

Autoimmune urticaria

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The term “autoimmune urticaria” increasingly is used to reflect advances in knowledge about functional autoantibodies that activate mast cells and basophils through cross-linking the high-affinity IgE receptor (FcεRI) to secrete histamine. Nonfunctional autoantibodies against the FcεRI have been detected by immunoassay in healthy subjects but seem to be nonpathogenic. Abnormalities of B and T cells have been described in chronic urticaria that lend support to the concept of an autoimmune disease. Confusingly for the clinician, there are no specific clinical features of autoimmune urticaria that clearly distinguish it from other causes of ordinary urticaria. There also is still no simple, reproducible clinical test for functional autoantibodies. Another difficulty in putting the concept of autoimmune urticaria into context is that most of the research has been done in secondary or tertiary referral centers and may not reflect the full spectrum of urticaria in the community. The purpose of this article is to

- Review the evidence for the autoimmune hypothesis and other nonantibody serum histamine-releasing factors in the etiopathogenesis of urticaria
- Define autoimmune urticaria
- Look at how autoimmune urticaria fits into existing classifications of urticaria
- Propose diagnostic criteria that may be useful to the clinician
- Review the management implications for patients with this subset of chronic disease

Evidence for autoimmune urticaria

Until recently, the cause of chronic idiopathic urticaria has remained an enigma because many of the cutaneous features mimic immediate-type hypersensitivity reactions caused by cross-linking of specific IgE on the FcεRI of skin mast cells by allergen. It also is rare for an extrinsic allergic cause to be found. Direct activation of the FcεRI on mast cells by autoantibodies can lead to the

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same cascade of events, resulting in the controlled release of proinflammatory mediators, including histamine, causing transient leakage of plasma from small blood vessels and recruitment of acute inflammatory cells into lesional skin.

Autologous serum skin test

The earliest indication that endogenous weal-producing factors are present in the blood of some patients with active chronic idiopathic urticaria came from an observation that autologous serum that was re-injected into normal-appearing skin could cause a localized wheal-and-flare response during disease activity but not during remission [1]. This observation now is used in the autologous serum skin test (ASST). The response was similar clinically to spontaneous urticaria wheals in that it would fade without residue within 24 hours and could be inhibited by oral antihistamines [2]. Most of the wheal-producing activity of the ASST-positive sera was confined to ultrafiltered fractions greater than 100 kD³, suggesting an immunoglobulin or immune-complex cause. The ASST response is positive in 50% to 60% of patients with active chronic idiopathic urticaria but has not been demonstrated in patients with physical urticarias (symptomatic dermographism, cholinergic urticaria) or healthy controls [4]. A high frequency of positive results has been described in patients with sensitivity to multiple nonsteroidal anti-inflammatory drugs (NSAIDs) presenting with acute urticaria [5], but the importance of this observation and relevance to clinical practice remains to be understood. The ASST has a reasonably high specificity (80%) and sensitivity (70%) for functional autoantibodies detected by *in vitro* histamine release from basophils of healthy donors in chronic idiopathic urticaria [6]. The ASST should not be regarded as a specific test for autoimmune urticaria, because uncharacterized wheal-producing factors remain after heat decomplexation and IgG depletion of ASST-positive chronic urticaria sera over Sepharose-coupled protein G [7]. It seems that a minority of patients with chronic urticaria and a positive ASST have a low-molecular-weight factor that releases histamine from mast cells but not basophils (known as a mast-cell specific factor) [4]. The frequency of positive skin tests with autologous heparinized plasma is lower than the frequency with autologous serum in patients with chronic urticaria [8]. The authors demonstrated a dose-dependent inhibition of basophil histamine release by heparin for immunologic and nonimmunologic stimuli *in vitro*, although the mechanism for this finding and potential clinical implications have not been explored.

Autoantibodies in urticaria

Autoantibodies against IgE

Autoantibodies against IgE (anti-IgE) have been detected in the blood of patients with atopic disorders, patients with hyper-IgE syndrome [9], and non-allergic healthy subjects [10]. Most investigators, however, have had great difficulty in demonstrating a functional role for anti-IgE in atopic disorders. Gruber et al described histamine release from healthy donor basophils challenged

with serum containing IgM anti-IgE from one patient with cold urticaria and low levels of release with four other cold urticaria sera containing IgG anti-IgE, detected by a nonfunctional enzyme immunoassay (ELISA) [11]. Serum containing IgG anti-IgE from patients with chronic idiopathic urticaria was nonfunctional. The first report of significant histamine release from basophils induced by sera from patients with chronic idiopathic urticaria was made by Grat-tan et al in 1991 [3]. Most of the releasers had a positive autologous serum skin test, and the whealing activity was confined to ultrafiltered fractions greater than 100 kD. Further characterization of some of the sera showed that the *in vitro* histamine-releasing activity was present in the IgG fraction and had functional properties of anti-IgE. It has since been shown that only about 9% of patients with chronic ordinary urticaria have functional autoantibodies to IgE, and most autoantibodies are directed against the high-affinity IgE receptor (Fc ϵ RI) [4].

