AAITO POSITION PAPER.
CHRONIC URTICARIA: DIAGNOSTIC WORKUP AND TREATMENT

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INTRODUCTION

Definition of chronic urticaria

A traditional and generally accepted definition of chronic urticaria (CU) is the presence of hives (with or without angioedema) for at least 6 weeks (1). Such definition includes chronic autoimmune urticaria, chronic idiopathic urticaria, and physically induced urticarias such as dermographism, solar urticaria and cholinergic urticaria.

Epidemiology

Studies aiming to assess the exact prevalence of CU in the general population are still missing. It has been estimated that this disease affects about 0.1% of the general population (2) but the real prevalence possibly exceeds this figure (3). CU occurs predominantly in adults; women are more commonly affected than men (4, 5), and the disease frequently shows a familiar pattern (6).

Clinical features

Urticaria is characterized by wheals, which manifest as pink to red swellings. Wheals are frequently paler than the surrounding skin due to the compressing effect of dermal edema (2). Individual wheals come and go rapidly, usually within 24 hours (3). When typical wheals disappear no alterations are left in the skin. Wheals may be a few millimeter in diameter or as large as a hand, and be single or very numerous. They may occur anywhere on the skin (including the scalp, palms and soles) but are rarely present on mucous membranes, where angioedema is frequent. Pruritus is almost invariably present, and is frequently more severe in the evening or nighttime (7). Angioedema is present in at least 50% of patients with CU (8). Angioedema is characterized by a swelling without erythema, and is not associated with pruritus. CU frequently follows a remitting and relapsing course. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAID) that inhibit cycloxygenase-1 (COX-1) exacerbate CU in about 30% of cases (9). In some women CU is more severe immediately before and during menses.
CU is frequently associated with autoimmune thyroid diseases; these may precede or follow by years the onset of CU. Urticarial lesions may be part of a number of dermatologic disorders. The most common include urticarial dermatitis, maculo-papular drug eruptions, insect bite reactions, and the pre-pemphigoid rash. Moreover, urticaria and urticaria-like lesions can be seen in several systemic disorders, including genetic diseases, and immune and hematological disorders. Therefore the first question to ask is whether the patient has urticaria or another disease characterized by urticaria-like lesions. A careful and detailed interview is generally sufficient to suggest associated disorders. Thereafter a practical approach to CU requires that at least the 3 main subtypes, physical urticaria, urticarial vasculitis and chronic urticaria be considered.

Diagnostic workup

Based on the available evidence, the diagnostic workup to patients with CU should be rather standardized.

What to do:

© Exacerbations induced by aspirin or other NSAIDs and/or frequent/chronic use of these drugs should be carefully and repeatedly ascertained by interview.

© The presence of individual wheals lasting longer than 24 hours along with ecchimotic lesions, purpura and hyper pigmentation as well as systemic symptoms including fever, fatigue, arthralgia, and

abdominal pain should be excluded. These symptoms are suggestive of urticarial vasculitis and require a biopsy of a skin lesion to ascertain the presence of leukocytoclastic vascultis. In order to increase the likelihood of a correct diagnosis of vasculitis the lesion chosen for histological examination should not be too young or too old.

© Urticaria may occur as result of an IgE-mediated reaction induced by food, hymenoptera, latex and drug allergens. In these cases, urticaria occurs soon after exposure to the offending antigen and *is acute or relapsing rather than chronic*. If involvement of food, hymenoptera, latex or drug allergens is suspected, skin prick tests or determination of specific IgE should be carried out.

© Specific diagnostic tests to exclude physical urticarias should be performed where needed:

- Exercise or hot shower for cholinergic urticaria (10);
- Ice cube test (10 min application; reading after further 10 min) for cold urticaria (11);
- Light stroking of skin for symptomatic dermatographism (12);
- Exposure of the skin to selected electromagnetic wavelengths (visible light, UVA, UVB, narrow band UVB) for solar urticaria
- Contact with water of any temperature for aquagenic urticaria
- Application of a pressure perpendicular to the skin (reading after 1-4 h) for delayed pressure urticaria (13);

© A limited number of laboratory investigations should be performed in order to rule out conditions such as hereditary or acquired C1 inhibitor deficiency, urticarial vasculitis, rare urticarial syndromes such as Schnitzler syndrome, and systemic autoimmune disorders associated with urticaria, and to exclude an association with autoimmune thyroid disorders. We suggest the following panel:

