REVIEW

Arch. Immunol. Ther. Exp., 2008, **56**, 103–114
PL ISSN 0004-069X

DOI 10.1007/s00005-008-0013-6

Current advances in the management of urticaria

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Received: 2007.08.26, **Accepted:** 2007.12.28, **Published online first:** 2008.03.31

Abstract

Urticaria is a relatively common autoimmune/autoreactive skin disorder that may severely impair quality of life. Although rarely life-threatening, widespread urticaria and its associated angioedema can be an extremely disabling and difficult-to--treat condition. Patients may suffer symptoms such as pruritus and disfigurement due to wheals for years or decades. Urticaria is caused by cutaneous mast-cell degranulation attributed to immunological, non-immunological, and idiopathic causes. The last decade has seen some notable advances in the understanding of the etiology and pathogenesis of common forms of urticaria and their management. Furthermore, the wide diversity in urticaria subtypes has been identified and this reflects a partial understanding of the causes or factors that trigger it as well as the molecular and cellular mechanisms that are involved in its physiopathology. In addition, new instruments for diagnosing urticaria variants and for assessing quality of life in urticaria patients have been developed. Finally, several clinical trials have demonstrated the efficacy of novel treatment approaches for urticaria, while other therapeutic concepts are under development. The objective of this article was to review the literature to be able to offer the readers comprehensive and updated information on the basic etiological and physiopathological mechanisms and to make special emphasis on the current management of urticaria, thus promoting continuous medical education.

Key words: urticaria, wheal, autologous serum skin test, autoimmune urticaria, mast cells, antihistamines, FcεRIα autoantibodies.

Abbreviations: CU – chronic urticaria, CIU – chronic idiopathic urticaria, ASST – autologous serum skin test, ELISA – enzyme--linked immunosorbent assay, ACE – angiotensin-converting enzyme, NSAIDs – nonsteroidal anti-inflammatory drugs.

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INTRODUCTON

Urticaria has been known as a disease since ancient times. It is one of the most common and, in its chronic course, frustrating skin diseases for both patients and physicians. Urticaria (from Latin *urtica disica*: "stinging nettle") was described in 1772 by Herberden [49] as "little elevations upon the skin in the 'nettle' rash that often appears involuntarily and seldom stay many hours in the same place". Urticaria is a vascular reaction with primary wheal lesions which appear suddenly as red, raised, itchy circumscribed areas of dermal edema, last for a few hours, and then fade away to reappear in the same or other places. Deeper swellings of the skin and alimentary tract are called angioedema. These may be painful rather than itchy and tend to last longer [111]. Wheals and angioedema often coexist, but either may occur alone. Though rarely life-threatening, widespread urticaria and its associated angioedema can be both debilitating and frightening. In some cases, lingual swelling requires treatment with epinephrine. Accurate data on the prevalence of urticaria are unavailable; however, on the basis of published data [19], a prevalence 15–23% of the population who may have had this condition seems probable, which in many cases is prolonged and relapsing.

While most cases of acute urticaria are self-limited in nature and are often due to allergic reactions to food or medication, extensive medical intervention may not uncover the etiology of chronic urticaria (CU) [57]. Approximately 30% of patients with urticaria present CU [41]. By CU we mean the occurrence of widespread wheals daily or almost daily for at least 6 weeks, and in around 30% of patients with urticaria, attacks often recur for months or years [22]. Since the cause of CU cannot be determined in most cases, it is considered idiopathic. CU predominantly affects adults, and it is approximately

twice as common in women as in men [95]. Up to 40% of patients who have CU for more than 6 months still have urticarial wheals 10 years later [19]. CU is an extremely distressing condition and patients suffer disability, handicap, and sleep disturbance, mainly as a result of itching lesions, fatigue, social isolation, energy loss, and emotional/sexual difficulties [76]. Hence it has been shown that the quality-of-life impact in patients with CU is comparable to that seen in patients with severe coronary heart disease and out-patients with psoriasis [76, 84].

The objective of this article was to make a review of the literature to be able to offer the readers comprehensive information and updating on the basic etiological and physiopathological mechanisms and to make special emphasis on the current management of urticaria, thus promoting continuous medical education.

CLINICAL APPEARANCE

Urticaria is characterized by a rapid arising of wheals, which may be accompanied by angioedema. A wheal is a primary skin lesion comprising three typical features: 1) central edema of variable size surrounded by reflex erythema, 2) associated itching sensation, and 3) a transitory nature, the skin usually returning to normal within 1–24 h. Angioedema is characterized by: 1) sudden and pronounced swelling of the dermis and the subcutaneous layer, 2) pain rather than itching, 3) frequent involvement of mucous membranes, and 4) resolution of the condition is slower than for wheals and can take up to 72 h [110].

Whereas most cases of urticaria are acute in nature and resolve without medical intervention in less than 6 weeks, CU usually follows a relactant and relapsing course over 6 weeks, but the wheals usually last less than 24 h. However, in urticarial vasculitis the wheals last more than 24 h, with red, purple, or violet erythema, and burn or pain rather than itching. In physical urticaria, such as from cold, vibration, and water, the application of a physical stimulus to the skin causes the formation of local wheals, itching and, in some cases, angioedema. It is reproducibly induced by the same physical stimulus within minutes of the trigger stimulus and usually clears within 2 h. Physical urticarias may occur alone or together with ordinary urticaria, including dermatographism (applying mechanical force to skin) and delayed-pressure urticaria. Wheals in delayed-pressure urticaria arise after 3–8 h at places of sustained pressure applied to the skin and may last up to three days. In contact urticaria, wheals are induced within minutes of skin exposure to the contactant. Cholinergic urticaria is evoked by an increase in body temperature [102, 111].

CLASSIFICATION

The spectrum of clinical manifestations of different urticaria subtypes is very wide. Additionally, in one patient two or more different subtypes of urticaria can coexist. However, urticaria and angioedema may be broadly classified by duration and trigger factors [38]. Urticaria is classified as acute or chronic. When urticaria is present for less than 6 weeks, urticaria can be termed acute. If wheals continue on most days for longer than 6 weeks, the urticaria can be termed chronic. A cause is more likely to be found in acute urticaria than in CU. The term "ordinary urticaria" can be used when predominantly physical, immune complex, and contact urticarias have been excluded. Up to 30% of chronic "idiopathic" urticarias have an autoimmune basis [27]. Table 1 presents a classification for clinical use.

Table 1. Classification of urticaria and angioedema

Acute urticaria "ordinary urticaria", <6 weeks' duration
idiopathic
allergic
non-allergic
Chronic urticaria, >6 weeks' duration,
identifiable provoking factors (5–10%)
autoimmune (>30%)
idiopathic (50%)
Physical urticaria
aquagenic urticaria
cholinergic urticaria
cold urticaria
delayed-pressure urticaria
dermographism
localized heat urticaria
solar urticaria
vibratory angioedema
Contact urticaria (due to contact with the skin)
Chemical
Urticarial vasculitis
Angioedema (without wheals)

GENETICS

There are reports that HLA-DRB1*4, HLADQB1*0302, and HLA-DOB1*06 have been found with increased frequency in patients with chronic idiopathic urticaria (CIU) compared with a control population [58]. HLADRB1*4, HLA-DQB1*0301/4, and HLA-DQB1*0302 have been found in increased frequency in patients with anti-FcεRIα autoantibodies. Furthermore, it is speculated that the promoter polymorphism of the transforming growth factor (TGF)-β1 gene may be involved in ICU. A study of the influence of genetic variability at the promoter of the TGF-β1 gene (–509C>T) on the occurrence of ICU has shown it to be a useful genetic change [54].

HISTOPATHOLOGICAL FEATURES

The classical fleeting wheal demonstrates edema with an upregulation of endothelial adhesion molecules,

a mixed inflammatory perivascular infiltrate of variable intensity consisting of neutrophils and/or eosinophils, macrophages, and T-helper lymphocytes [46]. In delayed-pressure urticaria the infiltrate is located typically in the mid to lower dermis [9]. Frequently, alterations of adhesion molecules [114] and cytokine expression are also seen in uninvolved skin [34, 50].