Autoantibodies against anti-Fc ϵ RI

Hide et al made the novel discovery of autoantibodies that could stimulate histamine release by binding the Fc ϵ RI directly rather than through cross-linking IgE [12]. They demonstrated that the autoantibodies could be neutralized by previous incubation of the sera and their IgG fractions with the soluble extra-cellular fragment of the α -subunit (sFc ϵ RI α). After studying a larger number of chronic urticaria sera, it became clear that most functional autoantibodies bound the Fc ϵ RI despite the presence of IgE (noncompetitive binding), but a minority of autoantibodies only were able to bind Fc ϵ RI in the absence of IgE by competing for the receptor [13]. The work on functional Fc ϵ RI autoantibodies in urticaria was repeated and extended by groups in Vienna [14,15], Philadelphia [16], and New York [17]. As with anti-IgE, it became apparent that autoantibodies against anti-Fc ϵ RI (anti-Fc ϵ RI) could be detected in the sera of patients with chronic urticaria by immunoassays but did not necessarily have a demonstrable effect on basophils. Fiebiger et al developed an ELISA system for measuring IgG autoantibodies to the α -chain of the Fc ϵ RI in serum. The autoantibodies were present in 38% of patients with chronic urticaria but not in patients with atopic dermatitis or psoriasis or healthy controls [15]. The autoantibodies belonged predominantly to the complement-fixing subtypes IgG₁ and IgG₃. They also found anti-Fc ϵ RI α in other autoimmune diseases (pemphigus, bullous pemphi-goid, dermatomyositis, systemic lupus erythematosus), but these autoantibodies were mainly of the IgG₂ and IgG₄ subtypes, which are not complement fixing. Five distinct subsets of chronic idiopathic urticaria sera could be classified on the strength of their immunoreactivity by Western blot and functional properties on basophils or cutaneous mast cells: sera that were immunoreactive against Fc ϵ RI and released histamine (26% of 78 patients in this series), those that were immunoreactive against Fc ϵ RI but showed no histamine release (15%), those with functional autoantibodies like anti-IgE (9%), those releasing histamine from mast cells but not basophils (9%), and those with no identifiable factor (41%) [4].

Although the original definition of functional autoantibodies was made based on basophils, it was important to establish that autoantibodies also could stimulate cutaneous mast cells to release mediators of inflammation, because mast cells are believed to be the primary effector cell of urticaria. Niimi et al used thin slices of human foreskin obtained at circumcision as a source of mast cells for histamine release assays [18]. They found that all 12 sera samples from chronic idiopathic urticaria patients with positive ASST results induced histamine release, whereas sera from patients with negative ASST results and healthy controls did not. The sera also released histamine from basophils, confirming their functional relevance to target cells expressing the FcεRI. Histamine release from skin slices that was induced by IgG from the sera of three patients was inhibited by preincubation with sFcεRIα, indicating that the stimulus for histamine release was acting through the mast cell FcεRI. Ferrer et al used newborn foreskins as a source of dispersed mast cells and found a good correlation between mast cell and basophil histamine release [19]. Immunoblotting for anti-FcεRIα on the same sera showed that a few sera tested negative but evoked basophil histamine release, indicating the presence of another stimulus, possibly anti-IgE.

Complement dependence of autoantibody-induced histamine release

Although it seemed from the results of early studies that heat treatment of sera at 56°C for 1 hour caused only a small reduction of basophil histamine release [18], later work showed that heat decomplexation of sera for 4 hours at 56°C led to a 50% overall reduction [16]. The degree of inhibition of histamine release by heating correlated well with inhibition by C5a receptor blockade in most, but not all, sera [15]. Ferrer et al convincingly showed that human mast cell dispersions released histamine with exposure to sera from patients with chronic idiopathic urticaria but not with exposure to IgG derived from the sera, unless an external source of complement was added [20]. When these studies were extended to basophils, it was clear that basophil histamine release with IgG derived from sera from patients with chronic urticaria was largely dependent on or augmented by complement [21]. These results show that complement is a necessary cofactor for histamine release in mast cells and that most basophils are activated by autoantibodies through the FcεRI. It seems that binding of the autoantibody to the autoantigen (FcεRI or IgE) activates the early components of the complement cascade, as with immune complexes, and that binding of C5a to complement receptors on the mast cell or basophil causes or augments histamine release. Fiebiger et al argue that the restriction of histamine release by anti-FcεRI to cutaneous mast cells in urticaria may be caused by a lack of expression of C5a receptors in lung and intestinal mucosa [15].

Conditional autoimmunity

Horn et al have demonstrated nonfunctional anti-FcεRIα by a sensitive ELISA in the sera of healthy individuals and multidonor intravenous immunoglobulin

(IVIG) preparations and chronic urticaria [22]. They propose that these naturally occurring autoantibodies can become pathogenic in certain circumstances and that this occurrence is dependent on the state of occupancy of the Fc ϵ RI by its natural ligand IgE [23]. The development of urticaria is caused by alterations in tissue binding of a preexisting autoantibody in susceptible individuals rather than its production *de novo*. They argue that any perturbation in the skin from physical or other stimuli that would expose or increase expression of the Fc ϵ RI would promote mast cell degranulation. The story is similar to the competitive anti-Fc ϵ RI α that was defined functionally 8 years earlier by Hide [13]; these autoantibodies also were inhibited by sensitization of the receptor by IgE, although they were present in only a small proportion of the urticaria sera that showed anti-Fc ϵ RI activity. More studies are needed to define whether natural autoantibodies can become pathogenic in certain circumstances, such as by increased production, or whether other factors, including epitope specificity, immunoglobulin subclass, or complement fixation, are more important in determining functionality in urticaria.

