

Chronic Urticaria

A Role for Newer Immunomodulatory Drugs?

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Abstract

Chronic urticaria is now recognized as an autoreactive disorder in a substantial fraction of patients. A serologic mediator of whealing has been demonstrated in 50–60% of patients with chronic urticaria, and autoantibodies against the high affinity IgE receptor or IgE have been detected in about half of these patients. The demonstration that chronic urticaria is frequently autoimmune has encouraged a more aggressive therapeutic approach, with the use of immunomodulatory drugs.

A step-by-step approach to the management of chronic urticaria is proposed, based on our personal experience and review of current medical literature, identified through Medline research and hand searching in medical journals.

The non- or low-sedating H₁ receptor antagonists (antihistamines), such as cetirizine, fexofenadine, loratadine, mizolastine and, more recently, levocetirizine, desloratadine and ebastine, represent the basic therapy for all chronic urticaria patients. Older sedating antihistamines, such as hydroxyzine and diphenhydramine, may be indicated if symptoms are severe, are associated with angioedema, and if the patient is anxious and disturbed at night.

Corticosteroid therapy with prednisone or methylprednisolone can be administered for a few days (7–14) if urticarial symptoms are not controlled by antihistamines and a rapid clinical response is needed. In cases of relapse after corticosteroid suspension, leukotriene receptor antagonists, such as montelukast and zafirlukast, should be tried. In our experience, remission of urticarial symptoms can be achieved in 20–50% of chronic urticaria patients unresponsive to antihistamines alone. When urticaria is unremitting and is not controlled by combined therapy with antihistamines and leukotriene receptor antagonists, prolonged corticosteroid therapy may be needed. Long-term corticosteroid therapy should be administered at the lowest dose able to control urticarial symptoms, in order to minimize adverse effects. In a few patients, however, high-dose corticosteroid therapy may have to be administered for long periods. In these patients, immunosuppressive treatment with low-dose cyclosporine can be started. This type of treatment has a corticosteroid-sparing effect and is also generally effective in patients with severe, unremitting urticaria, but requires careful monitoring of cyclosporine plasma concentration and possible adverse effects.

Other immunomodulating drugs that have been tried in chronic urticaria patients include hydroxychloroquine, dapsone, sulfasalazine and methotrexate, but their efficacy has not been proven in large controlled studies. Warfarin therapy may also be considered in some patients with chronic urticaria and angioedema unresponsive to antihistamines.

1. Background

Chronic urticaria is characterized by the repeated occurrence of short-lived cutaneous wheals accompanied by redness and itching for >6 weeks. Chronic urticaria has long been considered as a 'mysterious' disorder and has been often been ascribed to anxiety or intolerance to foods, food dyes and food additives.^[1-3] For many years hypoallergenic diets have been prescribed to chronic urticaria patients, but the clinical benefit was little or none.^[4-6] It is now clear that food allergy/intolerance underlies chronic urticaria only in a very small percentage of patients and that dietary restrictions are most often useless. According to some authors, however, a diet low in pseudoallergens may be beneficial,^[7,8] perhaps because it reduces the exposure to aromatic components of foods that are supposed to cause pseudoallergic reactions in patients with chronic urticaria.^[9]

The association of chronic urticaria with chronic infections has been thoroughly investigated, but convincing evidence that infectious agents may provoke chronic urticaria has not been provided. The association of chronic urticaria with *Helicobacter pylori* infection has been postulated, and some authors have found a beneficial effect from eradication therapy.^[10,11] However, other reports have failed to confirm the possible link between *H. pylori* infection and chronic urticaria.^[12,13] Occasionally, parasite infestations are associated with urticarial rash, especially in regions where parasitoses are endemic.^[14,15] In summary, until recently, a clear etiology of chronic urticaria was not identified in most patients. New light on the pathogenesis of the disease was shed by the demonstration of a serologic mediator of whealing in many chronic urticaria patients.

In 1986 Grattan et al.^[16] demonstrated that intradermal injection of autologous serum induced a wheal and flare reaction in many chronic urticaria patients. Furthermore, Gruber et al.^[17] found that circulating anti-Ig-E autoantibodies are present in some patients with chronic urticaria. Subsequently, two studies by Grattan and colleagues^[18] and Hide et al.^[19] showed that the main serologic mediator of whealing was an autoantibody directed against the α subunit of the high affinity IgE receptor Fc ϵ RI, which was found in 25% of chronic urticaria patients. This observation was confirmed by independent researchers.^[20,21] Only in a minority of chronic urticaria patients (about 5%) can circulating autoantibodies directed against IgE be detected. These autoantibodies cause direct cross-linking of adjacent Fc ϵ RI receptors or IgE, thus inducing mast cell activation and release of inflammatory

mediators. In addition, monovalent combination of autoantibodies and receptors may occur, with complement activation and generation of anaphylatoxins. Complement dependence of histamine release in chronic urticaria has been suggested by Ferrer and colleagues.^[22] Furthermore, C5a has a role in augmenting IgG-dependent histamine release from basophils in chronic urticaria.^[23]

It has been suggested that anti-Fc ϵ RI autoantibodies are not always pathogenic and in fact they have been detected in chronic urticaria patients who went into remission after being treated for suspected causes of the disease (food or drug intolerance, *Helicobacter pylori* infection).^[24] Stadler et al.^[25] have proposed that anti-Fc ϵ RI autoantibodies are part of a conditional autoimmune reaction, leading to urticaria in relation to other cofactors and only if a sufficient number of free Fc ϵ RI is available. The state of occupancy of Fc ϵ RI, in turn, may depend on the consumption of local IgE, e.g. after an immediate reaction.^[26] This hypothesis can explain why the presence of anti-Fc ϵ RI autoantibodies in the serum is not always accompanied by urticaria and why some patients have intermittent urticaria.

