‐hour activity and consistency of activity of levocetirizine and desloratadine in the skin. *Br J Clin Pharmacol* 2003; **56**:388-94.

48 Lever L, Hill S, Marks R *et al.* Effects of cetirizine, loratadine and terfenadine on histamine weal and flare reactions. *Skin Pharmacol Physiol* 1992; **5**:29-33.

49 Phinyo P, Koompawichit P, Nochaiwong S *et al.* Comparative Efficacy and Acceptability of Licensed Dose Second-Generation Antihistamines in Chronic Spontaneous Urticaria: A Network Meta-Analysis. *J Allergy Clin Immunol* 2021; **9**:956-70. e57.

50 Guillen‐Aguinaga S, Jauregui Presa I, Aguinaga‐Ontoso E *et al.* Updosing nonsedating antihistamines in patients with chronic spontaneous urticaria: a systematic review and meta‐analysis. *Br J Dermatol* 2016; **175**:1153-65.

51 Maurer M, Church M, Gonçalo M *et al.* Management and treatment of chronic urticaria (CU). *J Eur Acad Dermatol Venereol* 2015; **29**:16-32.

52 Casale TB, Blaiss MS, Gelfand E *et al.* First do no harm: managing antihistamine impairment in patients with allergic rhinitis. *J Allergy Clin Immunol* 2003; **111**:S835-S42.

53 Weller K, Ziege C, Staubach P *et al.* H1-antihistamine up-dosing in chronic spontaneous urticaria: patients' perspective of effectiveness and side effects–a retrospective survey study. *PLoS One* 2011; **6**.

54 Cataldi M, Maurer M, Taglialatela M *et al.* Cardiac safety of second‐generation H1‐antihistamines when updosed in chronic spontaneous urticaria. *Clin Exp Allergy* 2019; **49**:1615-23.

55 de Silva NL, Damayanthi H, Rajapakse AC *et al.* Leukotriene receptor antagonists for chronic urticaria: a systematic review. *Allergy Asthma Clin Immunol* 2014; **10**:1-6.

56 Nettis E, Colanardi M, Soccio A *et al.* Desloratadine in combination with montelukast suppresses the dermographometer challenge test papule, and is effective in the treatment of delayed pressure urticaria: a randomized, double‐blind, placebo‐controlled study. *Br J Dermatol* 2006; **155**:1279-82.

57 Pacor M, Di Lorenzo G, Corrocher R. Efficacy of leukotriene receptor antagonist in chronic urticaria. A double‐blind, placebo‐controlled comparison of treatment with montelukast and cetirizine in patients with chronic urticaria with intolerance to food additive and/or acetylsalicylic acid. *Clin Exp Allergy* 2001; **31**:1607-14.

58 Akenroye AT, McEwan C, Saini SS. Montelukast reduces symptom severity and frequency in patients with angioedema-predominant chronic spontaneous urticaria. *J Allergy Clin Immunol* 2018; **6**:1403-5.

59 Fedorowicz Z, van Zuuren EJ, Hu N. Histamine H2‐receptor antagonists for urticaria. *Cochrane Database Syst Rev* 2012; **3**.

60 Bleehen S, Thomas S, Greaves M *et al.* Cimetidine and chlorpheniramine in the treatment of chronic idiopathic urticaria: a multi‐centre randomized double‐blind study. *Br J Dermatol* 1987; **117**:81-8.

61 MHRA. Ranitidine – MHRA drug alert issued for Teva UK recall. In, Vol. 2020. 2019.

62 Zuberbier T, Aberer W, Asero R *et al.* The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy* 2018; **73**:1393-414.

63 Kone-Paut I, Piram M. Targeting interleukin-1beta in CAPS (cryopyrin-associated periodic) syndromes: what did we learn? *Autoimmun Rev.* 2012; **12**:77-80.

64 Kolkhir P, Altrichter S, Munoz M *et al.* New treatments for chronic urticaria. *Ann Allergy Asthma Immunol* 2020; **124**:2-12.

65 Humphreys F, Hunter JA. The characteristics of urticaria in 390 patients. *Br J Dermatol.* 1998; **138**:635-8.

66 Tharp MD, Bernstein JA, Kavati A *et al.* Benefits and Harms of Omalizumab Treatment in Adolescent and Adult Patients With Chronic Idiopathic (Spontaneous) Urticaria: A Meta-analysis of "Real-world" Evidence. *JAMA Dermatol.* 2019; **155**:29-38.

67 Kulthanan K, Chaweekulrat P, Komoltri C *et al.* Cyclosporine for chronic spontaneous urticaria: a meta-analysis and systematic review. *J Allergy Clin Immunol* 2018; **6**:586-99.

68 Champion RH, Roberts SO, Carpenter RG *et al.* Urticaria and angio-oedema. A review of 554 patients. *Br J Dermatol* 1969; **81**:588-97.

69 Netchiporouk E, Sasseville D, Moreau L *et al.* Evaluating comorbidities, natural history, and predictors of early resolution in a cohort of children with chronic urticaria. *JAMA dermatology* 2017; **153**:1236-42.

70 Fitzsimons R, van der Poel LA, Thornhill W *et al.* Antihistamine use in children. *Arch Dis Child Educ Pract Ed.* 2015; **100**:122-31.

71 Gabrielli S, Le M, Netchiporouk E *et al.* Chronic urticaria in children can be controlled effectively with updosing second-generation antihistamines. *J Am Acad Dermatol* 2020; **82**:1535-7.

72 Al-Shaikhly T, Rosenthal JA, Ayars AG *et al.* Omalizumab for chronic urticaria in children younger than 12 years. *Ann Allergy Asthma Immunol.* 2019; **123**:208-10.

73 Doshi DR, Weinberger MM. Experience with cyclosporine in children with chronic idiopathic urticaria. *Pediatr Dermatol* 2009; **26**:409-13.

74 Giuliodori K, Ganzetti G, Campanati A *et al.* A non-responsive chronic autoimmune urticaria in a 12-year-old autistic girl treated with cyclosporin. *J Eur Acad Dermatol Venereol* 2009; **23**:619-20.

75 Neverman L, Weinberger M. Treatment of chronic urticaria in children with antihistamines and cyclosporine. *J Allergy Clin Immunol Pract* 2014; **2**:434-8.