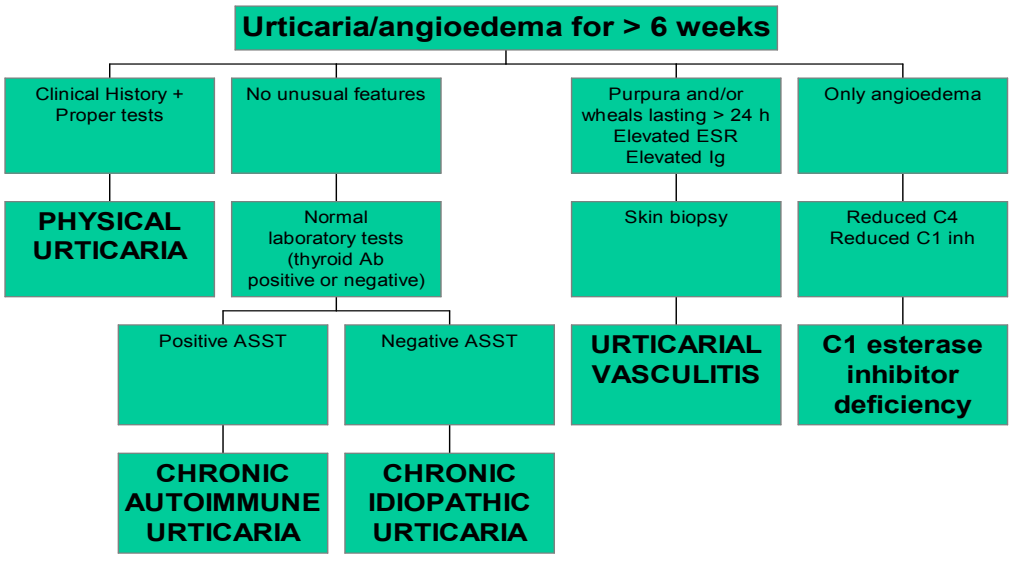
- erythrocyte sedimentation rate ;
- complete blood count and differential ;
- electrophoresis of serum proteins ;
- C3 and C4 complement fractions ;
- antinuclear antibodies ;
- thyrotropin ;
- autoantibodies to thyroglobulin and thyroid peroxydase.

No further test is necessary if the panel is negative; clearly, further investigations are needed if one or more tests in the panel are not normal (see figure 1).

© Autologous serum skin test (ASST). Its technique has been reported in detail elsewhere (2). A positive test is strongly suggestive of an autoimmune origin for CU (14); recent studies showed that chronic autoimmune urticaria is generally more severe than chronic idiopathic urticaria (15-17).

© Autologous plasma skin test. Recent studies showed that in patients with CU intradermal testing with autologous plasma anticoagulated with Na citrate (APST) scores much more frequently positive than ASST, suggesting the presence of plasma factors involved in whealing. In effect, CU patients show signs of thrombin generation, as suggested by the increased plasma levels of the prothrombin fragment F_{1+2} (18); recent studies showed that this is the result of the activation of the tissue factor pathway of coagulation cascade (19). Notably, thrombin is a serine protease that has been shown to activate mast cells in animal models. Severe exacerbations of CU are associated with a strong activation of coagulation cascade that may lead to fibrin formation and fibrinolysis, as show by elevated D-dimer plasma levels (20).

Figure 1: Diagnostic workup in patients with chronic urticaria.



Controversial investigations

There is a large number of studies dealing with possible causes of CU, including psychological reactions, food allergies and intolerances, and infections, but probably none of these are really involved in CU (21).

Psychological factors: CU has been shown to affect everyday life, limiting and impairing physical and emotional functioning, and provoking a heavy impact on the quality of life (22). Some psychological investigations have shown a higher prevalence of alexithymia and of depressant features in chronic urticaria patients than in normal controls (23). Whether psychological disorders precede or follow the onset of the skin disease is still unknown; as a consequence, further studies are needed before the psychological approach can be recommended in the current routine evaluation of chronic urticaria patients.

Parasites: Stool examination for ova and parasites is unnecessary in the absence of eosinophilia. Although some cases of CU occurring in association with *Anisakis, Echinococcus granulosus* and *Blastocytis hominis* infections have been reported (24-26), the association of parasitoses and CU is rather weak. In the absence of eosinophilia and/or a clinical story suggesting a high risk of parasitic infections, there is no need to perform stool examination and serological tests for parasites. However, it has to be considered that *Giardia lamblia* infection does not provoke eosinophilia, although this parasite has not been unequivocally associated with CU yet.

Food allergy: Although there is presently no evidence that IgE-mediated food allergy may present as CU, most patients with CU presenting at allergy centers are strongly convinced they have some kind of food allergy. A negative skin prick test with a standard panel of well-chosen commercial food extracts will help the physicians to demonstrate their patients that the disease is not caused by a food allergy.

