

Chronic Urticaria: Recent Advances

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Abstract Chronic urticaria is an umbrella term, which encompasses physical urticarias, chronic “idiopathic” urticaria and urticarial vasculitis. It is important to recognize patients with physical urticarias as the investigation and treatment differs in important ways from patients with idiopathic chronic urticaria or urticarial vasculitis. Although relatively uncommon, urticarial vasculitis is an important diagnosis to make and requires histological confirmation by biopsy. Underlying systemic disease and systemic involvement, especially of the kidneys, should be sought. It is now recognized that chronic “idiopathic” urticaria includes a subset with an autoimmune basis caused by circulating autoantibodies against the high affinity IgE receptor (FcεR1) and less commonly against IgE. Although the autologous serum skin test has been proven useful in prompting search for and characterization of circulating wheal-producing factors in chronic urticaria, its specificity as a screening test for presence of functional anti-FcεR1 is low, and confirmation by demonstration of histamine-releasing activity in the patient’s serum must be the benchmark test in establishing this diagnosis. Improved screening tests are being sought; for example, ability of the chronic urticaria patient’s serum to evoke expression of CD

203c on donor human basophils is showing some promise. The strong association between autoimmune thyroid disease and autoimmune urticaria is also an area of ongoing research. Drug treatment continues to be centered on the H1 antihistamines, and the newer second-generation compounds appear to be safe and effective even in off-label dosage. Use of systemic steroids should be confined to special circumstances such as tapering regimens for acute flare-ups. Use of leukotriene antagonists is becoming popular, but the evidence for efficacy is conflicting. Cyclosporin is also effective and can be used in selected cases of autoimmune urticaria, and it is also effective in non-autoimmune cases, although less so.

Keywords Urticaria · Vasculitis · Angioedema · Autoimmune

Introduction

Urticaria affects 15–30% of the population [1, 2], and in 0.5–1%, it persists daily or almost daily for more than 6 weeks and is therefore conventionally deemed to be chronic [3]. In this form, it causes severe impairment of quality of life, comparable with that experienced by patients with triple coronary arterial disease [4].

However, patients with chronic urticaria (CU) are too often poorly served by dermatologists and allergists alike, especially with regard to investigations. The important diagnosis of urticarial vasculitis is frequently not considered, leading to under—investigation. But more often, patients with CU are grossly over—investigated due to failure to recognize common physical urticarias such as symptomatic dermographism and cholinergic urticaria. Prevailing uncertainty about the aetiology and pathogenesis of CU is one

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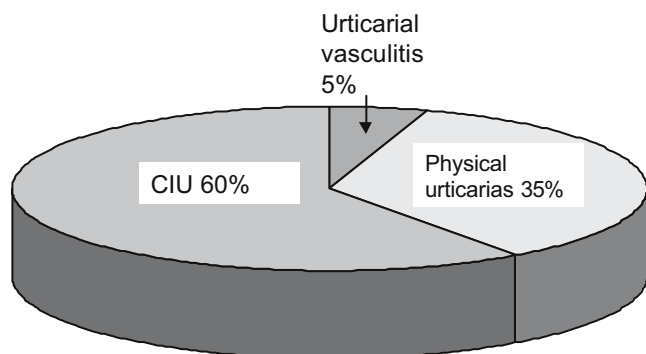


Fig. 1 Subtypes of chronic urticaria

underlying factor—hence the frequency with which the diagnostic label of chronic idiopathic urticaria (CIU) is used. Although in many patients with CU the disease remains “idiopathic”, a significant number of patients with non-physical CU are now generally recognized to have an autoimmune basis for their urticaria, and this carries important implications for investigation and treatment.

It is the purpose of this review to highlight the significant progress that has recently been made, to outline the level of evidence upon which it is based, and to point up the more important problems that still await solution. For the purposes of this discussion, angioedema which occurs only rarely in physical urticarias (except cholinergic urticaria where it is frequent), more commonly in urticarial vasculitis and in 90% of CIU patients [5], will be deemed to be caused by essentially the same underlying pathomechanisms as urticaria.

Sub-Types of Chronic Urticaria

The three main subtypes of CU are illustrated in Fig. 1.

