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Management and diagnostic guidelines for urticaria and angio-oedema

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Summary These guidelines for management of urticaria and angio-oedema have been prepared for dermatologists on behalf of the British Association of Dermatologists. They present evidence-based guidance for treatment, with identification of the strength of evidence available at the time of preparation of the guidelines, and a brief overview of aetiology, diagnosis and investigation.

Disclaimer

These guidelines have been prepared for dermatologists on behalf of the British Association of Dermatologists and reflect the best data available at the time the report was prepared. Caution should be exercised in interpreting the data; the results of future studies may require attention to the conclusions or recommendations in this report.

It may be necessary, or even desirable, to depart from the guidelines in the interests of specific patients and special circumstances. Just as adherence to the guidelines may not constitute defence against a claim of negligence, so deviation from them should not be deemed negligent.

Definition

Superficial itchy swellings of the skin due to transient plasma leakage from small blood vessels are known as weals. Deeper swellings of the skin and alimentary tract are called angio-oedema. These may be painful rather than itchy and tend to last longer. Weals and angio-oedema often coexist but either may occur alone. Most urticaria patients do not have systemic reactions but, very rarely, physical urticarias may progress to anaphylaxis. Conversely, urticaria is often a feature of anaphylactic and anaphylactoid reactions.

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Clinical classification

It is usually possible to classify urticaria on the clinical presentation supported, where appropriate, by challenge tests and skin biopsy (Table 1). The duration of individual weals can be helpful: they typically last from 2 to 24 h in ordinary urticaria and up 2 h in contact urticaria. The weals of physical urticaria are gone within an hour except those in delayed pressure urticaria, which take longer to develop and to fade. C1 esterase inhibitor (C1 inh) deficiency should be excluded if recurrent angio-oedema presents without weals. Patients with C1 inh deficiency may have a family history of this disorder or may present with abdominal pain. Contact urticaria may present with symptoms ranging from burning and stinging at the site of skin contact to localized wealing and, rarely, generalized urticaria following percutaneous absorption of the eliciting substance. The lesions of urticarial vasculitis usually persist for days but may look indistinguishable from ordinary urticaria, which is why this presentation of vasculitis is usually included in classifications of urticaria. Other urticarial rashes, such as drug eruptions, are not urticaria.

Aetiology

It may be possible to assign a specific aetiology to individual cases of urticaria but many cases remain

Table 1. Clinical classification of urticaria and angio-oedema

Ordinary urticaria
acute (up to 6 weeks of continuous activity)
chronic (6 weeks or more of continuous activity)
episodic (intermittent)
Physical urticaria (reproducibly induced by the same physical stimulus)
aquagenic urticaria
cholinergic urticaria
cold urticaria
delayed pressure urticaria
dermographism
localized heat urticaria
solar urticaria
vibratory angio-oedema
Angio-oedema (without weals)
Contact urticaria (induced by biological or chemical skin contact)
Urticarial vasculitis (defined by vasculitis on skin biopsy)

unexplained ('idiopathic') despite thorough evaluation (Table 2).

Immunological urticaria

At least 30% of patients with chronic 'idiopathic' urticaria (CIU) have histamine-releasing autoantibodies which degranulate mast cells and basophils by binding high affinity IgE receptors or IgE bound to them.[1] These cases are increasingly being known as autoimmune urticaria. Cross-linking of specific IgE on mast cells and basophils by allergens can cause contact urticaria, anaphylaxis and some cases of acute ordinary urticaria, but immediate hypersensitivity reactions are hardly ever the cause of chronic disease. Urticarial vasculitis and urticarial reactions to blood products are thought to result from the lodging of immune complexes in small blood vessels. The angio-oedema of C1 esterase inhibitor deficiency is caused by complement-derived kinins.

Non-immunological urticaria

Degranulation of mast cells and basophils can occur without involvement of the IgE receptor after exposure to certain drugs (e.g. codeine) and other agents (e.g. radiocontrast media). The mechanism by which aspirin, non-steroidal anti-inflammatory drugs and dietary pseudoallergens (such as salicylates, azo dyes and food preservatives) cause or aggravate urticaria remains uncertain but may involve leukotriene formation. The angio-oedema or urticaria occasionally seen with angiotensin-converting enzyme (ACE) inhibitors is believed to result from inhibition of kinin breakdown by ACE.

