

Italian position paper on urticaria

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The Italian Board on Urticaria has prepared a document focusing on the definition and classification of urticaria, taking into account the recent progress in identifying the causes, eliciting factors, and pathomechanisms of this disease. As urticaria has a profound impact on the quality of life, effective treatment is important. Therefore, specific treatment options for the management of urticaria are evaluated on the basis of the recent literature. Non-sedating H₁ antihistamines are recommended as the first-line treatment as they have proven effective in several randomized double-blind controlled studies. Dosages higher than those recommended may be necessary in some cases. However, additional or alternative therapies may be required for different urticaria subtypes and in view of individual variations in the course of the disease and response to treatment. Immunosuppressive drugs such as corticosteroids are not recommended for long-term treatment due to unavoidable, severe adverse effects.

KEY WORDS: Urticaria - Immunosuppressive agents - Adrenal cortex hormones.

Urticaria was described as a distinct entity by Hippocrates, but the different subtypes were recognized only during the early 1900s. This disease is characterized by transient, more or less diffuse, and intensely pruritic wheals that disappear within a few hours. The wheals tend to have a relapsing-remitting course, resulting in transitory worsening for a duration rang-

ing from 1 to 24 hours. In a number of patients, urticaria is associated with angioedema, which is a serious and life threatening condition. Urticaria without angioedema, urticaria with angioedema, and angioedema without urticaria account for nearly 50%, 40%, and 10% of cases, respectively.¹ The lifetime prevalence of urticaria is 15-20%¹⁻³ and the peak age is between 20-40 years. It is more prevalent in women than men.¹ Acute urticaria is present in two-thirds of patients, whereas chronic urticaria (CU), which has a lifetime prevalence of 0.5-1% affects one-third of urticaria patients.^{2, 4} Patients with CU have a poor quality of life (QoL) in comparison to patients with other dermatological and medical conditions.⁵ The major concern that compromises their QoL is uncertainty. Other contributing factors include

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The present publication and its topics are based on and are the fruit of a collaboration between the authors and Schering-Plough SpA.

Received on April 3, 2009.

Accepted for publication on May 4, 2009.

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TABLE I.—*Classification of urticaria.*

Spontaneous	Urticaria	Acute	Spontaneous wheals for less than 6 weeks
		Chronic	Spontaneous wheals for more than 6 weeks — Intermittent — Persistent
Inducible	Physical urticaria		
	Other urticaria disorders	Aquagenic urticaria	Elicited by water
		Cholinergic urticaria	Elicited by increase in body temperature
		Contact urticaria	Elicited by contact with urticariogenic substances
		Exercise induced anaphylaxis/ urticaria	Elicited by physical exercise (alone or with foods, either specific or non-specific foods)

patients' frustration. A new tool of evidence-based medicine, the Chronic Urticaria Quality of Life Questionnaire, has been assessed and validated for determining health status and is used worldwide by both dermatologists and patients for further research in this field.

Classification of urticaria

From a strictly morphological point of view, there is no significant difference between the various forms of urticaria, and their causes frequently remain unclear.⁶ Urticaria is classified as spontaneous or inducible (Table I). Spontaneous urticaria is further divided on the basis of simple chronological criteria into: acute (when it lasts less than six weeks) and chronic (when it lasts more than six weeks). The average activity of CU is three to five years, although cases that last 20 years or more have been described. CU seriously impairs patients' QoL because of sleep disturbances, troublesome symptoms, and secondary psychosocial problems.

Clinical manifestations

Urticaria is easily diagnosed by morphology, but the distribution and duration of wheals and the presence of associated symptoms can contribute to further etiological research. Hives are the clinical hallmark of urticaria; they are raised lesions that vary in color from red to pale pink with a slightly depressed central area and blurred reddish edges. The number of lesions is variable.

There are no preferential locations: mucous mem-

branes (lips, tongue, throat) are less frequently involved in CU but more in acute urticaria. The shapes of hives are also highly variable: they can be single or multiple, round or oval, or sometimes have bizarre shapes, from which the terms circinated and "figured" urticaria derive. Even their dimensions are variable: from pinpoint wheals (typically seen, for instance, in cholinergic or aquagenic urticarias) to wheals that are several centimeters in diameter ("giant" urticaria). Hives are usually temporary and typically persist for less than 24 hours, but they can also vanish completely a few minutes after their occurrence and leave no signs. Physical urticaria arises as a result of different kinds of physical stimuli, from less severe forms such as dermographism to life-threatening eruptions (see below).

Diagnosis

Clinical diagnosis of urticaria/angioedema is very easy. By contrast, the etiological diagnosis remains a very complex issue with a potentially high economic cost. The patient's history should include all possible eliciting factors and significant aspects of urticaria. Factors that should always be investigated in urticaria are shown in Table II.⁷ The second step includes a physical examination of the patient together with an evaluation of dermographism (see physical urticaria). Other relevant diagnostic tests are summarized in Table III. In acute urticaria, no test is needed unless a strong suspicion arises from the patient's history. In CU, a limited number of screening tests are useful in a preliminary phase; where results are positive, other extended tests should be considered.