Urticarial vasculitis represents no more than 5% of all cases of CU. Individual wheals last more than 24 h in contrast with wheals of CIU each of which lasts 12–24 h. This diagnosis, which needs to be confirmed by histological

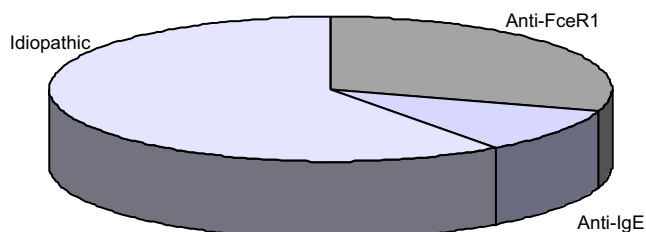


Fig. 3 Subsets of chronic “idiopathic” urticaria

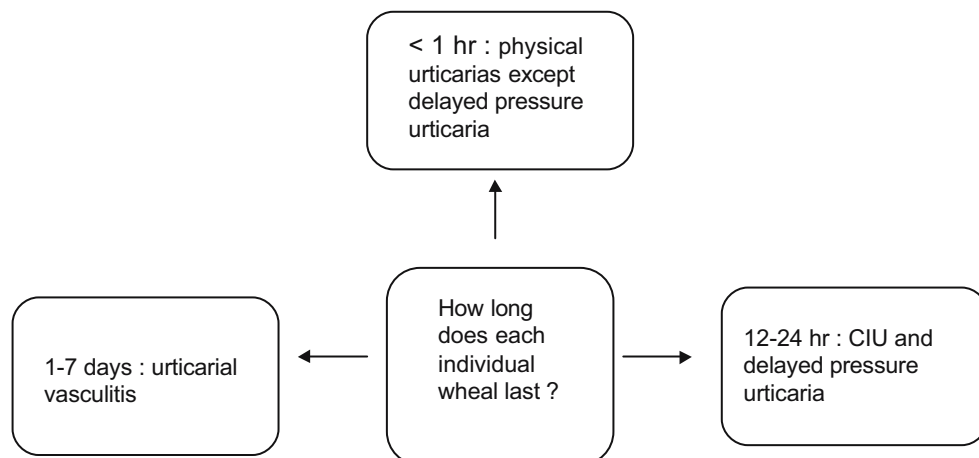
examination of a skin biopsy, is important, as a detailed search will need to be made for underlying causes including autoimmune connective tissue diseases, inflammatory bowel disease, viral hepatitis and paraproteinaemia, as well as for evidence of involvement of other organs, especially the kidneys [6].

Physical urticarias represent about 45% of CU. Characteristically, individual wheals last less than 1 h except for delayed pressure urticaria, individual wheals in which are of at least 24 h duration. The commonest are symptomatic dermographism and cholinergic urticaria. Delayed pressure urticaria frequently co-exists with CIU [5]. If a physical urticaria turns out to be the patient’s sole or predominant problem then apart from confirming the diagnosis by appropriate physical urticaria challenge—testing no further investigations are warranted, and symptomatic control using H1 antihistamines should be sought. The physical urticarias have recently been reviewed [7].

The significance of wheal duration in assisting in clinical diagnosis of CU is illustrated in Fig. 2.

Chronic idiopathic urticaria (CIU) The wheals and itching and the histological appearances of a late-phase reaction [8] that characterize CIU are due to activation of dermal mast cells (Fig. 3). Although a large number of naturally occurring immunological and nonimmunological agents (some of which are illustrated in Fig. 4) are known to be capable of activating dermal mast cells, only allergen-

Fig. 2 Estimating duration of individual wheals aids in diagnosis of chronic urticaria



specific IgE reactions, anti-IgE and anti-FcεR1 autoantibodies and complement C5a are of established importance in urticaria. Dermal mast cells secrete preformed mediators including histamine (mainly the cause of pruritus), proteases, interleukin-1 and tumour necrosis factor-α. The cytokines cause increased expression of adhesion molecules by endothelium of post capillary venules. De novo synthesized mediators include leukotrienes, prostaglandins, cytokines, and chemokines resulting in leukocyte recruitment including eosinophils, which characterize the late phase reaction [8]. An MHC classII-dependent signaling pathway enables mast cells to behave as antigen presenting cells [9], which by activating T cells are able to maintain the longevity of the wheals.

Although a variety of causative factors have been advocated over the years including food additives [10] and chronic infections, most recently *Helicobacter pylori* [11], only recently has evidence emerged that at least some of these patients have an autoimmune disease manifesting itself as CU (Fig. 4). This type of chronic urticaria is conventionally designated as chronic autoimmune urticaria (CAU).