Skin biopsies at sites of urticarial lesions have demonstrated a perivascular infiltration of lymphocytes which are predominantly cell cluster differentiation 4 (CD4) positive, monocytes, neutrophils and eosinophils, a picture recalling late-phase antigen-induced reactions.^[27,28] This suggests that the cellular and biochemical events underlying urticarial symptoms are similar to those involved in IgE-mediated antigen-induced reactions.

Wedi et al.^[29] have demonstrated that sera from chronic urticaria patients induce not only histamine release, but also the production of leukotriene C4 by stimulated basophils. Since intradermal injection of leukotriene C4 induces a wheal and flare reaction in humans, this arachidonic acid derivative can be considered as a mediator of urticaria.^[30] Other mediators, such as platelet-activating factor, cytokines and chemokines, can be released by activated mast cells, but little evidence is available so far that they are involved in the pathogenesis of urticarial lesions.^[31,32] As chronic urticaria is an autoimmune disorder due to mast cells stimulating autoantibodies in several patients, it has many similarities with Graves disease, which is characterized by thyroid-stimulating antibodies. The coexistence of chronic urticaria and Graves disease has been described only occasionally.^[33]

Conversely, an association of chronic urticaria with autoimmune thyroiditis has been clearly demonstrated, since antithyroglobulin and/or antithyroid peroxidase antibodies have been detected in 25–30% of chronic urticaria patients.^[34] A role for

thyroid autoimmunity in the pathogenesis of chronic urticaria has been suggested, but not proven. Thyroid-peroxidase specific IgE have been detected in one patient with chronic urticaria and autoimmune thyroiditis,^[35] and it has been suggested that these antibodies could trigger histamine release from mast cells. However, the presence of thyroid-peroxidase specific IgE is an occasional finding and most chronic urticaria patients do not have these antibodies.^[36] A role for thyroid autoimmunity in the mechanism of chronic urticaria is unlikely, although the two autoimmune diseases are significantly associated. Recurrent hives may occur in patients with systemic autoimmune disorders, such as systemic lupus erythematosus, but in these cases histologic examination of the skin reveals a leukocytoclastic vasculitis rather than the non-necrotizing vasculopathy which is usually seen in chronic urticaria patients. Chronic hives due to cutaneous vasculitis occurs in a very small proportion (<1%) of chronic urticaria patients.

In our experience, intradermal injection of autologous serum (measured using the autologous serum skin test [ASST]) elicits a wheal and flare reaction in about 60% of chronic urticaria patients, in whom the disease can indeed be considered as autoreactive.^[37] However, functional IgG autoantibodies for the high affinity IgE receptor, FcεRI, can be detected only in 20–30% of the chronic urticaria patients.^[38] Furthermore, it has been demonstrated that sera from chronic urticaria patients containing anti-FcεRI antibodies retained their *in vivo* ability to induce a wheal and flare reaction also after depletion of IgG.^[39] It is, therefore, conceivable that histamine-releasing factors other than anti-FcεRI and anti-IgE autoantibodies account for the *in vivo* activity of sera from chronic urticaria patients. A preliminary, partial characterization of a histamine-releasing factor with a molecular weight in excess of 30 kDa was reported by Kermani et al.^[40] A histamine-releasing factor potentially involved in chronic urticaria was also described by Claveau et al.^[41]

The pathogenesis of chronic urticaria remains elusive in about 40% of patients, in whom an autoimmune or autoreactive phenomenon cannot be demonstrated. A few of these patients have food or additive intolerance; although the remainder do not show any serologic mediator of whealing on ASST, it is possible that they have a disease due to endogenous factors (chemokines, neuropeptides) capable of inducing the release of histamine.

From a clinical point of view, the management of autoimmune and nonautoimmune chronic urticaria is similar. However, the demonstration of an autoimmune mechanism in patients with severe symptoms may support a more aggressive approach.

2. Diagnosis

We perform skin testing with autologous serum in all patients with chronic urticaria. Chronic urticaria is a frustrating disorder and many patients are seriously concerned about their health; a positive ASST suggests that an autoimmune mechanism underlies the disease and most patients are happy to know that their disorder has a defined origin and can be properly treated. ASST requires minimal technical equipment and can be performed routinely in all allergy or dermatology outpatient clinics. We recommend the method by Sabroe et al.^[42] where 0.05ml of freshly drawn serum is injected intradermally into uninvolved skin, generally in the volar aspect of the forearm. Intradermal injection with saline solution (0.9% weight/volume sodium chloride) is considered as negative control. A positive reaction is when the wheal has a diameter at least 1.5mm greater than that induced by saline solution. A positive ASST is suggestive, but not a certain diagnosis, of autoimmune urticaria; *in vitro* tests may help to identify patients with autoimmune urticaria.

Since a satisfactory immunoassay for anti-FcεRI and anti-IgE antibodies is not available, a functional *in vitro* assay using basophils from normal donors may help to identify those patients with chronic urticaria who presumably have histamine-releasing autoantibodies. Serum filtration may allow a further characterization of the histamine-releasing factors in ASST-positive patients, and we have found that serum histamine-releasing activity is retained by fractions with molecular weight >100 kDa.^[37] Furthermore, basophils from normal donors can be stimulated with sera from patients with chronic urticaria before and after the stripping of membrane IgE with lactic acid in order to differentiate patients with anti-FcεRI autoantibodies from those with anti-IgE autoantibodies. *In vitro* basophil histamine release assay is available in few centers, and therefore can not be performed as routine examination. In addition to ASST and basophil histamine release assay, routine hematologic examinations, thyroid function tests and antithyroid peroxidase and antithyroglobulin antibodies are recommended in all patients with chronic urticaria. Antinuclear antibodies and other serologic tests for systemic autoimmunity, complement profile, cryoglobulins, hepatitis B and C serologies and serum protein electrophoresis are indicated if the erythrocyte sedimentation rate is elevated. A skin biopsy may be required if systemic autoimmunity and cutaneous vasculitis are suspected. C4 and C1 inhibition should be determined if the patient reports angioedema.