Basophils and mast cells as targets for autoantibodies in urticaria

The pivotal studies described earlier that defined functional autoantibodies in urticaria sera used basophils or mast cells from healthy subjects to demonstrate a response, but what happens to the basophils and mast cells in patients with urticaria?

Basophils

Reduced numbers of circulating basophils, detected by metachromatic granule stains, were found in patients with chronic urticaria as early as 1961 by Rorsman [24]. He found no evidence of reduced formation in the bone marrow or marked accumulation in wheals and concluded that degranulation or destruction of the basophils in the circulation or in lesional skin was the cause of the basopenia. He recognized that basopenia was not present in patients with predominantly physical chronic urticaria and was worse in patients with angioedema and patients with extensive whealing [25]. His observations have been extended by the finding that basopenia in chronic urticaria is related closely to serum histamine-releasing activity [26]. A comparable reduction of blood cellular histamine levels (containing basophils) also has been noted [27]. A negative linear correlation between blood basophil numbers and urticarial activity is consistent with the hypothesis that basophils are recruited actively from blood into wheals during disease activity [28].

Functional and numerical changes have been described in basophils of patients with chronic urticaria. Circulating basophils show reduced histamine release in response to anti-IgE, a standard experimental immunologic releasing stimulus [29–31], and to a monoclonal anti-Fc ϵ RI antibody but not the nonimmunologic

degranulating agent formyl-methionyl-leucyl-phenylalanine [27]. The reduced response to immunologic stimuli working through the Fc ϵ RI probably is caused by desensitization of the receptor by autoantibodies. In preliminary studies, basophils from patients with chronic urticaria that were incubated with the sera from healthy controls and sera from other patients with chronic urticaria showed considerably higher histamine release than did basophils from healthy controls, suggesting a state of hyper-responsiveness to some unknown factor or factors in the serum despite the relative unresponsiveness to known immunologic secretagogues [32].

Mast cells

Numbers of lesional mast cells in patients with chronic idiopathic urticaria that were counted by conventional histochemical stains have been reported to be increased 10-fold [33] but were no different from the numbers in healthy controls or uninvolved skin when counted by a double-labeling immunochemical technique for tryptase and chymase [34]. It is possible that this difference relates to the inclusion of basophils in the study by Natbony et al, because basophils have been shown to infiltrate chronic urticaria wheals using the specific monoclonal BB1 [35]. Mast cell numbers seemed to be reduced in pressure-induced wheals 6 hours after pressure challenge [36].

Little research has been done on the functional changes in mast cells from patients with chronic urticaria, although there is general agreement that the mast cells seem to be more releasable to nonimmunologic stimuli. This observation is derived largely from skin testing studies with the experimental mast cell-releasing agent, compound 48/80 [37], and codeine [38]. The influence of an immunologic stimulus was explored in a small study of dispersed mast cells from nonlesional urticaria skin biopsies in which no reduction of histamine release in response to anti-IgE was found, in contrast to basophils [31]. Immunohistochemical staining for tumor necrosis factor α (TNF- α) and interleukin 3 (IL-3) of wheals that were estimated to be between 2 and 6 hours old showed increased staining of perivascular cells for both of these cytokines, but only a few cells showed double staining with tryptase, so up-regulated secretion could not be confirmed [39]. It has been shown that sera from patients with chronic urticaria containing anti-Fc ϵ RI α release TNF- α from dispersed neonatal human foreskins, leading to expression of adhesion molecules on human dermal microvascular endothelial cells [40]. Expression of nerve growth factor receptor (p75NGFR) was decreased on c-kit-positive dermal mast cells, but expression of the nerve growth factor receptor tyrosine kinase and granulocyte-macrophage colony-stimulating factor receptors was unchanged [41].

Clinical associations with autoimmune urticaria

The most convincing evidence of a genetic predisposition for autoimmune disease in chronic idiopathic urticaria comes from studies of major histocompatibility complex class II association. There was a strikingly increased frequency of

HLA-DRB1*04 (DR4) and its associated allele DQB1*0302 (DQ8) in patients with chronic idiopathic urticaria compared with a healthy control population [42]. The HLA-DR4 association was strong for patients with in vitro and in vivo evidence of histamine-releasing activity but also was highly significant for patients with a positive ASST and no basophil histamine release in their sera. Patients with a negative ASST and no evidence of in vitro histamine release showed a similar frequency of HLA-DR4 and HLA-DQ8 compared with that of controls. An increased frequency of the HLA-DR4 and HLA-DQ8 haplotype also has been shown in Ashkenazi Jews with pemphigus vulgaris, another condition in which anti-Fc ϵ RI α have been detected, albeit, they are nonfunctional.

