British Association of Dermatologists *draft* guidelines for the management of people with urticaria 2020

R.A. Sabroe,¹ F. Lawlor,² C.E.H. Grattan,² M.R. Ardem-Jones,³ A. Bewley,⁴ L. Campbell,⁵ C. Flohr,² F. Humphreys,⁶ T.A. Leslie,⁷ A.M. Marsland,⁸ G. Ogg,⁹ W.A.C. Sewell,¹⁰ M. Hashme,⁶ L.S. Exton,⁶ M.F. Mohd Mustapa,⁶ M.C. Ezejimofor⁶ 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.
³ Clinical 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 British Association of Dermatologists, Willan House, 4 Fitzroy Square, London W1T 5HQ, U.K.
⁷ Royal Free London NHS Foundation Trust, Pond St, London NW3 2QG, U.K.
⁸ University of Manchester & Salford Royal Hospital, Salford M6 8HD, U.K.
⁹ MRC 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.
¹⁰ University of Lincoln, Lincoln LN6 7TS, U.K.

**Corresponding author:** Ruth A Sabroe, rsabroe@doctors.org.uk; guidelines@bad.org.uk

Produced in 2001 by the British Association of Dermatology

Reviewed and updated 2010, 2020

**Key words:** urticaria, chronic spontaneous urticaria, inducible urticarias, guidelines, management, treatment.
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 (Chairman T&G), M Hashme (BAD Information Scientist), LS Exton (BAD Guideline Research Fellow), MC Ezejimofo (BAD Guideline Research Fellow), MF Mohd Mustapa (BAD Clinical Standards Manager).

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 2015 initially, which will be updated in 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 website, www.bad.org.uk/leaflets).

1.1 Exclusions
Other than providing background information, the guideline does not cover angio-oedema without weals, hereditary angio-oedema, auto-inflammatory syndromes and 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 K (see Supporting Information) with reference to the Appraisal of Guidelines Research and Evaluation (AGREE II) instrument (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 consultant dermatologists managing adults, children and young people, a consultant immunologist, a consultant psychodermatologist, a drug allergy specialist, 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 B – 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 2015 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 will be run officially ahead of journal submission to ensure currency. Search terms and strategies are detailed in Appendix L (see supporting information). Additional references relevant to the topic were also isolated from citations in reviewed literature and the previous version of the guideline. Evidence from included studies was graded according to the GRADE system (high, moderate, low or very low quality).

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 desirable 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 is insufficient evidence from the literature, informal consensus is reached based on the experience of the GDG.

The summary of findings with forest plots (see Appendix C), tables Linking the Evidence To the Recommendations (LETR – see Appendix D), GRADE evidence profiles indicating the quality of evidence (see Appendix E), PRISMA flow diagram (see Appendix H) and list of excluded studies (see Appendix I) 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**

<table>
<thead>
<tr>
<th>Strength</th>
<th>Wording</th>
<th>Symbols</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strong</strong> recommendation for the use of an intervention</td>
<td>“Offer” (or similar, e.g. “Use”, “Provide”, “Take”, “Investigate”, etc.)</td>
<td>↑↑</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Weak</strong> recommendation for the use of an intervention</td>
<td>“Consider”</td>
<td>↑</td>
<td>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.</td>
</tr>
<tr>
<td>No recommendation</td>
<td></td>
<td>Θ</td>
<td>Insufficient evidence to support any recommendation.</td>
</tr>
</tbody>
</table>
**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.

### 2.1 Clinical questions and outcomes

The GDG established the following clinical questions pertinent to the scope of the guideline (Table 2).