These findings underline the complex nature of the pathogenesis of urticaria, which has many features in addition to the release of histamine from dermal mast cells. These changes are also seen in a wide variety of inflammatory reactions and are thus not specific or of diagnostic value. A search for more specific histological markers for different subtypes of urticaria is desirable.

ETIOLOGY AND PATHOGENESIS

Acute idiopathic urticaria is present in 50% of patients with acute urticaria. In the others, the most common causes are upper respiratory tract infection (40%), usually viral, followed by drug ingestion (9%), but allergy or intolerance to food is rare (1%) [38]. Allergic urticaria is usually due to the reaction of an antigen with its specific IgE antibody bound to the mast cell and is more common in people who are atopic and have elevated IgE levels. Although it is unusual to find an allergic cause for acute urticaria, any drug, food, food additive, injection, implant, contactant, and inhalant should be considered as a potential allergen. Acute urticarial reactions from drugs are common, occurring within 36 h of administration of antibiotics; especially penicillins, cephalosporins, tetracyclines, and sulfonomides are common causes of urticaria [43]. Increased risk factors include previous exposure and reaction to the drug or a chemically related drug. Acute urticarial reactions to food are believed to be common. Reactions usually occur within minutes, but sometimes allergic urticaria develops many hours after food ingestion. A recent multicenter study found food allergy to be the cause of 10.2% of anaphylactic shocks. [72] The most frequently implicated food allergens are eggs, fish, shellfish, fruits, rice, nuts, sour food, and crustaceans. Some urticaria cases were found to be due to a foodstuff cross-reacting with birch pollen [52], and there are reports of patients who had wheat-induced urticaria [86, 104]. Both genetic and environmental causes are under consideration, and the foods involved in allergic reactions depend mostly on age and the dietary habits of the community [24, 56]. Though food allergy is a known cause of acute urticaria, there is no such evidence to support this assumption in CU [6]. Patients looking for a cause for their urticaria usually blame food, but an allergic cause for all ordinary urticarias has been found in fewer than 3.5% [6].

Allergic reactions to bee-sting venom are not uncommon and may be fatal. Some substances evoking IgE-mediated anaphylactic [23] reactions more readily include penicillins, peanuts, latex, and *Hymenoptera* stings. Prodromal symptoms include itching or tingling of the mouth, palms, and soles. Widespread urticaria and angioedema, bronchospasm, laryngeal edema, hypotension, or cardiac arrythmias may subsequently develop and can rarely lead to death [94]. This is a medical emergency and the first-line treatment is with adrenaline. Acute urticarias from ingested substances may be nonallergic. Mast-cell histamine release is not immunological and may occur after the first exposure to a substance. Histamine-releasing agents, including morphine and codeine, and antibiotics such as ciprofloxacin, rifampicin, and vancomycin can cause urticaria [30]. While the exact role of food dyes and preservatives in exacerbating urticaria is controversial, tartrazine and other dyes have been implicated in causing pseudoallergic reactions. Food preservatives are rarely implicated. Alcoholic beverages such as white wine often include sulfites, which may cause urticaria. Food may also contain vasoactive amines, including histamine (such as cheese, fish, meat, tomatoes, pineapple, and avocados) or histamine-releasing substances (such as egg white, cheese, and strawberries). However, the role of food additives, preservatives, dyes, and biogenic amines should not be overestimated and useless diets prescribed, because well-documented studies have shown that food additives and foods containing vasoactive amines have little or no role in CU [51, 55].

Urticaria may also follow infections, e.g. Epstein-Barr, hepatitis B and C, and other viral and possibly parasitic infections. This inflammatory pathway is triggered by complement activation from immune complex formation [96]. Infection with *Helicobacter pylori* has been proposed as a possible cause, but its role in urticaria is still controversial [106]. Other chronic bacterial infections, e.g. with streptococci, staphylococci, or *Yersinia*, can provoke urticaria [108]. There is no link between dental abscess, *Candida* colonization of the gut, or malignancy and CU [58]. Association between CU and house dust mite sensitivity has been proposed by a recent report [71]. Stress may trigger or aggravate urticaria from a variety of causes; on the other hand, urticaria and angioedema can cause considerable stress [81]. While angioedema of C1 esterase inhibitor deficiency is caused by complement-derived kinins, acquired angioedema may be idiopathic or due to various medications, transfusion reactions, foods, food additives, infective agents, or connective tissue diseases [97]. Some cases of angioedema have been found to be due to angiotensin-converting enzyme (ACE) inhibitors and to angiotensin II receptor antagonist [26, 74].

Even after evaluation for evidence of immunological and other provoking factors, about 50% cases of CU remain unexplained and are categorized as CIU. In most series, this subgroup represents a substantial number of patients, but it must remain a diagnosis of exclusion [28]. Table 2 lists the etiologies of urticaria and angioedema.

Table 2. Etiopathogenesis of urticaria and angioedema

Idiopathic
Immunological
IgE-dependent (type I hypersensitivity)
autoimmune (autoantibodies against Fc1RI or IgE)
immune complexes (urticarial vasculitis)
complement-dependent (C1 esterase inhibitor deficiency)
Non-immunological
direct mast-cell releasing agents (e.g. opioids and others)
aspirin, NSAIDs and food pseudoallergens
angiotensin-converting enzyme inhibitors (ACE inhibitors)

Mechanisms

Urticaria can occur by three of the four immunological reactions as classified by Gell and Coombs. Type I, or the immediate IgE-mediated mechanism ("allergic" hive or acute urticaria), type II or the cytotoxic mechanism (urticarial phase of bullous pemphigoid), and type III or immune-complex disease, as seen in serum sickness, systemic lupus erythematosus, and rheumatoid arthritis, in which lesions are less pruritic, more persistent, often painful, and may be associated with arthritis and other systemic features of vasculitis. Noxious stimuli, on encountering keratinocytes, induce the release of a melange of cytokines, such as interleukin (IL)-1, IL-3, IL-6, IL-8, granulocyte macrophage colony-stimulating factor, and tumor necrosis factor α. These cytokines then signal to the migratory dendritic professional antigen-presenting epidermal Langerhan's cells or (dermal) mast cells the appropriate inflammatory response to rally against that stimulus. On this signal, mast cells, which patrol the vasculature and nerve endings, release their many (combinations of) preformed and newly synthesized mediators [98]. Antigen-induced mast-cell degranulation is a unique feature of type I (Gell and Coombs) reactions (acute urticaria). These type I reactions are often biphasic, with an early immediate phase, resulting from the release of the mast cell's preformed mediators and occurring within 30 min, and a late phase, owing partly to the release of newly formed mediators and partly to the release of mediators from other infiltrating inflammatory cells that may occur 6–8 h later [28]. It has been noted that patients with CIU exhibit no recognizable late-phase reaction, suggesting that "allergy" (IgE) is probably not the dominant pathogenic mechanism. CU lesions demonstrate an infiltration of basophils, eosinophils, and monocytes. A "concoction" of chemical mediators, determined by the specific secretagogue or trigger, is then released by this cellular infiltrate. Mast cells and basophils, the predominant sources of the body's histamine, have much in common in their mediator content and mechanism of release. Mast cells themselves, in different locations, however, have differences in mediator content, sensitivity to secretagogues, and response to pharmacological agents [98].

The mechanism of degranulation has been best studied with IgE as a secretagogue. IgE antibody binds with its specific high-affinity receptor on the surface of the mast cell. The binding is rapid, tight, persistent, and sensitive. When a threshold number of receptors are "bridged" (1% or fewer of a cell's receptors), the mast cell membrane becomes activated (via the arachidonic acid metabolic pathway) and there is a rapid influx of Ca^{2+} ions from the intercellular space into the mast cell. Basophil activation is calcium dependent and also some IgE-independent secretagogues (e.g. A23187, FMLP) require calcium for activation. A concomitant generation of intracellular cAMP and the presence of Ca^{2+} initiate the movement of the granules toward the cell surface, where they fuse with the cell membrane and secrete their contents into the extracellular space [91].

