Guidelines for evaluation and management of urticaria in adults and children

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Summary

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Conflicts of interest

None declared.

Members of the British Association of Dermatologists Therapy Guidelines and Audit Subcommittee are: A.D. Ormerod (Chair), H. Bell, F. Humphreys, D. Mitchell, R. Bull, M. Tidman, D.J. Eedy, S. Joseph and S. Wagle. Appropriate management of urticaria depends on the correct evaluation of clinical patterns and causes where these can be identified. Guidance for treatment is presented, based on the strength of evidence available at the time of preparation. As many of the recommendations relate to the off-licence use of drugs, it is particularly important that clinicians should be familiar with dosing and side-effects of treatment in the context of managing urticaria.

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 alterations of 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 necessarily be deemed negligent.

Definition

The term urticaria is widely used to describe an eruption of weals. It is now also increasingly being used to define a disease characterized by short-lived itchy weals, angio-oedema or both together. Most patients with urticaria do not have systemic reactions, but allergic and some physical urticarias may occasionally progress to anaphylaxis. Conversely, urticaria is often a feature of anaphylactic and anaphylactoid reactions.

Clinical classification

For clinical purposes it is often more helpful to classify urticaria by presentation than by aetiology, which is often difficult to establish. A classification based on clinical features may be used to guide appropriate investigation and management. It is usually possible to distinguish clearly recognizable patterns of urticaria on the clinical presentation, supported, where appropriate, by challenge tests and skin biopsy (Table 1). The presentation of urticaria in childhood is similar to that in adults. Clinical and aetiological classifications should be complementary rather than exclusive: for example, chronic ordinary urticaria (COU) is most appropriate when the aetiology remains uncertain. Where there is evidence of histaminereleasing autoantibodies the patient has autoimmune COU (syn. chronic autoimmune urticaria) but where there is no evidence of functional autoantibodies the patient has idiopathic COU (syn. chronic idiopathic urticaria).

Ordinary urticaria is the commonest pattern, presenting with spontaneous weals anywhere on the body with or without angio-oedema. Although the underlying tendency to urticaria is spontaneous it is often possible to identify aggravating factors, such as heat or pressure from clothing, that appear

Table 1 Clinical classification of the urticarias

Ordinary urticaria

Acute (up to 6 weeks of continuous activity)

Chronic (6 weeks or more of continuous activity)

Episodic (acute intermittent or recurrent activity)

Physical urticarias (reproducibly induced by the same

physical stimulus)

Mechanical

Delayed pressure urticaria

Symptomatic dermographism

Vibratory angio-oedema

Thermal

Cholinergic urticaria

Cold contact urticaria

Localized heat urticaria

Other

Aquagenic urticaria

Solar urticaria

Exercise-induced anaphylaxis

Angio-oedema without weals

Idiopathic

Drug-induced

C1 esterase inhibitor deficiency

Contact urticaria (contact with allergens or chemicals)

Urticarial vasculitis (defined by vasculitis on skin biopsy)

Autoinflammatory syndromes

Hereditary

Cryopyrin-associated periodic syndromes (CIAS1 mutations)

Acquired

Schnitzler syndrome

to encourage urticarial lesions. It may follow an acute, episodic (syn. intermittent) or chronic course. Weals occur continuously every day or almost daily while the disease is active.

Physical urticarias are triggered reproducibly by one or more physical stimuli. Swellings are induced rather than spontaneous. Defining the stimulus provides an opportunity to minimize or prevent urticaria through lifestyle changes. The most readily identifiable triggers are mechanical or thermal. Some authorities distinguish cholinergic urticaria from the physical urticarias because it is primarily induced by the stimulus for sweating rather than overheating per se (even though the usual reason for sweating is a raised core temperature).

Angio-oedema without weals should be distinguished from angio-oedema occurring with weals as it may be caused by angiotensin-converting enzyme (ACE) inhibitors or be a presentation of C1 esterase inhibitor (C1 inh) deficiency. Patients with C1 inh deficiency may present with abdominal pain without obvious angio-oedema. Angio-oedema without weals may also be idiopathic.

Contact urticaria occurs only when the eliciting substance is absorbed percutaneously or through mucous membranes. It is never spontaneous. Percutaneous or mucosal absorption of an allergen may result in a localized or a systemic reaction. The

latter may occasionally progress to anaphylaxis in a highly sensitized individual (e.g. latex allergy).