Food additives: Restriction diets are not warranted unless a clear-cut relationship between the ingestion of certain preserved foods and a flare of hives is reported. In these (few) cases double blind, placebo-controlled oral challenges with food additives will be needed to confirm food additives intolerance. In a large study only 0.63% of 1100 patients with CU were found to have an exacerbation of their disease following the ingestion of some specific food additive, but none of them reacted again on re-challenge (27).

Histamine-free diets and salycilates-free diets: As previously pointed out, restriction diets are not warranted as no clear evidence exists that CU can be exacerbated by histamine or salyciclates contained in foods (28).

Helicobacter pylori infection: Recently some studies claimed a role of Helicobacter pylori in chronic urticaria (29, 30), but other studies did not confirm a cause-effect relationship and suggested that such association occurs by chance (31-33). A truly causative effect of Helicobacter pylori infection in chronic urticaria has not been observed yet (2).

Step-by-step approach to the treatment of chronic urticaria

Some general measures can be suggested to all CU patients; for instance, it is advisable to avoid overheating and alcohol consumption since they can exacerbate urticaria symptoms. Other measures should be adopted in specific cases. Patients reporting exacerbations following the ingestion of acetylsalicylic acid should not take NSAID, with the exception of those exerting little or no inhibitory effect on COX-1 (e.g., paracetamol, nimesulide, etoricoxib) which are in most cases better tolerated by these patients. Patients with angioedema should avoid angiotensin-converting enzyme inhibitors. Exclusion diets are recommended only when hypersensitivity to food allergens or intolerance food additives has been clearly demonstrated.

Drug therapy of CU relies mainly on H1 antihistamines, systemic steroids and immunomodulating drugs. A step-by-step approach can be conveniently followed in all cases, although it is now clear that chronic autoimmune urticaria tends to be more severe and to relapse more frequently than chronic idiopathic urticaria (15,16). Therefore, a more aggressive approach might be justified in patients with chronic autoimmune urticaria.

The first step in the management of CU is represented by the new low-sedating H1 receptor antagonists, such as cetirizine, loratadine, fexofenadine, mizolastine and ebastine. These drugs at the daily doses suggested (10 mg in all cases except 180 mg for fexofenadine), will control pruritus and hives in most urticaria patients (34-38). Levocetirizine, the active enantiomer of cetirizine, and desloratadine, the biologically active metabolite of loratadine, both given at the daily dosage of 5 mg, seem effective as well, with even less risk of sedation and interaction with other drugs than older compounds (39,40). At least during the first period of treatment, the drugs should be taken regularly and not on demand in order to maximize benefit. If symptoms are severe, associated with angioedema, and the patient is anxious and disturbed at night, old sedating H1 antihistamines, such as hydroxizine (25 to 50 mg/day) and diphenydramine (25 mg twice a day) may be used instead of the new generation

H1 antihistamines. The drugs are usually administered in a single nocturnal dose to minimize daily sedation.

Some authors suggest to give doses higher than those recommended or to add a second H1 antihistamine or an H2 antihistamine in patients reporting little effect from H1 antihistamine treatment (41). However, as there is presently no clear evidence that such approaches represent an advantage over the use of a single antihistamine at licensed doses but are likely to increase the risk of side effects without providing significant clinical benefits they cannot be presently recommended; in effect, in a recent study most patients with severe CU did not show any benefit taking daily doses of cetirizine of 30 mg (i.e., 3 times higher than the recommended doses) (42). combined treatments with a H1 and a H2 antihistamine or with two H1 antihistamines do not seem to provide any clear advantage over H1 antihistamine monotherapy (43, 44).

The second step in the pharmacological treatment of chronic urticaria is represented by systemic steroids (45). Short courses of oral steroids (for example prednisone 0.3-0-5 mg/kg daily or methylprednisolone 16 mg daily to be tapered and stopped within 3-4 weeks) can be prescribed if urticaria symptoms are severe and disturbing and if the patient needs a rapid relief and complete disease control for special circumstances. Steroid therapy is highly effective, but long-term administration cannot be proposed because of the well-known side-effects, such as hypertension, diabetes and osteoporosis. In some cases, oral steroid therapy can be prolonged, but it has to be kept at the lowest effective dose (for example, prednisone 5 mg daily or every other day).