Historical note on CAU Although the concept of CU as an autoimmune disease is fairly new, evidence pointing to the importance of autoimmunity in CU has been accumulating for over 40 years. Rorsman's prescient observation in 1962 [12] that, in CU, "...antigen-antibody reactions...bring about degranulation of leucocytes" was followed by the observation that circulating thyroid autoantibodies and, more controversially, dysfunctional thyroid disease showed a significant association with CIU leading Leznoff [13] to propose a "syndrome" of autoimmune thyroid disease and CU.

Finally, the seminal report of Hide et al. appeared in 1993 [14, 15] showing that autoantibodies against the high affinity IgE receptor or less commonly IgE itself were the cause of whealing in some patients with CU. The findings

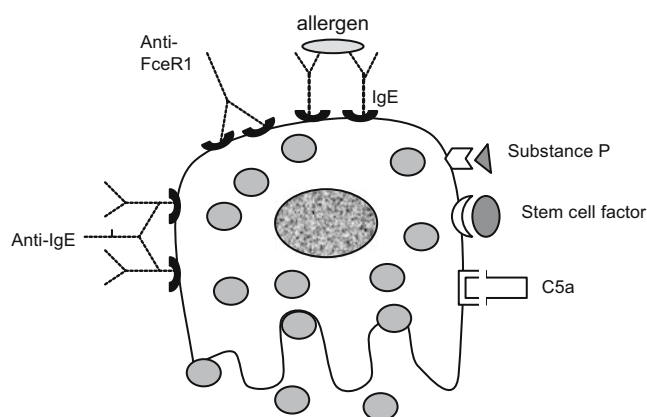


Fig. 4 Immunological and non-immunological modes of activation of dermal mast cells

- 1962 : basopenia in CIU noted by Rorsman who suggested "antigen-antibody reactions... bring about degranulation of basophil leucocytes"
- 1974 : basophils in CIU reported to be "desensitised" to anti- IgE (Greaves et al)
- 1986 : Grattan used the autologous serum skin test to demonstrate circulating wheal – producing factors in blood of some CIU patients
- 1988 : Kaplan detected serum anti-IgE autoantibodies in chronic urticaria by ELISA
- 1989 : "syndrome" of autoimmune thyroid disease and chronic urticaria proposed by Leznoff
- 1993 : presence of histamine releasing anti - FcεR1α and (less often) anti-IgE autoantibodies reported in a subset of 30% of CIU and proposed to be the cause of the disease in these patients (Hide et al)

Fig. 5 Historical milestones in recognition of autoimmune chronic urticaria

were subsequently independently confirmed by several groups [16, 17]. These and other important milestones are listed in Fig. 5.

Immunopathology of CAU

IgG autoantibodies in CAU Little or no anti-FcεR1 immunoreactivity is found in the IgM fraction. Isolation of IgG high affinity IgE receptor autoantibody subclasses using protein G affinity chromatography in patients' sera has shown that the majority of the histamine-releasing activity co-localises with IgG subclasses IgG1 and IgG3 [18] and similar results were also reported using immunoblotting [19]. Occasional sera contained histamine-releasing IgG4 but no histamine-releasing autoantibody activity was found in subclass IgG2. Significant amounts of non-functional (non-histamine releasing) IgG anti-FcεR1 immunoreactivity was found concurrently with histamine releasing IgG in all subclasses studied.

The precise binding sites for anti-FcεR1 autoantibodies have yet to be elucidated. The high affinity IgE receptor, FcεR1 consists of four peptide chains (Fig. 6): intracellular γ1, γ2, and β chains and an α-chain with an extracellular portion, which bears the binding site for IgE. Competitive inhibition studies using human recombinant α-chain of FcεR1 have established that the binding sites for IgG anti-FcεR1 autoantibodies are located on the external portion of the α-chain [14]. Binding can occur on at least two domains in this region of the α-chain as inhibition experiments utilizing myeloma IgE have demonstrated blockade of some but not all of these autoantibodies, an effect which could be reversed by lactic acid stripping to remove basophil or mast cell-bound IgE [14, 15]. These autoantibodies cross-link and dimerise FcεR1 leading to mast cell