Urticarial vasculitis presents with urticaria clinically but small vessel vasculitis histologically. Other features of this systemic disease may include joint and renal involvement.

Autoinflammatory syndromes presenting with urticaria typically develop spontaneous weals, pyrexia and malaise, with other features that define the disease phenotype (such as renal amyloidosis and sensorineural deafness in Muckle–Wells syndrome). The inherited patterns usually present in early childhood.

The duration of individual weals can be very helpful in distinguishing between these clinical patterns: weals typically last from 2 to 24 h in ordinary urticaria and up to 2 h in contact urticaria. The weals of physical urticaria are gone within an hour except those in delayed pressure urticaria, which take 2–6 h to develop and up to 48 h to fade. The weals of urticarial vasculitis usually persist for days. Angio-oedema may last up to 3 days without treatment.

Aetiology

Despite thorough evaluation many cases remain unexplained ('idiopathic') but it may be possible to assign a specific aetiology to individual cases of urticaria (Table 2).

Immunological urticaria

At least 30% of patients with COU have histamine-releasing autoantibodies. These degranulate mast cells and basophils in vitro by activating high-affinity IgE receptors directly or IgE bound to them. Patients with evidence of functional autoantibodies are increasingly being regarded as having an autoimmune subset of urticaria. Cross-linking of specific IgE on cutaneous mast cells by allergens can cause contact urticaria, anaphylaxis and some cases of acute or episodic ordinary urticaria, but experience shows that allergy is not the cause of chronic continuous disease in adults. Urticarial vasculitis and acute urticarial reactions to drugs or blood products (serum sickness) are thought to result from the lodging of immune complexes in small blood vessels. The angio-oedema of C1 inh deficiency is mediated by kinins resulting from

Table 2 Aetiologies of urticaria

Idiopathic

Immunological

Autoimmune (autoantibodies against $Fc \in RI$ or IgE)

Allergic (IgE-mediated type I hypersensitivity reactions)

Immune complex (urticarial vasculitis)

Complement-dependent (C1 esterase inhibitor deficiency)

Nonimmunological

Direct mast cell-releasing agents (e.g. opiates)

Aspirin, nonsteroidal anti-inflammatories and dietary pseudoallergens

Angiotensin-converting enzyme inhibitors

complement activation and bradykinin formation rather than histamine.

Nonimmunological urticaria

Degranulation of mast cells and basophils can occur independently of IgE receptor activation after exposure to certain drugs (e.g. codeine) and other agents (e.g. radiocontrast media). The mechanism by which aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs) and dietary pseudoallergens (such as salicylates, azo dyes and food preservatives) cause or aggravate urticaria remains uncertain but probably involves leukotriene formation as well as histamine release. Angio-oedema due to ACE inhibitors is believed to result from inhibition of kinin breakdown by ACE.

Associations

Thyroid autoimmunity in COU (14%) is more prevalent than in population controls (6%)² (Quality of evidence II-ii; see Appendix 1). A significantly higher prevalence of coeliac disease in children and adolescents with severe chronic urticaria than in case-matched controls has been reported.³ Associations between chronic urticaria and occult infection (e.g. dental abscess⁴ and gastrointestinal candidiasis⁵) have been proposed but there is little evidence to support them (Quality of evidence III). A meta-analysis of therapeutic trials for Helicobacter pylori found that resolution of chronic urticaria was more likely when antibiotic therapy was successful than when it was not (Quality of evidence I, Strength of recommendation B).⁶ There is no statistical association between malignancy and urticaria² (Quality of evidence II-ii) although individual case reports have been published.

Appropriate investigations

The diagnosis of urticaria is primarily clinical.⁸ Any investigations should be guided by the history and should not be

performed in all patients. Relevant clinical and laboratory tests for the different clinical patterns 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 allergic or contact urticaria can be confirmed by skin-prick testing (where there are facilities) and CAP fluoroimmunoassay (previously radioallergosorbent tests, RAST) on blood. Results of both have to be interpreted in the clinical context. Single-blind oral challenge with food additives or aspirin may be appropriate in the evaluation of episodic urticaria in the appropriate clinical setting in centres where challenge capsules are available.

