

Chronic autoimmune urticaria : Where we stand ?

CL Goh, KT Tan

Department of Dermatology, National Skin Center, Singapore

Date of Web Publication 10-Sep-2009

Correspondence Address:

C L Goh

1 Mandalay Road, 308205

Singapore

 Login to access the email ID

Source of Support: None, **Conflict of Interest:** None

DOI: 10.4103/0019-5154.55640

PMID: 20161862

 Get Permissions

 Abstract

It is well-recognized that 30-40% of chronic idiopathic urticaria is autoimmune in nature. Chronic autoimmune urticaria is caused by anti-Fc ϵ RI and less frequently, by anti-IgE autoantibodies that lead to mast cell and basophil activation, thereby giving rise to the release of histamine and other proinflammatory mediators. Activation of the classical complement pathway and formation of C5a are important in dermal mast cell activation. C5a is also a neutrophil and eosinophil chemoattractant. Chronic autoimmune urticaria has been found to be associated with autoimmune thyroid disease. The autologous serum skin test is used as a screening test for chronic autoimmune urticaria and has a sensitivity and specificity of about 70 and 80%, respectively. The current gold standard diagnostic test is the basophil histamine release assay. The treatment of chronic autoimmune urticaria, as in chronic idiopathic urticaria, is with H1 antihistamines. Oral corticosteroids may be used during acute flares. Refractory cases have been shown to respond to cyclosporine and other immunomodulators. The prevalence of chronic autoimmune urticaria in Singapore is similar to that reported in Western countries at about 42%. The presence of thyroid autoimmunity appears to be higher than reported, with 22.5% of patients with chronic idiopathic urticaria here, exhibiting presence of thyroid autoantibodies.

Keywords: Chronic autoimmune urticaria, urticaria, chronic urticaria

How to cite this article:

Goh CL, Tan KT. Chronic autoimmune urticaria : Where we stand ?. Indian J Dermatol 2009;54:269-74

How to cite this URL:

Goh CL, Tan KT. Chronic autoimmune urticaria : Where we stand ?. Indian J Dermatol [serial online] 2009 [cited 2010 Feb 19];54:269-74. Available from: <http://www.e-ijd.org/text.asp?2009/54/3/269/55640>

▼ Introduction



This is a review article of an update on chronic autoimmune urticaria.

Chronic urticaria (CU) is defined as urticaria persisting daily or almost daily for more than six weeks. It causes severe impairment on the quality of life. ^[1] CU includes physical urticaria, chronic "idiopathic" urticaria (CIU), and urticarial vasculitis. It is important to recognize patients with physical urticaria, as the need for investigation and treatment modalities differ from patients with CIU or urticarial vasculitis.

Although in many patients with CU the disease remains "idiopathic", in recent years, a significant number of patients with non-physical CU have been reported to have an autoimmune basis for their urticaria. This has important implications when investigating CIU and when planning treatment for patients with CIU.

Hence, if we eliminate physical urticaria and urticarial vasculitis from all patients with CU, the remainder can be divided into chronic autoimmune urticaria (CAU) (45%) and CIU (55%). The autoimmune subgroup is associated with the IgG anti-IgE receptor alpha subunit in 35-40% of the patients, and IgG anti-IgE in an additional 5-10%. These autoantibodies have been shown to activate blood basophils and cutaneous mast cells *in vitro*, with augmentation of basophil activation by complement and release of C5a. Unfortunately antibody binding tests (immunoblot and ELISA) can yield positive tests in many autoimmune diseases, normal subjects, or patients with other forms of urticaria, but most such sera are nonfunctional and cannot be used to diagnose CAU. At this point in time, the gold standard for detecting clinically relevant autoantibodies to FcεRI is the functional *in vitro* donor basophil histamine release assay. Activation of basophils or mast cells causing histamine release is quite specific to chronic urticaria and defines the autoimmune subgroup. Although pathogenicity is not formally proven, the antibodies cause whealing upon intradermal injection, and removal of the autoantibody leads to remission. ^[2] CAU has been reported to occur in children as well. ^[3]

▼ What is Chronic Autoimmune Urticaria?