Less direct evidence for an association of chronic idiopathic urticaria with autoimmune disease comes from an association with autoimmune thyroid disease, first described by Leznoff in 1983 [43] and confirmed in several subsequent reports [44–47]. It has been shown that patients with chronic urticaria and thyroid autoimmunity are more likely to have in vitro basophil histamine release [48] than those without it. A history of autoimmune conditions was given significantly more often by patients with anti-Fc ϵ RI or anti-IgE than by patients without such a history [49].

In the same report, Sabroe compared the clinical features with and without autoantibodies, as demonstrated by histamine release from basophils. There was no sharp definition between the two patient groups, suggesting that the clinical expression of urticaria is determined by the outcome of mast cell degranulation rather than by its trigger. Patients with evidence of autoimmune urticaria had significantly higher wheal scores at more sites, higher itch scores for the most severe episodes of itching, and more systemic symptoms than did patients without such evidence. The urticaria of the former patients tended to be more severe, but a later report from the same group illustrated that the differences in clinical features of autoimmune and nonautoimmune urticaria were not marked [4]. Other clinical indicators of autoimmune urticaria include lower median serum IgE levels [49] and absent or markedly reduced levels of peripheral blood basophils [26]. There were no consistent differences on routine histology of early (<4 h) and late (> 12 h) wheals between patients with and without autoantibodies [50].

Immunologic profiles in chronic urticaria

Extensive immunologic screening for organ and nonorgan specific autoantibodies, immune complexes, immunoglobulins, and complement abnormalities is invariably unrewarding in nonvasculitic chronic urticaria and should not be undertaken in routine clinical practice. The complex pathways involved in triggering, maintaining, and controlling autoantibody formation against the Fc ϵ RI, IgE, and, perhaps, other autoantigens still need evaluation. Some reports offer insight into the immunologic aberrations that may underlie and accompany chronic urticaria, although more work needs to be done. The possibility that other autoantibodies may be involved in disease pathogenesis was highlighted by the demonstration of anti-endothelial cell antibodies in 3 of 20 patients with chronic

idiopathic urticaria, two of whom also had weak histamine-releasing activity [51]. Anti-endothelial cell autoantibodies also have been found in systemic lupus erythematosus and urticarial vasculitis, but systematic searching for these autoantibodies in urticaria has not been done. CD_{40L} expression on activated T cells was higher in patients with chronic urticaria than in healthy controls and patients with contact dermatitis, implying that the co-stimulatory signals for B-cell activation leading to proliferation and antibody formation are enhanced [52]. Bcl-2 expression on B and T cells was increased in patients with more severe chronic urticaria. Bcl-2 protein rescues B cells from apoptosis and contributes to cell survival and proliferation. Aberrant signaling of the p21 Ras pathway, which is involved in T-cell receptor and IL-2 receptor activation, has been detected in chronic urticaria similar to other autoimmune diseases [53]. Stimulated peripheral blood mononuclear cells from patients with chronic idiopathic urticaria produced more TNF- α , IL-10, and the chemokines macrophage inflammatory protein (MIP)-1 α and RANTES than did the cells from healthy controls [54]. Cytokine production was higher in patients with negative ASSTs than in patients with positive ASSTs. Expression of adhesion ligands on CD4 and CD8 cells also was augmented.

Model of autoimmune urticaria pathogenesis

As in other autoimmune disorders, the trigger for autoantibody formation in urticaria is unknown. Chronic bacterial infection with abscess formation has been suspected as a cause of urticaria, but this theory remains unproven. Infection of the stomach with *Helicobacter pylori* has been suggested as a potential cause of chronic urticaria; however, in the absence of double-blinded trials of eradication therapies, this theory also remains to be proved. A report linking *H pylori* infection with autoimmune thyroiditis in patients with chronic urticaria and positive ASSTs [55] lends tentative support to the proposal that *H pylori* infection may predispose patients to autoimmune urticaria by molecular mimicry [56]. Strong cross-reactivity between antibodies to tetanus toxoid and nonfunctional anti-Fc ϵ RI has been reported [22], but the clinical significance of this finding remains uncertain. It seems likely that local events, including heat, pressure, and, perhaps, local retrograde nerve pathway stimulation, lead to vascular leakage, which allows extravasation of plasma proteins (including autoantibodies) into the perivascular space. Binding of the autoantibody to IgE or Fc ϵ RI leads to cross-linking of the receptor, complement activation, and a series of intracellular events, including protein-kinase activation; calcium influx; and release of pre-formed granule contents, including histamine, heparin, tryptase, and TNF- α with synthesis of other proinflammatory cytokines and eicosanoids. Up-regulation of adhesion molecules on endothelial cells actively recruits into the dermis acute inflammatory cells, including neutrophils, eosinophils, mononuclear cells, and basophils, which sustain the immediate wheal response by releasing histamine and sulphidopeptide leukotrienes. The signals for resolution of the inflammatory

process are unknown but presumably involve down-regulation of the histamine receptor, reconstitution of the integrity of the endothelial cell lining, apoptosis of the inflammatory cells, clearance of cellular debris by macrophages, and drainage of the edema fluid into the vascular circulation by lymphatics. Clinical experience indicates that the activity of urticaria is influenced adversely by many factors, including viral infections, NSAIDs, dietary pseudoallergens, and stress. The factors that influence or predict remission are unknown. Some evidence shows that the functional autoantibody levels decrease as the disease abates. Positive ASSTs became negative in remission [1]. Serum histamine-releasing activity decreased significantly during successful treatment with plasmapheresis [57] and ciclosporin [58]. Information from long-term longitudinal studies of autoantibody activity in chronic urticaria is not available, just as there is no information concerning the age of onset of the immune response.