**Table 2. Clinical questions**

<table>
<thead>
<tr>
<th>In people with urticaria:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Investigation</strong></td>
<td><strong>Question 1:</strong> Do tests, such as blood tests and the autologous serum skin test (ASST), alter the management of urticaria?</td>
</tr>
</tbody>
</table>
| **Treatment** | **Question 2:** What is the clinical effectiveness of H\(_1\)-antihistamines compared with each other for the treatment of urticaria?  
**Question 3:** Would changing from one H\(_1\)-antihistamine to another lead to benefit in the treatment of urticaria?  
**Question 4:** Would adding an H\(_2\)-antihistamine to an H\(_1\)-antihistamine lead to benefit in the treatment of urticaria?  
**Question 5:** What is the effectiveness of leukotriene receptor antagonists in the treatment of urticaria?  
**Question 6:** What is the effectiveness and safety of increasing doses of H\(_1\)-antihistamines?  
**Question 7:** Would adding other therapies to an H\(_1\)-antihistamine lead to benefit in the treatment of urticaria, including sulfasalazine, dapsone, thyroxine, tricyclic antidepressants, hydroxychloroquine, methotrexate, danazol, tranexamic acid, mycophenolate mofetil, intravenous immunoglobulins (IVlg) and anticoagulants?  
**Question 8:** What is the effectiveness of taking systemic corticosteroids for the treatment of urticaria?  
**Question 9:** What is the effectiveness of dietary exclusions or supplements for the treatment of urticaria?  
**Question 10:** What is the effectiveness of *Helicobacter pylori* eradication for the treatment of urticaria?  
**Question 11:** What is the effectiveness of avoiding non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of urticaria?  
**Question 12:** What is the effectiveness of ciclosporin for the treatment of urticaria and are there any long-term benefits? |
The GDG also established two sets of outcome measures of importance to patients (for treatment and investigation), ranked according to the GRADE methodology, by the patient representatives (see Appendix B for full review protocol; supporting information). In the investigation protocol, the outcome is either Yes or No. However, the treatment outcomes (Table 3) are ranked 9, 8 or 7. These 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 3. Outcome measures and ranking

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ranking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease control</td>
<td>9</td>
</tr>
<tr>
<td>Decrease in urticarial activity</td>
<td>9</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>9</td>
</tr>
<tr>
<td>Quality of life</td>
<td>9</td>
</tr>
<tr>
<td>Time to clinical effect</td>
<td>7</td>
</tr>
<tr>
<td>Relapse</td>
<td>6</td>
</tr>
<tr>
<td>When to stop treatment</td>
<td>3</td>
</tr>
</tbody>
</table>

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 C-F (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 amongst 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.

Licensing information, dosages and monitoring requirements for specific drugs are not included. Except where otherwise stated, we recommend adherence to published guidelines, for example by the manufacturer, the British Association of Dermatologists or, in the U.K., the British National Formulary (www.bnf.org). In particular, note licensed dosages for people aged less than 14 years.

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) 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.

**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, 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 (www.bad.org.uk/leaflets).

**R4 (GPP)** Offer access to support and treatment for anxiety, depression and the psychosocial impact of the disease, where appropriate.

**R5 (GPP)** Consider topical anti-pruritic agents, such as 2% menthol in aqueous cream.

**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 inhibitors (ACEi) in people with angio-oedema without weals.

GENERAL MANAGEMENT FOR PEOPLE WITH CSU

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

R9 (↑) 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),6 British Society of Allergy and Clinical Immunology (BSACI)7 or European Academy of Allergy and Clinical Immunology (EAACI) guidance8 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 other dietary supplementation.

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

First-line treatment options for people with CSU

R12 (↑↑) 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

<table>
<thead>
<tr>
<th>First generation</th>
<th>Chlorphenamine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cyproheptadine</td>
</tr>
<tr>
<td></td>
<td>Hydroxyzine</td>
</tr>
<tr>
<td></td>
<td>Promethazine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Second generation</th>
<th>Acrivastine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cetirizine</td>
</tr>
<tr>
<td></td>
<td>Desloratadine</td>
</tr>
<tr>
<td></td>
<td>Fexofenadine</td>
</tr>
<tr>
<td></td>
<td>Loratadine</td>
</tr>
<tr>
<td></td>
<td>Levocetirizine</td>
</tr>
<tr>
<td></td>
<td>Mizolastine</td>
</tr>
</tbody>
</table>

R13 (↓↓) 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 (↑↑) 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 D (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 (↓↓) Do not up-dose mizolastine.