It is now recognized that approximately 30-40% of patients with CIU have histamine-releasing autoantibodies directed against either the high-affinity IgE receptor, or less frequently, IgE. The presence of autoantibodies may be important clinically in a small group of severely affected, treatment-resistant patients, where immunomodulatory treatments may be helpful.

▼ History of CAU



Although the concept of CAU as an autoimmune disease is fairly new, Rorsman's report in 1962 ^[4]

that in CU, "antigen-antibody reactions bring about degranulation of leucocytes" was followed by the observation that circulating thyroid autoantibodies, and more controversially, dysfunctional thyroid disease, showed a significant association with CIU. Leznoff later proposed a "syndrome" of autoimmune thyroid disease and CU. ^[5]

Hide *et al.*, ^[6] in 1993 and Nimii *et al.*, ^[7] in 1996 showed that autoantibodies against the high affinity IgE receptor or less commonly IgE itself were the cause of whealing in some patients with CU. The findings were subsequently independently confirmed by several groups. ^{[8],[9]}

❖ Pathogenesis of CAU



Although a large number of naturally occurring immunological and nonimmunological agents are known to be capable of activating dermal mast cells, only allergen-specific IgE reactions, anti-IgE and anti-FcεRI autoantibodies, and complement C5a are of significant importance in CU.

Dermal mast cells secrete preformed mediators including histamine, proteases, interleukin-1, and tumor necrosis factor- α (TNF- α). These cytokines cause increased expression of adhesion molecules by the endothelium of the post capillary venules. *De novo* synthesized mediators include leukotrienes, prostaglandins, cytokines, and chemokines resulting in leukocyte recruitment including eosinophils, which characterize the late phase reaction. ^[10] An MHC class II-dependent signaling pathway enables mast cells to behave as antigen presenting cells, ^[11] which by activating T cells are able to maintain the duration of the wheals.

Little or no anti-FcεRI immunoreactivity is found in the IgM fraction. Isolation of IgG high affinity IgE receptor autoantibody subclasses using protein G affinity chromatography in patients' sera has shown that a majority of the histamine-releasing activity co-localizes with the IgG subclasses IgG1 and IgG3 ^[12] and similar results are also reported on using immunoblotting. ^[13] Occasionally sera contained histamine-releasing IgG4, but no histamine-releasing autoantibody activity was found in subclass IgG2.

The high affinity IgE receptor FcεRI consists of four peptide chains: intracellular α 1, α 2, and β chains and an γ -chain with an extracellular portion, which bears the binding site for IgE. Competitive inhibition studies, using a human recombinant α -chain of FcεRI, have established that the binding sites for IgG anti-FcεRI autoantibodies are located on the external portion of the α -chain. ^[14] Binding can occur on at least two domains in this region of the α -chain. These autoantibodies cross-link and dimerise FcεRI, leading to mast cell basophil activation and release of histamine and other mediators.

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

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

Role of complement

Complement depletion or inactivation diminishes histamine release evoked by anti-FcεRI autoantibodies *in vitro*.^[15] Subsequent studies established the involvement of C5a and the classical complement activation pathway.^[16] This finding explains the otherwise puzzling observation that symptoms and signs consequent upon interaction between anti-FcεRI autoantibodies, and their antigenic targets on mast cell membranes are limited to the skin, as pulmonary mast cells are devoid of C5a receptors. Activation of the classical complement pathway and formation of C5a is important in bringing about dermal mast cell activation. C5a is also a neutrophil and eosinophil chemoattractant, giving rise to the observed accumulation of these cells in the lesional skin.

❖ Diagnostic Tests for CAU



It is often not possible to distinguish CAU from those without autoantibodies, clinically or histologically. The autologous serum skin test (ASST) is used as a screening test. Gratten *et al.*, reported that the histological features of a positive ASST resemble an IgE-mediated late phase reaction.^[10]

The ASST is a useful tool for picking up patients with circulating wheal-producing factors in CIU. However, its specificity as a screening test for the presence of functional anti-FcεRI is low, and confirmation by demonstration of histamine-releasing activity in the patient's serum is needed for establishing this diagnosis. The ASST is at best 80% sensitive and specific. Improved screening tests are being sought.