Table 2. Aetiologies of urticaria and angio-oedema

Idiopathic
Immunological
Autoimmune (autoantibodies against FcεRI or IgE)
IgE-dependent (Type I hypersensitivity reactions)
Immune complex (urticarial vasculitis)
Complement-dependent (C1 esterase inhibitor deficiency)
Non-immunological
Direct mast cell releasing agents (e.g. opiates)
Aspirin, nonsteroidal anti-inflammatories and dietary pseudoallergens
Angiotensin-converting enzyme inhibitors

Associations

Associations between CIU and occult infections (e.g. dental abscess[2] and gastrointestinal candidiasis[3]) have been proposed but there is little evidence to support them (*Quality of evidence III*). Thyroid autoimmunity in CIU (14%) is more prevalent than in population controls (6%)[4] (*Quality of evidence II.ii*). The role of *Helicobacter pylori* in chronic urticaria is currently being investigated. There is no association between malignancy and urticaria[5] (*Quality of evidence II.ii*).

Appropriate investigations

The diagnosis of urticaria is primarily clinical.[6] Any investigations should be guided by the history and should not be performed in all patients. Relevant clinical and laboratory tests for the different presentations of urticaria are summarized in Table 3.

Acute or episodic ordinary urticaria

No investigations are required except where suggested by the history. IgE-mediated reactions to environmental allergens (such as latex, nuts or fish) as a cause of acute urticaria and contact urticaria can be confirmed by skin-prick testing (where there are facilities) and radioallergosorbent tests (RAST) on blood. Results of both have to be interpreted in the clinical context.

Chronic ordinary urticaria

No investigations are required for the majority of patients with mild disease responding to antihistamines. A useful screening profile for non-responders with more severe disease could include a full blood count and white cell differential (for instance, to detect the eosinophilia of bowel helminth infections), and

Table 3. Relevant investigations

	FBC	ESR	TA/TFT	C4	Biopsy	Challenge
Ordinary urticaria acute/episodic	–	–	–	–	–	–
chronic	(v)	(v)	(v)	–	–	–
Physical urticaria	–	–	–	–	–	v
Angio-oedema without weals	–	–	–	v	–	–
Contact urticaria	–	–	–	–	–	(v)
Urticarial vasculitis	v	v	–	(v)	v	–

FBC, full blood count; ESR, erythrocyte sedimentation rate; TA, Thyroid autoantibodies; TFT, thyroid function tests; C4, C_4 component of complement as a marker for C1 esterase inhibitor deficiency and in hypocomplementaemic urticarial vasculitis; (v), discretionary investigations

erythrocyte sedimentation rate (usually normal in CIU but may be raised in urticarial vasculitis). Thyroid autoantibodies should be considered and thyroid function tests performed if thyroid dysfunction is likely. There is currently no routine laboratory test for histamine-releasing autoantibodies but intradermal injection of autologous serum (the autologous serum skin test) offers a reasonably sensitive and specific screening test[7] in centres with experience.

Physical urticarias

Physical urticarias may occur alone or coexist with ordinary urticaria. International standards for the diagnosis of physical urticarias and definitions of challenge testing have been proposed.[8]

Urticarial vasculitis

Lesional skin biopsy is essential to confirm the presence of small-vessel vasculitis histologically (endothelial cell damage, leucocytoclasia and fibrin deposition are cardinal features). Patients with urticarial vasculitis need a full vasculitis screen, including serum complement assays.

Angio-oedema without weals

Hereditary and acquired C1 inh deficiency should be screened by assaying serum C4, which is rapid and inexpensive with very high sensitivity but low specificity. If low, C1 inh deficiency can be confirmed by quantitative and functional C1 inh assays.

Interventions

General measures

Non-specific aggravating factors, such as overheating, stress, alcohol and drugs with the potential to worsen urticaria (e.g. aspirin and codeine) should be minimized. The risk of cross-reactions between aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) is difficult to quantify but may relate to potency of cyclo-oxygenase inhibition and dose. In general, NSAIDs should be avoided in aspirin-sensitive urticaria patients. ACE inhibitors should be used with caution in patients with concurrent angio-oedema or urticaria not caused by the drug. Cooling antipruritic lotions, such as 1% menthol in aqueous cream and calamine lotion can be soothing (*Strength of Recommendation A, Quality of Evidence III*). Clearly written information sheets, such as the British Association of Dermatologists' publication on Urticaria and Angio-oedema, can be very helpful to patients. It is important to explain to the patient that a cause of the condition is unlikely to be found.

Antihistamines

The efficacy and safety of antihistamines in urticaria is undisputed although not all patients respond and some, very occasionally, become worse. Four non-sedating H1 receptor antagonists are currently licensed for urticaria in the UK. Fexofenadine, loratadine and mizolastine are taken once daily. Acrivastine is taken three times a day in view of its short half-life (1·5 h). Cetirizine (the active metabolite of hydroxyzine) is minimally sedating. Mizolastine is contraindicated in heart failure and when there is prolongation of the Q-T interval. It should be avoided with drugs which inhibit hepatic metabolism via cytochrome P450 (including macrolide antibiotics and imidazole antifungals) and with drugs that have potential arrythmic properties (including tricyclic antidepressants, such as doxepin).