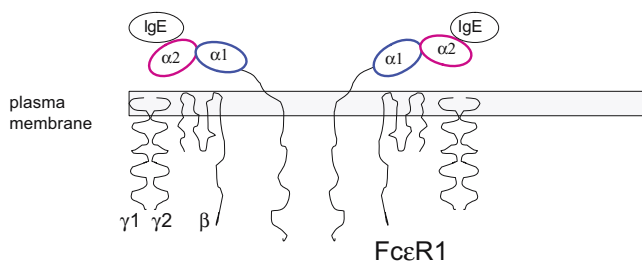


Fig. 6 The four peptide chains which comprise the high affinity IgE receptor FcεR1

or basophil activation and release of histamine and other mediators. Up to 5–10% of patients with CAU have autoantibodies with a specificity for IgE itself. These combine with and cross-link receptor-bound IgE and, by dimerising mast cell-bound IgE, evoke release of histamine. Removal of IgE from mast cells or basophils by lactic acid stripping renders these autoantibodies inactive [15].

Anti-FcεR1 and anti-IgE autoantibodies are functional, leading to mast cell and basophil activation and release of histamine and other pro-inflammatory mediators. The molecular cascade of events linking the autoantibody–antigen reaction with mediator synthesis and release have not been fully characterized.

Role of complement Complement depletion or inactivation diminishes histamine release evoked by anti-FcεR1 autoantibodies in vitro [19]. Subsequent studies established the involvement of C5a and the classical complement activation pathway [20, 21]. This finding may also explain the otherwise puzzling observation that symptoms and signs consequent upon interaction between anti-FcεR1 autoantibodies and their antigenic targets on mast cell membranes are limited to the skin since pulmonary mast cells are devoid of C5a receptors. If receptors are too far apart (i.e., low cell membrane population density of receptors), the Fc regions of 2 adjacent IgG molecules may each be unable to bind to the globular heads of C1q and thus be incapable of initiating complement activation and release of mediators although binding of antibody to receptor has occurred. Activation of the classical complement pathway and formation of C5a is important not only to bring about dermal mast cell activation but also because C5a is a neutrophil and eosinophil chemoattractant leading to the observed accumulation of these cells in lesional skin.

Histamine releasability in CAU Basophils of patients with CU have long been known to be hyporesponsive to histamine release evoked by anti-IgE [22]. This observation has recently been confirmed and extended [23]. Examination of in vitro histamine release from basophils of patients with CU in response to the anti-FcεR1 monoclonal antibody 22E7, polyclonal anti-IgE, and formyl-methionyl-leucyl-phenyl-

alanine (fMLP) showed that basophils from CIU patients released reduced amounts of histamine compared with basophils of control subjects. This subsensitivity correlates with basopenia and segregates with the autoimmune group of CU.

Its cause is unclear but it could represent immunological desensitization or a feature of a surviving subpopulation of functionally impaired basophils. It is of interest that evidence of an abnormal signaling pathway has been reported in peripheral blood mononuclear cells of some patients with CU [24].

Diagnosis of CAU

Clinical and histological features Although there are clinical differences between CAU and CIU, none of these is sufficiently distinctive to be clinically useful. Sabroe [5], in a detailed study of 107 patients with CIU, concluded that those with CAU (demonstrable autoantibodies directed against FcεR1 or anti-IgE), amounting to 31% of the total, had more severe CU judging from wheal counts, extent of distribution of wheals, itch scores, and frequency of systemic symptoms. However, each of these differences, although statistically significant, did not manifest sufficient specificity to use as a “rule in–rule out” test. As noted previously [25], patients with CAU had a significantly lower serum IgE than those with no autoantibodies. The significance of this finding is unclear. Attempts to compute a clinical diagnostic index, with appropriate weightings attached to the above clinical attributes, to help discriminate between the two subsets of CU would be of interest.

The histological appearances of the skin in CIU resemble those of a late phase reaction [8]. Although the infiltrate in patients with CAU was characterized by more prominent granulocyte infiltrate than that of nonautoimmune patients [26] the frequency of other infiltrating cells was similar in both groups, although there was a slight increase in serum tryptase and cytokines in the CAU patients. These small differences are insufficient to assist in diagnosis.