Classification of autoimmune urticaria

Classifications of urticaria based on etiopathogenesis may be satisfying academically but are of little practical clinical value. This fact is true partly because relevant tests may not be available to clinicians, partly because the urticarias often overlap and partly because, in many instances, the cause remains unknown after full evaluation. It is helpful to dissociate causes from aggravating events or triggers. The cause of the physical urticarias is unknown, but the specific physical trigger that brings out wheals almost always can be defined by history taking and challenge testing. Even when the activity of urticaria is caused by histamine-releasing autoantibodies, it may be influenced day to day by exogenous aggravating factors. A clinical classification based on the overall clinical pattern of urticaria (Fig. 1) is more useful for managing urticaria than an

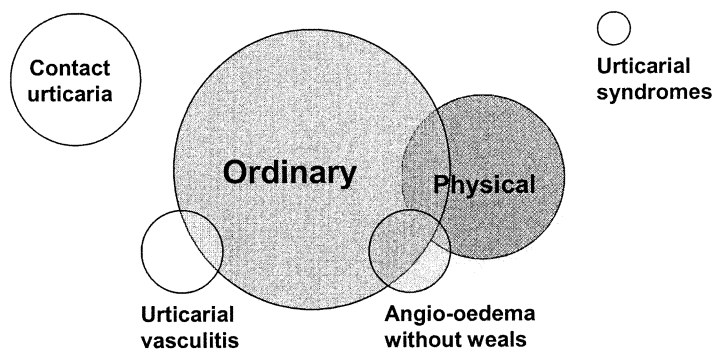


Fig. 1. Classification of urticaria by clinical presentation rather than cause. The term “ordinary urticaria” includes autoimmune and idiopathic urticaria. Whether the cause is autoimmunity, allergy, pseudoallergy, or infection or is unexplained (idiopathic), the disease tends to present with the same clinical picture. Rare urticarial syndromes include Muckle-Wells syndrome, familial cold urticaria, Schnitzler’s syndrome, and the autoinflammatory syndromes (such as TNF receptor–associated periodic syndrome).

etiologic classification [59]. The term “ordinary urticaria” embraces autoimmunity, allergy, pseudoallergy, infection, and idiopathic disease as possible causes and does not imply a specific cause. Because 30% to 40% of cases of chronic ordinary urticaria are autoimmune, it is not appropriate to use the term “idiopathic urticaria” as synonymous with “ordinary urticaria.”

Diagnosis of autoimmune urticaria

Although the current gold standard of diagnosis hinges on functional release assays with basophils or mast cells, these investigations remain confined to a few research centers; in practice, the diagnosis of autoimmune urticaria relies primarily on clinical suspicion that is supported by tests when available (Fig. 2).

Functional in vitro tests

Most of the studies that support the concept of autoimmune urticaria have relied on the release of histamine from basophils of healthy donors as a marker of activation and degranulation. Assays for other products of degranulation,

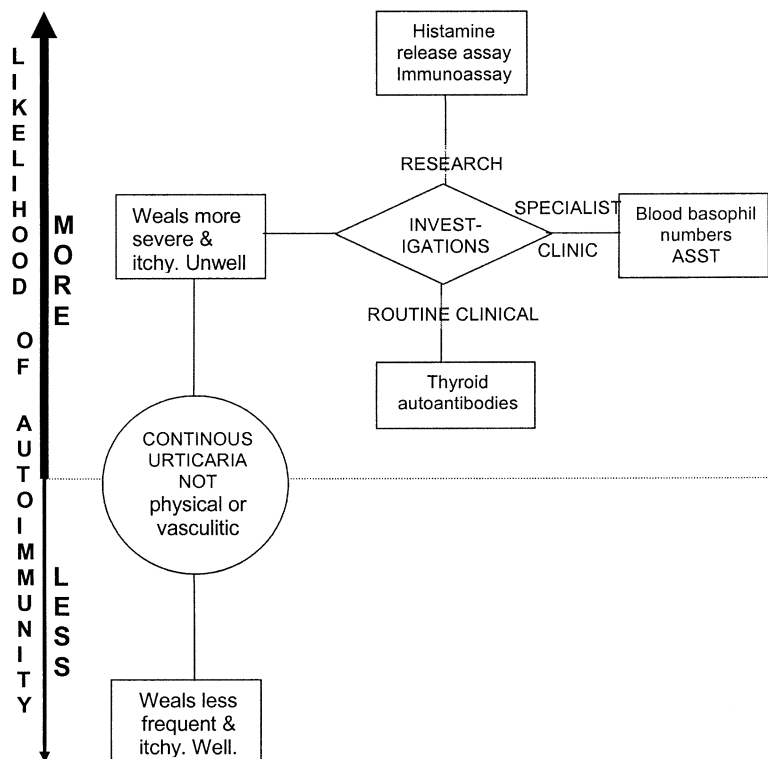


Fig. 2. The diagnosis of autoimmune urticaria more or less likely depends on the clinical features and any investigations that may be available.