If urticaria relapses after a short course of steroid therapy, and symptoms are not adequately controlled by H1 antihistamines, leukotriene-receptor antagonists could be tried. In a variable proportion of CU patients montelukast and zafirlukast at the usual daily doses of 10 mg and 20 mg b.i.d., respectively, can achieve urticaria control when added to H1 antihistamine therapy (46-51). Patients who are likely to benefit from leukotriene receptor antagonists are those positive on ASST and experiencing urticaria exacerbations following the ingestion of NSAID (52, 53).

The third step in chronic urticaria treatment are immunosuppressive agents, namely ciclosporin. When H1 antihistamines, steroids and leukotriene antagonists fail to achieve urticaria control or when the minimum dose of oral steroid required exposes the patient to unacceptable side effects, immunosuppressive therapy with ciclosporin can be started. This drug is effective in patients with severe unremitting urticaria and a poor response to conventional treatment (54-56). In a recent study 8/19 patients receiving ciclosporin had a remission of urticaria accompanied by a decrease of serum histamine-releasing activity (57). Treatment with ciclosporin at the daily dose of 3-4 mg Kg^{-1} should last for 3-6 months, performing blood pressure and renal function controls at regular intervals. According to literature data and to our personal experience, urticaria remission can be achieved in 50-80% of patients receiving ciclosporin for 3-6 months. Given the potentially serious side effects, it is generally agreed that ciclosporin should be given to patients with severe unremitting urticaria, requiring prolonged high dose steroid therapy.

Immunomodulators drugs other than ciclosporin have been tried as well, but the experience is limited and these drugs can be recommended only in cases of severe refractory urticaria. In a recent open study low-dose tacrolimus achieved a clinical response in 12/17 (70.5%) patients with severe CU (58). Preliminary data are indeed promising, but further studies are needed to clearly establish the place of tacrolimus in the therapy of CU. Low-dose methotrexate has been favorably employed in two patients with autoantibody-negative, refractory CU (59). Successful treatment with oral or intravenous-pulse cyclophosphamide has also been reported in single patients with refractory urticaria (60,61). Plasmapheresis has been used to treat some autoantibody-positive patients with severe unremitting chronic urticaria (62). This approach is effective, but unpractical and can not be proposed for long-term management of chronic urticaria patients. High dose intravenous immunoglobulin (IVIG) has been employed to treat some immune-mediated diseases. An attempt to treat chronic urticaria patients with IVIG was done by O'Donnell *et al.* (63) with apparent benefit, but the study was small and the effectiveness was not confirmed by others (64). Hydroxychloroquine has been used to treat hypocomplementemic urticarial-vasculitis syndrome (65) and, more recently, has been administered in combination with H1 antihistamines in patients with chronic autoimmune urticaria (66). Although the results of this study have shown a favorable effect, hydroxychloroquine cannot be recommended routinely in patients with CU, either autoimmune or idiopathic, and its primary indication remains hypocomplementemic urticarial-vasculitis syndrome, in combination with systemic steroids. Some small studies have suggested the efficacy of sulfasalazine and dapsone, which have immunomodulatory properties, in the treatment of CU (67-69). However, the experience is limited and the routine use of these drugs can not be recommended. Levothyroxine administration had reportedly a favorable effect in some patients with chronic urticaria and associated autoimmune thyroiditis (70). However, efficacy

was not confirmed by other studies (71). Our opinion is that this treatment should be reserved to those patients with both hypothyroidism and CU.
Finally, in view of the recent findings of the involvement of the coagulation factors in patients with CU (18-20) it is possible that drugs active on the coagulation system will increase their relevance in the treatment of this disorder in the next future. To date treatment of chronic urticaria with warfarin and tranexamic acid has been tried by some authors with variable results (72-74); in addition, a case of CU responding to heparin sodium administration has been recently described (75). A small but controlled study by Parslew et al. (72) showed a response to warfarin in some patients with CU and angioedema unresponsive to H1 antihistamines. Interestingly, these patients were negative on ASST and had therefore chronic idiopathic (not autoimmune) urticaria. We suggest that warfarin, heparin or tranexamic acid may be tried in patients with refractory CU associated with angioedema who are negative on ASST.

THE GENERAL PRACTITIONER BOX

1/Chronic urticaria lasts more than 6 weeks
2/It is not caused by food allergy or intolerance.
3/Most patients respond well to anti-histamine treatment.
4/Address patients to the allergologist to carry out intradermal testing with autologous serum and plasma, and in case of ongoing disease or poor response to antihistamines.