3. Treatment

Treatment of chronic autoimmune and nonautoimmune urticaria does not differ substantially; a lack of response to conventional therapy and demonstration of an autoimmune mechanism represent an indication to provide more aggressive treatment and the use of immunosuppressive drugs. It must be noted, however, that studies comparing different immunomodulatory drugs in autoimmune and nonautoimmune chronic urticaria are still lacking.

3.1 Antihistamines

Histamine is the main mediator of urticaria and histamine H₁-receptor antagonists (antihistamines) represent the treatment of choice in all chronic urticaria patients.^[43] The non- or low-sedating antihistamines (second generation antihistamines), such as cetirizine, fexofenadine, loratadine, mizolastine and ebastine at the daily doses suggested (10mg for all except for fexofenadine, which is recommended at the dose of 180mg) will control pruritus and hives in most urticaria patients.^[44-49] Desloratadine, the biologically active metabolite of loratadine, and levocetirizine, the active enantiomer of cetirizine, both given at the daily dosage of 5mg, seem to be effective as well, with even less risk of sedation and interaction with other drugs than with other antihistamines.^[50-52] According to some authors, concentrations of H₁ antihistamines higher than those recommended may be necessary to achieve disease control.^[53] However, according to our personal experience and to published literature, chronic urticaria patients are unlikely to obtain added benefits from the use of H₁ antihistamines at higher doses, whereas they are certainly more exposed to the risk of sedation and other adverse effects.^[54] At least during the first period of treatment, the drugs should be taken regularly and not as needed to obtain maximum benefit. When patients complain of severe pruritus at night, older sedating antihistamines, such as hydroxyzine (25–50 mg/day) diphenhydramine (25mg twice a day) or the tricyclic antidepressant doxepin (25–50 mg/day) may be indicated to achieve control of urticarial symptoms.^[2,3,55] The drugs are usually administered in a single nocturnal dose.

H₂-receptor antagonists have been used in combination with antihistamines to treat patients with urticaria.^[56] The basis of this combined pharmacological treatment is provided by the representation of H₂-receptors in the skin, where they account for approximately 15% of total histamine receptors. Some controlled studies have shown that the addition of H₂-receptor antagonists to antihistamines may provide a statistically significant benefit.^[57,58] Ac-

cording to Simons et al.,^[59] co-administration of hydroxyzine with cimetidine resulted in significantly increased serum hydroxyzine concentrations and increased wheal and flare suppression, suggesting that a combined therapy with these drugs might be useful in some chronic urticaria patients who are unresponsive to an H₁ antihistamine alone. In contrast, cetirizine levels were not affected by cimetidine administration and no enhancement of wheal and flare suppression was found.^[59] In our experience there is no indication of a benefit with a combined therapy with hydroxyzine and cimetidine, in fact, this combination exposes the patient to a high risk of sedation. However, a combined H₁ and H₂ antagonist therapy may be administered if the patient complains of dyspepsia or gastric hyperacidity. Gastrosocopy and search for *H. pylori* are indicated in patients with persisting digestive symptoms, and appropriate therapy should be prescribed if necessary.

3.2 Corticosteroids

Oral corticosteroids are prescribed in a minority of patients with chronic urticaria with persisting clinical symptoms that are not controlled by antihistamines. The efficacy of corticosteroid therapy is high,^[3] but long-term therapy cannot be proposed because of known adverse effects, such as diabetes mellitus, hypertension, osteoporosis and gastrointestinal bleeding. Short courses of systemic corticosteroids (for example prednisone 25mg daily or methylprednisolone 16mg daily to be tapered and suspended within 7–14 days) can be prescribed if urticarial symptoms are severe and disturbing and if the patient needs a rapid and complete disease control for special circumstances. In some cases, oral corticosteroid therapy can be prolonged, but it has to be kept at the lowest effective dose (for example, prednisone 5mg daily or every other day).

3.3 New Therapeutic Options

3.3.1 Leukotriene Antagonists

Peptide-leukotrienes are potent inflammatory mediators derived from arachidonic acid through the 5-lipoxygenase pathway and produced by several cell types.^[60] Some lines of evidence indicate that peptide-leukotrienes are mediators of urticaria,^[29,30] providing the rationale for the clinical use of leukotriene receptor antagonists. Wedi et al.^[29] demonstrated that sera from chronic urticaria patients induced *de novo* generation of peptide-leukotrienes by basophils of normal donors, in addition to histamine release. Intradermal injection of peptide-leukotrienes (leukotriene

C4, D4 and E4) elicits a wheal and flare reaction either in chronic urticaria patients or in healthy patients.^[30] On a molar basis, peptide-leukotrienes are 100 times more potent than histamine in inducing wheal and flare reactions. *In vitro* experiments have shown that peptide-leukotrienes are generated and released by human mast cells following IgE-mediated stimulation and it is reasonable to suppose that they are released *in vivo* by human skin mast cells activated by anti-FcεRI or anti-IgE autoantibodies, which are present in many chronic urticaria patients.