The complement pathway plays an important role in skin mast-cell degranulation [29, 31, 61, 62]. The anti-FcεRIα autoantibodies in CU patients belong mainly to the complement-fixing subtypes IgGI and IgG3 [31]. These autoantibodies can directly activate histamine release by binding with their receptors. However, the amount of released histamine is increased by complement activation with broad variability within patients [61]. Complement activation liberates component C5a, which directly participates in skin mast-cell degranulation in urticaria patients with anti-FcεRIα autoantibodies. The complement-activating property of anti-FcεRIα is undoubtedly of pathogenic relevance because C5a receptor blockade on basophils as well as decomplementation drastically reduced the histamine-releasing capacity of most anti-FcεRIα-reactive CU sera [62]. Non-immunological direct mast-cell degranulation can occur without involvement of the IgE receptor after exposure to certain drugs. The mechanism by which aspirin and other non-steroidal anti-inflammatory agents induce or exacerbate urticaria remains uncertain, but it is thought to be related to their activity in inhibiting the cyclo-oxygenase pathway of arachidonic acid metabolism and diverting it to pro-inflammatory lipoxygenase pathway products [94].

Although ACE inhibitors are known to cause angioedema alone or along with urticaria [26], the exact pathomechanism is still unknown. Nevertheless, there is evidence that increased levels of bradykinin have a crucial role in the pathogenesis of ACE inhibitor-induced angioedema [11]. ACE inhibitors delay the degradation of potent vasodilators such as bradykinin and substance P through their interaction with the kallikrein-kinin system. The combined effect of decreased peripheral vascular resistance and increased concentration of vasodilators is believed to be the likely mechanism leading to angioedema [97].

Autoimmunity in urticaria

CU appears to be an autoimmune disorder in a substantial fraction of patients. Approximately 35–40% of patients have circulating IgG antibody directed against a subunit of the IgE receptor [53]. An additional 5–10% have antibodies against a subunit of IgE [45]. These anti-

bodies activate basophils and mast cells to release histamine, and complement fixation augments histamine release by the formation of C5a anaphylatoxin [62]. It is not clear whether the numbers of cutaneous mast cells in CU are increased or unchanged, but they definitely respond with a lowered threshold of releasability [35]. Secretagogues trigger mast cell and basophil mediator release immunologically through identifiable receptors on the mast cell surface and non-immunologically without receptor mediation. Therefore CU can be classified as immunological (mediated by IgE or IgE receptors), complement-mediated due to direct mast-cell degranulation, and related to abnormal arachidonic acid metabolism. The concept of autoimmune urticaria has evolved over the past decade as evidence for histamine-releasing autoantibodies and their relationship to disease activity has accrued. Several lines of evidence support this concept. The frequency of atopy in these patients is equal to that in the general population and serum IgE levels are usually normal. Biopsies of CU lesions reveal a perivascular accumulation of eosinophils, mast cells, and activated $CD4^+$ T cells, in contrast to biopsies of lesions in acute urticaria, which are devoid of cellular infiltrates. Recently, IgG class autoantibodies against IgE and/or the high-affinity IgE receptor on mast cells (FcεRI) have been demonstrated in the serum of patients with CU [102]. Many autoimmune diseases have also been reported as associated with CU, including thyroid disease, celiac disease, type 1 diabetes, ulcerative colitis, and others [1, 89]. The response was not seen in healthy subjects. It was also found that the presence of this serum factor related to overall disease activity and might therefore be relevant to its pathogenesis. This skin reactivity to serum from CU patients could be transferred to healthy volunteers.

Pretreatment with alcohol, amphetamine, rifampicin, thiamine, thiopental antihistamines, or the mast cell--degranulating chemical compound 48/80 substantially reduced the response, suggesting that it was histamine and mast-cell dependent [35]. Detailed study of these sera and IgG purified from them showed that they contained functional autoantibodies directed against the alpha subunit of the high-affinity IgE receptor (FcεRIα) on basophils and mast cells [36]. These FcεRIα autoantibodies can be either competitive or noncompetitive.

Autoimmune conditions (thyroid disease, vitiligo, type 1 diabetes, rheumatoid arthritis, and pernicious anemia) are associated more frequently with CU patients having functional autoantibodies than those without autoantibodies [68, 73]. A strong association has recently been shown between *in vitro* basophil histamine-releasing activity and HLA-DR4 and its associated allele DQ8 in CU patients with a positive autologous serum skin test (ASST) response [77]. In autoantibody assays, skin mast cells have been used as target cells in a few studies, but they are more difficult to obtain and require a different source for each experiment. Most immunoassays therefore use donor basophils [98], have found anti-FcεRIα autoantibodies by Western blotting in a high proportion of CU sera [31], and have developed an enzyme-linked immunosorbent assay (ELISA) for FcεRIα autoantibodies, which allows large numbers of serum samples to be screened. The basophil histamine release assay, currently the "gold standard" for detecting functional autoantibodies in the serum of patients with CU, is difficult to standardize because it requires fresh basophils from healthy donors and is time consuming. Western blotting and other nonfunctional assays, including ELISA and flow cytometry using chimeric cell lines expressing the human FcεRIα, may be useful for screening sera in the future, but they need to be validated [32, 92]. The finding that peripheral blood basophils are reduced or absent in patients with CU with histamine-releasing autoantibodies [41, 42] suggests that CU has an autoimmune origin and can be a helpful clinical marker of autoimmune urticaria once rapid and reliable methods for measuring small numbers of circulating basophils are available.

INVESTIGATIONS

The diagnosis of urticaria is primarily clinical [65]. Any investigations should be guided by the history and should not be performed in all patients. Relevant clinical and laboratory tests for the different presentations of urticaria are summarized in Table 3.

Acute urticaria

No investigations are required except where suggested by the history. IgE-mediated reactions to environmental allergens (such as latex, nuts, or fish) as a cause of acute urticaria and contact urticaria can be confirmed by skin-prick testing (where there are facilities) and radioallergosorbent tests on blood [44]. Results of both have to be interpreted in the clinical context.

Chronic urticaria

No investigations are required for the majority of patients with mild disease responding to antihistamines. A useful screening profile for non-responders with more severe disease could include a full blood count and white cell differential (for instance, to detect the eosinophilia of bowel helminth infections) and erythrocyte sedimentation rate (usually normal in CIU but may be raised in urticarial vasculitis). Thyroid autoantibodies should be considered and thyroid function tests performed if thyroid dysfunction is likely. There is currently no routine laboratory test for histamine-releasing autoantibodies, but intradermal injection of autologous serum (ASST) offers a reasonably sensitive and specific screening test [90] in centers with experience.

Physical urticarias

Physical urticarias may occur alone or coexist with ordinary urticaria. International standards for the diag-

Table 3. Recommended diagnostic tests in frequent urticaria subtypes

Group	Subgroup	Routine diagnostic tests	Extended diagnostic program
Spontaneous urticaria	acute urticaria	none	none
	CU	differential blood count and ESR/CRP omission of suspected drugs (e.g. NSAIDs) TSH thyroid autoantibodies C3 and C4	test for: 1) infectious diseases (e.g. *H. pylori*), 2) type I allergy, 3) autoantibodies, 4) physical tests, 5) pseudoallergen-free diet for 3 weeks and tryptase, biopsy
Physical urticaria	cold contact urticaria	cold provocation and threshold test (ice cube, cold water, cold wind)	differential blood count and ESR/CRP
	delayed-pressure urticaria	pressure test (0.2–1.5 kg/cm^2 for 10 and 20 min)	none
	heat contact urticaria	heat provocation and threshold test (warm water)	none
	solar urticaria	UV and visible light of different wave lengths	rule out other light-induced dermatoses
	dermographic urticaria/urticaria factitia	elicit dermographism	differential blood count, ESR/CRP
Other urticaria disorders	aquagenic urticaria	wet cloths at body temperature applied for 20 min	none
	cholinergic urticaria	exercise and hot bath	none
	contact urticaria	prick/patch test read after 20 min	none
	exercise-induced anaphylaxis/urticaria	according to history exercise test with/without food	none

ESR – erythrocyte sedimentation rate, CRP – C-reactive protein, NSAIDs – nonsteroidal anti-inflammatory drugs, TSH – thyroid hormones.

nosis of physical urticarias and definitions of challenge testing have been proposed [63].