Autologous serum skin test Although first described by Grattan [27], this test was fully characterized by Sabroe et al. in 1999 [28]. Briefly, serum is obtained from the patient preferably when the urticaria is in relapse. This is injected intradermally into the same patient’s uninvolved skin and the injected skin examined for wheal formation 30 min later. Necessary controls include intradermal histamine and saline injections into adjacent skin. The test is positive if the diameter of the serum-induced wheal is at least 1.5 mm greater than the saline wheal. A typical



Fig. 7 The autologous serum skin test (ASST). *Se*, patient's serum; *H*, histamine (positive control); *Na*, saline (negative control)

positive test is illustrated in Fig. 7 and the test has a sensitivity of about 70% and specificity of about 80% if performed as described above. However, as we pointed out in a recent review [29] “...experience is required to obtain reproducible results”. In a recent study [30], we found that of 78 patients with CIU, 35% had a positive ASST. However histamine-releasing activity against donor basophils was found in sera of only 25%. Presumably, the “false” positive ASSTs were due to presence in serum of other wheal-inducing factors such as the mast cell specific factor [15] or to vasoactive kinin-like products released during the course of coagulation. Thus, there are marked differences between *in vivo* ASST findings and the results of histamine release tests *in vitro* since only a proportion of ASST positive sera is able to release histamine from donor basophils *in vitro*. [30]. The ASST et al. is at best a crude screening test and should not be used as a specific test for circulating auto-antibodies [31].

***In vitro* histamine release tests** Demonstration that the patient's serum will release histamine (or other mediator) from donor basophils or dermal mast cells remains the benchmark confirmatory test for autoimmune urticaria [31–33]. Although human basophils are widely used, human mast cells (utilizing thin slices of foreskin or suspensions of partially purified dermal mast cells) are effective alternatives [15, 20]. A rat basophil cell line in which the basophils have been transfected with genes encoding for the α - γ 1- and γ 2-chains of Fc ϵ R1 has also been used successfully [17]. Donor basophils can be made more sensitive to the histamine releasing action of positive sera by preincubation with interleukin-3, but this procedure does not increase the numbers of positive sera [34]. Utilising human donor basophils sera from 78 CIU patients 27 (35%) were positive indicative of the presence of functional anti-Fc ϵ R1 or anti-IgE autoantibodies, the corresponding figures

using dermal mast cells in this study being 31 (40%) [29]. Table 1 summarizes data on histamine release evoked by CIU sera in several published studies.

In addition, recent studies in 52 children have shown that approximately 45% of children with CIU had autoimmune urticaria as judged by basophil histamine release evoked by these patients' sera [38].

Immunoreactive autoantibodies Initially, it was hoped that the diagnosis of autoimmune urticaria could be confirmed using a simple and convenient immunoassay. However, numerous attempts to develop immunoassays that will measure serum levels of IgG anti-Fc ϵ R1 or anti-IgE, although successful, have shown low specificity and poor correlation with *in vitro* serum histamine releasing and urticarial disease activity. Positive immunoreactivity has been found in several non-urticarial autoimmune diseases [19, 36].

Recently, there have been reports of the presence of innate anti-Fc ϵ R1 autoantibody activity in normal serum. These antibodies, which are primarily IgM, show cross reactivity with tetanus toxoid [39–41] and may be functional if basophils that have had IgE removed by lactic acid are used. These investigators have suggested that a state of “conditional autoimmunity” may exist in CU, dermal mast cell activation only occurring if these autoantibodies encounter mast cells devoid of IgE. However, other investigators have been unable to neutralize anti-Fc ϵ R1 α using tetanus toxoid or inhibit histamine release by this means [33], and little or no evidence of histamine-releasing activity has been detected in healthy sera although large numbers of samples have been screened. It seems reasonable at present to rely on demonstration of histamine release from donor basophils as the benchmark diagnostic test for autoimmune urticaria.

Table 1 Frequency of autoimmune urticaria in some published studies of CIU utilizing a functional assay

Reference	Target cells	No. of positive CIU sera (%)
Nimii (1996) [15]	basophils	47/163 (29)
Zweiman (1996) [35]	basophils	21/70 (30)
Tong (1997) [17]	basophils	26/50 (52)
Tong (1997) [17]	RBL cells	38/50 (78)
Fiebiger (1998) [19]	basophils	39/86 (45)
Ferrer (1998) [36]	basophils	31/68 (48)
Ferrer (1998) [36]	dermal mast cells	28/65 (46)
Asero (2001) [30]	basophils	20/121 (17)
Kikuchi (2001) [37]	basophils	111/280 (43)
Sabroe (2002) [29]	basophils	27/78 (35)
Sabroe (2002) [29]	dermal mast cells	31/78 (40)

RBL=rat basophil leukaemia

General Management of Chronic Urticaria

Diagnostic workup Patients with CU are frequently over-investigated, and a recent study failed to show that increasing the number of laboratory tests performed increased the number of identified diagnoses [42]. Guidelines for diagnosis have recently been formulated [43]. The first step requires exclusion of physical urticarias by appropriate challenge testing. This includes stroking the skin firmly for symptomatic dermatographism, exercise testing for cholinergic urticaria and ice cube challenge testing for cold urticaria. These and other procedures have recently been reviewed [7]. Identification of physical urticarias is important as, once the diagnosis is confirmed, no further investigations are warranted, and response to avoidance of provoking stimuli coupled with H1 antihistamine treatment is all that is needed.

