

# Chronic idiopathic urticaria

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## Purpose of review

Chronic idiopathic urticaria has long been a demoralizing disease, baffling allergists and dermatologists alike, to the detriment of the patient. Recent findings, however, have shed light on causation in many, though not all, of these patients. The purpose of this review is to bring the reader up to date on the current position regarding aetiology and pathogenesis and the strength of the evidence. The review also seeks to point up rational approaches to diagnosis and treatment in the light of these developments.

## Recent findings

Chronic idiopathic urticaria encompasses at least two subgroups. One of these is the now well-established entity of autoimmune chronic urticaria, due to autoantibodies against either the high-affinity IgE receptor Fc $\epsilon$ R1 or, less commonly, IgE. These patients, who co-segregate with chronic idiopathic urticaria patients having an increased frequency of antithyroid autoantibodies, represent 30–50% of the patients previously designated as having chronic idiopathic urticaria. Convenient routine diagnostic tests for this subset remain elusive. The remaining 50% of patients with chronic idiopathic urticaria remain truly 'idiopathic', although the condition in some may have an autoimmune basis, autoantibodies having eluded current techniques for detection. Selected patients with autoimmune urticaria may benefit from immunotherapy.

## Summary

It is now known that in 30–50% of patients with chronic idiopathic urticaria, the condition has an autoimmune basis, although confirmation of the diagnosis in these patients is not straightforward. In selected patients, attempts to establish this diagnosis are worthwhile since there are important therapeutic implications.

## Keywords

autoimmune chronic urticaria, autoimmunity, chronic idiopathic urticaria, high-affinity IgE receptor, immunotherapy

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## Abbreviations

AICU autoimmune chronic urticaria  
CIU chronic idiopathic urticaria

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## Introduction

Chronic idiopathic urticaria (CIU), defined as the occurrence of daily, or almost daily, wheals and itching for at least 6 weeks, with no obvious cause, has not been the subject of detailed epidemiological studies. Published figures for frequency are confounded by uncertainty of the diagnosis, since the term 'chronic idiopathic urticaria' is often taken to encompass physical urticarias as well as CIU. However, a figure of 0.5% for the lifelong prevalence is probably not wide of the mark and this figure does not seem to vary greatly across different regions of the world. In any case, it is widely acknowledged that CIU is a major affliction causing serious disability [1] to a degree equal to that experienced by sufferers from triple coronary arterial disease.

Physical urticarias, especially delayed pressure urticaria [2], also frequently occur concurrently with CIU in the same patients, and the prognosis and treatment for these two very different types of chronic urticaria may also be very different. It is therefore important to tease these entities out from the patient's history and clinical assessment, in order to determine which urticarial disorder is principally responsible for the patient's disabilities. About 90% of patients with CIU also have angio-oedema [2], and, in the ensuing text, the abbreviation CIU includes both entities.

The major advance in our understanding of CIU in recent years has been the discovery that in 30–50% of patients with CIU the disease is due to an autoimmune process, and therefore is not strictly 'idiopathic'. In autoimmune urticaria, circulating IgG autoantibodies react specifically with the  $\alpha$ -chain of the high-affinity IgE receptor on dermal mast cells and basophils, evoking release of histamine and other mediators, which cause urticaria and angio-oedema [3–6]. The remainder of this review deals with the differential diagnosis of CIU, the pathophysiology of autoimmune chronic urticaria (AICU) and its diagnosis, significance, clinical and laboratory features and treatment. The problem of patients with CIU that is not autoimmune is also discussed, and approaches to its investigation and management are proposed. These issues have been reviewed elsewhere recently [7,8,9\*].

## Differential diagnosis of chronic idiopathic urticaria

Patients are frequently referred to the allergist or dermatologist with a diagnostic label of CIU that turns out to be mistaken. Skin conditions that frequently

mimic CIU are listed in Table 1, and a few of these are discussed here in more detail.