including leukotriene C4 tryptase and TNF- α , have not been used, because histamine is the major mediator of most patterns of urticaria and is also relatively simple and inexpensive to measure. For subgroups of patients, including patients who are relatively unresponsive to antihistamines, assays for other mediators may be informative. Several restrictions apply to the basophil histamine release assay and illustrate the potential pitfalls of relying on this test as a gold-standard investigation.

1. Basophils from different donors respond differently to immunologic stimulation. IgE-sensitized (atopic) donors may respond to anti-IgE or non-competitive anti-Fc ϵ RI but do not bind autoantibodies that compete with IgE for Fc ϵ RI. Conversely, IgE-depleted basophils bind competitive and noncompetitive anti-Fc ϵ RI but not anti-IgE. A few basophil donors are unresponsive to all immunologic stimuli but respond to nonimmunologic, stimuli such as calcium ionophore or the cytokine macrophage chemotactic protein (MCP)-1. This state of nonreleasability is believed to be caused by a functional abnormality in the tyrosine kinase product syk. Priming basophils with IL-3 before incubation with sera from patients with chronic urticaria has been reported to increase the amount of histamine release but does not seem to convert nonreleasing sera into positive releasers [60]. Modifications of this type may help to standardize the basophil histamine-release assay in the future by reducing the variations between donors.
2. Many publications have defined functional autoantibodies by incubating basophils with whole sera rather than purified IgG, inferring that histamine release has been stimulated immunologically through the Fc ϵ RI, because the purification process for IgG is time consuming. This assumption, however, leaves open the possibility that other immunoglobulin classes in serum, such as natural IgM autoantibodies, may be relevant to some patients and that nonimmune stimulation may account for low levels of histamine release in other patients. The distinction between competitive and noncompetitive binding of the Fc ϵ RI and binding of IgE cannot be made without assaying sera on IgE-sensitized and IgE-depleted basophils.
3. The third consideration relates to the applicability of basophil assays to a primarily cutaneous condition in which the initial target cell is the mast cell. Although there are many functional and structural similarities between these cell types, it is not clear whether the basophil is an adequate substitute for assessing functional autoantibodies in urticaria, because positive results on basophils correlate well with mast cells. The converse is not always true, however (mast cell specific factor). The frequency of positive basophil histamine-release assays in most series (25%–40%) is less than the frequency of positive autologous serum skin tests (50%–60%), which may offer a more relevant test for endogenous histamine-releasing factors. Continuing efforts are needed to find sensitive and specific detection systems, including mast cell lines and perhaps chimeric cell lines transfected with the human Fc ϵ RI for detection by flow cytometry.

Immunoassays

Immunoassays depend on the binding of autoantibody to a specific autoantigen (in this case, the soluble chain of Fc ϵ RI α or IgE) rather than the detection of a secreted mediator from the target cell (in this case, histamine) as evidence of functionality. Comparative studies have shown that positive detection of anti-Fc ϵ RI α by immunoblot does not correlate well with basophil histamine release [21]. The reasons for this finding are unclear, but false-positive results may relate to the aberrant binding of the autoantibody to carbohydrate moieties in the cloned autoantigen or to the noncomplement fixing IgG₂ and IgG₄ subclasses that are detected by immunoassay. False-negative results could be caused by the insensitivity of Western blotting at the low concentrations of anti-Fc ϵ RI present in sera of patients with chronic urticaria. An ELISA would increase sensitivity and allow quantitation of the autoantibody, but attempts to develop a suitable system for general use have been unsuccessful. The ELISA published by Fiebiger et al [15] was a complex assay involving two reaction steps and using a human recombinant soluble Fc ϵ RI α that is generated by baculovirus-infected insect cells. This assay has not been repeated by other investigators. Horn et al [22] subsequently compared two recombinant Fc ϵ RI α proteins that were produced similarly in insect cells or in mammalian Chinese hamster ovary (CHO) cells. They concluded that the CHO protein showed a superior biologic activity for ELISA. They went on to show that similar levels of anti-Fc ϵ RI α could be detected in patients with chronic idiopathic urticaria, patients with chronic urticaria of other causes, and a small number of controls. There was no apparent relationship between the ELISA results and histamine-releasing activity. Future research should develop a sensitive ELISA that can distinguish pathogenic autoantibodies above background levels of natural autoantibody and that measures only functional anti-Fc ϵ RI α .