R16 (↑) 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 different second-generation H₁-antihistamines concurrently.

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

R18 (↑) 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 (↑↑) Offer* progression of therapy, through first-line treatment options (see R12 to R18) every 2 to 4 weeks.

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 (although some people may benefit from the addition of ranitidine [expert clinical experience]). Please see section 7.4. N.B. during the writing of this guideline, ranitidine has been recalled by the manufacturers, and suspended by the European Medicines Agency, due to the risk of contamination with a potential carcinogen.

R20 (↑) 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 (↓↓) Do not offer* long-term systemic corticosteroids, unless there is no other option. Use the lowest effective dose for the shortest possible period.⁹

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 (↓↓) Do not offer autologous serum or plasma skin tests (ASST/APST) 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 D [LETR narratives – see supporting information]).

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

R26 (↑↑) 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 (↑↑) 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 (↑) 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
- colchicine
- dapsone
- doxepin (but there are concerns about CNS effects, such as sedation in the short term, and dementia in the long term)
- hydroxychloroquine (particularly for urticaria occurring with systemic lupus erythematosus)
- intravenous immunoglobulins (IVIg)
- methotrexate
- mycophenolate mofetil
- narrowband UVB (only as a short-term option)
- sulfasalazine
- tacrolimus
- tranexamic acid (only if predominantly angio-oedema)

Θ5 There is insufficient evidence to recommend the following interventions (in alphabetical order):
• 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 and other anticoagulants

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 H₁-antihistamine, using a regular daily licensed dose.

R30 (↓↓) 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 (↑↑) 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 D [LETTR 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 (↓↓) Do not up-dose mizolastine.

R33 (↑) 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 different second-generation H₁-antihistamines concurrently.

R34 (↓↓) 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 (↑) 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, cholinergic or solar 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.

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 desensitization/hardening to the wavelength of light relevant to the individual person.

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

Symptomatic dermographism

R43 (↑↑) Offer* narrow band UVB.

R44 (GPP) Offer psoralen-UVA.

CONSIDERATIONS

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 for information on safety during pregnancy) and discussion in Appendix D (LETR narratives) – see supporting information.

R45 (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 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 A randomized controlled trials (RCTs) evaluating the safety and efficacy of up-dosing one second-generation H1-antihistamine compared with using different second-generation H1-antihistamines concurrently 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 H4 receptor antagonists, C5a receptor antagonists and drugs targeting inhibitory mast cells 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/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 D – 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 the course of 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.
PATIENT MANAGEMENT PATHWAY – CHRONIC SPONTANEOUS / INDUCIBLE URTICARIA

Please use in conjunction with the summary of recommendations and discussions in the guideline and supporting information document
© British Association of Dermatologists

**DIAGNOSIS**
Chronic spontaneous / inducible urticaria
(see section 4.2 and Table 1)

**FIRST LINE**
2nd generation H1-antihistamine (licensed doses)
2nd generation H1-antihistamine (up to four-fold the licensed doses – see section 7.2)
Switch 2nd generation H1-antihistamine
Montelukast, in addition to a 2nd generation H1-antihistamine
Progress through first-line options every 2-4 weeks

Consider BHRA / total IgE

**SECOND LINE**
(in addition to a 2nd generation H1-antihistamine)

Omalizumab
Ciclosporin

**THIRD LINE**
(in addition to a 2nd generation H1-antihistamine)

1st generation H1-antihistamine, H2-antihistamine, azathioprine, dapsone, dexamethasone, hydroxychloroquine, IVg, methotrexate, mycophenolate mofetil, NB-UVB (short-term only), sulfasalazine, tacrolimus or tranexamic acid (the latter only for angio-oedema without weals)