Questions to be asked:

© How long have you been suffering from hives and how long do hives last?
© Is urticaria triggered by light skin stroking, exercise, hot shower, water contact, cold or sun exposure and application of a pressure to the skin?
© Are urticarial symptoms related to drug or food intake?
© Is urticaria exacerbated by intake of aspirin or other nonsteroidal anti-inflammatory drugs?
© Is urticaria associated with other symptoms, such as arthralgias, abdominal pains and fever?

What to do:

© General physical examination, careful observation of urticarial weals and differential diagnosis with other dermatological disorders such as purpura, urticarial-vasculitis and urticaria pigmentosa.
© A limited number of laboratory investigations should be performed including erythrocyte sedimentation rate, complete blood count and differential, electrophoresis of serum proteins, measurement of C3 and C4 complement fractions, detection of antinuclear antibodies, measurement of thyrotropin and detection of autoantibodies to thyroglobulin and thyroid peroxydase.

What to prescribe: Most CU patients respond to the last generation anti-H1 antagonists. If the patient is anxious and disturbed at night, older sedating anti-H1 antagonists may be preferred. In case of symptom persistence and for further investigations, address the patient to the allergologist

THE THERAPY BOX: A PRACTICAL APPROACH TO THE PHARMACOTHERAPY OF CHRONIC URTICARIA

Fist line

© *New low-sedating H1 antihistamines:* Levocetirizine, desloratadine, ebastine, cetirizine, fexofenadine, loratadine, mizolastine.
If the patient is anxious and disturbed at night, prefer old sedating H1 antihistamines: Hydroxizine, diphenydramine.

Second line

© *Steroid therapy:* Prednisone, methylprednisolone.
© *If the patient reports NSAID hypersensitivity, try leukotriene receptor antagonists:* Montelukast, zafirlukast

Third line

© *Immunosuppressive therapy:* Ciclosporin.
Other therapies that have been used in patients with chronic urticaria unresponsive to H1 antihistamines and steroids are: tacrolimus, cyclophosphamide, methotrexate, hydroxycloroquine,

dapsone, sulphasalazine, plasmapheresis, warfarin and tranexamic acid. Experience with these therapies is anedoctal or limited and therefore they cannot be recommended for routine use.
In patients with hypothyroidism and chronic urticaria, treatment with levothyroxine is indicated.