All patients should be offered the choice of at least two non-sedating H1 antagonists because responses and tolerance vary between individuals (*Strength of recommendation A*). It is common practice to increase the dose above the manufacturer's licensed recommendation

when the potential benefits are considered to outweigh any risks (*Quality of evidence III*). 'Antiallergic' effects on mast-cell mediator release of possible clinical importance have been shown with cetirizine[9] and loratadine,[10] especially at higher doses. Adjustments to the timing of medication can be helpful to ensure that the highest drug levels are obtained when urticaria is expected to be most active. The use of sedating antihistamines as monotherapy is now uncommon because of concerns about reduced cognitive functions but they can be effective and well-tolerated by some individuals. Doxepin has useful antihistaminic properties but has sedating and anticholinergic side-effects.

Addition of a sedating antihistamine (e.g. chlorpheniramine 4–12 mg, hydroxyzine 10–50 mg) at night to a non-sedating antihistamine may help patients sleep better although they probably add little to existing H1 receptor blockade. The addition of an H2 antagonist, on the other hand, may give better control of urticaria than H1 antagonists alone (*Quality of evidence I, Strength of recommendation B*)[11,12] although a benefit is not always seen.

Antihistamines in pregnancy

If possible, it is best to avoid all antihistamines in pregnancy, especially during the first trimester, although none have been shown to be teratogenic in humans. Current manufacturers' Data Sheets recommend that cetirizine, loratadine and mizolastine should be avoided in pregnancy and breast feeding. Chlorpheniramine is often chosen by clinicians when antihistamine therapy is necessary because of its long safety record.

Antihistamines in childhood

None of the antihistamines are contraindicated in children over 12 years. As dosing and age restrictions for individual products vary widely in younger children, it is recommended that the relevant Data Sheets are consulted before prescribing.

Mast cell stabilizing drugs

Drugs with mast-cell stabilizing properties are not licensed for urticaria. Ketotifen has been used for its antihistaminic properties but is sedating. Oral sodium cromoglycate is not effective for urticaria. Nifedipine has been shown to reduce pruritus and wealing in CIU[13,14] (*Quality of evidence I, Strength of Recommendation B*), presumably by modifying calcium influx into cutaneous mast cells, but the overall clinical benefit is often disappointing.

Corticosteroids

Oral corticosteroids may shorten the duration of acute urticaria (e.g. prednisolone 50 mg/day for 3 days in adults).[15] Intravenous hydrocortisone is a useful adjunct for severe laryngeal oedema and anaphylaxis when given as a stat dose although its action is delayed. Short tapering courses of oral steroids over 3–4 weeks may be necessary for urticarial vasculitis and severe delayed pressure urticaria (*Quality of evidence III*) but longterm oral corticosteroids should not be used in chronic urticaria (*Strength of recommendation A*) except in very selected cases under regular specialist supervision.

Epinephrine (syn. adrenaline)

Intramuscular or subcutaneous epinephrine can be life-saving in anaphylaxis and in severe laryngeal angio-oedema but should be used with caution in hypertension and ischaemic heart disease. Dosing is weight-dependent. The British National Formulary (Issue 40) currently recommends 0·5 mL of 1 : 1000 [500 μg] epinephrine by intramuscular injection for adults and adolescents. Fixed-dose epinephrine pens delivering 300 μg for adults or 150 μg in children between 15 and 30 kg may be carried by patients for emergency self-administration if the history indicates that the individual is at risk of further life-threatening attacks. If after the first dose of epinephrine there is no significant relief of symptoms, a further dose should be given. Epinephrine is not considered helpful for angio-oedema caused by C1 inh deficiency (*Quality of evidence III*). There is currently no licensed epinephrine aerosol inhaler available in the UK.

Immunosuppressive therapies

Plasmapheresis[16] and intravenous immunoglobulin[17] may be effective in severe autoimmune chronic urticaria (*Quality of evidence II.ii*). Cyclosporin A has recently been shown to be effective for patients with severe autoimmune urticaria unresponsive to antihistamines[18] (*Quality of evidence I, Strength of recommendation A*) but only 25% of the responders remained clear or much improved 4–5 months later.

Other interventions

Although some food additives and natural salicylates may aggravate aspirin-sensitive chronic urticaria[19] the value of avoidance is controversial. In one prospective open study of chronic urticaria inpatients, 73% of 64 improved within 2 weeks of a strict pseudoallergen diet but confirmed exacerbations on provocation testing with individual pseudoallergens were only demonstrated in 19% of them[20] (*Quality of evidence III, Strength of recommendation B*). Thyroxine treatment of euthyroid patients with CIU and with evidence of thyroid autoimmunity may lead to remission of urticaria[21] (*Quality of evidence III, Strength of recommendation C*). Psoralen photochemotherapy,[22] ultraviolet B phototherapy[23] and relaxation therapies[24] for chronic urticaria have yielded unconvincing results (*Quality of evidence VI, Strength of Recommendation D*). Although some immediate benefit from using very potent topical steroids under occlusion for chronic urticaria has been reported,[25] the use of topical steroids is not recommended.