Autologous serum skin test

The ASST was first described by Grattan^[18] and subsequently characterized by Sabroe *et al.*^[19] Briefly, serum is obtained from the patient, preferably with active urticaria. This is injected intradermally into the same patient's uninvolved skin, and the injected skin is examined for wheal formation 30 minutes later. Positive and negative controls with intradermal histamine and saline injections are carried out on the adjacent skin. The test is positive if the serum-induced wheal is at least 1.5 mm greater than the saline wheal. The ASST has a sensitivity of about 70% and specificity of about 80%. However, experience is required to produce reliable results.^[20] In a recent study, Asero *et al.*, found that out of 78 patients with CIU, 35% had a positive ASST, but only 25% was positive for histamine-releasing activity against donor basophils.^[21] Presumably, the "false" positive ASSTs were due to the presence of other wheal-inducing factors in the serum, such as, the mast cell specific factor or vasoactive kinin-like products released during the course of coagulation. Thus, there are marked differences between *in vivo* ASST findings and the results of the histamine release tests *in vitro*, as only a proportion of the ASST positive sera are able to release histamine from donor basophils *in vitro*. The ASST should be considered a crude screening test and should not be used as a specific test for the detection of circulating autoantibodies.^[22]

The ASST positivity has also been reported to correlate with the duration of CIU attacks and with disease severity,^[23] although it was also reported that the test was persistent in some patients even when the disease had gone into remission.

It has been reported that positive ASST also correlated strongly with patients who have multiple intolerances to nonsteroidal anti-inflammatory drugs^[24] and in some cases may be related to the presence of *Helicobacter pylori* (*H. pylori*) IgG antibodies. The relationship between *H. pylori* and CIU has been reviewed.^[25]

Confirmatory in vitro tests for CAU

Because immunoreactive but non-histamine releasing anti- FcεRI autoantibodies are also detectable in sera from some patients with autoimmune connective tissue diseases, and in a small proportion in patients with other types of urticaria, immunoassays for CAU antibodies have poor specificity. At present the most useful *in vitro* method for the diagnosis of CAU antibodies is the demonstration of the release of histamine (or another reactant) from target basophils or dermal mast cells. ^[26] At this point in time, the gold standard for detecting clinically relevant autoantibodies to FcεRI is the functional *in vitro* donor basophil histamine release assay. Several laboratories now offer the basophil histamine release assay as a commercial service.

Other laboratory findings in CAU

Patients with CAU had a significantly lower serum IgE than those with no autoantibody. The significance of this finding is unclear.

That basopenia is a feature of CAU has long been recognized. ^[4] Histological studies of wheals suggest that one reason for these low values may be the sequestration of basophils within the affected skin. ^[28] Enumeration of blood basophils, possibly by an automated method might form the basis of a screening test for CAU.

In recent times, an alternative screening test has been proposed based upon the observation that sera from ASST-positive patients with CAU when incubated with basophils from an atopic donor cause CD63 expression on the target basophils. ^[29] Similarly, donor basophil CD203c expression appears to correlate with autologous serum skin test positivity. ^[30] Expression of these basophil activation markers can be detected using flow cytometry. This may be developed as a screening test for CAU antibodies, but as yet still requires validation against the basophil histamine release assay.

Histology

The histological appearance of the skin in CIU resembles that of a late phase reaction. ^[10] Although the infiltrate in patients with CAU is characterized by more prominent granulocyte infiltrate than that of non-autoimmune patients, the frequency of other infiltrating cells is similar in both groups, although there is a slight increase in serum tryptase and cytokines in CAU patients. These small differences are too insignificant to be used as a diagnostic tool.