Two leukotriene receptor antagonists – zafirlukast and montelukast – are now available in most countries for the treatment of asthma. In controlled studies, zafirlukast (20mg twice daily) and montelukast (10mg once daily) were shown to be superior to placebo in the treatment of patients with chronic urticaria symptoms.^[61-65] The efficacy of leukotriene receptor antagonists was also reported in single cases of delayed pressure or chronic autoreactive urticaria.^[66,67] A recent controlled study by Erbagci^[68] demonstrated the beneficial effect of montelukast when added to antihistamines in patients with refractory chronic urticaria. However, in another controlled study by Reimers et al.,^[69] zafirlukast did not provide any significant benefit when administered as monotherapy to patients with chronic urticaria. In our experience, leukotriene receptor antagonists can control urticaria symptoms in a variable proportion of chronic urticaria patients (20–50%) who are unresponsive to antihistamines alone; the proportion is possibly dependent upon the coexistence of intolerance to acetylsalicylic acid or additives.^[70] In some patients with chronic urticaria, leukotriene receptor antagonists have been able to prevent NSAID-induced exacerbations.^[71] Accordingly, Pacor et al.^[64] found that montelukast was effective in the treatment of patients with chronic urticaria who had positive challenge to acetylsalicylic acid and/or food additives. Clinical responses to leukotriene receptor antagonists are likely to depend on the mechanism of chronic urticaria, which may be different and involve peptide-leukotrienes only in some subgroups of patients. The 5-lipoxygenase inhibitor zileuton, which inhibits peptide-leukotriene generation, has also been employed with success in the treatment of chronic urticaria, but experience with this agent is limited and the drug is available in few countries.^[62]

3.3.2 Cyclosporine

Cyclosporine is an immunosuppressive and anti-inflammatory drug, which is currently employed to avoid graft rejection in transplanted patients and to treat some autoimmune diseases. Oral

cyclosporine was shown to be effective in patients with severe unremitting urticaria who had a poor response to conventional treatment with antihistamines.^[72] This observation was confirmed by some controlled studies.^[73,74] In a recent randomized, double-blind study by Grattan et al.,^[75] 8 out of 19 patients receiving cyclosporine (4 mg/kg/day), compared with none of the 10 patients receiving placebo, had a remission of urticarial symptoms, accompanied by a decrease of serum histamine-releasing activity. However, given the potentially serious adverse effects, the administration of cyclosporine should be limited to patients with severe unremitting urticaria, requiring prolonged high dose corticosteroid therapy.

3.3.3 High Dose Intravenous Immunoglobulin

High dose intravenous immunoglobulin (IVIG) has been employed to treat some immune-mediated diseases, such as vasculitis and connective-tissue disorders, corticosteroid-dependent bronchial asthma and myocarditis.^[76] IVIG exerts a complex immunomodulating effect, resulting in immunosuppression.^[77] O'Donnell et al.^[78] found some apparent benefits with IVIG in the treatment of chronic urticaria patients; however, the study was small and the effectiveness was not confirmed by others.^[79]

3.3.4 Plasmapheresis

Plasmapheresis has been used to treat some patients with autoantibody-positive severe chronic urticaria.^[80] This approach is effective, but can not be adopted for long-term management of patients with chronic urticaria.

3.3.5 Methotrexate

The efficacy of low-dose methotrexate in the control of urticarial symptoms has been reported in two patients with autoantibody-negative chronic urticaria refractory to conventional therapies.^[81] So far, the experience with methotrexate is limited and its clinical use can be proposed only in cases of severe, unremitting corticosteroid-dependent chronic urticaria.

3.3.6 Hydroxychloroquine, Sulfasalazine, and Dapsone

Some case reports have suggested that hydroxychloroquine, sulfasalazine, and dapsone, which have immunomodulatory properties, are effective in the treatment of chronic urticaria.^[82-85] In particular, a favorable response to hydroxychloroquine has been described in patients with hypocomplementemic urticarial-vasculitis syndrome.^[82] However, the experience is limited and routine use of these drugs in patients with chronic urticaria cannot be recommended.

3.3.7 Thyroxine

The efficacy of treatment with thyroxine (levothyroxine) has been described in some patients with chronic urticaria and thyroid autoimmunity,^[86,87] but not confirmed in others.^[88] Our opinion is that this treatment should be reserved to those patients with both hypothyroidism and chronic urticaria.

3.3.8 Warfarin

Berth-Jones et al.^[89] found a beneficial effect of warfarin therapy in some patients with chronic urticaria, but no improvement was observed in another study.^[90] Recently, a double-blind placebo-controlled study showed a response to warfarin in some patients with chronic urticaria and angioedema unresponsive to antihistamines.^[91] It is interesting to note that these patients were ASST-negative and had chronic urticaria associated with angioedema. The lack of response to antihistamines and the beneficial effect of warfarin suggest that their symptoms were not histamine-dependent, but related to coagulation-dependent mediators, perhaps kinins. Warfarin therapy can indeed be considered in a subgroup of patients with ASST-negative chronic urticaria and angioedema.

3.4 A Step-By-Step Guide to Practical Treatment

Figure 1 provides a step-by-step approach to the treatment of chronic urticaria. The first step in the treatment of chronic urticaria is represented by the low-sedating antihistamines, such as cetirizine and its active enantiomer levocetirizine, loratadine and its metabolite desloratadine, fexofenadine, mizolastine and ebastine. If symptoms are severe, associated with angioedema, and the patient is anxious and disturbed at night, old sedating antihistamines, such as hydroxyzine and diphenhydramine may be used instead of the new generation antihistamines.

When the disease is unrelenting and urticarial symptoms are incompletely controlled by antihistamines, a short course of corticosteroid therapy (for example prednisone 25 mg/day to be tapered and suspended in 1–2 weeks) can be administered. If urticaria relapses after corticosteroid suspension, leukotriene receptor antagonists, such as montelukast and zafirlukast, should be tried. In a variable proportion of the patients with partial response to antihistamines, sufficient control of the disease may be achieved with the addition of a leukotriene receptor antagonist.