Chronic ordinary urticaria

No investigations are required for the majority of patients with mild disease responding to H1 antihistamines. A useful screening profile for nonresponders with more severe disease could include a full blood count and white cell differential (for instance, to detect the eosinophilia of bowel helminth infections or the leucopenia of systemic lupus erythematosus), and erythrocyte sedimentation rate (usually normal in COU but may be raised in urticarial vasculitis and always raised in autoinflammatory syndromes). Thyroid autoantibodies and thyroid function tests should be performed, especially if an autoimmune aetiology of urticaria is likely. There is currently no routine laboratory test for histamine-releasing autoantibodies but intradermal injection of autologous serum (the autologous serum skin test, ASST) offers a reasonably sensitive and specific screening test⁹ in centres with experience of doing it. The basophil histamine release assay remains the gold standard investigation for functional autoantibodies in centres where it is available.

						Skin	Physical
	FBC	ESR	TA/TFT	IgE	C4	biopsy	challenge
Ordinary urticaria							
Acute/episodic	-	-	_	(+)	-	-	_
Chronic	(+)	(+)	(+)	-	-	-	-
Physical urticaria	-	-	_	-	-	-	+
Angio-oedema without weals	_	_	_	_	+	-	_
Contact urticaria	-	-	_	(+)	-	-	-
Urticarial vasculitis	+	+	-	-	+	+	-
Autoinflammatory syndrome	+	+	-	-	-	-	-

FBC, full blood count; ESR, erythrocyte sedimentation rate; TA, thyroid autoantibodies; TFT, thyroid function tests; IgE, specific IgE (CAP) or skin prick tests; C4, component of complement as a marker for C1 esterase inhibitor deficiency and in hypocomplementaemic urticarial vasculitis; (+), discretionary investigations.

Table 3 Relevant investigations

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.¹⁰

Angio-oedema without weals

Serum C4 should be used as an initial screening test for hereditary and acquired C1 inh deficiency. A low C4 level between and during attacks (< 30% mean normal) has a very high sensitivity but low specificity for C1 inh deficiency. If low, C1 inh deficiency can be confirmed by quantitative and functional C1 inh assays. Immunochemical and functional C1 inh are both low in type I hereditary angio-oedema (HAE) whereas only functional activity is low in type II HAE. C1q is also reduced in acquired C1 inh deficiency.

Urticarial vasculitis

Lesional skin biopsy is essential to confirm the presence of small-vessel vasculitis histologically (leucocytoclasia, endothelial cell damage, perivascular fibrin deposition and red cell extravasation are key changes although there is no single defining feature). Patients with urticarial vasculitis need a full vasculitis screen, including serum complement assays for C3 and C4 to distinguish normocomplementaemic from hypocomplementaemic disease, which carries a worse prognosis.

Interventions

General measures

Nonspecific 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 NSAIDs is difficult to quantify but may relate to potency of cyclooxygenase inhibition and dose. NSAIDs should be avoided in aspirin-sensitive patients with urticaria. ACE inhibitors should be avoided in patients with angio-oedema without weals and used with caution in urticaria if angio-oedema is also present. Oestrogens should be avoided in HAE. Cooling antipruritic lotions, such as calamine or 1% menthol in aqueous cream, can be soothing (Quality of evidence III, Strength of recommendation A). 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 but the prognosis for eventual recovery from ordinary, physical and vasculitic urticarias is excellent. Some physical urticarias may be especially persistent.

Pharmacological agents

Antihistamines

The efficacy and safety of antihistamines in urticaria is undisputed although not all patients respond and some, very occasionally, become worse. The outcome of randomized controlled studies of nonsedating H1 antihistamines has been summarized.12 Seven nonsedating H1 antihistamines are currently licensed for urticaria in the U.K. Cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine and mizolastine are taken once daily. Acrivastine is taken three times a day in view of its short half-life ($T\frac{1}{2}$). It is now available in the U.K. only in a nonprescription presentation. Cetirizine (the active metabolite of hydroxyzine) may be sedating, especially at higher doses. Mizolastine is contraindicated in clinically significant cardiac disease and when there is prolongation of the Q-T interval. It should not be taken concurrently with drugs that 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). Cetirizine has the shortest time to attain maximum concentration, which may be an advantage where rapid availability is clinically important. Desloratadine has the longest elimination T1/2 at 27 h and should therefore be discontinued 6 days before skin prick testing.