ASST

The ASST remains the most accessible and useful test for demonstrating endogenous vasoactive factors in the blood of patients with ordinary urticaria. It is not a specific test for autoimmune urticaria. Although it has a reasonable sensitivity (about 70%) and specificity (about 80%) for basophil histamine release using the criteria described (a red serum-induced wheal with a diameter that is 1.5 mm or greater than the diameter of the edema caused by an adjacent normal saline control injection at 30 minutes) [6], it does not specifically imply mast cell degranulation or autoimmune stimulation as a cause of the wheal response. The ASST offers a simple screening test for potentially relevant biologic activity and may help to define a subgroup of patients with urticaria who are more likely to have an endogenous cause for their disease than do patients without a positive test. The significance of a negative ASST remains less clear. Although it is unusual for patients with a negative ASST to show significant *in vitro* release of basophils, the histology of positive and negative ASSTs has shown marked neutrophil-rich infiltrates between 90 and 135 minutes, in contrast to injection of autologous serum in healthy controls in whom the serum response was similar to

that seen with saline injection [1]. The presence of this cellular infiltrate suggests that circulating proinflammatory factors still may be relevant in patients with chronic urticaria and negative ASSTs, but the role of histamine and other vaso-active mediators in the response is diminished.

Various practical considerations may influence the outcome of the test, including the use of antihistamines within 3 days of the test, injection over the sites of recent wheals, and health and safety issues in relation to preparation of the serum. Standardization of the skin test technique and definition of a positive response would be helpful to facilitate comparison of results between centers and the definition of patient groups most likely to respond to targeted therapies.

Clinical assessment in the diagnosis of autoimmune urticaria

The diagnosis of autoimmune urticaria often can be suspected from a history of highly symptomatic, severe continuous whealing linked with systemic features of malaise, indigestion, and feeling hot or cold. A past or family history of autoimmune disease, especially thyroiditis, can be indicative. Routine clinical workup might include a complete blood cell count, erythrocyte sedimentation rate, measurement of levels of total IgE and thyroid autoantibodies. Blood basophil enumeration and an ASST are useful if facilities for them are available, but the diagnosis often has to be made on clinical suspicion and after exclusion of other recognizable patterns of urticaria, including patterns triggered by physical stimuli or those linked with drugs, infections, or dietary pseudoallergens.

Management of autoimmune urticaria

The initial management of patients with suspected or proven autoimmune urticaria is the same as that for patients with ordinary urticaria (Fig. 3) [59]. Patients should be given information about their condition and advice to avoid exposures that might aggravate it, including overheating; stress; exposure to alcohol, opiates, NSAIDs, and dietary pseudoallergens. Pseudoallergens include food additives, salicylates, and as yet unidentified aromatic substances in tomato, white wine, and herbs [61]. A strict low-pseudoallergen-avoidance diet for 3 weeks seems to benefit some patients with chronic ordinary urticaria [62], especially those with milder antihistamine-responsive disease. About 25% of patients with ordinary urticaria are aspirin sensitive [63]. Pharmacologic therapies generally should be offered sequentially, starting with first-line drugs (antihistamines) and moving onto second-line drugs for specific indications (including short courses of oral corticosteroids for acute exacerbations) before considering third-line immunomodulating therapies for cases of severe disabling ordinary urticaria that do not respond to other treatments. Most early trials of immunotherapy stipulated that patients had to have some evidence of histamine-releasing autoantibodies to justify their recruitment into the studies (such as a positive ASST or in vitro evidence of functional autoantibodies). Because of the difficulty in proving autoimmunity as a cause of urticaria, it has become common practice

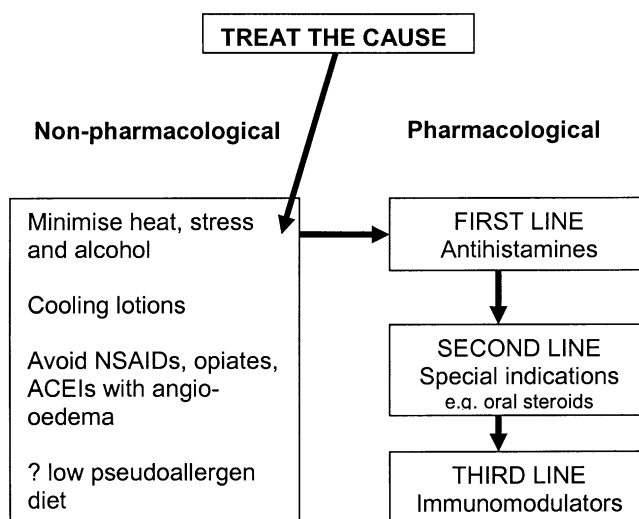


Fig. 3. A management scheme for ordinary urticaria (including autoimmune urticaria) involves non-pharmacologic measures and drug treatments, starting with first-line antihistamines and progressing to third-line (immunomodulating) treatments according to clinical need. ACEIs, angiotensin-converting enzyme inhibitors.

to offer a trial of immunotherapies to patients with severe disabling chronic ordinary disease, particularly if they are corticosteroid dependent. Clinical experience suggests that good responses may be achieved with or without proof of functional autoantibodies, although it seems that patients with strongly positive basophil histamine release are more likely to respond well to ciclosporin [58]. Immunotherapies that have been reported include plasmapheresis, interferon γ , IVIGs, and ciclosporin. Encouraging anecdotal experience with methotrexate and azathioprine indicates that a wide range of drugs that influence T- and B-cell function may have a role in selected patients.