Urticarial vasculitis

Lesional skin biopsy is essential to confirm the presence of small-vessel vasculitis histologically (endothelial cell damage, leukocytoclasia, and fibrin deposition are cardinal features). Patients with urticarial vasculitis need a full vasculitis screen, including serum complement assays.

Angioedema without wheals

Hereditary and acquired C1 inhibitor deficiency should be screened by assaying serum C4, which is rapid and inexpensive and with very high sensitivity but low specificity. If low, C1 inhibitor deficiency can be confirmed by quantitative and functional C1 inhibitor assays. However, the diagnosis of hereditary angioedema is not excluded by normal levels of complement C4. Studies of C1 inhibitor should be performed regardless of serum C4 where a high index of clinical suspicion exists [101].

Diagnosis of autoimmune urticaria

The ASST is currently the best *in vivo* clinical test for detecting skin mast-cell histamine-releasing factors and it is a surrogate test for *in vitro* basophil histamine-releasing activity [40]. The ASST a useful screening test for autoimmune CU [17]. In this test, 0.05 ml of the patient's own serum, removed during a period of disease activity, is injected intradermally into the uninvolved forearm skin along with equal volumes of saline and histamine (10 μg/ml) at adjacent sites. The test is read 30 min later. A positive result is recorded if the diameter of the wheal at the serum-injected site is 1.5 mm greater than that of the bleb at the saline-injected site. The standard laboratory test for autoimmune CU is the demonstration and measurement of histamine release from target basophils or dermal mast cells [90].

MANAGEMENT AND THERAPEUTIC OPTIONS

General measures

Nonspecific aggravating factors, such as overheating, stress, alcohol, and drugs with the potential to worsen urticaria (e.g. aspirin and codeine), should be minimized. The risk of cross-reactions between aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) is difficult to quantify, but it may relate to the potency of cyclooxygenase inhibition and dose. In general, NSAIDs should be avoided in aspirin-sensitive urticaria patients. ACE inhibitors should be used with caution in patients with concurrent angioedema or urticaria not caused by the drug. Cooling antipruritic lotions, such as 1% menthol in aqueous cream and calamine lotion, can be soothing. Clearly written information sheets on urticaria and angioedema can be very helpful to patients. It is

important to explain to the patient that the cause of the condition is unlikely to be found.

First line of treatment

Antihistamines. The efficacy and safety of antihistamines in urticaria is undisputed. Nearly all symptoms of urticaria are primarily mediated by H1-receptors located on nerves and endothelials. Thus H1-receptor antagonists are of eminent importance in the treatment of urticaria, although not all patients respond and some, very occasionally, become worse. The development of second-generation non-sedating or low-sedating antihistamines has allowed improvement in the quality of life of urticaria patients. New-generation antihistamines also exert anti-inflammatory effects such as cytokine release from basophils and mast cells [69, 70]. The effect of antihistamines in urticaria is dose dependent [64, 113] and higher dosages are usually well tolerated, but care must be taken as side-effects such as sedation can occur more frequently in some cases at higher dosages. Fexofenadine, loratadine, and mizolastine are taken once daily. Acrivastine is taken three times a day in view of its short half-life (1.5 h). Cetirizine, the active metabolite of hydroxyzine, is minimally sedating. Mizolastine is contraindicated in heart failure and when there is prolongation of the Q-T interval. It should be avoided with drugs which inhibit hepatic metabolism via cytochrome P450 (including macrolide antibiotics and imidazole antifungals) and with drugs that have potential arrythmic properties (including tricyclic antidepressants, such as doxepin).

Third-generation antihistamines significantly suppress the release by mast cells of histamine as well as the secretion, by various effector cells, of pro-inflammatory eicosanoids and leukotrienes, cytokines including interleukins, and chemokines as well as adhesion molecules. They inhibit eosinophil migration through endothelial cells, downregulate vascular cell adhesion molecule (VCAM)-1 mRNA activation and VCAM-1 expression in endothelial cells, and block NF-κB induction. There are no untoward or neurobehavioral effects such as sedation or motor impairment. They do not induce QTc prolongation or other adverse electrocardiographic effects (cardiac arrythmias/torsade de pointes). There is no concern about possible cardiac arrythmias as there are no drug interactions with co-administration with erythromycin or ketoconazole. They do not interact with cytochrome P450 inhibitors such as cimetidine, cyclosporine, and nifedipine. They have rapid absorption and its extent is not altered by food. They also have a high affinity, persistent binding, and specificity for H1 receptors. There is no problem of tachyphylaxis, which is seen with the sedative antihistamines. Safe and well tolerated, they represent a major advance in the management of urticaria. Levocetirazine is the active enantiomer of the racemate cetirizine, fexofenadine the active metabolite of terfinadine, and desloratadine an active metabolite of loratadine [66]. Levocetirizine is from the latest generation approved for CU and also demonstrated a broad anti-inflammatory effect in patients with CU [18, 59]. The majority of patients with urticaria can be controlled on the above-mentioned new-generation antihistamines. In cases of severe refractory CIU, the new-generation antihistamine dosage can be doubled. A recent randomized double-blind study of 116 CU patients comparing cetirizine (10 mg) with fexofenadine (180 mg) showed that with cetirizine a significantly higher proportion of patients responded with clearance (52%) of symptoms than with fexofenadine (4%) after one month of treatment. Similar proportions of patients showed partial improvements (37 and 42%, respectively) [47].

All patients should be offered the choice of at least two non-sedating H1 antagonists because responses and tolerance vary among individuals. It is common practice to increase the dose above the manufacturer's licensed recommendation when the potential benefits are considered to outweigh any risks. "Antiallergic" effects on mast-cell mediator release of possible clinical importance have been shown with cetirizine [99] and loratadine [15], especially at higher doses. Adjustments to the timing of medication can be helpful to ensure that the highest drug levels are obtained when urticaria is expected to be most active. The addition of an H2 antagonist, on the other hand, may give better control of urticaria than H1 antagonists alone [13, 82], although a benefit is not always seen.

Management plan for CU and angioedema. It should be started by the identification of triggers, education, and avoidance of these triggers. Although the subtypes of urticaria are elicited by a great variety of factors, their treatment mainly follows some basic principles [85]. These are: 1) start with the standard dose of a non-sedating H1 anti-histamine such as cetirizine, levocetirizine, desloratadine, fexafenadine, loratadine, etc., 2) alternative H1-antihistamine or a higher dose, 3) add a second non-sedating H1-antihistamine or add a first-generation H1-antihistamine to be taken in the evening; different types or combinations should be tried for the best response, 4) consider adding anti-leukotriene, and 5) immune modifiers and other specialist treatments.

Second-line of treatment

The second-step therapies should be used in cases of CU and angioedema resistant to high-dose antihistamines. There is no accepted second-line therapy, but treatment options may be considered depending on the presenting clinical symptoms, specific trigger factors, and underlying pathology.

Corticosteroids. There are no controlled studies on the use of corticosteroids in urticaria and angioedema, but their effectiveness is generally accepted. Oral corticosteroids may shorten the duration of acute urticaria (e.g. prednisolone 50 mg/day for 3 days in adults) [112]. Intravenous hydrocortisone is a useful adjunct for severe laryngeal edema and anaphylaxis when given as

a stat dose, although its action is delayed. Short tapering courses of oral steroids over 3–4 weeks may be necessary for urticarial vasculitis and severe delayed-pressure urticaria, but long-term oral corticosteroids should not be used in CU except in very selected cases under regular specialist supervision.

Leukotriene receptor antagonists (Montelukast, Zafirlukast). These are more effective in combination with antihistamines for treating autoimmune urticaria, CU with positive challenge to food, food additives, or aspirin, and delayed-pressure urticaria [8, 25, 78, 83, 88].