### Allergic contact dermatitis

Patients with swollen, itchy eyelids may have urticaria and angio-oedema, contact allergic dermatitis or dermatomyositis (discussed below). Contact allergic dermatitis may be intermittent, relapsing or chronic, depending on the exposure to a specific antigen. Typical antigens for eyelid contact dermatitis include nail varnish, nickel, latex, and eyedrops containing sulphonamide or benzalkonium. However, in these cases, unlike CIU, there is persistent oedema and, when the swelling subsides, peeling – a sign never seen in CIU. Patch-testing should confirm the diagnosis.

### Dermatomyositis

Eyelid oedema associated with erythema and telangiectasia is a common feature of dermatomyositis, and itching may also be troublesome. Thus, the facial rash of dermatomyositis may be easily mistaken for CIU. However, the presence of digital Gottron's papules and nail-fold telangiectasia should reveal the correct diagnosis, and determination of the serum creatinine phosphokinase level may also be helpful.

### Recurrent erythema multiforme

The development of red en cocarde (targetoid) lesions symmetrically on the limbs, hands and feet in recurrent (often monthly) crops, with swelling and crusting of the mucocutaneous junctions, may occasionally lead to a mistaken diagnosis of relapsing CIU. Recurrent erythema multiforme lesions leave residual pigmentation and desquamation – sequelae rarely seen in straightforward CIU, which, in addition, does not manifest erosive mucosal lesions. A skin biopsy in recurrent erythema multiforme will show a mononuclear cell interface dermatitis with exocytosis of CD8<sup>+</sup> cells into the epidermis and satellite-cell necrosis.

### Cellulitis

Recurrent cellulitis of the face or limbs can be mistaken for relapsing angio-oedema, especially when it occurs

against a background of lymphoedema, as in the Melkersson–Rosenthal syndrome (facial lymphoedema, scrotal tongue, Bell's palsy). The lesions of cellulitis are warm red and usually painful rather than itchy, but they can arise very rapidly suggesting angio-oedema. The distinction between the two is made on clinical grounds: pain, tenderness and desquamation are usual in resolving cellulitis but not in the angio-oedema of CIU.

### Fixed drug eruption

Because the lesions of fixed drug eruption, like the angio-oedema of CIU, show a predilection for the mucocutaneous junctions, develop rapidly, and are often red and oedematous in the early stages, they can be mistaken for CIU. However, they almost invariably blister, and leave residual pigmentation – features not seen in CIU. A careful drug history must be taken.

### Autoimmune urticaria

The wheals, redness and itching of CIU are due to release of histamine and other mediators, including eicosanoids, cytokines and proteases, from dermal mast cells. In CIU, the triggering stimulus causing the characteristically unpredictable dermal mast-cell activation has proved elusive. That an antibody-mediated reaction might be responsible was suggested early on by authors such as Rorsman [10] and Gruber *et al.* [11]. There was also some indirect evidence to suggest that CIU might have an autoimmune basis, at least in some patients, since the incidence of autoimmune thyroid disease is significantly raised in these patients [12–15], and there is a high frequency of human leukocyte antigen alleles that are characteristically associated with autoimmune disease [16].

### Evidence that chronic idiopathic urticaria in some patients is cause by autoimmunity

Prima facie evidence of the involvement of functional autoantibodies against the high-affinity receptor (FcεR1) of dermal mast cells and basophils was first reported in 1993 and 1996 by Hide *et al.* [3,4]. These investigators used basophils and dermal mast cells of healthy human donors to show that the serum and purified IgG of a subset of about 25% of patients with CIU would release histamine from these cells, and that release could be inhibited by preincubation with recombinant FcεR1α, the α-chain of the high-affinity IgE receptor. In a further 5% of patients, the histamine-releasing factor was inhibited not by the α-chain of FcεR1 but by IgE itself. Thus, patients with CIU appear to have functional autoantibodies of the IgG subclass with specificity for FcεR1 or IgE. That these autoantibodies are the cause of the lesions in the CIU patients who have them is supported by their ability to cause whealing upon intradermal injection in skin of human volunteers [17] and to release histamine from healthy donor basophils