Plasmapheresis

Only one open series of plasmapheresis for chronic autoimmune urticaria has been reported [56]. Eight patients with severe chronic urticaria and serum histamine-releasing activity were treated three times over 5 days (volume of plasma removed, 4.2–9.0 L). Two patients cleared for 8 and 4 weeks, four patients improved symptomatically for up to 2 months, but two patients showed only a slight benefit. The study showed that serum histamine-releasing activity corresponded well with clinical disease activity and supported the hypothesis that autoantibodies could be pathogenic in urticaria. It also demonstrated that the clinical improvement from removal of functional autoantibodies was short-lived because the autoantibodies reaccumulated afterward and that plasmapheresis as monotherapy was difficult to justify.

Interferon α

There have been two reports of interferon α (IFN- α) treatment for chronic urticaria. In the first report, patients with mastocytosis and several patterns of chronic urticaria were treated with subcutaneous injections of IFN- α 2a for at least 8 weeks [64]. The only patient with chronic idiopathic urticaria failed to respond. Open administration of intramuscular IFN- α 2a at 3×10^6 IU three times a week for at least 2 weeks in eight patients with severe refractory chronic idiopathic urticaria seemed to result in a “good response” in 50% of patients, but this response was not maintained despite continuing treatment at the same dosage [65]. The authors of this report did not attempt to assess the patients for functional autoantibodies. The conclusion that can be drawn from these uncontrolled reports is that IFN- α treatment of urticaria is unproven and probably should not be used.

Intravenous immunoglobulin

Pooled gammaglobulin containing predominantly IgG from multiple healthy donors has been used to treat a wide range of autoinflammatory disorders, including idiopathic thrombocytopenic purpura and vasculitis. Ten patients with severe chronic autoimmune urticaria evidenced by positive in vitro basophil histamine release were treated over 5 days with 2-g/kg IVIG [66]. Clinical benefit was noted in nine patients. Two patients had prolonged complete remissions lasting at least 3 years, and three patients showed temporary complete remissions. The reduced urticarial activity corresponded with a reduction in the size of the ASST response in most patients. This encouraging open study has not been repeated or controlled, so it remains difficult to assess the likely benefits of IVIG. Further studies are needed to explore different dosing regimens.

Cyclosporine

Cyclosporine has been used widely off license for treatment of severe chronic urticaria over the past few years as a result of encouraging early reports [67,68]. A randomized double-blind controlled study of patients with severe chronic urticaria shows good evidence of efficacy [58]. All 30 patients had a positive ASST, and 14/27 patients tested had significant in vitro basophil histamine release. Patients were randomized to receive cyclosporine at 4 mg/kg/d or placebo for the first 4 weeks of treatment. Nonresponders were offered open-label cyclosporine at the same dosage for another month. All patients took 20 mg/d of cetirizine throughout the treatment and follow-up period for a duration of up to 5 months. In the randomized phase of the study, the number of responders to cyclosporine was significantly greater than the number of responders to placebo. About two thirds of the patients responded overall, with a reduction of their urticaria activity to less than 25% of baseline overall, but only 26% of responders remained clear or almost clear near the end of the study. Histamine-releasing activity of sera decreased significantly after cyclosporine treatment began, and

13 of 18 of the responders showed significant in vitro histamine release. It is likely that the early response to cyclosporine seen in some subjects (within 48 hours) was a result of the stabilizing effects of the drug on basophils and mast cells rather than the inhibition of functional autoantibodies, although the rate of autoantibody reduction was not assessed. Preliminary data from a multicenter study of cyclosporine given at 5 mg/kg/d for 2 weeks, 4 mg/kg/d for the next 2 weeks, and then 3 mg/kg/d for the remainder of the study confirmed a good therapeutic response and indicated that relapses were more frequent in patients treated for 8 weeks rather than 16 weeks [69]. Optimal treatment protocols with cyclosporine still need to be defined.

Summary

A growing body of evidence shows that at least 40% of patients with unexplained (idiopathic) chronic urticaria have clinically relevant functional autoantibodies to the high-affinity IgE receptor on basophils and mast cells. The term “autoimmune urticaria” is used for this subgroup of patients presenting with continuous ordinary urticaria. Although immunoassays have been used in a research setting to screen sera for anti-FcεRI, there is a poor correlation between these results and in vitro functional histamine-release assays on basophils and cutaneous mast cells. Better laboratory assays need to be routinely available to clinicians to facilitate diagnosis. The simplest test of functional factors in the blood of patients with endogenous urticaria is the whealing response to intra-dermal injection with autologous serum, known as the ASST. Diagnosis of autoimmune urticaria hinges mainly on clinical suspicion in patients with the most severe presentations of chronic urticaria and without any other known cause or physical trigger. The use of immunotherapies may be helpful for patients with this pattern of severe refractory urticaria, especially when there is evidence of underlying autoimmunity or dependence on oral corticosteroid therapy for disease control.

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