References

1. Kaplan A.-P. - Urticaria and angioedema. In: Adkinson NF, Yunginger JW, Busse WW, Bochner BS, Holgate ST, Simons FER, editors. Allergy: principles and practice. Philadelphia: *Mosby* 2003;1537-58.
2. Greaves M.-W. - Chronic urticaria. *J Allergy Clin Immunol* 2000;105:664-72.
3. Greaves M.-W. - Chronic urticaria. N Engl J Med 1995;332:1767-72.
4. Monroe E.-W., Jones H.-E. - Urticaria: an updated review: *Arch Dermatol* 1977;113:80-90.
5. Sibbald R.-G., Cheema A.-S., Lozinski A., Tarlo S. - Chronic urticaria: evaluation of the role of physical, immunologic, and other contributory factors. *Int J Dermatol* 1991;30:381-386.
6. Asero R. - Chronic idiopathic urticaria: a family study. *Ann Allergy Asthma Immunol* 2002;89:195-6.
7. Sabroe R.-A., Seed P.-T., Francis D.-M., Barr R.-M., Black A.-K., Greaves M.-W. - Chronic idiopathic urticaria: comparison of the clinical features of patients with and without FceRI or anti-IgE autoantibodies. *J Am Acad Dermatol* 1999;40:443-50.
8. Champion R.-H., Roberts SOB., Carpenter R.-G., Roger J.-H. - Urticaria and angioedema- a review of 554 patients. *Br J Dermatol* 1969;81:588-97.
9. Warin R.-P. - The effect of aspirin in chronic urticaria. *Br J Dermatol* 1960;72:350-1.
10. Commens C.-A., Greaves M.-W. - Tests to establish the diagnosis in cholinergic urticaria. *Br J Dermatol* 1978;98:47-51.
11.Kaplan A.-P., Beaven M.-A. - *In vivo* studies of the pathogenesis of cold urticaria, cholinergic urticaria, and vibration-induced swelling. *J Invest Dermatol* 1976;67:327-32.
12. Breathnach S.-M., Allen R., Ward A.-M., Greaves M.-W. - Symptomatic dermographism: natural history, clinical features, laboratory investigations and response to therapy. *Clin Exp Dermatol* 1983;8:463-76.
13. Barlow J., Warburton F., Watson K., Black A.-K., Greaves M.-W. - Diagnosis and incidence of delayed pressure urticaria in patients of chronic urticaria. *J Am Acad Dermatol* 1993;29:954-8.
14. Sabroe R.-A., Grattan C.-E., Francio D.-M., Barr R.-M., Kobza Black A., Greaves M.-W. - The autologous serum skin test: a screening test for autoantibodies in chronic idiopathic urticaria. *Br J Dermatol* 1999;140:446-59.
15. Sabroe R.-A., Fiebiger E., Francis D.-M., Maurer D., Seed P.-T., Grattan C.-E., Black A.-K., Stingl G., Greaves M.-W., Barr R.-M. - Classification of anti-FceRI and anti-IgE autoantibodies in chronic idiopathic urticaria and correlation with disease severity. *J Allergy Clin Immunol* 2002;110:492-9.
16. Toubi E., Kessel A., Avshovich N., Bamberger E., Sabo E., Nusem D., Panasoff J. - Clinical and laboratory parameters in predicting chronic urticaria duration: a prospective study of 139 patients. *Allergy* 2004;59:869-73.
17. Fusari A., Colangelo C., Bonifazi F., Antonicelli L. - The autologous serum skin test in the follow-up of patients with chronic urticaria. *Allergy* 2005;60:256-8.
18. Asero R., Tedeschi A., Riboldi P., Cugno M. - Plasma of chronic urticaria patients shows signs of thrombin generation and its intradermal injection causes wheal and flare reactions much more frequently than autologous serum. *J Allergy Clin Immunol* 2006;117:1113-7.
19. Asero R., Tedeschi A., Coppola R., Griffini S., Paparella P., Riboldi P., Marzano A.-V., Fanoni D., Cugno M. - Activation of the tissue factor pathway of blood coagulation in patients with chronic urticaria. *J Allergy Clin Immunol* 2007;119:705-10.
20. Asero R., Tedeschi A., Riboldi P., Griffini S., Bonanni E., Cugno M. - Severe chronic urticaria is associated with elevated plasma levels of D-dimer. *Allergy* 2007; (in press).
21. Kaplan A.-P. - Chronic urticaria: pathogenesis and treatment. *J Allergy Clin Immunol* 2004;114:465-74.
22. Baiardini I., Giardini A., Pasquali M., Dignetti P., Guerra L., Specchia C., Braido F., Majani G., Canonica G.-W. - Quality of life and patients' satisfaction in chronic urticaria and respiratory allergy. A*llergy* 2003;58:621-3.
23. Maniaci G., Epifanio M.-S., Marino M.-A., Amoroso S. - The presence of alexithymia investigated by the TAS-20 in chronic urticaria patients: a preliminary report. *Eur Ann Aller Clin Immunol* 2006;38:15-9.
24. Scala E., Giani M., Pirrotta L., Guerra E.-C., Cadoni S., Girardelli C.-R., De Pita O., Puddu P. - Occupational generalised urticaria and allergic airborne asthma due to anisakis simplex. *Eur J Dermatol* 2001;11:249-50.