Epinephrine (syn. adrenaline). Intramuscular or subcutaneous epinephrine can be life-saving in anaphylaxis and in severe laryngeal angioedema, but it should be used with caution in hypertension and ischemic heart disease.

Cyclosporine. This is an immunosuppressive agent, i.e. it requires monitoring of blood pressure, renal and liver functions, and serum levels if indicated. The potential side effects of cyclosporine preclude long-term high dosages in the treatment of urticaria, but it may be an effective alternative to corticosteroids for short-term crisis management to break the cycle of a resistant episode [39, 10]. The common side effects are gastrointestinal disturbance, headache, insomnia, tremor, and numbness. These accompanying effects resolve after treatment is stopped or the dose is reduced [103]. More serious side effects are seen with higher doses, i.e. more than 5 mg/kg/day; they include nephrotoxicity, hypertension, and abnormal liver functions. Cyclosporine should be retained for recalcitrant cases of CU, especially those which appear to be of autoimmune origin. Consequently, it can lower the levels of both IgG anti-IgE or anti-FcεRIα autoantibodies [6, 10, 39, 71, 103]. Low-dose cyclosporin (3 mg/kg/day) given as two doses for 6 weeks followed by 3 weeks at 2 mg/kg/day and finally 1 mg/kg/day for another 3 weeks is effective and safe in patients with CU whose response to conventional therapy is dissatisfactory [6, 39, 71, 103]. An evidence-based update report considered cyclosporine as one of the most useful and rather well-studied alternative drug for treating severely affected patients [107]. The effectiveness of cyclosporine (4 mg/kg daily) in combination with cetirizine for the treatment of CIU was shown in a recent multicenter randomized controlled trial [105].

Nifedipine has showed benefits in CU when added to maximum doses of H1 and H2 antihistamines [16].

Other therapeutic options

Alternative treatments are needed for patients with unremitting and extremely severe disease unresponsive to standard treatments. As the side effects of many of these substances are considerable, it may be wise to try to use them as add-on therapy to antihistamines first, or to use combinations to be able to have lower dosages of these medications. Many of the alternatives are based on open trials or case reports.

For chronic autoimmune urticaria, a high dose of intravenous immunoglobulin has been found to be associated with some apparent benefits [37]. Plasmapheresis has been used to treat some patients with autoantibody-positive severe CU [75].

Tacrolimus has value in severe, steroid-dependent CU, but needs further randomized controlled studies [21, 60]. Tranexamic acid showed reduced frequency of angioedema attacks [21, 67]. Micofenolate, an immunosuppressive agent, has shown a promising role in treating patients with refractory CIU [93]. Danazol, an anabolic steroid which is normally used to treat angioedema as part of C1 esterase inhibitor deficiency, may be used for severe cholinergic urticaria [79]. There is a clear rationale for treating the hypothyroid state with thyroxin; however, the use of thyroxin in a euthyroid subject is controversial and not recommended [7]. In a recent placebo-controlled study, autohemotherapy has shown a beneficial role in ASST-positive CU patients [100]. According to some reports, colchicine (neutrophil inhibitor), low-dose methotrexate, hydroxychloroquine, cyclophosphamide, sulfasalazine, and dapsone, which have immunomodulatory properties, are effective in the treatment of CU [5, 12, 14, 33, 48, 87].

These studies lack underpinning by controlled trial data and should be limited for use in difficult cases and only considered in specialist centers.

Future directions-emerging treatments for CU

Interestingly, published studies showed that warfarin, an anticoagulant drug, induced a dramatic response in some patients with CU unresponsive to antihistamines in a double-blinded placebo-controlled study [80]. Furthermore, published case reports showed the effectiveness of heparin as a treatment for CU [20]. This supported the possibility that patients with CU could derive clinical benefit from anticoagulants, and the therapy may interfere with pathogenic mechanisms involved in CU. Evidence supporting this was obtained in recent findings that in patients with CU, plasma shows signs of thrombin generation and autologous plasma skin tests score positive in as many as 95% of cases, and that plasma from patients with both autoimmune and "idiopathic" CU is frequently characterized by signs of thrombin activation (plasma levels of prothrombin fragment F1.2 are significantly increased), suggesting that the clotting cascade might be somehow involved in the pathogenesis of CU [2–4, 109].

Finally, the results of these current studies seem to open some new insights into the effect of drugs active on the coagulation system in the management of CU. Nonetheless, the long-term effects of these medications on plasma thrombin are pending further observations and remain to be studied further.

CONCLUSION

Urticaria often remains idiopathic after allergic, infectious, physical, and drug-related causes have been

excluded as far as possible. At least 30% of patients with chronic idiopathic disease appear to have an autoimmune etiology. An impressive number of studies carried out during the last decade succeeded in shedding some light on the pathogenic mechanisms underlying a relevant proportion of CU cases. The activation of cutaneous mast cells appears to be caused by a combination of direct cross-linking of the high-affinity IgE receptor (or IgE) and the anaphylatoxin C5a. However, several aspects, including the true effects of autoantibodies *in vivo*, remain controversial and deserve further investigation. New strategies in the management of urticaria include the introduction of third-generation antihistamines, including levocetirizine, fexafenadine, and desloratadine. Chronic idiopathic urticaria is no longer the diagnosis of despair that it used to be. Establishing an autoimmune basis helps patients to cope with the problem and the use of immunosuppressive therapy is becoming a realistic option. Furthermore, the involvement of the coagulation pathway in CU opens new perspectives for a better understanding of the pathogenesis and, possibly, the treatment of this disease.