It must be stressed that most of the above reports are derived from studies of Caucasian patients in occidental countries. The correlations between certain autoantibodies and corresponding diseases while holding good in Caucasian patients, may not be applicable to Asians.

☛ CAU and Thyroid Disease



The frequency with which autoimmune thyroid disease is associated with CU has already been remarked upon. ^[5] The strong association between autoimmune thyroid disease and CAU is also an area of interest in CAU research. There is a generally recognized association between CIU and autoimmune thyroid disease. ^{[31],[32]} In a recent report, half of the 182 Caucasian (UK) patients with CIU had a positive ASST and there was clear evidence of an association of CAU with thyroid microsomal autoantibodies. These autoantibodies were present in 36/182 CIU patients with

cosegregation of anti-FcεRI autoantibodies. Most of these patients are euthyroid, but occasionally, they are hyper- or hypothyroid.^[33] Although claims have been made that correcting thyroid dysfunction, if present, also ameliorated the associated urticaria, the evidence is not convincing. However, the association between thyroid disease and CU is sufficiently strong, to prompt adding measurement of the plasma level of thyroid stimulating hormone level (as a screen for thyroid dysfunction) and thyroid autoantibodies to the routine workup of CU patients.^[34]

CAU in Singapore



The prevalence of CAU in Singapore has been found to be about 42%. This does not differ from the established findings. However, thyroid autoimmunity in our patients with CIU appears to be higher than that reported in Western countries. Twenty-one percent of our CIU patients with positive ASST and 24% with negative ASST had serological evidence of thyroid autoimmunity. This number is more than twice that reported in Caucasians. Thyroid autoantibody titers were generally found to be lower in patients with negative ASST compared to those who were ASST positive.

General Management of CAU



Patients with CU often undergo numerous unnecessary laboratory investigations. A recent study failed to show that increasing the number of laboratory tests would improve the identification of the cause of CU.^[35] Guidelines for classification and diagnosis of CU have recently been formulated.^[36]

Generally, if no obvious underlying cause for the CU can be found, the patient should be treated with H1 antihistamines supplemented by short tapering courses of prednisolone for flare-ups if necessary. If this is unsuccessful, and the patient's quality of life is impaired, a search for the evidence of CAU should be carried out. Commercial laboratories offering a satisfactory serodiagnostic service for CAU based upon the basophil histamine release assay are available.

Treatment for all forms of CU should include a sound, basic lifestyle. These include avoidance of stress, overtiredness, alcohol, NSAIDs, and tight fitting garments. Nocturnal pruritus can be reduced by tepid showering and keeping the ambient temperature of the bedroom cool. Cooling lotions such as calamine with 1% menthol are popular with patients. H1 antihistamines remain the cornerstone of drug treatment for all types of CU.

Treatment of CAU: Special Considerations



Patients with proven CAU are initially treated in exactly the same way as patients with CIU. H1 antihistamines remain the initial treatment of choice. The newer second-generation compounds appear to be safe and effective even in off-label dosages.

The treatment of CIU has recently been reviewed.^{[37],[38]} After making the diagnosis of CIU, patients with CAU should initially be treated in the same way as those without autoantibodies.

Oral antihistamines

This includes the use of low-sedation H1 antihistamines in licensed dosages. It is recommended that the period in which the patient is maximally symptomatic be identified, in order to fine-tune the antihistamine therapy to the patient's individual requirements. Most patients experience maximum pruritus at night, so a sedating antihistamine such as hydroxyzine 10-25 mg at night is recommended. However, the patient should be warned about impairment of cognitive function the following day even though there may be no overt symptom of sedation. Dosage of low-sedation antihistamines above those licensed could be tried in non-responders, for example, fexofenadine 360mg daily. Doxepin 10-30 mg can be used instead of night time hydroxyzine.

Leukotriene antagonists

Early enthusiasm about the value of montelukast, a leukotriene antagonist, has not been borne out by subsequent studies, although it may be of benefit in a small number of patients.