TABLE II.—*Patient's history.*

1) Time of onset of disease
2) Frequency and duration of wheals
3) Diurnal and seasonal variations
4) Shape, size and distribution of wheals
5) Associated angioedema
6) Associated subjective symptoms of lesion, e.g. itching, pain
7) Personal and family history regarding urticaria, atopy, allergies, infections, autoimmune and other diseases
8) Induction by physical agents or exercise
9) Use of drugs (non-steroidal anti-inflammatory drugs, injections, immunotherapy, hormones, laxatives, suppositories, ear and eye drops, alternative remedies and alimentary supplements)
10) Foods and beverages
11) Work, hobbies, sport and leisure activities
12) Occurrence in relation to weekends, holidays and travel abroad
13) Surgical implants and procedures
14) Reactions to insect stings
15) Relationship to the menstrual cycle
16) Stressful events
17) Response to therapy
18) Quality of life related to urticaria

Adapted and modified from Zuberbier *et al.*⁷

Physical urticarias

Various exogenous stimuli such as rubbing, pressure, cold, heat, exercise, vibration, or electromagnetic waves have been described to elicit whealing reactions, the so-called physical urticarias (Table IV).⁸ Patients suffering from physical urticaria very often have a suggestive history with specific eliciting stimuli (*e.g.*, cold, heat, sun) since a sharp limitation of the lesions to the areas of physical stimuli is almost always observed. Inducibility by physical stimuli and the tendency not to occur at night (with the exception of pressure urticaria) represent the main characteristics of these forms of urticaria. Overlap between groups is common and often occurs as an added feature of chronic ordinary urticaria. With a few exceptions, urticarial lesions develop in exposed skin areas within minutes of application of the appropriate external stimulus and tend to disappear rapidly over a few hours. Delayed forms, characterized by a time-lag of several hours in lesion appearance, may cause diagnostic problems since a direct relationship between the stimulus and the whealing reaction may not be suspected. After whealing has been evoked and has subsided, the affected skin is frequently refractory to further provocation for a period ranging from a few hours to a day or two. Most forms of

TABLE III.—*Routine and extended tests in spontaneous urticaria.*

Group	Routine diagnostic tests	Extended diagnostic program
Acute	None	None
Chronic	Differential blood count and ESR/ CRP, omission of suspected drugs (<i>e.g.</i> , non-steroidal anti-inflammatory drugs)	Test for 1) infectious diseases; 2) type I allergy; 3) autoantibodies; 4) thyroid hormones; 5) physical tests; 6) pseudoallergen-free diet for three weeks and tryptase, biopsy

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

TABELLA IV.—*Clinical classification of physical urticarias.*

Type	Usual triggers
Dermographic	Minor trauma caused by mechanical shearing forces
Delayed pressure	Vertical pressure. Lying, sitting, tight clothing
Cholinergic urticaria	Exercise, increase in body temperature
Cold	Cold objects/foods/beverages/water; cold environment
Heat contact	Localized heat; hot objects
Vibratory angioedema	Vibrating tools
Solar	Sun exposure (UV/visible light)

urticaria are acquired and have their onset during young adulthood. As a rule, physical urticarias remit spontaneously; however, long-lasting forms may occur. Aquagenic and purely emotion-induced urticarias can no longer be considered as physical varieties, due to the absence of true physical-inducing causes. Many questions concerning the pathomechanisms of physical urticarias remain to be clarified. A comprehensive history is essential for diagnosis. Patients with physical urticarias often undergo unnecessary investigations and diet restrictions at the first examination by a dermatologist. Instead, different tests are needed to confirm the diagnosis suggested by patient history (Tables V, VI).

Dermographism

Dermographism means the ability to write on the skin. This is the most common type of physical urticarias, presenting with linear wheals at sites of scratching or friction and occurring in about 5% of

TABELLA V.—*Provocation test in physical urticaria.*

Challenges	Provocation test (threshold testing should be performed, when possible)
Dermographic	Dermographometer (palpable linear wheal by 10 arbitrary units or less); moderate stroking with a blunt-pointed object across the skin (linear wheals appearing within 10 minutes)
Delayed pressure	Firm sustained pressure obtained by means of a weight applied to the anterior thigh or back (0.2-1.5 kg/cm ²); dermatographometer applied perpendicularly to the skin: firm wheal at that site hours later
Cholinergic urticaria	Cyclette at room temperature or other physical exercise in a warm environment to the point of perspiration: positive if pruritic erythematous flare, often with punctate wheals, within 5 to 15 minutes
Cold	Place an ice cube in a sealed plastic bag over the anterior thigh or forearm for 3-5 min. If positive history and negative response, place the entire forearm in cold water. Search for serum cryoproteins and underlying diseases, when suspected
Heat contact	Local application of heat induces a wheal within minutes
Vibratory angioedema	Vibration using a laboratory Vortex (mixer) apparatus induces angioedema of the vibrated site within minutes
Solar	Exposure of the skin to artificial UVB, UVA or visible radiation (or natural sunlight) induces wheals within minutes

the population. While many people with CU present some of the features of dermatographism, people with true dermatographism have friction and/or pressure as the only trigger(s) for their symptoms. Stroking of the skin with a firm object or a dermatographometer will cause a corresponding urticarial response within minutes.