25. Veraldi S., Miadonna A. - Chronic “idiopathic” urticaria and hydatid disease. *Allergy* 1998;53:1234-5.
26. Armentia A., Mendez J., Gomez A., Sanchis E., Fernandez A., de la Fuente R., Sanchez P. - Urticaria by Blastocystis hominis. Successful treatment with paromomycin. *Allergol Immunopathol* 1993;21:149-51.
27. Hernandez-Garcia J., Garcia-Selles J., Negro-Alvarez J.-M., Pagan Aleman J.-A., Lopez Sanchez J.-D. - Incidence of adverse reactions to additives. Our experience over 10 years. *Allergol Immunopathol* 1994;22:233-42.
28. Jansen S.-C., van Dusseldorp M., Bottega K.-C., Dubois A.-E. - Intolerance to dietary biogenic amines: a review. *Ann Allergy Asthma Immunol* 2003;91:233-40.
29. Wedi B., Wagner S., Werfel T., Manns M.-P., Kapp A. - Prevalence of Helicobacter pylori associated gastritis in chronic urticaria. *Int Arch Allergy Immunol* 1998;116:288-94.
30. Di Campli C., Gasbarrini A., Nucera E., Franceschi F., Ojetti V., Sanz Torre E., Schiavino D., Pola P., Patriarca G., Gasbarrini G. - Beneficial effects of Helicobacter pylori eradication on chronic idiopathic urticaria. *Dig Dis Sci* 1998;43:1226-9.
31. Valsecchi R., Pigatto P. - Chronic urticaria and Helicobacter pylori. *Acta Dermatol Venereol* 1998;78:440-2.
32. Schnyder B., Helbling A., Pichler W.-J. - Chronic idiopathic urticaria: natural cause and association with H pilori infection. *Int Arch Allergy Immunol* 1999;119:60-3.
33. Liutu M., Kalimo K., Uksila J., Kalimo H. - Etiological aspects of chronic urticaria. *Int J Dermatol* 1998;37:515-9.
34. Ring J., Brockow K., Ollert M., Engst R. - Antihistamines in urticaria. *Clin Exp Allergy* 1999;29(Suppl 1):31-7.
35. Kalivas J., Breneman D., Tharp D., Bruce S., Bigby M. - Urticaria: clinical efficacy of cetirizine in comparison with hydroxyzine and placebo. *J Allergy Clin Immunol* 1990;86:1014-8.
36. Finn A.-F. Jr, Kaplan A.-P., Fretwell R., Qu R., Long J. - A double-blind, placebo-controlled trial of fexofenadine HCl in the treatment of chronic idiopathic urticaria. *J Allergy Clin Immunol* 1999;103:1071-8.
37. Monroe E.-W. - Loratadine in the treatment of urticaria. *Clin Ther* 1997;19:232-42.
38. Lorette G., Giannetti A., Pereira R.-S., Leynadier F., Murrieta-Aguttes M. - One-year treatment of chronic urticaria with mizolastine: efficacy and safety. URTOL study group. *J Eur Acad Dermatol Venereol* 2000:14:83-90.
39. Clough G.-F., Boutsiouki P., Church M.-K. - Comparison of the effects of levocetirizine and loratadine on histamine-induced wheal, flare and itch in human skin. *Allergy* 2001;56:985-8.
40. Ring J., Hein R., Gauger A. - Desloratadine in the treatment of chronic idiopathic urticaria. *Allergy* 2001;56(Suppl 65):28-32.
41. Zuberbier T., Bindslev-Jensen C., Canonica W., Grattan C.-E. *et al.* - EAACI/GA2LEN/EDF guideline: management of urticaria. Allergy 2006;61: 321-31.
Asero R. Chronic unremitting urticaria: is the use of antihistamines above the licensed dose effective? A preliminary study of cetirizine at licensed and above-licensed dose. *Clin Exp Dermatol* 2006;32:34-38.
42. Bleehen S.-S., Thomas S.-E., Greaves M.-W., Newton J., Kennedy C.-T., Hindley F., Marks R., Hazell M., Rowell N.-R., Fairiss G.-M. *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.
43. Simons F.-E., Sussman G.-L., Simons K.-J. - Effect of the H2-antagonist cimetidine on the pharmacokinetics and pharmacodynamics of the H2 antagonists hydroxizine and cetirizine in patients with chronic urticaria. *J Allergy Clin Immunol* 1995;95:685-93.
44. Tedeschi A., Airaghi L., Lorini M., Asero R. - Chronic urticaria. A role for newer immunomodulatory drugs? *Am J Clin Dermatol* 2003;4:297-305.
45. Spector S., Tan R.-A. - Antileukotrienes in chronic urticaria. *J Allergy Clin Immunol* 1998;101:572.
46. Ellis M.-H. - Successful treatment of chronic urticaria with leukotriene antagonists. *J Allergy Clin Immunol* 1998;102:876-7.
47. Berkun Y., Shalit M. - Successful treatment of delayed pressure urticaria with montelukast. *Allergy* 2000;203-4.
48. Tedeschi A., Lorini M., Suli C., Airaghi L. - Successful treatment of chronic urticaria. *Allergy* 2000; 55:1097-8.
49. Asero R, Tedeschi A, Lorini M. Leukotriene receptors antagonists in chronic urticaria. Allergy 2001; 56: 456-7.