It is not uncommon to find patients to be well controlled most of the time by these measures, punctuated by occasional distressing flares, due very often to personal, occupational, or economic factors, or other previously described exacerbating factors. These relapses are best controlled by brief courses of oral steroids. Prednisolone 30mg daily for five days followed by tapering over five to six days is usually effective, after which the patient can continue regular antihistamines.

Cyclosporine

Unfortunately, patients with CAU often have severe disease and are poorly responsive to antihistamines, even in high off-label dosages. Cyclosporine is effective and can be used in selected cases of CAU. Cyclosporine has been seen to be effective in selected patients who were ASST positive, in a double-blind placebo-controlled study. ^[39] Cyclosporine has also been seen to inhibit histamine release from basophils, triggered *in vitro* by sera from patients with CIU known to have anti-FcεRI autoantibodies. The recommended dose range is 4-6 mg/kg/day in addition to oral antihistamines. It is recommended that patients be treated up to three months. About 80% of the patients experience total or partial remission. In these, withdrawal of cyclosporine is followed by sustained remission in about one third. One third of the patients have a relapse, but they are responsive to regular dosages of H1 antihistamines. Although the remaining one third relapse to a severity approximating that suffered before initiating cyclosporine, ^[40] these patients can be offered further cyclosporine treatment. All patients receiving cyclosporine must be regularly monitored for renal function, serum cholesterol, triglycerides, and blood pressure.

Other immunomodulators that have been reported effective in selected patients with CAU include intravenous immunoglobulin and plasmapheresis. ^[41]

Other immunosuppressive measures that can be considered, and which have been shown to be helpful in small studies or case reports, include, tacrolimus, methotrexate, and hydroxychloroquine.

A recent report indicated that biologics may be effective in treating recalcitrant CAU. Treatment of allergic asthma with omalizumab produces rapid reduction in free IgE levels and a subsequent decrease in FcεRI expression on mast cells and basophils. If this occurs in CAU, cross-linking of IgE receptors by an autoantibody would be less likely, reducing cell activation and urticaria/angioedema. Twelve patients with CAU, identified by basophil histamine release assay and ASST, with persistent symptoms for at least 6 weeks despite antihistamines, were treated with placebo for 4 weeks followed by omalizumab every 2 or 4 weeks for 16 weeks. The findings suggest that omalizumab is an effective therapy for CAU resistant to antihistamines. ^[42]

On the current evidence, the pathogenic role of anti-FcεRI and anti-IgE autoantibodies in CAU is probable, but several problems remain unsolved. CAU fits many, but not all the criteria for autoimmune disease, but the pathogenic factor in patients without autoantibodies remains a mystery. Additionally, the detection of patients with autoantibodies remains a major stumbling block. The ASST is characterized by moderate sensitivity and specificity, but it is an indicator of the presence of circulating vasoactive factors and not specifically autoantibodies. Functional *in vitro* tests suffer from variability between donor basophils or mast cells, and immunoassays detect autoantibodies that may or may not be functional, and so are less specific. There is a need to develop a reliable and easily accessible *in vitro* test.