REFERENCES

1. Asero R., Orsatti A., Tedeschi A. and Lorini M. (2005): Autoimmune chronic urticaria associated with type 1 diabetes and Graves' disease. J. Allergy Clin. Immunol., **115**, 1088–1089.
2. Asero R. and Tedeschi A. (2006): Emerging drugs for chronic urticaria. Expert Opin. Emerg. Drugs, **11**, 265–274.
3. Asero R., Tedeschi A., Coppola R., Griffini S., Paparella P., Riboldi P., Marzano A., Fanoni D. and Cugno M. (2007): Activation of the tissue factor pathway of blood coagulation in patients with chronic urticaria. J. Allergy Clin. Immunol., **119**, 705–710.
4. Asero R., Tedeschi A., Riboldi P. and Cugno M. (2006): Plasma of patients with chronic urticaria shows signs of thrombin generation, and its intradermal injection causes wheal-and-flare reactions much more frequently than autologous serum. J. Allergy Clin. Immunol., **117**, 1113–1117.
5. Asherson R. A., Buchanan N., Kenwright S., Fletcher C. M. and Hughes G. R. (1991): The normocomplementemic urticarial vasculitis syndrome – report of a case and response to colchicine. Clin. Exp. Dermatol., **16**, 424–427.
6. Atkins F. M. (1991): Food induced urticaria. In Metcalfe D. D., Sampson H. A. and Simon R. A. (eds.): Food allergy: adverse reactions to food and food additives. Blackwell Scientific Publication, Oxford, pp. 129–138.
7. Aversano M., Caiazzo P., Iorio G., Ponticiello L., Lagana B., Leccese F. (2005): Improvement of chronic idiopathic urticaria with L-thyroxin: a new TSH role in immune response? Allergy, **60**, 489–493.
8. Bagenstose S. E., Levin L. and Bernstein J. A. (2004): The addition of zafirlukast to cetirizine improves the treatment of chronic urticaria in patients with positive autologous serum skin test results. J. Allergy Clin. Immunol., **113**, 134–140.
9. Barlow R. J., Ross E. L., MacDonald D., Black A. K. and Greaves M. W. (1994): Adhesion molecule expression and the inflammatory cell infiltrate in delayed pressure urticaria. Br. J. Dermatol., **131**, 341–347.
10. Baskan E. B., Tunali S., Turker T. and Saricaoglu H. (2004): Comparison of short and long term cyclosporine A therapy in chronic idiopathic urticaria. J. Dermatolog. Treat., **15**, 164–168.
11. Beltrami L., Zingale L. C., Carugo S. and Cicardi M. (2006): Angiotensin-converting enzyme inhibitor-related angioedema: how to deal with it. Expert Opin. Drug Saf., **5**, 643–649.
12. Bernstein J. A., Garramone S. M. and Lower E. G. (2002): Successful treatment of autoimmune chronic idiopathic urticaria with intravenous cyclophosphamide. Ann. Allergy Asthma Immunol., **89**, 212–214.
13. Bleehen S. S., Thomas S. E., Greaves M. W., Newton J., Kennedy C. T., Hindley F., Marks R., Hazell M., Rowell N. R. and Fairiss G. M. (1987): Cimetidine and chlorpheniramine in the treatment of chronic idiopathic urticaria: a multi-centre randomized double-blind study. Br. J. Dermatol., **117**, 81–88.
14. Boehm I., Bauer R. and Bieber T. (1999): Urticaria treated with dapsone. Allergy, **54**, 765–766.
15. Bousquet J., Czarlewski W. and Danzig M. R. (1995): Antiallergic properties of loratadine: a review. Adv. Ther., **12**, 283–328.
16. Bressler R. B., Sowell K. and Huston D. P. (1989): Therapy of chronic idiopathic urticaria with nifedipine: demonstration of beneficial effect in a double-blinded, placebo-controlled, crossover trial. J. Allergy Clin. Immunol., **83**, 756–763.
17. Caproni M., Giomi B., Volpi W., Melani L., Schincaglia E., Macchia D., Manfredi M., D'Agata A. and Fabbri P. (2005): Chronic idiopathic urticaria: infiltrating cells and related cytokines in autologous serum-induced wheals. Clin. Immunol., **114**, 284–292.
18. Caproni M., Volpi W., Giomi B., Torchia D., Del Bianco E. and Fabbri P. (2006): Cellular adhesion molecules in chronic urticaria: modulation of serum levels occurs during levocetirizine treatment Br. J. Dermatol., **155**, 1270–1274.
19. Champion R. H., Roberts S. O., Carpenter R. G. and Roger J. H. (1969): Urticaria and angiooedema: a review of 554 patients. Br. J. Dermatol., **81**, 588–597.
20. Chua S. L. and Gibbs S. (2005): Chronic urticaria responding to subcutaneous heparin sodium. Br. J. Dermatol., **153**, 216–217.
21. Cicardi M., Bergamaschini L., Zingale L. C., Gioffre D. and Agostoni A. (1999): Idiopathic nonhistaminergic angioedema. Am. J. Med., **106**, 650–654.
22. Clive E. H., Ruth A. and Malcom W. (2002): Chronic urticaria. J. Am. Acad. Dermatol., **46**, 645–657.
23. Coleman J. W. and Godfrey R. C. (1981): The number and affinity of IgE receptors on dispersed human lung mast cells. Immunology, **44**, 859–861.
24. Crespo J. F., Pascual C., Burks A. W., Helm R. M. and Esteban M. M. (1995): Frequency of food allergy in a pediatric population from Spain. Pediatr. Allergy Immunol., **6**, 39–43.
25. Di Lorenzo G., Pacor M., Mansueto P., Esposito Pellitteri M., Lo Bianco C., Ditta V., Martinelli N. and Rini G. B. (2004): Randomized placebo-controlled trial comparing desloratadine and montelukast in monotherapy and desloratadine plus montelukast in combined therapy for chronic idiopathic urticaria. J. Allergy Clin. Immunol., **114**, 619–625.
26. Dumpiérrez A. G., Almeida L., Blanco C., Castillo R., Ortega N. and Carrillo T. (2000): Angioedema caused by angiotensin converting enzyme inhibitors. Allergol. Immunol. Clin., **15**, 396–399.

27. Du Toit G. (2003): Chronic urticaria. Curr. Allergy Clin. Immunol., **16**, 106–111.
28. Elias J., Boss E. and Kaplan A. P. (1986): Studies of the cellular infiltrate of chronic idiopathic urticaria: prominence of T-lymphocytes, monocytes, and mast cells. J. Allergy Clin. Immunol., **78**, 914–918.
29. Fagiolo U., Kricek F., Ruf C., Peserico A., Amadori A. and Cancian M. (2000): Effects of complement inactivation and IgG depletion on skin reactivity to autologous serum in chronic idiopathic urticaria. J. Allergy Clin. Immunol., **106**, 567–572.
30. Ferrer M., Kinet J. P. and Kaplan A. P. (1998): Comparative studies of functional and binding assays for IgG anti-FcεRIα (α-subunit) in chronic urticaria. J. Allergy Clin. Immunol., **101**, 672–676.
31. Fiebiger E., Hammerschmid F., Stingl G. and Maurer D. (1998): Anti-FcεRIα autoantibodies in autoimmune disorders. Identification of a structure-function relationship. J. Clin. Invest., **101**, 243–251.
32. Fiebiger E., Maurer D., Holub H., Reininger B., Hartmann G., Woisetschlager M., Kinet J. P. and Stingl G. (1995): Serum IgG autoantibodies directed against the a chain of FcεRIα: a selective marker and pathogenetic factor for a distinct subset of chronic urticaria patients? J. Clin. Invest., **96**, 2606–2612.
33. Gach J. E., Sabroe R. A., Greaves M. W. and Black A. K. (2001): Methotrexate-responsive chronic idiopathic urticaria: A report of two cases. Br. J. Dermatol., **145**, 340–343.
34. Godse K. V. (2004): Autologous serum skin test in chronic idiopathic urticaria. Indian J. Dermatol. Venereol. Leprol., **70**, 283–284.
35. Grattan C. E. and Francis D. M. (1999): Autoimmune urticaria. Adv. Dermatol., **15**, 311–340.
36. Grattan C. E., Francis D. M., Hide M. and Greaves M. W. (1991): Detection of circulating histamine releasing autoantibodies with functional properties of anti-IgE in chronic urticaria. Clin. Exp. Allergy, **21**, 695–704.
37. Grattan C. E., Francis D. M., Slater N. G., Barlow R. J. and Greaves M. W. (1992): Plasmapheresis for severe, unremitting, chronic urticaria. Lancet, **339**, 1078–1080.
38. Grattan C. E. and Kobza Black A. (2003): Urticaria and angioedema. In Bolognia J. L., Jorizzo J. L. and Rapini R. D. (eds.): Dermatology. Mosby, Philadelphia, **1**, pp. 289–302.
39. Grattan C. E., O'Donnell B. F., Francis D. M., Niimi N., Barlow R. J., Seed P. T., Kobza Black A. and Greaves M. W. (2000): Randomized double-blind study of cyclosporin in chronic "idiopathic" urticaria. Br. J. Dermatol., **143**, 365–372.
40. Grattan C. E., Sabroe R. A. and Greaves M. W. (2002): Chronic urticaria. J. Am. Acad. Dermatol., **46**, 657–660.
41. Grattan C. E., Wallington T. B., Warin R. P., Kennedy C. T. and Bradfield J. W. (1986): A serological mediator in chronic idiopathic urticaria – a clinical, immunological and histological evaluation. Br. J. Dermatol., **114**, 583–590.
42. Grattan C. E., Walpole D., Francis D. M., Niimi N., Dootson G., Edler S., Corbett M. F. and Barr R. M. (1997): Flow cytometric analysis of basophil numbers in chronic urticaria: basopenia is related to serum histamine releasing activity. Clin. Exp. Allergy, **27**, 1417–1424.
43. Greaves M. W. (2001): Chronic idiopathic urticaria (CIU) and *Helicobacter pylori* not directly causative, but could there be a link? Allergy Clin. Immunol. Int., **13**, 23–26.
44. Greaves M. W. and Sabroe R. A. (1998): ABC of allergies. Allergy and the skin. I. Urticaria. BMJ, **316**, 1147–1150.
45. Gruber B. L., Baeza M., Marchese M., Agnello V. and Kaplan A. P. (1988): Prevalence and functional role of anti-IgE autoantibodies in urticarial syndromes. J. Invest. Dermatol., **90**, 213–217.
46. Haas N., Schadendorf D. and Henz B. M. (1998): Endothelial adhesion molecules in immediate and delayed urticarial whealing reactions. Int. Arch. Allergy Immunol., **115**, 210–214.
47. Handa S., Dogra S. and Kumar B. (2004): Comparative efficacy of cetirizine and fexofenadine in the treatment of chronic idiopathic urticaria. J. Dermatolog. Treat., **15**, 55–57.
48. Hartmann K., Hani N., Hinrichs R., Hunzelmann N. and Scharffetter-Kochanek K. (2001): Successful sulfasalazine treatment of severe chronic idiopathic urticaria associated with pressure urticaria. Acta Dermatol. Venereol., **81**, 71.
49. Herberden W. (1772): Of the Nettle Rash. Medical Transactions, College of Physicians, London, **2**, 173–191.
50. Hermes B., Prochazka A. K., Haas N., Jurgovsky K., Sticherling M. and Henz B. M. (1999): Upregulation of tumor necrosis and interleukin-3 expression in lesional and uninvolved skin in different types of urticaria. J. Allergy Clin. Immunol., **103**, 307–314.
51. Hernandez Garcia J., Garcia Selles J., Negro Alvarez J. M., Pagan Aleman J. A. and Lopez Sanchez J. D. (1994): Incidence of adverse reactions to additives. Our experience over ten years. Allergol. Immunopathol., **22**, 233–242.
52. Hesselmar B., Eriksson B. and Åberg N. (2007): Urticaria is associated with birch-pollen sensitization. Pediatr. Allergy Immunol., **18**, 692–695.
53. Hide M., Francis D. M., Grattan C. E., Hakimi J., Kochan J. P. and Greaves M. W. (1993): Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. N. Engl. J. Med., **328**, 1599–1604.
54. Hosseini-Farahabadi S., Tavakkol-Afshari J., Rafatpanah H., Farid-Hosseini R. and Khaje Daluei M. (2006): Association between the polymorphism of TGF-beta1 gene promoter (–509C>T) and idiopathic chronic urticaria. Iran J. Allergy Asthma Immunol., **5**, 109–113.
55. Jansen S. C., van Dusseldorp M., Bottema K. C. and Dubois A. E. (2003): Intolerance to biogenic amines: a review. Ann. Allergy Asthma Immunol., **91**, 233–241.
56. Joral A., Villas F., Garmendia J. and Villareal O. (1995): Adverse reactions to food in adults. J. Investig. Allergol. Clin. Immunol., **5**, 47–49.
57. Kaplan A. P. (1998): Urticaria and angioedema. In Middleton E. Jr., Reed C. E., Ellis E. F., Adkinson N. F. Jr., Yunginger J. W. and Busse W. W. (eds.): Allergy: principles and practice. 5th ed. Mosby, St. Louis, **2**, pp. 1104–1122.
58. Kaplan A. P. (2004): Chronic urticaria: pathogenesis and treatment. J. Allergy Clin. Immunol., **114**, 465–474.
59. Kapp A. and Pichler W. J. (2006): Levocetirizine is an effective treatment in patients suffering from chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled, parallel, multicenter study. Int. J. Dermatol., **45**, 469–474.
60. Kessel A., Bamberger E. and Toubi E. (2005): Tacrolimus in the treatment of severe chronic idiopathic urticaria: an open-label prospective study. J. Am. Acad. Dermatol., **52**, 145–148.
61. Kikuchi Y. and Kaplan A. P. (2001): Mechanisms of autoimmune activation of basophils in chronic urticaria. J. Allergy Clin. Immunol., **107**, 1056–1062.