**GENERAL MANAGEMENT**
Only consider baseline investigations if clinically indicated
Consider using appropriate validated scoring systems to assess disease activity and impact, e.g. DLQI, UAST, AAS, UCT
Offer educational material / PIL
Offer access to support and treatment for anxiety, depression and psychosocial impact
Consider topical anti-pruritic agents, e.g. 2% menthol in aqueous cream
Advise avoidance of identified triggers or exacerbating factors
Stop ACE inhibitors in people with angio-oedema without weals

**RESOLUTION TREATMENT**
Short-term prednisolone, e.g. 0.5 mg/kg/d for 2-3 days

**FIRST LINE**
2nd generation H1-antihistamine (licensed doses)
2nd generation H1-antihistamine (up to four-fold the licensed doses – see section 7.2)
Switch 2nd generation H1-antihistamine

SECOND LINE
(in addition to a 2nd generation H1-antihistamine)
Omalizumab

THIRD LINE
(in addition to a 2nd generation H1-antihistamine)
Treat as per phenotype (see below)

**CHOLETERGIC URTICARIA**
Anticholinergics, propranolol or danazol

**COLD URTICARIA**
Ciclosporin

**DELAYED-PRESSURE URTICARIA**
Dapsone or sulfasalazine

**SOLAR URTICARIA**
Advice about sun avoidance & protection, UV desensitisation / hardening

**SYMPTOMATIC DERMATOGRAPHISM**
NB-UVB or PUVA
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.\(^{11-13}\) The point prevalence of chronic urticaria varies from 0.1% in North America to 1.4% in Asia.\(^{14}\) 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.\(^{15,16}\)

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. To complicate matters, 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.\(^4\)

<table>
<thead>
<tr>
<th>Spontaneous urticaria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Acute</td>
</tr>
<tr>
<td>• Chronic (6 weeks or more of continuous activity)</td>
</tr>
<tr>
<td>• Episodic (acute intermittent or recurrent activity)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inducible urticarias (reproducibly induced by the same physical stimulus)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Aquagenic</td>
</tr>
<tr>
<td>• Cholinergic</td>
</tr>
<tr>
<td>• Cold contact</td>
</tr>
<tr>
<td>• Delayed pressure</td>
</tr>
<tr>
<td>• Exercise-induced anaphylaxis</td>
</tr>
<tr>
<td>• Localized heat contact</td>
</tr>
<tr>
<td>• Solar</td>
</tr>
<tr>
<td>• Symptomatic dermographism</td>
</tr>
<tr>
<td>• Vibratory</td>
</tr>
</tbody>
</table>

Angio-oedema without weals
- Idiopathic (now classified as part of chronic spontaneous urticaria)
- Drug-induced, e.g. angiotensin-converting enzyme (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)

### 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 angiotensin-converting enzyme (ACE) inhibitors, where the angio-oedema may occur soon or many years after drug initiation), 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 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
Wheels 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, 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).19

5.2.6 Autoinflammatory syndromes
Those presenting with urticaria-like rashes include the cryopyrin-associated periodic syndromes (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 inflammatory markers20,21