References

1. O'Donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on quality of life. *Br J Dermatol* 1997;136:197-201. [↑](#)
2. Kaplan AP, Greaves M. Pathogenesis of chronic urticaria. *Clin Exp Allergy* 2009;39:777-87. [↑](#)
3. Dodig S, Richter D. Chronic autoimmune urticaria in children. *Acta Dermatovenerol Croat* 2008;16:65-71. [↑](#)
4. Rorsman H. Basophilic leucopenia in different forms of urticaria. *Acta Allergologica* 1962;17:168-84. [↑](#)
5. 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. [↑](#)
6. Hide M, Francis DM, Grattan CE, Hakimi J, Kochan JP, Greaves MW. Autoantibodies against the high affinity IgE receptor as a cause for histamine release in chronic urticaria. *N Engl J Med* 1993;328:1599-604. [↑](#)
7. Nimii N, Francis DM, Kermani F, O'Donnell BF, Hide M, Kobza-Black A, *et al* . Dermal mast cell activation by autoantibody against the high affinity IgE receptor in chronic urticaria. *J Invest Dermatol* 1996;106:1001-6. [↑](#)
8. Fiebiger E, Maurer D, Holub H, Reininger B, Hartmann G, Woisetschläger M, *et al* . Autoantibodies directed against the α-chain of Fcεpsilon R1; A selective marker and pathogenetic factor for a distinct subset of chronic urticaria patients. *J Clin Invest* 1995;96:2606-12. [↑](#)
9. Tong LJ, Balakrishnan G, Kochan JP, Kinét JP, Kaplan AP. Assessment of autoimmunity in patients with chronic urticaria. *J Allergy Clin Immunol* 1997;99:461-5. [↑](#)
10. Grattan CE, Boon AP, Eady RA, Winkelmann RK. The pathology of the autologous serum skin test response in chronic urticaria resembles IgE-mediated late phase reactions. *Int Arch Allergy Immunol* 1990;93:198-204. [↑](#)
11. Frandji P, Mourad W, Tkaczyk C, Singer M, David B, Colle JH, *et al* . IL-4 mRNA transcription is induced in mouse bone marrow-derived mast cells through an MHC class II-dependent signaling pathway. *Eur J Immunol* 1998;28:844-55. [↑](#)
12. Soundararajan S, Kikuchi K, Joseph K, Kaplan AP. Functional assessment of pathogenic IgG subclasses in chronic autoimmune urticaria. *J Allergy Clin Immunol* 2005;115:815-21. [↑](#)
13. Fiebiger E, Hammaerschmid F, Stingl G, Maurer D. Anti-Fcεpsilon R1 autoantibodies in autoimmune-mediated disorders: Identification of a structure function relationship. *J Clin Invest* 1998;101:243-51. [↑](#)
14. Hide M, Francis DM, Grattan CE, Hakimi J, Kochan JP, Greaves MW. Autoantibodies against the high affinity IgE receptor as a cause for histamine release in chronic urticaria. *N Engl J*