If physical urticarias can be excluded, consideration should be given to the possibility that the patient has urticarial vasculitis. Clinical features to look for include the duration of individual wheals (>24 h), staining of the skin or purpura, pain and tenderness of involved skin and associated systemic symptoms such as arthralgia. Patients with urticarial vasculitis are frequently poorly responsive to H1 antihistamines. However the clinical picture in urticarial vasculitis may be unremarkable. In all cases, the diagnosis must be confirmed by a skin biopsy, histological examination of which should reveal leucocytoclastic vasculitis. Direct immunofluorescence examination of the skin biopsy is unhelpful. If the diagnosis is confirmed, then underlying causes must be sought as previously indicated (*vide supra*) and investigation should include a search for evidence of associated systemic vasculitic disease. Patients with urticarial vasculitis associated with hypocomplementaemia are more likely to have systemic involvement than those without [44].

A total white blood cell count and differential is worth doing to exclude parasitic infestation—especially in developing countries. Absence of a blood eosinophilia obviates the necessity for stool examinations for ova.

The frequency with which autoimmune thyroid disease is associated with CU has already been remarked [13], and there is recent clear evidence of an association of CAU with thyroid microsomal autoantibodies [45]. These autoantibodies were present in 36/182 CIU patients, cosegregating with anti-FcεR1 autoantibodies. Most of these patients are euthyroid, but occasionally, they are hyper—or hypothyroid. Although claims have been made that correcting thyroid dysfunction, if present, also ameliorated the associated urticaria, the evidence is not convincing. However the association between thyroid disease and CU is sufficiently strong to prompt adding measurement of the plasma level of thyroid stimulating hormone level (as a screen for thyroid

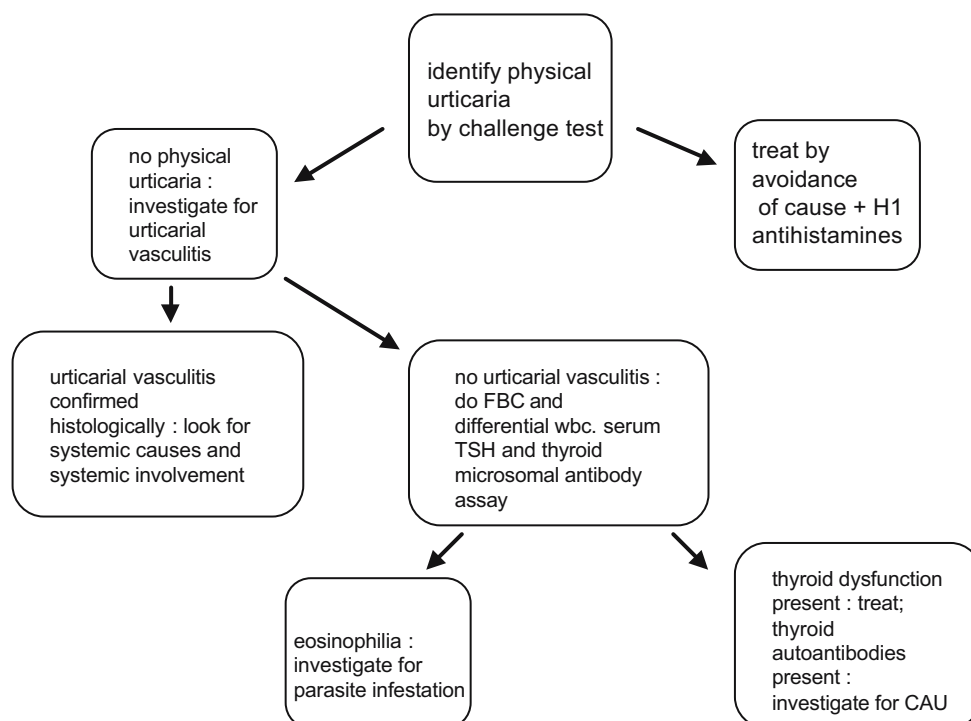
dysfunction) and thyroid autoantibodies to the routine workup of the CU patient [46, 47].