In patients whose disease is not controlled by combination therapy with antihistamines and leukotriene receptor antagonists,

prolonged systemic corticosteroid therapy may be needed. Corticosteroids should be continued at the lowest dose sufficient enough to control urticarial symptoms (for example 5mg every other day), in order to minimize adverse effects. In a few cases, high-dose corticosteroid therapy has to be administered for long periods. In these patients, actually a small minority, immunosuppressive treatment with low-dose cyclosporine (3 mg/kg/day) can be started. This type of treatment has a corticosteroid-sparing effect and is also generally effective in patients with severe unremitting urticaria. However, cyclosporine plasma concentrations and possible adverse effects must be carefully monitored. Alternative treatments to cyclosporine are hydroxychloroquine, sulfasalazine or dapsone. The efficacy of these agents, however, has not been proven in large controlled studies. Plasmapheresis may also be effective in patients with severe chronic urticaria, but certainly represents an impractical approach and has a temporary effect. Warfarin therapy may be considered in a subgroup of patients with chronic urticaria and angioedema unresponsive to antihistamines.

4. Possible Future Studies

Much remains to be done in order to identify the best therapeutic approach in each patient with chronic urticaria. For example, studies comparing the effects of different immunomodulatory drugs in patients with either autoimmune or nonautoimmune chronic urticaria are still lacking and should be performed. Cyclosporine seems to be a very effective drug in the treatment of most chronic urticaria patients, but it is not known whether its efficacy varies according to positivity or negativity of ASST. Furthermore, the optimal dose and duration of treatment have to be identified. The place of other immunomodulatory drugs also remains to be defined. For example, it would be worth evaluating in a double-blind, placebo-controlled study whether leukotriene receptor antagonists provide an added benefit in chronic urticaria patients who are already receiving antihistamines. It should also be ascertained whether the patients who are likely to benefit from leukotriene receptor antagonists are those with chronic urticaria and intolerance to acetylsalicylic acid and food additives. Lastly, the experience with the oral anticoagulant warfarin should be expanded, particularly in those patients who have presumably nonautoimmune chronic urticaria associated with angioedema.

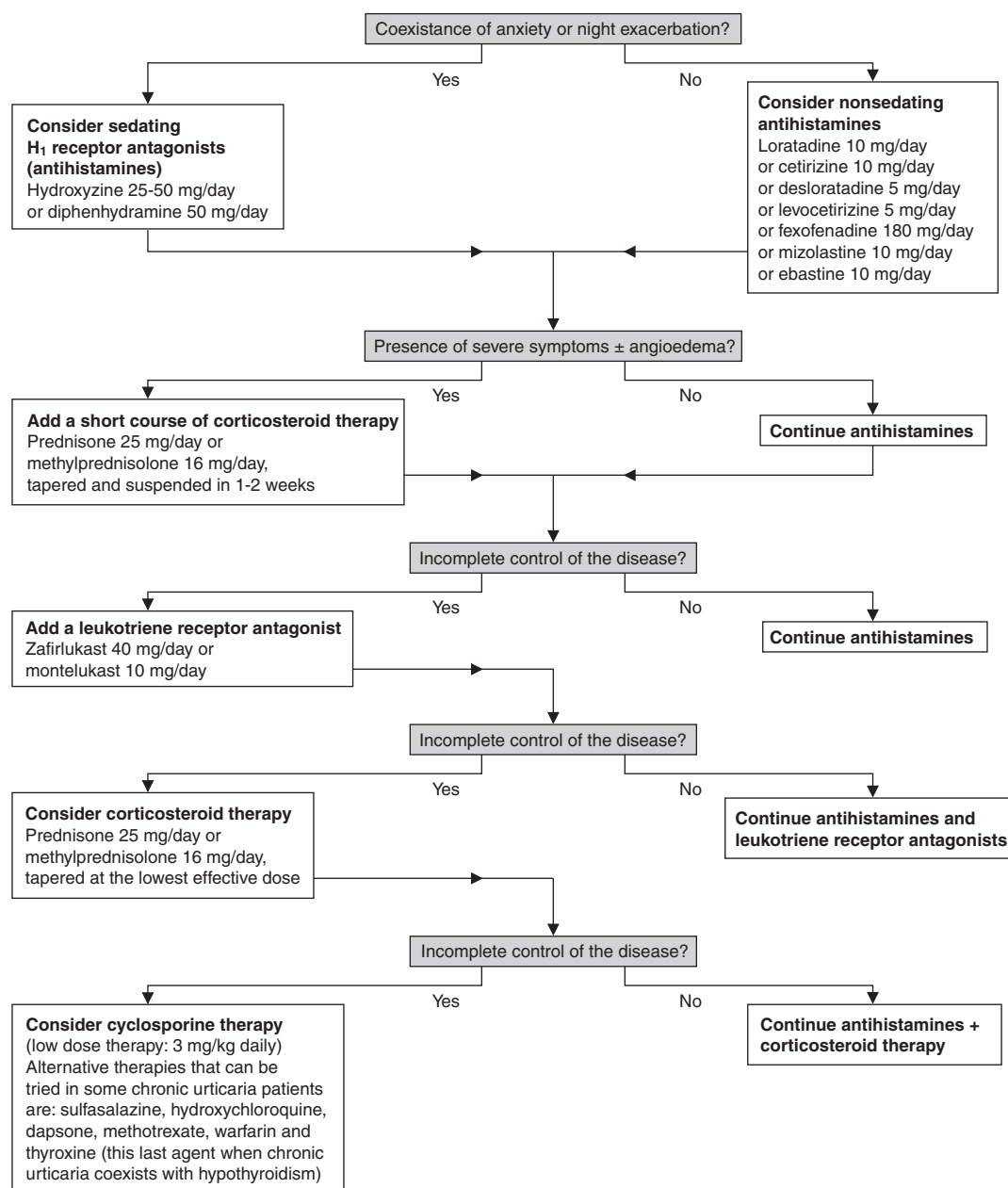


Fig. 1. Step-by-step treatment of chronic urticaria.