Med 1993;328:1599-604. †

15. Fiebiger E, Hammaerschmid F, Stingl G, Maurer D. Anti-FcepsilonRI alpha autoantibodies in autoimmune-mediated disorders. Identification of a structure function relationship. J Clin Invest 1998;101:243-51. †
16. Kikuchi Y, Kaplan AP. A role for C5a in augmenting IgG dependent histamine release from basophils in chronic urticaria. J Allergy Clin Immunol 2002;109:114-8. †
17. Sabroe RA, Francis DM, Barr RM, Black AK, Greaves MW. Anti-Fcepsilon R1 autoantibodies and basophil histamine releasability in chronic idiopathic urticaria. J Allergy Clin Immunol 1998;102:651-8. †
18. Grattan CE, Wallington TB, Warin RP, Kennedy CT, Bradfield JW. A serological mediator in chronic idiopathic urticaria: A clinical Immunological and histological evaluation. Br J Dermatol 1986;114:583-90. †
19. Sabroe RA, Grattan CE, Francis DM, Barr RM, Kobza Black A, Greaves MW, *et al* . The autologous serum skin test: A screening test for autoantibodies in chronic idiopathic urticaria. Br J Dermatol 1999;140:446-52. †
20. Sabroe RA, Fiebiger E, Francis DM. Classification of anti-FceR1 and anti-IgE autoantibodies in chronic urticaria and correlation with disease activity. J Allergy Clin Immunol 2002;40:492-9. †
21. Asero R, Tedeschi A, Lorini M, Salimbeni R, Zanoletti T, Miadonna A. Chronic urticaria: Novel clinical and serological aspects. Clin Exp Allergy 2001;31:1105-10. †
22. Grattan CE, Sabroe RA, Greaves MW. Chronic urticaria. J Am Acad Dermatol 2002;46:645-57. †
23. 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. †
24. Erbagci Z. Multiple NSAID intolerance in chronic idiopathic urticaria is correlated with delayed, pronounced and prolonged autoreactivity. J Dermatol 2004;31:376-82. †
25. Greaves MW. Chronic idiopathic urticaria (CIU) and Helicobacter pylori - not directly causative, but could there be a link? ACI Int 2001;13:23-6. †
26. Kikuchi Y, Kaplan AP. Mechanisms of autoimmune activation of basophils in chronic urticaria. J Allergy Clin Immunol 2001;107:1056-62. †
27. Sabroe RA, Seed PT, Francis DM, Barr RM, Black AK, Greaves MW. Chronic idiopathic urticaria: Comparison of clinical features of patients with and without anti-FceR1 or anti-IgE autoantibodies. J Am Acad Dermatol 1999;40:443-50. †
28. Hoskin SL, Wilson SJ, Sabroe RA. Basophil infiltration of weals in chronic idiopathic urticaria. J Allergy Clin Immunol 2002;109:A22. †
29. Gyimesi E, Sipka S, Danko K, Kiss E, Hídvégi B, Gál M, *et al* . Basophil CD63 expression assay on highly sensitized atopic donor leucocytes: A useful method in chronic autoimmune urticaria. Br J Dermatol 2004;151:388-96. †
30. Yasnowsky KM, Dreskin SC, Efaw B, Schoen D, Vedanthan PK, Alam R, *et al* . Chronic urticaria sera increase basophil CD203c surface expression. J Allergy Clin Immunol 2006;117:1430-4. †
31. Leznoff A, Josse RG, Denburg J, Dolovich J. Association of chronic urticaria and angioedema with thyroid autoimmunity. Arch Dermatol 1983;119:636-40. †
32. Gangemi S, Saitta S, Lombardo G, Patafi M, Benvenga S. Serum thyroid autoantibodies in patients with idiopathic either acute or chronic urticaria. J Endocrinol Invest 2009;32:107-10. †
33. O'Donnell BF, Francis DM, Swana GT, Seed PT, Kobza Black A, Greaves MW. Thyroid autoimmunity in chronic urticaria. Br J Dermatol 2005;153:331-5. †
34. Kaplan AP, Finn A. Autoimmunity and the etiology of chronic urticaria. Canad J Allergy Clin Immunol 1999;4:286-92. †
35. Kozel MM, Bossuyt PM, Mekkes JR, Bos JD. Laboratory tests and identified diagnoses in

patients with physical and chronic urticaria and angioedema: A systematic review. *J Am Acad Dermatol* 2003;48:409-16. [✚](#)

[36.](#) Zuberbier T, Bindslev-Jensen C, Canonica W, Grattan CE, Greaves MW, Henz BM, *et al* . EAACI/GA2LEN/EDF guideline: Definition, classification and diagnosis of urticaria. *Allergy* 2006;61:321-31. [✚](#)

[37.](#) Greaves MW. Chronic idiopathic urticaria. *Curr Opin Allergy Clin Immunol* 2003;3:363-8. [✚](#)

[38.](#) Kozel MM, Sabroe RA. Chronic urticaria: Aetiology, management and current and future treatment options. *Drugs* 2004;64:2515-36. [✚](#)

[39.](#) Grattan CE, O'Donnell BF, Francis DM, Niimi N, Barlow RJ, Seed PT, *et al* . Randomised double blind study of cyclosporine in chronic idiopathic urticaria. *Br J Dermatol* 2000;143:365-72. [✚](#)

[40.](#) Greaves MW, KT Tan. Chronic urticaria: Recent advances. *Clin Rev Allerg Immunol* 2007;33:134-43. [✚](#)

[41.](#) O'Donnell BF, Barr RM, Black AK, Francis DM, Kermani F, Niimi N, *et al* . Intravenous immunoglobulin in chronic urticaria. *Br J Dermatol* 1998;138:101-6. [✚](#)

[42.](#) Kaplan AP, Joseph K, Maykut RJ, Geba GP, Zeldin RK. Treatment of chronic autoimmune urticaria with omalizumab. *J Allergy Clin Immunol* 2008;122:569-73. [✚](#)