**Table 1. Skin and other disorders commonly incorrectly diagnosed as chronic idiopathic urticaria with or without angio-oedema**

| Skin disorder                                | Comment                        |
|----------------------------------------------|--------------------------------|
| Contact allergic dermatitis                  | Mainly facial                  |
| Dermatomyositis                              | Mainly facial                  |
| Cellulitis                                   | Mainly limbs and face          |
| Lymphoedema                                  | Mainly limbs and face          |
| Recurrent erythema multiforme                | Mainly limbs and face          |
| Hypoalbuminaemia,<br>e.g. nephrotic syndrome | Angio-oedema of face and limbs |
| Polymorphous light eruption                  | Mainly facial                  |
| Fixed drug eruption                          | Mucocutaneous junctions        |
| Crohn's disease                              | Angio-oedema of lips           |

and mast cells [3,4]. The plasma levels of these autoantibodies vary in proportion with disease activity [18], and removal (by plasmapheresis) causes remission [19]. These findings have been confirmed by a number of independent groups, the percentage of patients with CIU and anti-Fc $\epsilon$ R1 autoantibodies varying from 35 to 55% of the total [5,6,20].

#### **Does identification of these patients matter?**

Patients with AICU are more treatment-resistant, and their disease runs a more aggressive course, than those with non-autoimmune CIU [2]. Thus, if a patient with AICU proves unresponsive to H<sub>1</sub> antihistamines, even in off-label dosage, and is suffering serious disability as a result of the disease, then immunosuppressive therapy (cyclosporin [21], intravenous Ig [22], or even plasmapheresis [18]) may be warranted. Even in those autoantibody-positive patients for whom immunotherapy is deemed inappropriate, an understanding of the autoantibody basis of his/her urticaria may help the patient to cope with the problem and avoid unnecessary investigations.

#### **Diagnosis of autoimmune urticaria: the autologous serum skin test**

Unfortunately, there is no straightforward rule-in/rule-out test for autoimmune urticaria. Clinical and histological evaluations are unhelpful. Although there are subtle differences [2,23], these do not provide adequate discrimination between CIU and AICU. We have found the autologous serum skin test to be a useful screening test for AICU. In this test, 0.05 ml of the patient's serum, removed during a period of disease activity, is injected intradermally volume 0.05 ml into the same patient's uninvolved forearm skin, along with equal volumes of saline and histamine (10  $\mu$ g/ml) at adjacent sites. The test is read 30 min later. A positive result is recorded if the diameter of the wheal at the serum-injected site is 1.5 mm greater than that of the bleb at the saline-injected site. The sensitivity and specificity of the test were calculated as 65–81% and 71–78%, respectively [24]. Using in-vitro release of histamine from healthy donor basophils (see below) as the 'gold standard', the autologous serum skin test was negative in 39/40 healthy controls, in 23/24 patients with a physical urticaria (symptomatic dermographism, cholinergic urticaria), and in 10/10 patients with atopic eczema. We advise that a positive result should be confirmed by in-vitro testing.

#### **Diagnosis of autoimmune urticaria: in-vitro tests**

Numerous attempts have been made to devise specific and sensitive in-vitro tests for AICU, including enzyme-linked immunosorbent assay and other immunobinding assays [25], but, in terms of specificity, the results have been disappointing; Kikuchi and Kaplan [26] were

recently obliged to conclude, on the basis of a study of 260 patients with chronic urticaria, that immunobinding assays were unacceptable as a method for diagnosis of AICU, and that functional assays are required. Furthermore, immunoreactive anti-Fc $\epsilon$ R1 autoantibodies are also occasionally found in autoimmune connective tissue and immunobullous diseases [25]. The 'gold standard' laboratory test for AICU is the demonstration and measurement of histamine (or other mediator) release from target basophils or dermal mast cells. Basophils are normally obtained from healthy donors. Basophils from both low-IgE and high-IgE donors should be used to enable identification of patients with anti-Fc $\epsilon$ R1 or anti-IgE autoantibodies. Dermal mast cells are obtained from skin removed during circumcision [3,4]. Alternatively, a rat basophil leukaemia cell line transfected with the genes that code for the  $\alpha$ ,  $\gamma$ 1 and  $\gamma$ 2 chains of Fc $\epsilon$ R1 can be used [6]. These cells express functioning high-affinity IgE receptors, and can be used to detect anti-Fc $\epsilon$ R1 autoantibodies by using release of  $\beta$ -glucuronidase histamine or serotonin as quantitative markers of activation.