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References

- Greaves MW. Chronic urticaria. *N Engl J Med* 1995; 332: 1767-72
- Greaves M. Chronic urticaria. *J Allergy Clin Immunol* 2000; 105: 664-72
- Kaplan AP. Chronic urticaria and angioedema. *N Engl J Med* 2002; 346: 175-9
- May CD. Are confusion and controversy about food hypersensitivity really necessary? *J Allergy Clin Immunol* 1985; 75: 329-33
- Doeglas HMG. Reactions to aspirin and food additives in patients with chronic urticaria including the physical urticarias. *Br J Dermatol* 1975; 93: 135-44
- Kaplan AP. Urticaria and angioedema. In: Middleton Jr E, Reed CE, Ellis EF, et al., editors. *Allergy: principles & practice*. 5th ed., vol 2, St Louis: Mosby-Year book, 1998: 1104-22
- Zuberbier T, Chantraine-Hess S, et al. Pseudoallergen-free diet in the treatment of chronic urticaria: a prospective study. *Acta Derm Venereol* 1995; 75: 484-7
- Pigatto PD, Valsecchi RH. Chronic urticaria: a mystery. *Allergy* 2000; 55: 306-8
- Zuberbier T, Pfrommer C, Specht K, et al. Aromatic components of food as novel eliciting factors of pseudoallergic reactions in chronic urticaria. *J Allergy Clin Immunol* 2002; 109: 343-8
- Di Campli C, Gasbarrini A, Nucera E, et al. Beneficial effects of *Helicobacter pylori* eradication on idiopathic chronic urticaria. *Dig Dis Sci* 1998; 43: 1226-9