All patients should be offered the choice of at least two nonsedating H1 antihistamines because responses and tolerance vary between individuals (Strength of recommendation A). It has become common practice to increase the dose above the manufacturer's licensed recommendation for patients who do not respond when the potential benefits are considered to outweigh any risks (Quality of evidence III, Strength of recommendation C). 'Antiallergic' effects on mast-cell mediator release of possible clinical importance have been shown with cetirizine 13 and loratadine, 14 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 anticipated. The use of sedating antihistamines as monotherapy is now less common because of concerns about reduced concentration and performance 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 at night [e.g. chlorphenamine (chlorpheniramine) 4-12 mg, hydroxyzine 10-50 mg] to a nonsedating antihistamine by day may help patients sleep better although it probably has little additional clinical effect on urticaria if the H1 receptor is already saturated. The off-licence addition of an H2 antihistamine, on the other hand, may sometimes give better control of urticaria than an H1 antihistamine taken alone (Quality of evidence II, Strength of recommendation C)^{15,16} although, in practice, it may be more helpful for dyspepsia that may accompany severe urticaria.

Renal impairment. Acrivastine should be avoided in moderate renal impairment (creatinine clearance $10-20~\text{mL min}^{-1}$) and

the dose of cetirizine, levocetirizine and hydroxyzine should be halved. Cetirizine, levocetirizine and alimemazine (trime-prazine) should be avoided in severe renal impairment (creatinine clearance < 10 mL min⁻¹). Loratadine and desloratadine should be used with caution in severe renal impairment.

Hepatic impairment. Mizolastine is contraindicated by significant hepatic impairment. Alimemazine should be avoided in hepatic impairment because it is hepatotoxic and may precipitate coma in severe liver disease. Chlorphenamine and hydroxyzine should also be avoided in severe liver disease because their sedating effect is inappropriate.

Antihistamines in pregnancy. It is best to avoid all antihistamines in pregnancy, especially during the first trimester, although none has been shown to be teratogenic in humans. Hydroxyzine is the only antihistamine to be specifically contraindicated during the early stages of pregnancy in its current U.K. manufacturer's Summary of Product Characteristics. Avoidance or caution is recommended for the others, particularly in the first trimester and during lactation. Chlorphenamine is often chosen by clinicians in the U.K. when antihistamine therapy is necessary because of its long safety record. Loratadine and cetirizine are classified as U.S. Food and Drug Administration Pregnancy Category B drugs, implying there is no evidence of harm to the fetus during pregnancy, although well-controlled studies in humans are not available to exclude harmful effects.

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

Antileukotrienes

Antileukotrienes may be taken in addition to an H1 antihistamine for poorly controlled urticaria but there is little evidence that they are useful as monotherapy. They appear more likely to benefit aspirin-sensitive and ASST-positive COU than other patterns of urticaria¹⁷ but a good response is unpredictable. Montelukast is usually chosen.

Corticosteroids

Oral corticosteroids may shorten the duration of acute urticaria (e.g. prednisolone 50 mg daily for 3 days in adults¹⁸) although lower doses are often effective. Parenteral hydrocortisone is often given as an adjunct for severe laryngeal oedema and anaphylaxis 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 long-term 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 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 recommends 0.5 mL of 1:1000 (500 μg) epinephrine by intramuscular injection for adults and adolescents older than 12 years. Fixeddose 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 U.K., although Primatene® Mist (Wyeth, Madison, NJ, U.S.A.) is available as a named patient import from the U.S.A. where it is licensed for asthma. It should be sprayed directly on to the affected area of the mouth rather than inhaled or used sublingually with the intention of achieving systemic absorption.