Treatment of C1esterase inhibitor deficiency

Treatment options are summarized in Table 4. Maintenance therapy is only necessary for patients with symptomatic recurring angio-oedema or related abdominal pain. Anabolic steroids are the treatment of choice for most patients (*Quality of evidence III, Strength of Recommendation B*). Virilizing side-effects may occur even at the low doses needed for long-term maintenance. Regular monitoring for hepatic inflammation and tumours is essential. Tranexamic acid may be used for maintenance but is contraindicated in patients with a history of thrombosis. Regular eye examinations and liver function tests are recommended by the manufacturer in the long-term treatment of hereditary angiooedema.

Prophylaxis before planned surgery or dental procedures includes taking tranexamic acid 3–4 days beforehand or increasing the dose of established maintenance therapies with tranexamic acid or anabolic steroids. C1 inhibitor concentrate or fresh frozen plasma should be given for emergency treatment of serious angio-oedema attacks or as prophylaxis before emergency surgery, especially when intubation is necessary.

Prognosis

A comprehensive survey published in 1969 before the advent of non-sedating antihistamines showed that 50% of hospital chronic urticaria patients with weals alone were clear by 6 months. By contrast, over 50% of patients with weals and angio-oedema still had active disease after 5 years[26] and therefore had a poorer outlook. A retrospective survey in 1998 did not address prognosis directly but found that 44% of hospital urticaria patients reported a good response to antihistamines.[27] It is possible that the more potent antihistamines now available result in better disease control although the prognosis for complete recovery has probably not changed over 30 years.

Key points

1 Urticaria can usually be classified on the clinical presentation without extensive investigation. The weals of physical urticaria usually last less than 1 h (except delayed pressure urticaria) whereas those of ordinary urticaria typically last from 2–24 h. Urticarial vasculitis should be sought by skin biopsy if weals last longer.

Table 4. Summary of treatments for C1 esterase inhibitor deficiency

Drug	Maintenance	Prophylaxis	Emergency	Side-effects
Stanozolol	2·5 mg alternate daily to 10 mg daily	–	–	Androgenic Liver disturbance C/I in pregnancy
*Danazol	200 mg Mon-Fri to 800 mg on-demand	– –	– –	Androgenic Liver disturbance C/I with thrombosis C/I in pregnancy
Tranexamic acid	0·5–3·0 g daily change for 3–4 days	1·5 g 3 times day^{-1}	–	Colour vision C/I with thrombosis
C 1 inhibitor concentrate	–	–	3 vials stat	
Fresh frozen plasma	–	–	3 units stat	

*not licensed for hereditary angio-oedema in the UK. C/I; contra-indicated;.

2 Urticaria often remains idiopathic after allergic, infectious, physical and drug-related causes have been excluded as far as possible. At least 30% of patients with chronic idiopathic disease appear to have an autoimmune aetiology. The autologous serum skin test is a reasonably sensitive and specific marker for histamine releasing autoantibodies in this group.

3 Advice on general measures and information can be helpful for most patients with urticaria. Over 40% of hospital urticaria patients show a good response to antihistamines, which are the mainstay of therapy.

4 Combinations of non-sedating H1 antagonists with other agents, such as H2 antagonists and sedating antihistamines at night can be useful for resistant cases.

5 Oral corticosteroids should be restricted to short courses for severe acute urticaria or angio-oedema affecting the mouth although more prolonged treatment may be necessary for delayed pressure urticaria or urticarial vasculitis.

6 Immunosuppressive therapies for autoimmune urticaria should be restricted to patients with disabling disease who have not responded to optimal conventional treatments.

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Appendix 1

Strength of recommendations

A There is good evidence to support the use of the procedure
B There is fair evidence to support the use of the procedure
C There is poor evidence to support the use of the procedure
D There is fair evidence to support the rejection of the procedure
E There is good evidence to support the rejection of the procedure

Appendix 2

Quality of evidence

I Evidence obtained from at least one properly designed, randomised controlled trial.
II-i Evidence obtained from well designed control trials without randomization.
II-ii Evidence obtained from well designed cohort or case control analytic studies, preferably from more than one centre or research group.
II-iii Evidence obtained from mulitple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III Opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees.
IV Evidence inadequate owing to problems of methodology (e.g. sample size, or length of comprehensiveness of follow-up or conflicts in evidence).

Audit Points

1 The value of laboratory investigations not indicated by the history.
2 Additional clinical benefit from exceeding the licensed dose of antihistamines.
3 The outcome of unlicensed therapies and other interventions (including diet) for the treatment of urticaria.