62. Kikuchi Y. and Kaplan A. P. (2002): A role of C5a in augmenting IgG-dependent histamine release from basophils in chronic urticaria. J. Allergy Clin. Immunol., **109**, 114–118.
63. Kobza Black A., Lawlor F. and Greaves M. W. (1996): Consensus meeting on the definition of physical urticarias and urticarial vasculitis. Clin. Exp. Dermatol., **21**, 424–426.
64. Kontou-Fili K., Maniakatou G., Demaka P. and Paleologos G. (1989): Therapeutic effect of cetirizine 2HCl in delayed pressure urticaria. Health Sci. Rev., **3**, 23–25.
65. Kozel M. M., Mekkes J. R., Bossuyt P. M. and Bos J. D. (1998): The effectiveness of a history-based diagnostic approach in chronic urticaria and angioedema. Arch. Dermatol., **134**, 1575–1580.
66. Lachapelle J. M., Decroix J., Henrijean A., Roquet-Gravy P. P., De Swerdt A., Boonen H., Lecuyer M., Suys E., Speelman G. and Vastesaeger N. (2006): Desloratadine 5 mg once daily improves the quality of life of patients with chronic idiopathic urticaria. J. Eur. Acad. Dermatol. Venereol., **20**, 288–292.
67. Laurberg G. (1977): Tranexamic acid (Cyklokapron) in chronic urticaria: a double-blind study. Acta Dermatol. Venereol., **57**, 369–370.
68. Leznoff A. and Sussman G. L. (1989): Syndrome of idiopathic chronic urticaria and angioedema with thyroid autoimmunity: a study of 90 patients. J. Allergy Clin. Immunol., **84**, 66–671.
69. Lippert U., Kruger-Krasagakes S., Moller A., Kiessling U. and Czarnetzki B. M. (1995): Pharmacological modulation of IL-6 and IL-8 secretion by the H1-antagonist descarboethoxy-loratadine and dexamethasone from human mast and basophilic cell lines. Exp. Dermatol., **4**, 272–276.
70. Lippert U., Moller A., Welker P., Artuc M., Grutzkau A. and Henz B. M. (2000): Inhibition of cytokine secretion from human mast cells and basophils by H1- and H2--receptor antagonists. Exp. Dermatol., **9**, 118–124.
71. Mahesh P. A., Kushalappa P. A., Holla Amrutha D. and Vedanthan P. K. (2005): House dust mite sensitivity is a factor in chronic urticaria. Indian J. Dermatol. Venereol. Leprol., **71**, 99–101.
72. Moneret-Vautrin D. A. and Kanny G. (1995): Food induced anaphylaxis. A new French multicenter survey. Ann. Gastroenterol. Hepatol., **31**, 256–263.
73. Monge C., Demarco P., Burman K. D. and Wartofsky L. (2007): Autoimmune thyroid disease and chronic urticaria. Clin. Endocrinol., **67**, 473–475.
74. Nielsen E. W. (2005): Hypotensive shock and angio-oedema from angiotensin II receptor blocker: a class effect in spite of tripled tryptase values. J. Intern. Med., **258**, 385–387.
75. O'Donnell B. F., Barr R. M., Kobza Black A., Francis D. M., Kermani F., Niimi N., Barlow R. J., Winkelmann R. K. and Greaves M. W. (1998): Intravenous immunoglobulin in autoimmune chronic urticaria. Br. J. Dermatol., **138**, 101–106.
76. O'Donnell B. F., Lawlor F., Simpson J., Morgan M. and Greaves M. W. (1997): The impact of chronic urticaria on the quality of life. Br. J. Dermatol., **136**, 197–201.
77. O'Donnell B. F., O'Neill C. M., Francis D. M., Niimi N., Barr R. M., Barlow R. J., Kobza Black A., Welsh K. I. and Greaves M. W. (1999): Human leucocyte antigen class II associations in chronic idiopathic urticaria. Br. J. Dermatol., **140**, 853–858.
78. Pacor M. L., Di Lorenzo G. and Corrocher R. (2001): 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, **31**, 1607–1614.
79. Parsad D., Pandhi R. and Juneja A. (2001): Stanozolol in chronic urticaria: a double blind, placebo controlled trial. J. Dermatol., **28**, 299–302.
80. Parslew R., Pryce D., Ashworth J. and Friedmann P. S. (2000): Warfarin treatment of chronic idiopathic urticaria and angio-oedema. Clin. Exp. Allergy, **30**, 1161–1165.
81. Pasaoglu G., Bavbek S., Tugcu H., Abadoglu O. and Misirligil Z. (2006): Psychological status of patients with chronic urticaria. J. Dermatol., **33**, 765–771.
82. Paul E. and Bodeker R. H. (1986): Treatment of chronic urticaria with terfenadine and ranitidine: a randomized double-blind study in 45 patients. Eur. J. Clin. Pharmacol., **31**, 277–280.
83. Perez C., Sanchez-Borges M. and Capriles E. (2001): Pretreatment with montelukast blocks NSAID-induced urticaria and angioedema. J. Allergy Clin. Immunol., **108**, 1060–1061.
84. Poon E., Seed P. T., Greaves M. W. and Kobza-Black A. (1999): The extent and nature of disability in different urticarial conditions. Br. J. Dermatol., **140**, 667–671.
85. Powell R. J., Du Toit G. L., Siddique N., Leech S. C., Dixon T. A., Clark A. T., Mirakian R., Walker S. M., Huber P. A. and Nasser S. M. (2007): BSACI guidelines for the management of chronic urticaria and angio-oedema. Clin. Exp. Allergy, **37**, 631–650.
86. Ramam M. (2005): Wheat induced urticaria? Indian J. Dermatol. Venereol. Leprol., **71**, 211–212.
87. Reeves G. E., Boyle M. J., Bonfield J., Dobson P. and Loewenthal M. (2004): Impact of hydroxychloroquine therapy on chronic urticaria: chronic autoimmune urticaria study and evaluation. Intern. Med. J., **34**, 182–186.
88. Reimers A., Pichler C., Helbling A., Pichler W. J. and Yawalkar N. (2002): Zafirlukast has no beneficial effects in the treatment of chronic urticaria. Clin. Exp. Allergy, **32**, 1763–1768.
89. Rottem M. (2003): Chronic urticaria and autoimmune thyroid disease: is there a link? Autoimmun. Rev., **2**, 69–72.
90. Sabroe R. A., Grattan C. E., Francis D. M., Barr R. M., Kobza Black A. and Greaves M. W. (1999): The autologous serum skin test: a screening test for autoantibodies in chronic idiopathic urticaria. Br. J. Dermatol., **140**, 446–453.
91. Sabroe R. A., Poon E., Orchard G. E., Lane D., Francis D. M., Barr R. M., Black M. M., Black A. K. and Greaves M. W. (1999): Cutaneous inflammatory cell infiltrate in chronic idiopathic urticaria: comparison of patients with and without anti-FcεRI or anti-IgE autoantibodies. J. Allergy Clin. Immunol., **103**, 484–493.
92. Sabroe R. A., Seed P. T., Francis D. M., Barr R. M., Kobza Black A. and Greaves M. W. (1999): Chronic idiopathic urticaria: comparisons of the clinical features of patients with and without anti-FcεRIα or anti-IgE autoantibodies. J. Am. Acad. Dermatol., **40**, 443–450.
93. Shahar E., Bergman R., Guttman-Yassky E. and Pollack S. (2006): Treatment of severe chronic idiopathic urticaria with oral mycophenolate mofetil in patients not responding to antihistamines and/or corticosteroids. Int. J. Dermatol., **45**, 1224–1227.
94. Shalit M., Schwartz L. B., von Allmen C., Atkins P. C., Lavker R. M. and Zweiman B. (1990): Release of histamine and tryptase during continuous and interrupted cutaneous challenge with allergens in humans. J. Allergy Clin. Immunol., **116**, 117–125.