If no underlying cause for the CU can be found, then an attempt should be made to treat the patient with H1 antihistamines, supplemented by short tapering courses of prednisolone for flareups as necessary. If this is unsuccessful, and the patient's quality of life is impaired, then a search for evidence of an autoimmune basis for the patient's CU should be carried out as indicated above. Commercial laboratories offering a satisfactory serodiagnostic service for CAU based upon the basophil histamine release assay as outlined above are available, and details can be obtained on request from the present authors. A paradigm for investigation is illustrated in Fig. 8. It is the authors' opinion that search for foci of infection, food allergy, and food pseudoallergy has no place in the routine investigation of CU.

Treatment For all forms of chronic urticaria, basic lifestyle ground rules need to be observed. These include avoidance of stress, overtiredness, alcohol, NSAIDs, and tight fitting garments. Nocturnal pruritus can be reduced by tepid showering and keeping the ambient temperature of the bedroom cool. Cooling lotions such as calamine with 1% menthol are popular with patients.

H1 antihistamines remain the cornerstone of drug treatment of all types of CU except urticarial vasculitis in which they are usually ineffective alone. Their clinical pharmacology and correct usage in urticaria has recently been reviewed [48]. Pruritus is the main symptom of most types of urticaria, and its diurnal periodicity should be determined in every patient. Many patients find that itching is less troublesome during the working day when attention is distracted, onset of itching occurring characteristically when they are relaxing at home in the evening. This needs to be taken into account in timing the dose schedule of the antihistamines used. However, for many patients, pruritus is troublesome day and night and for them a twice-daily dosage of a low sedation H1 antihistamine such as loratidine or cetirizine is adequate. Off-label dosages of H1 antihistamines such as fexofenadine 180 mg bd are useful in recalcitrant cases and, in our experience and that of others [49], devoid of adverse effects even after prolonged dosages. For persistent nighttime sleep disturbance, an additional nocturnal dose of a sedative antihistamine such as hydroxyzine or the tricyclic doxepin, a highly potent H1- and H2-receptor antagonist, can be added. However, the patient should be warned that impairment of cognitive function might persist throughout the following day [50, 51]. Doxepin should be used with extreme caution in patients with heart disease and in the elderly, and should never be withdrawn abruptly. It is also important to emphasize the importance of regular dosage of H1 antihistamines to avoid the problem of devel-

Fig. 8 Flow chart for investigation and diagnosis of chronic urticaria



opment of subsensitivity (“pseudotachyphylaxis”) [48]. For a small number of patients, especially those with CIU rather than a physical urticaria, even off-label dosages of H1 antihistamines are poorly effective. Although H2 antihistamines have a statistically significant beneficial effect in CIU [52], and in most physical urticarias it is only marginally clinically useful and better effects are achieved using off-label doses of low sedation antihistamines. Cimetidine or ranitidine may occasionally be useful in patients with severe urticaria who experience gastric hyperacidity due to elevated

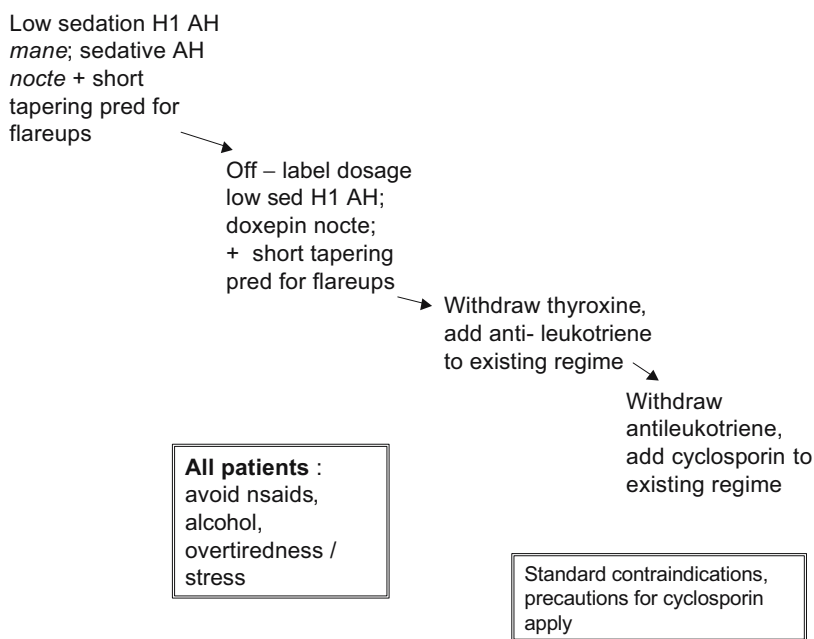
histamine levels, and in patients receiving short courses of oral steroids during relapses.