50. Nettis E., Colanardi M.-C., Paradiso M.-T., Ferrannini A. - Desloratadine in combination with montelukast in the treatment of chronic urticaria: a randomized, double-blind, placebo controlled study. *Clin Exp Allergy* 2004;34:1401-7.
51. Bagenstose S.-E., Levin L., Bernstein J.-A. - The addition of zafirlukast to cetirizine improves the treatment of chronic urticaria in patients with positive serum skin test results. *J Allergy Clin Immunol* 2004;113:134-40.
52. Asero R. - Leukotriene receptor antagonists may prevent NSAID-induced exacerbations in patients with chronic urticaria. *Ann Allergy Asthma Immunol* 2000;85:156-7.
53. Fradin M.-S., Ellis C.-N., Goldfarb M.-T., Voorhees J.-J. - Oral cyclosporine for severe chronic idiopathic urticaria and angioedema. *J Am Acad Dermatol.* 1991;25:1065-7.
54. Barlow R.-J., Kobza Black A., Greaves M.-W. - Treatment of severe, chronic urticaria with cyclosporin A. *Eur J Dermatol* 1993;3:273-5.
55. Toubi E., Blant A., Kessel A., Golan T.-D. - Low-dose cyclosporin A in the treatment of severe chronic idiopathic urticaria. *Allergy* 1997;52:312-6.
56. Grattan CEH., O'Donnell P.-F., Francis D.-M., Niimi N., Barlow R.-J., Seed P.-T., Kobza Black A., Greaves M.-W. - Randomised double blind study of cyclosporin in chronic "idiopathic" urticaria. *Br J Dermatol* 2000;143;365-72.
57. Kessel A., Bamberger E., Toubi E. - Tacrolimus in the treatment of severe chronic idiopathic urticaria: an open-label prospective study. J *Am Acad Dermatol* 2005;52:145-8.
58. Gach J.-E., Sabroe R.-A., Greaves M.-W., Kobza Black A. - Methotrexate-responsive chronic idiopathic urticaria: a report of two cases. *Br J Dermatol* 2001;145:340-3.
59. Asero R. - Oral cyclophosphamide in a case of cyclosporin and steroid-resistant chronic urticaria showing autoreactivity on autologous serum skin testing. *Clin Exp Dermatol* 2005;30:582-3.
60. Bernstein J.-A., Garramone S.-M., Lower E.-G. - Successful treatment of autoimmune chronic idiopathic urticaria with intravenous cyclophosphamide. *Ann Allergy Asthma Immunol* 2002;89:212-4.
61. Grattan CEH., Francis D.-M., Slater NGP., Barlow R.-J., Greaves M.-J. - Plasmapheresis for severe unremitting chronic urticaria. *Lancet* 1992;339:1078-80.
62. O'Donnell B.-F., Barr R.-M., Black A.-K., Francis D.-M., Kermani F., Niimi N., Barlow R.-J., Winkelmann R.-K., Greaves M.-W. - Intravenous immunoglobulin in chronic autoimmune urticaria. *Br J Dermatol* 1998;138;101-6.
63. Asero R. - Are IVIG for chronic unremitting urticaria effective? *Allergy* 2000;55:1099-101.
64. Lopez L.-R., Davis K.-C., Kohler P.-F., Schocket A.-L. - The hypocomplementemic urticarial-vasculitis syndrome: therapeutic response to hydroxychloroquine. *J Allergy Clin Immunol* 1984;73:600-3.
65. Reeves G.-E., Boyle M.-J., Bonfield J., Dobson P., Loewenthal M. - Impact of hydroxychloroquine therapy in chronic urticaria: chronic autoimmune urticaria study and evaluation. *Intern Med J* 2004;34:182-6.
66. Jaffer A.-M. - Sulfasalazine in the treatment of corticosteroid-dependent chronic idiopathic urticaria. *J Allergy Clin Immunol* 1991;88:964-5.
67. Hartmann K., Hani N., Hinrichs R., Hunzelmann N., Scharffetter-Kolhanek K. - Successful sulfasalazine treatment of severe chronic idiopathic urticaria associated with pressure urticaria. *Acta Derm Venereol* 2001;81:71.
68. Boehm I, Bauer R, Bieber T. Urticaria treated with dapsone. Allergy 1999; 54: 765-6.
69. Rumbyrt J.-S., Katz J.-L., Schocket A.-L. - Resolution of chronic urticaria in patients with thyroid autoimmunity. J *Allergy Clin Immunol* 1995;96:901-5.
70. Kandeel A.-A., Zeid M., Helm T., Lillie M.-A., Donahue E., Ambrus J.-L. Jr. - Evaluation of chronic urticaria in patients with Hashimoto thyroiditis. *J Clin Immunol* 2001;21:335-347.
71. Parslew R., Pryce D., Ashworth J., Friedmann P.-S. - Warfarin treatment of chronic idiopathic urticaria and angio-edema. *Clin Exp Allergy* 2000;30:1161-5.
72. Mortens BPM. - Clinical experience with tranexamic acid (cyclocapron) in urticaria and angio-edema. *Br J Dermatol* 1974 90:431-4.
73. Vita D., Passalacqua G., Caminiti L., Barberio G., Pajno G.-B. - Successful combined therapy for refractory chronic urticaria in a 10-year-old boy. *Allergy* 2004;59:1021-2.
75. Chua S.-L, Gibbs. - Chronic urticaria responding to subcutaneous heparin sodium. *Br J Dermatol* 2005;153:216-7.