5.3 Pathogenesis/Aetiology

Table 6. Pathogenesis/aetiology of urticaria.4

<table>
<thead>
<tr>
<th>Idiopathic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immunological</strong></td>
</tr>
<tr>
<td>Adaptive immune system</td>
</tr>
<tr>
<td>• Allergic (mediated by IgE – abnormal response to external antigen)</td>
</tr>
<tr>
<td>• Autoimmune (mediated by IgG (or possibly IgE “autoallergy”) – abnormal response to self-antigen)</td>
</tr>
<tr>
<td>• Immune complex (urticarial vasculitis, or acute urticaria due to blood products)</td>
</tr>
<tr>
<td>• Kallikrein-kinin system mediated (acquired or hereditary C1 esterase inhibitor deficiency/ hereditary angio-oedema with normal C1 esterase inhibitor)</td>
</tr>
<tr>
<td>Innate immune system</td>
</tr>
<tr>
<td>• Autoinflammatory (mediated by cytokines)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Direct mast cell-releasing agents (e.g. opiates, radiocontrast media)</td>
</tr>
<tr>
<td>• Leukotriene formation (e.g. aspirin, nonsteroidal anti-inflammatory drugs)</td>
</tr>
<tr>
<td>• Inhibition of kinin breakdown (e.g. angiotensin-converting enzyme (ACE) inhibitors)</td>
</tr>
</tbody>
</table>

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 of antigen-specific IgE (type 1 hypersensitivity).
5.3.2 Autoimmune urticaria
About 1/3 of people with CSU have functional, histamine-releasing, IgG autoantibodies. These either directly cross link high-affinity IgE receptors (FcεRI) or bind IgE.

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 FcεRI, thus reducing IgG mediated activation. 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.

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

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. 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 Helicobacter pylori alleviates CSU, although identified Helicobacter pylori infection should, in any case, be treated appropriately (see Appendix D [LETR narratives for Q10 – see supporting information]).

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; sleep and attendance at school/work. The severity of the disease should be measured (using, for example, the weekly urticaria activity score 7 (UAS7), the angio-oedema activity score (AAS),\textsuperscript{31,32} before embarking on second line treatment options.\textsuperscript{33,34}

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 not usually 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 R24).\textsuperscript{35-37} 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. Please see Appendix D (LETR narratives – see supporting information) for more detail.

6.3 Inducible urticarias
These should be confirmed by history and appropriate provocation tests.\textsuperscript{38}
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 37°C). If weals follow the cold trigger after a delay of few hours, are associated with systemic symptoms, start in early childhood and/or if 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. 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 and internal organ involvement.

6.6 Autoinflammatory syndromes
Inflammatory markers (CRP and ESR) are usually elevated, as is serum amyloid A which should be checked. Immunoglobulins and 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 for should be arranged if CAPS is 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 D (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. 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.

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. 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 different second-generation H₁-antihistamines concurrently to people with CSU, although it was noted that some people may benefit. 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. 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 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. For example, amongst other contraindications, mizolastine is contraindicated in: people with known or suspected QT prolongation or with electrolyte imbalance, in particular hypokalaemia or hypomagnesaeemia; clinically significant bradycardia; 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. Much less data is available for inducible urticarias, although there is some evidence for efficacy in delayed pressure urticaria, 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.\textsuperscript{51,52}

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 H\textsubscript{2}-antihistamines
There is insufficient evidence to recommend routine addition of H\textsubscript{2}-antihistamines to second-generation H\textsubscript{1}-antihistamines for people with chronic urticaria whose symptoms are inadequately controlled by the latter alone.\textsuperscript{53} However, some people may benefit, especially if urticaria is associated with dyspepsia. If an H\textsubscript{2}-antihistamine is used, this should usually be ranitidine rather than 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\textsubscript{1}-antihistamines, raising their plasma concentration, which may explain some of the beneficial effects of combination therapy demonstrated many years ago.\textsuperscript{54}

It is of note that during the writing of this guideline, ranitidine has been withdrawn by the manufacturers due to the risk of contamination with a potential carcinogen.\textsuperscript{55}

7.5 Oral corticosteroids for inducible urticarias
There is 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.\textsuperscript{56}

7.6 Avoidance of triggers in inducible urticarias
Avoidance of triggers may be helpful, especially where disease control is difficult, but avoidance can be disabling. However, where there is a risk of anaphylaxis, people should be warned about 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, 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.\textsuperscript{57}