#### **Current critical issues in autoimmune chronic urticaria: mode of action of anti-Fc $\epsilon$ R1 autoantibodies**

Initial studies argued against the involvement of complement activation in AICU [3,4]. Recent work suggests that this may be an oversimplification, on the basis of the following observations. The antibodies involved in AICU turn out to be predominantly IgG1 and IgG3, isotypes conventionally considered to be involved in complement activation [25]; using highly purified IgG anti-Fc $\epsilon$ R1 and patients' decomplexed sera, it was found that whole sera, but not decomplexed sera, would release histamine from dermal mast cells [26–28]. It was also shown that release of histamine from dermal mast cells by anti-Fc $\epsilon$ R1 could be inhibited by an antibody to the C5a receptor and was dependent on the concentration of C5a. Thus, release of histamine from dermal mast cells by Fc $\epsilon$ R1 appears to be at least augmented by complement activation. This finding may explain the well-known but puzzling fact that patients with severe AICU do not suffer from bronchospasm, since lung, but not skin, mast cells are devoid of complement receptors [29].

#### **The role of the basophil**

That basopenia is a regular feature of chronic urticaria [10] and of AICU [30] has long been recognized [31]. Lowered basophil numbers correlate well with lowered whole-blood histamine content [31]. Although the reason for the paucity of circulating basophils may be straightforward activation and depletion by circulating autoimmune factors, relocation to the urticated tissues of the skin and mucous membranes has been considered, but

not supported by recent quantitative histometric and cytometric studies in CIU and AICU [32]. In any case, basopenia has been considered as a diagnostic screening test for AICU [33\*\*], but, for this possibility to be carried forward, convenient and reproducible methods for counting basophils in the peripheral circulation need to be found.

### **Treatment of autoimmune chronic urticaria**

Patients with AICU are initially treated in the same way as patients with CIU. However, AICU tends to be resistant to routine H<sub>1</sub> antihistamine treatment and I often have recourse to off-label dosage of the newer non-sedative antihistamines such as fexofenadine (120 mg twice daily) and desloratidine (5 mg twice daily) [9\*]. The administration of sedative antihistamines, such as hydroxyzine (25 mg), at night may also help relieve nocturnal itching, but the patient must be warned of continuing impairment of cognitive function during the following day. For the above reasons this regime may prove inadequate, and in severely disabled patients immunosuppressive measures may be necessary. Although short tapering courses of oral corticosteroids may be reasonable in emergency situations, long-term corticosteroid therapy is not normally recommended for AICU. However, other authorities [34] have advocated alternate-day corticosteroid protocols for long-term management, evidently with satisfactory results. Cyclosporin is a satisfactory alternative, used frequently by the author in patients with AICU who are severely handicapped by their urticaria, and are unresponsive to antihistamines. Given in dosages of 3–5 mg/kg daily for up to 3 months, this treatment has proved effective in a placebo-controlled double-blind trial [21] in patients with CIU, all of whom gave positive results in the autologous serum skin test and had serum showing evidence of histamine-releasing activity, and were therefore highly likely to have AICU. Cyclosporin is contraindicated in patients with a history of cancer, a positive cervical smear or renal impairment. In the author's experience (unpublished observation), at least 75% of treated patients experience total, or almost total, remission. About one-third of patients treated successfully for 2–3 months remain in remission after withdrawal; one-third have a mild relapse that is easily controlled by routine antihistamines; however, one-third relapse badly upon withdrawal and may require a further course of treatment, or an alternative medication. Alternative immunotherapeutic treatments include intravenous immunoglobulin [22] or plasmapheresis [19].