11. Sakurane M, Shiotani A, Furukawa F. Therapeutic effects of antibacterial treatment for intractable skin diseases in *Helicobacter pylori*-positive Japanese patients. *J Dermatol* 2002; 29: 23-7
12. Wedi B, Kapp A. *Helicobacter pylori* infection in skin diseases: a critical appraisal. *Am J Clin Dermatol* 2002; 3: 273-82
13. Schnyder B, Hebling A, Pichler WJ. Chronic idiopathic urticaria: natural course and association with *Helicobacter pylori* infection. *Int Arch Allergy Immunol* 1999; 119: 60-3
14. Habte-Gabr E, Tiruneh M, Hailu M. Chronic urticaria: its relationship to intestinal parasitic infestation and response to antihelmintic drugs: a preliminary study. *Ethiop Med J* 1977; 15: 9-14
15. Oteifa NM, Moustafa MA, Elgozamy BM. Toxocariasis as a possible cause of allergic diseases in children. *J Egypt Soc Parasitol* 1998; 28: 365-72
16. Grattan CE, Wallington TB, Warin RP, et al. A serological mediator in chronic idiopathic urticaria: a clinical, immunological and histological evaluation. *Br J Dermatol* 1986; 114: 583-90
17. Gruber BL, Baeza ML, Marchese MJ, et al. Prevalence and functional role of anti-IgE autoantibodies in urticarial syndromes. *J Invest Dermatol* 1988; 90: 213-7
18. Grattan CEH, Francis DM, Hide M, et al. Detection of circulating histamine releasing autoantibodies with functional properties of anti IgE in chronic urticaria. *Clin Exp Allergy* 1991; 21: 695-704
19. Hide M, Francis DM, Grattan CEH, et al. Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. *N Engl J Med* 1993; 328: 1599-604
20. Fiebiger E, Maurer D, Holub H, et al. J. Serum IgG autoantibodies directed against the alpha chain of FcεRI: a selective marker and pathogenetic factor for a distinct subset of chronic urticaria patients? *J Clin Invest* 1995; 96: 2606-12
21. Ferrer M, Kinet JP, Kaplan AP. Comparative studies of functional and binding assays for IgG anti-FcεRIα (α-subunit). *J Allergy Clin Immunol* 1998; 101: 672-6
22. Ferrer M, Nakazawa K, Kaplan AP. Complement dependence of histamine release in chronic urticaria. *J Allergy Clin Immunol* 1999; 104: 169-72
23. Kikuchi Y, Kaplan AP. A role for C5a in augmenting IgE-dependent histamine release from basophils in chronic urticaria. *J Allergy Clin Immunol* 2002; 109: 114-8
24. Zuberbier T, Henz BM, Fiebiger E, et al. Anti-FcεRIα serum autoantibodies in different subtypes of urticaria. *Allergy* 2000; 55: 951-4
25. Stadler BM, Miescher S, Horn M, et al. Allergic manifestations as the results of a conditional autoimmune response. *Int Arch Allergy Immunol* 2001; 124: 411-3
26. Horn MP, Pachlopnik JM, Vogel M, et al. Conditional autoimmunity mediated by human natural anti-FcεRI alpha autoantibodies? *FASEB J* 2001; 15: 2268-74
27. Elias J, Boss E, Kaplan AP. Studies of the cellular infiltrate of chronic idiopathic urticaria: prominence of T-lymphocytes, monocytes, and mast cells. *J Allergy Clin Immunol* 1986; 78: 914-8
28. Sabroe RA, Poon E, Orchard GE, et al. Cutaneous inflammatory cell infiltrate in chronic idiopathic urticaria: comparison of patients with and without anti-FcεRIα or anti-IgE autoantibodies. *J Allergy Clin Immunol* 1999; 103: 484-93
29. Wedi B, Novacevic V, Koerner M, et al. Chronic urticaria serum induces histamine release, leukotriene production, and basophil CD63 surface expression: inhibitory effects of anti-inflammatory drugs. *J Allergy Clin Immunol* 2000; 105: 552-60
30. Maxwell DL, Atkinson BA, Spur BW, et al. Skin responses to intradermal histamine and leukotrienes C4, D4, and E4 in patients with chronic idiopathic urticaria and in normal subjects. *J Allergy Clin Immunol* 1990; 86: 759-65
31. Cunningham F. Lipid mediators in inflammatory skin disorders. *J Lipid Mediat* 1990; 2: 61-74
32. Norris JG, Sullivan TJ. Leukotriene and cytokines in steroid dependent chronic urticaria [abstract]. *J Allergy Clin Immunol* 1998; 101 (pt 2): S128
33. Irani C, Gordon ND, Zweiman B, et al. Chronic urticaria/angioedema and Graves' disease: coexistence of 2 antireceptor antibody-mediated diseases. *J Allergy Clin Immunol* 2001; 108: 874
34. Leznoff A, Sussman GL. Syndrome of idiopathic chronic urticaria and angioedema with thyroid autoimmunity: a study of 90 patients. *J Allergy Clin Immunol* 1989; 84: 66-71
35. Bar-Sela S, Reshef T, Mekori Y. IgE antithyroid microsomal antibodies in a patient with chronic urticaria. *J Allergy Clin Immunol* 1999; 103: 1216-7
36. Tedeschi A, Lorini M, Asero R. Anti-thyroid peroxidase IgE in patients with chronic urticaria. *J Allergy Clin Immunol* 2001; 108: 467-8
37. Asero R, Tedeschi A, Lorini M, et al. Chronic urticaria: clinical and serological aspects. *Clin Exp Allergy* 2001; 31: 1105-10
38. Greaves MW, O'Donnell BF. Not all chronic urticaria is "idiopathic". *Exp Dermatol* 1998; 7: 11-3
39. Fagiolo U, Krick F, Ruf C, et al. Effects of complement inactivation and IgG depletion on skin reactivity to autologous serum in chronic idiopathic urticaria. *J Allergy Clin Immunol* 2000; 106: 567-72
40. Kermani F, Niimi N, Francis DM, et al. Characterization of a novel mast-cell specific histamine releasing activity in chronic idiopathic urticaria (CIU) [abstract]. *J Invest Dermatol* 1995; 105: 452
41. Claveau J, Lavoie A, Brunet C, et al. Chronic idiopathic urticaria: possible contribution of histamine releasing factor to the pathogenesis. *J Allergy Clin Immunol* 1993; 92: 132-7
42. Sabroe RA, Grattan CE, Francis DM, et al. The autologous serum skin test: a screening test for autoantibodies in chronic idiopathic urticaria. *Br J Dermatol* 1999; 140: 446-52
43. Ring J, Brockow K, Ollert M, et al. Antihistamines in urticaria. *Clin Exp Allergy* 1999; 29 Suppl. 1: 31-7
44. Kalivas J, Breneman D, Sharp D, et al. Urticaria: clinical efficacy of cetirizine in comparison with hydroxyzine and placebo. *J Allergy Clin Immunol* 1990; 86: 1014-8
45. Breneman DL. Cetirizine versus hydroxyzine and placebo in chronic idiopathic urticaria. *Ann Pharmacother* 1996; 30: 1075-9
46. Finn Jr AF, Kaplan AP, Fretwell R, et al. A double-blind, placebo-controlled trial of fexofenadine HCl in the treatment of chronic idiopathic urticaria. *J Allergy Clin Immunol* 1999; 103: 1071-8
47. Monroe EW. Loratadine in the treatment of urticaria. *Clin Ther* 1997; 19: 232-42
48. Lorette G, Giannetti A, Pereira RS, et al. One-year treatment of chronic urticaria with mizolastine: efficacy and safety. URTOL study group. *J Eur Acad Dermatol Venerol* 2000; 14: 83-90
49. Kalis B. Double-blind multicentre comparative study of ebastine, terfenadine and placebo in the treatment of chronic idiopathic urticaria in adults. *Drugs* 1996; 52 Suppl. 1: 30-4
50. Ring J, Hein R, Gauger A. Desloratadine in the treatment of chronic idiopathic urticaria. *Allergy* 2001; 56 Suppl. 65: 28-32
51. Clough GF, Boutsouki P, Church MK. Comparison of the effects of levocetirizine and loratadine on histamine-induced wheal, flare and itch in human skin. *Allergy* 2001; 56: 985-8
52. Gandon JM, Allain H. Lack of effect of single and repeated doses of levocetirizine, a new antihistamine drug, on cognitive and psychomotor functions in healthy volunteers. *Br J Clin Pharmacol* 2002; 54: 51-8
53. Zuberbier T, Greaves MW, Juhlin L, et al. Management of urticaria: a consensus report. *J Invest Dermatol Symp Proc* 2001; 6: 128-31
54. Chowdhury BA. Chronic urticaria and angioedema. *N Engl J Med* 2002; 347: 220-1
55. Goldsobel AB, Rohr AS, Siegel SC, et al. Efficacy of doxepin in the treatment of chronic idiopathic urticaria. *J Allergy Clin Immunol* 1986; 78: 867-73
56. Harvey RP, Wegs J, Schocket AL. A controlled trial of therapy in chronic urticaria. *J Allergy Clin Immunol* 1981; 68: 262-6
57. Commens CA, Greaves MW. Cimetidine in chronic idiopathic urticaria: a randomised double-blind study. *Br J Dermatol* 1978; 99: 675-6
58. Bleehe SS, Thomas SE, Greaves MW, et al. Cimetidine and chlorpheniramine in the treatment of chronic idiopathic urticaria: a multi-centre randomized double-blind study. *Br J Dermatol* 1987; 117: 81-8