Immunomodulating therapies

Ciclosporin has been the best studied immunsuppressive drug for COU to date. It was effective in about two thirds of patients with severe autoimmune urticaria unresponsive to antihistamines at 4 mg kg⁻¹ daily¹⁹ for up to 2 months (Quality of evidence I, Strength of recommendation A) but only 25% of the responders remained clear or much improved 4-5 months later. In a recent large multicentre study, there were fewer therapeutic failures when ciclosporin was taken for 16 weeks than 8 weeks.²⁰ Optimal patient selection, dose and duration of treatment still need to be defined. Some patients with chronic urticaria without evidence of functional autoantibodies (with a negative ASST) also respond, although this is not well documented in the literature and a beneficial outcome from immunosuppressive treatment is less predictable. Similar overall responses have been seen in open studies of tacrolimus²¹ and mycophenolate mofetil.²² Plasmapheresis²³ and intravenous immunoglobulins²⁴ may also be effective in severe autoimmune chronic urticaria (Quality of evidence II-ii) but are expensive and not widely available. There have been anecdotal reports of success with methotrexate²⁵ and cyclophosphamide.26,27 Resolution of cold urticaria has been noted in a patient treated with omalizumab for asthma, 28 improvement of delayed pressure urticaria occurred during treatment of psoriasis with etanercept²⁹ but no improvement was seen in a patient with severe corticosteroid-dependent COU given rituximab.³⁰

Other interventions

Although some food additives and natural salicylates may aggravate aspirin-sensitive chronic urticaria³¹ the value of avoidance is controversial. In one prospective open study of

Treatment of C1 esterase inhibitor deficiency

The management of C1 inh has been comprehensively reviewed¹¹ (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 adults (Quality of evidence III, Strength of recommendation B) but should be avoided in children if possible. Virilizing side-effects may occur even at the low doses needed for long-term maintenance. Regular monitoring for hepatic inflammation and hepatocellular adenomas 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 HAE. Prophylaxis before planned surgery or dental procedures includes taking tranexamic acid 2 days before and afterwards or increasing the dose of established maintenance therapies with tranexamic acid or anabolic steroids. C1 inh concentrate should be given for emergency treatment of serious angiooedema attacks or as prophylaxis before surgery, especially when intubation or dental extractions are necessary. Fresh frozen plasma may be used as a substitute in an emergency if C1 inh is not available.

Prognosis

A comprehensive survey published in 1969 before the advent of nonsedating antihistamines showed that 50% of patients with chronic urticaria attending a hospital clinic 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 46 and therefore had a poorer outlook. A retrospective survey in 1998 did not address prognosis directly but found that 44% of hospitalized patients with urticaria reported a good response to antihistamines. 47 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 40 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 to 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	Short-term prophylaxis	Emergency
Stanozolol ^a	2 mg alternate days to 10 mg daily	10 mg, 48 h before and after procedure	_
Danazol ^b	200 mg Mon–Fri to 400 mg daily	600 mg, 48 h before and after procedure	_
Tranexamic acid	0·5-3·0 g daily	≤ 4.5 g, 48 h before and after procedure	_
C1 esterase inhibitor concentrate	-	1000 U, 1 h before procedure	500-1500 U
Fresh frozen plasma	_	_	3 units

^aNo longer available in the U.K. but obtainable through IDIS World Medicines (Weybridge, U.K.). ^bNot licensed for hereditary angio-oedema in the U.K. Dose ranges given are for adults only.

- 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 the ordinary presentation of chronic urticaria appear to have an autoimmune aetiology. The ASST 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, especially if an avoidable physical or dietary trigger can be identified. Over 40% of hospitalized patients with urticaria show a good response to antihistamines, which are the mainstay of therapy.
- 4 It has become common practice to increase the dose of second-generation H1 antihistamines above the manufacturer's licensed recommendation for patients when the potential benefits are considered to outweigh any risks.
- 5 Combinations of nonsedating H1 antihistamines with other agents, such as H2 antihistamines, sedating antihistamines at night or the addition of antileukotrienes, can be useful for resistant cases.
- 6 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.
- 7 Immunomodulating therapies for chronic autoimmune urticaria should be restricted to patients with disabling disease who have not responded to optimal conventional treatments.

Audit points

- 1 The use of investigations above the minimum standard for the different clinical presentations of urticaria.
- 2 Use of antihistamines above the manufacturers' recommended dose.

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Appendix 1

Strength of recommendations and quality of evidence

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 use of the procedure
- E There is good evidence to support the rejection of the use of the procedure

Quality of evidence

- I Evidence obtained from at least one properly designed, randomized controlled trial
- II-ii Evidence obtained from well-designed cohort or case control analytical studies, preferably from more than one centre or research group
- II-iii Evidence obtained from multiple 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
- IV Evidence inadequate owing to problems of methodology (e.g. sample size, or length or comprehensiveness of follow-up or conflicts in evidence)