### **Chronic idiopathic urticaria**

At least 50% of patients with an initial diagnosis of CIU do not have detectable autoantibodies; these are properly designated as cases of presumptive chronic 'idiopathic' urticaria. This does not absolve the clinician

of the responsibility for ensuring that relevant investigations for an underlying cause are carried out, as occasionally a positive result may emerge. However, in most patients no cause can be found and the diagnosis of CIU remains. These patients are often burdened with a voluminous file of irrelevant but expensive investigations.

### **Clinical features and diagnosis of chronic idiopathic urticaria**

The detailed clinical features of CIU have been comprehensively described elsewhere [34,35]. As previously noted, the clinical features of CIU and AICU are essentially indistinguishable [2], angio-oedema occurring concurrently in about 90% of patients. At least 50% of patients also have accompanying delayed pressure urticaria. Associated systemic symptoms are rare. If they are prominent (dyspnoea, gastrointestinal symptoms, flushing), then the alternative diagnosis of idiopathic anaphylaxis should be considered. Urticarial vasculitis, though rare, can present as a picture clinically indistinguishable from CIU [36]. The diagnosis should be suspected in patients with persistent, treatment-resistant, chronic urticaria. Individual wheals last for more than 24 h and may leave residual pigmentation, but these features may not be present. A skin biopsy is essential to clinch the diagnosis.

### **Food constituents as a cause of chronic 'idiopathic' urticaria**

This issue has recently been reviewed [37]. Food allergy is a recognized cause of acute, but not chronic, urticaria, but non-allergic reactions to food additives (preservatives, colouring agents) have been proposed as a cause of chronic urticaria by mainly European writers [38–40]. These studies were inadequately controlled, and reproducibility of results was not confirmed. In a series of 1200 patients from 1995–2003, the incidence of food allergy as a cause of chronic urticaria was zero (A.P. Kaplan, personal communication), and this is not dissimilar from my own personal experience. I tend to agree with Mathews [41] that 'as a cause for chronic urticaria or angio-oedema, food allergy can only be rarely implicated'.

### **Chronic idiopathic urticaria and thyroid disease**

Hashimoto's thyroiditis and Graves' disease are positively associated with CIU [12,13]; antithyroid autoantibodies are found in 27% of patients with CIU, and 19% have abnormal thyroid function [14]. However, there is no evidence that treating the underlying thyroid dysfunction alters the course of the accompanying urticaria. Thyroid disease and chronic urticaria are frequently associated but there is no evidence that the thyroid autoantibodies are pathogenic in the context of chronic urticaria. The significance of the association lies

in the different autoimmune mechanisms found in both disorders [15].

### ***Helicobacter pylori***

Although several anecdotal accounts have implicated *Helicobacter pylori* in the aetiology of CIU, this has not been substantiated. This topic has recently been reviewed [42].

Up to 50% of the population show evidence of past or present *H. pylori* infection and at least 30% of patients with CIU have infection with this organism, but treatment of the infection has no influence on the CIU [43]. Greaves [42] has proposed that *H. pylori* might have an indirect role since it is known to bring about autoantibody formation due to the immunogenicity of its cell-envelope polysaccharide Lewis x and y blood-group antigens. Autoantibodies could be formed by molecular mimicry analogous with the role of *Campylobacter jejuni* in the Guillain-Barré syndrome. Thus, *H. pylori* may have an indirect role in the aetiology of CIU by reducing immune tolerance and inducing autoantibody formation, including that of anti-FcεR1 autoantibodies.

### **Investigation of chronic idiopathic urticaria**

This topic has been covered extensively in several recent reviews [44,45,46] and is not considered further here.

### **Conclusion**

Chronic idiopathic urticaria is no longer the diagnosis of despair that it used to be. Establishing an autoimmune basis helps patients to cope with the problem and may lead to effective treatment in selected cases. In the remainder, symptomatic treatment can be satisfactory, and, equally importantly, the patient can also be helped by advice on the avoidance of unnecessary and expensive laboratory tests, dietary manipulations and the like.

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