59. Simons FE, Sussman GL, Simons KJ. Effect of the H2-antagonist cimetidine on the pharmacokinetics and pharmacodynamics of the H1-antagonists hydroxyzine and cetirizine in patients with chronic urticaria. *J Allergy Clin Immunol* 1995; 95: 685-93
60. Lewis RA, Austen KF, Soberman RJ. Leukotrienes and other products of the 5-lipoxygenase pathway. *N Engl J Med* 1990; 323: 645
61. Spector S, Tan RA. Antileukotrienes in chronic urticaria [letter]. *J Allergy Clin Immunol* 1998; 101: 572
62. Ellis MH. Successful treatment of chronic urticaria with leukotriene antagonists. *J Allergy Clin Immunol* 1998; 102: 876-7
63. Chu TJ, Warren MS. Zafirlukast (ACCOLATE®) in the treatment of chronic idiopathic urticaria: a case series [abstract]. *J Allergy Clin Immunol* 1998; 101 (part 2): S155
64. Pacor ML, Di Lorenzo G, Corrocher R. Efficacy of leukotriene receptor antagonist in chronic urticaria: a double-blind, placebo-controlled comparison of treatment with montelukast and cetirizine in patients with chronic urticaria with intolerance to food additive and/or acetylsalicylic acid. *Clin Exp Allergy* 2001; 31: 1607-14
65. Bensch G, Borish L. Leukotriene modifiers in chronic urticaria. *Ann Allergy Asthma Immunol* 1999; 83: 348
66. Berkun Y, Shalit M. Successful treatment of delayed pressure urticaria with montelukast. *Allergy* 2000; 55 (2): 203-4
67. Tedeschi A, Lorini M, Suli C, et al. Successful treatment of chronic urticaria. *Allergy* 2000; 55: 1097-8
68. Erbagci Z. The leukotriene receptor antagonist montelukast in the treatment of chronic idiopathic urticaria: a single-blind, placebo-controlled, crossover clinical study. *J Allergy Clin Immunol* 2002; 110 (3): 484-8
69. Reimers A, Pichler C, Helbling A, et al. Zafirlukast has no beneficial effects in the treatment of chronic urticaria. *Clin Exp Allergy* 2002; 32 (12): 1763-8
70. Asero R, Tedeschi A, Lorini M. Leukotriene receptors antagonists in chronic urticaria. *Allergy* 2001; 56: 456-7
71. Asero R. Leukotriene receptor antagonists may prevent NSAID-induced exacerbations in patients with chronic urticaria. *Ann Allergy Asthma Immunol* 2000; 85: 156-7
72. Fradin MS, Ellis CN, Goldfarb MT, et al. Oral cyclosporine for severe chronic idiopathic urticaria and angioedema. *J Am Acad Dermatol* 1991; 25: 1065-7
73. Toubi E, Blant A, Kessel A, et al. Low-dose cyclosporin A in the treatment of severe chronic idiopathic urticaria. *Allergy* 1997; 52: 312-6
74. Barlow RJ, Kobza Black A, et al. Treatment of severe, chronic urticaria with cyclosporin A. *Eur J Dermatol* 1993; 3: 273-5
75. Grattan CEH, O'Donnell BF, Francis DM, et al. Randomized double-blind study of cyclosporin in chronic "idiopathic" urticaria. *Br J Dermatol* 2000; 143: 365-72
76. Kazatchkine MD, Kaveri SV. Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin. *N Engl J Med* 2001; 345: 747-55
77. Mouthon L, Kaveri SV, Spalter SH, et al. Mechanisms of action of intravenous immune globulin in immune-mediated diseases. *Clin Exp Immunol* 1996; 104 Suppl. 1: 3-9
78. O'Donnell BF, Barr RM, Black AK, et al. Intravenous immunoglobulin in chronic autoimmune urticaria. *Br J Dermatol* 1998; 138: 101-6
79. Asero R. Are IVIG for chronic unremitting urticaria effective? *Allergy* 2000; 55: 1099-101
80. Grattan CEH, Francis DM, Slater NGP, et al. Plasmapheresis for severe unremitting chronic urticaria. *Lancet* 1992; 339: 1078-80
81. Gach JE, Sabroe RA, Greaves MW, et al. Methotrexate-responsive chronic idiopathic urticaria: a report of two cases. *Br J Dermatol* 2001; 145: 340-3
82. Lopez LR, Davis KC, Kohler PF, et al. The hypocomplementemic urticarial-vasculitis syndrome: therapeutic response to hydroxychloroquine-. *J Allergy Clin Immunol* 1984; 73: 600-3
83. Jaffer AM. Sulfasalazine in the treatment of corticosteroid-dependent chronic idiopathic urticaria. *J Allergy Clin Immunol* 1991; 88: 964-5
84. Hartmann K, Hani N, Hinrichs R, et al. Successful sulfasalazine treatment of severe chronic idiopathic urticaria associated with pressure urticaria [letter]. *Acta Derm Venereol* 2001; 81: 71
85. Boehm I, Bauer R, Bieber T. Urticaria treated with dapsone. *Allergy* 1999; 54: 765-6
86. Rumbly JS, Katz JL, Schocket AL. Resolution of chronic urticaria in patients with thyroid autoimmunity. *J Allergy Clin Immunol* 1995; 96: 901-5
87. Heymann WR. Chronic urticaria and angioedema associated with thyroid autoimmunity: review and therapeutic implications. *J Am Acad Dermatol* 1999; 40: 229-32
88. Kandeel AA, Zeid M, Helm T, et al. Evaluation of chronic urticaria in patients with Hashimoto thyroiditis. *J Clin Immunol* 2001; 21: 335-47
89. Berth-Jones J, Hutchinson PE, Wicks ACB, et al. Chronic urticaria with angioedema controlled by warfarin. *BMJ* 1988; 297: 1382-3
90. Barlow RJ, Greaves MW. Warfarin in the treatment of chronic urticaria/angioedema. *Br J Dermatol* 1992; 126: 415-6
91. Parslew R, Pryce D, Ashworth J, et al. Warfarin treatment of chronic idiopathic urticaria and angio-oedema. *Clin Exp Allergy* 2000; 30: 1161-5

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