The value of adding a leukotriene antagonist such as montelukast 10 mg daily is controversial. A review of the literature (Table 2) suggests that although there is no clear evidence of efficacy, addition of a leukotriene antagonist does appear to help some patients especially those experiencing flare-ups due to aspirin and other NSAIDs. Adverse effects are rare but Churg-Strauss vasculopathy has been reported [61].

Table 2 Antileukotrienes in the treatment of CU: literature review

Antileukotriene	Reference no.	Outcome	EBM rating (Sackett) [53]
Zafirlukast 20 mg bd	54	“successful treatment”	D
Zafirlukast 20 mg bd+cetirizine 10 mg daily	55	Combination showed “modest but significantly greater improvement” than cetirizine alone	B
Montelukast 10 mg daily vs cetirizine 10 mg daily vs placebo	56	“more effective for treatment of cutaneous symptoms than cetirizine or placebo” (<i>in patients with CU sensitive to NSAIDs</i>)	B
Montelukast 10 mg daily vs fexofenadine 180 mg daily	57	Equally effective	C
Montelukast 20 mg single dose	58	NSAID-exacerbated urticaria suppressed	C
Montelukast 10 mg daily+cetirizine 10 mg daily as required	59	Reduced activity scores and antihistamine usage in montelukast treated patients vs placebo	B
Montelukast 10 mg daily vs desloratidine 5 mg daily vs desloratidine 5 mg daily+montelukast 10 mg daily vs placebo	60	“No additional benefit for any outcome with addition of montelukast”	A

Fig. 9 Drug treatment “step ladder” for chronic urticaria (excluding urticarial vasculitis)



Systemic corticosteroids are occasionally useful in patients experiencing severe flare-ups, which cannot be controlled by antihistamines. Brief tapering courses (e.g., 30 mg daily for 3 days; 20 mg daily for 3 days; 10 mg daily for 3 days; 5 mg daily for 3 days then cease) should be tried. We do not recommend systemic steroids as long-term treatment, although some authorities report satisfactory results using long-term alternate day prednisolone treatment [62].

Anabolic steroids given orally, have been found effective in the physical urticaria cholinergic urticaria [63]. The results of a recent double-blind placebo-controlled trial of stanozolol [64] suggest it may possibly be a useful adjunct to H1 antihistamines in CIU, although the authors have no personal experience of its use for this indication. Oral cyclosporine, a calcineurin inhibitor that inhibits T cell activation recently introduced for the treatment of CAU (see below), is also effective in CIU [33] but not in physical urticarias. We occasionally use it in selected patients with severe handicap who are recalcitrant to antihistamines. Oral tacrolimus, also a calcineurin inhibitor, can be considered as an alternative to cyclosporine [65] for the same indication.

Treatment of CAU: special considerations Patients with proven CAU are initially treated in exactly the same way

as patients with CIU. However, they usually have severe disease and frequently prove poorly responsive to antihistamines, even in off-label dosage. Cyclosporin was shown to be effective in selected patients who were ASST positive in a double-blind placebo-controlled study [66]. The dose range used is 4–6 mg/kg/day in addition to antihistamines. Our practice is to offer a course of up to 3 months. Eighty percent of patients experience total or partial remission. In these, withdrawal of cyclosporine is followed by sustained remission in about one third. One third relapse but are responsive to regular dosages of H1 antihistamines. Although the remaining one third relapse to a severity approximating to that suffered before initiating cyclosporine, we have not experienced a rebound effect such as that frequently occurring after withdrawal of oral steroids. These patients can be offered further cyclosporine treatment. All patients receiving cyclosporine must be regularly monitored for renal function, serum cholesterol and triglycerides and blood pressure. Other immunomodulators that have been reported effective in selected patients with CAU include intravenous immunoglobulin and plasmapheresis [67, 68].

A treatment stepladder for drug therapy of chronic urticaria (excluding urticarial vasculitis) is illustrated in Fig. 9.

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