95. Sibbald R. G., Cheema A. S., Lozinski A. and Tarlo S. (1991): Chronic urticaria: evaluation of the role of physical, immunologic, and other contributory factors. Int. J. Dermatol., **30**, 381–386.
96. Siddique N., Pereira B. N. and Hasan Arshad S. (2004): Hepatitis C and urticaria: cause and effect? Allergy, **59**, 668.
97. Slater E. E., Merrill D. D., Guess H. A., Roylance P. J., Cooper W. D., Inman W. H. and Ewan P. W. (1988): Clinical profile of angioedema associated with angiotensin converting enzyme inhibition. JAMA, **260**, 967–970.
98. Soter N. A. and Kaplan A. P. (2003): Urticaria and angioedema. In Freedberg I. M., Eisen A. Z. and Wolff K. (eds.): Fitzpatrick's, dermatology in general medicine. McGraw-Hill, New York, pp. 1129–1139.
99. Spencer C. M., Faulds D. and Peters D. H. (1993): Cetirizine: A reappraisal of its pharmacological properties and therapeutic use in selected allergic disorders. Drug, **46**, 1055–1080.
100. Staubach P., Onnen K., Vonend A., Metz M., Siebenhaar F., Tschentscher I., Opper B., Magerl M., Lüdtke R., Kromminga A. and Maurer M. (2006): Autologous whole blood injections to patients with chronic urticaria and a positive autologous serum skin test: A placebo-controlled trial. Dermatology, **212**, 150–159.
101. Tarzi M. D., Hickey A., Förster T., Mohammadi M. and Longhurst H. J. (2007): An evaluation of tests used for the diagnosis and monitoring of C1 inhibitor deficiency: normal serum C4 does not exclude hereditary angio-oedema. Clin. Exp. Immunol., **149**, 513–516.
102. Toubi E. (2004): Clinical and laboratory parameters in predicting chronic urticaria duration: a prospective study of 139 patients. Allergy, **59**, 869–873.
103. Toubi E., Blant A., Kessel A. and Golan T. D. (1997): Low-dose cyclosporin A in the treatment of severe chronic idiopathic urticaria. Allergy, **52**, 312–316.
104. Uppal M. and Srinivas C. R. (2004): Wheat induced urticaria. Indian J. Dermatol. Venereol. Leprol., **70**, 298–299.
105. Vena G. A., Cassano N., Colombo D., Peruzzi E. and Pigatto P. (2006): Cyclosporine in chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled trial. J. Am. Acad. Dermatol., **55**, 705–709.
106. Wedi B. and Kapp A. (2002): *Helicobacter pylori* infection in skin diseases: a critical appraisal. Am. J. Clin. Dermatol., **3**, 273–282.
107. Wedi B. and Kapp A. (2007): Evidence-based therapy of chronic urticaria. J. Dtsch. Dermatol. Ges., **5**, 146–157.
108. Wedi B., Raap U. and Kapp A. (2004): Chronic urticaria and infections. Curr. Opin. Allergy Clin. Immunol., **4**, 387–396.
109. Xiaoming L., Wanxiang S., Khalaf A. T., Jiquan S. and Jinquan T. (2007): Relation between autoimmunity chronic urticaria and the levels of plasma prothrombin F1+2. Am. J. App. Sc., **4**, 965–969.
110. Zuberbier T., Bindslev-Jensen C., Canonica W., Grattan C. E., Greaves M. W., Henz B. M., Kapp A., Kozel M. M., Maurer M., Merk H. F., Schäfer T., Simon D., Vena G. A. and Wedi B. (2006): EAACI/GA2LEN/EDF guideline: definition, classification and diagnosis of urticaria. Allergy, **61**, 316–320.
111. Zuberbier T., Greaves M. W., Juhlin L., Kobza-Black A., Maurer D., Stingl G. and Henz B. M. (2001): Definition, classification, and routine diagnosis of urticaria: a consensus report. J. Investig. Dermatol. Symp. Proc., **6**, 123–127.
112. Zuberbier T., Ifflander J., Semmler C. and Henz B. M. (1996): Acute urticaria: clinical aspects and therapeutic responsiveness. Acta Dermatol. Venereol., **76**, 295–297.
113. Zuberbier T., Munzberger C., Haustein U., Trippas E., Mariz S. D. and Czarnetzki B. M. (1996): Double-blind crossover study of high dose cetirizine in cholinergic urticaria. Dermatology, **193**, 324–327.
114. Zuberbier T., Schadendorf D., Haas N., Hartmann K. and Henz B. M. (1997): Enhanced P-selectin expression in chronic and dermographic urticaria. Int. Arch. Allergy Clin. Immunol., **114**, 86–89.