7.8 Potential new treatments for chronic spontaneous urticaria
A number of drugs are under investigation and/or in clinical trials for CSU.\textsuperscript{58} 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,⁵⁹ and reports estimate that up to two thirds of those unresponsive may respond to up-dosing.⁴⁴ About two thirds of those unresponsive to H₁-antihistamines respond to omalizumab,⁶⁰ and a similar, probably different but overlapping, proportion to ciclosporin, although there is less evidence for the latter.⁶¹

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.⁵⁹,⁶²

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 urticarias⁶³ and both can co-exist. However, there are a few important management aspects to consider when seeing children and adolescents:

1. Have a low threshold to consider an underlying autoinflammatory disease if a child is systemically unwell and/or has raised inflammatory markers.
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 high eosinophilia, gastrointestinal symptoms or a recent travel history to a tropical country.
3. CSU may be of longer duration in children compared with adults.
4. The same proportion of children with CSU have a positive BHRA, but there is a lack of evidence that this influences treatment response or disease remission.
5. Second generation H₁-antihistamines can be up-dosed with care (section 7.2) as for adults, taking into consideration cautions and contraindications, following the manufacturers' recommendations for age/weight.⁶⁴
6. H₁-antihistamines currently authorized for use in children aged 2 to 11 years include cetirizine, levocetirizine, loratadine, and rupatadine (the latter is not available in the U.K.).⁶⁵ Desloratadine is licensed from age 1 year and chlorphenamine from age 1 month (the latter allowed in the U.K. according to the British National Formulary)
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 licenced, 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.⁶⁶ The same applies to ciclosporin (typically 3-4 mg/kg/day).⁶⁷-⁶⁹
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 (such as swimming in cold water for those with cold urticaria), especially in children with a history of systemic symptoms.
10. There is very little published evidence for treatment interventions in children under 12 years.

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. Please refer to manufacturers’ summary of product characteristics,¹⁰ 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 D [LETR narratives – see supporting information] for available information on antihistamines).

Similarly, to date there is little 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 M (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 finalized 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 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.

13.0 PLANS FOR GUIDELINE REVISION

The proposed revision date for this set of recommendations is scheduled for 2025; 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:

Appendix A: Abbreviations
Appendix B: Systematic review protocols and clinical questions
Appendix C: Forest plots for comparative studies
Appendix D: Linking Evidence To Recommendations (LETR)
Appendix E: GRADE evidence tables
Appendix F: Summary of included comparative studies
Appendix G: Narrative findings for non-comparative studies
Appendix H: PRISMA diagram – study selection
Appendix I: Papers excluded from quantitative analysis
Appendix J: A MeaSurement Tool to Assess systematic Reviews (AMSTAR 2)
Appendix K: Methodology
Appendix L: Search strategy
Appendix M: 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, Ms Linda Campbell and Ms Alana Thomas, 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

23 Kolkhir P, Church MK, Weller K et al. Autoimmune chronic spontaneous urticaria: what we know and what we do not know. Journal of Allergy and Clinical Immunology 2017; 139:1772-81. e1.
24 Sánchez J, Sánchez A, Cardona R. Causal relationship between anti-TPO IgE and chronic urticaria by in vitro and in vivo tests. Allergy, asthma & immunology research 2019; 11:29-42.
25 Schmetzer O, Lakin E, Topal FA et al. IL-24 is a common and specific autoantigen of IgE in patients with chronic spontaneous urticaria. Journal of Allergy and Clinical Immunology 2018; 142:876-82.
35 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.


46 Casale TB, Blaiss MS, Gelfand E et al. First do no harm: managing antihistamine impairment in patients with allergic rhinitis. *Journal of Allergy and Clinical Immunology* 2003; **111**:S835-S42.


53 Fedorowicz Z, van Zuuren EJ, Hu N. Histamine H2-receptor antagonists for urticaria. *Cochrane Database of Systematic Reviews* 2012; **3**.