Pressure urticaria

Delayed pressure urticaria is the development of deep, painful hives after pressure is applied perpendicularly to the skin. This type of urticaria is actually very common. People with pressure urticaria may notice deep, light erythematous swellings on the buttocks after sitting on a hard surface for a long time. They may also present swelling of the soles after standing for a long time. Pressure urticaria also occurs in areas where clothing is tight. Reactions develop 3-12

TABLE VI.—*Management of patients with physical urticarias.*

— Avoid type-related physical stimuli
— Give a once-daily dose of a long acting, non-sedating antihistamine. At times, patients may benefit from taking antihistamine one hour before a predictable stimulus (e.g., cholinergic or cold urticaria)
— If resistant, double the dose of antihistamine and/or add a second antihistamine of different chemical class
— Consider further increase in dose of antihistamine
— Delayed pressure urticaria responds to systemic corticosteroids but prolonged use results in unacceptable side-effects

hours after the application. Swellings are usually pruritic or painful and may persist for several hours or days.

Constant perpendicular pressure applied to the skin results in delayed cutaneous erythema, and dermal and subcutaneous swelling.

Cholinergic urticaria

Cholinergic urticarial lesions occur within a few minutes of sweat-inducing stimuli such as physical exercise, heat (environmental or a hot bath or shower), or alcohol. Patients develop highly pruritic, punctate symmetrical wheals of 1-3 mm in diameter, which are surrounded by large areas of erythema. The rash usually subsides within minutes if the patient loses heat. The palms and soles are always spared. Some patients will only present the rash in conjunction with food ingestion followed by exercise.

Cold urticaria

There are two main subtypes of cold urticaria: primary ("essential") acquired cold urticaria (ACU) and secondary ACU. Wheals usually arise at the site of localized cooling, but may also be generalized following lowering of the body temperature. They are more persistent, last more than 24 hours, and may show features of vasculitis. This finding should lead to investigation for an underlying cause, as idiopathic ACU is caused by a variety of antigenic stimuli (e.g. Epstein-Barr virus) that induce cold-sensitive immune complexes of IgG and/or IgM anti-IgE autoantibodies. A pivotal role for IgE in idiopathic cold urticaria has been suggested. However, no putative skin antigen has been reported to date.

Secondary forms of cold urticaria may be caused by cryoproteins (i.e., IgG⁴ cryoglobulins and IgG-

IgM² mixed immune complexes). Complement activation may also be involved. Although the underlying causes of ACU still remain to be clarified in detail, a wide range of diseases has been reported to be associated with ACU. ACU symptoms typically occur minutes after the skin is exposed to cold air, liquids, or objects. Symptoms of ACU are usually limited to cold-exposed skin areas, but extensive cold contact may result in generalized urticarial symptoms and/or systemic reactions including headache, dyspnea, hypotension, and loss of consciousness, which most frequently result from extensive cold contact during water exposure. The use of an objective electronic device providing reproducible standardized cold stimulation over a wide range of temperatures is especially important when evaluating patients with a negative cold stimulation standard test and when retesting after treatment.⁹

Localized heat (or heat contact) urticaria

This is a rare condition in which urticaria only appears at the site where heat is applied, usually within minutes after stimulation. Common triggers include warm water, heating pads, oven steam, hair dryers, and hot utensils or plates. Systemic symptoms including wheezing, dyspnea, flushing, nausea, vomiting, abdominal pain, diarrhea, and syncope can occur but are not mandatory.

Vibratory angioedema

Vibratory angioedema is a rare form of urticaria that develops in response to vibratory stimuli such as horse riding, motorcycle riding, and the use of tools such as pneumatic drills, lawn mowers, and electric drills. Symptoms develop within a few minutes after contact with the eliciting object and resolve after about one hour.

Solar urticaria

Solar urticaria is caused by exposure to sunlight and characterized by the appearance of erythema and whealing immediately after exposure. It tends to disappear quickly (less than a day) after sun exposure has stopped. All sun-exposed body areas can manifest solar urticaria; nevertheless, chronically exposed skin is sometimes more tolerant. Wheals may also occur under thin clothing.

Urticaria in pediatric age

Acute as well as chronic forms of urticaria can occur at any age, but due to the fact that acute urticaria is more common in all ages, its exact frequency is unknown because it regresses in most patients before a careful evaluation is made. This is especially true in children, in whom acute forms are more common, whereas chronic idiopathic urticaria is more common in adults.

In the pediatric population, several studies indicate that 3% of preschool-aged children and 2% of older children are affected. Other findings from the United Kingdom suggest that acute urticaria is more common and affects 4.5-15% of children, whereas CU is thought to affect 0.1-3% of children. Approximately 50-80% of children with CU also have accompanying angioedema. In children affected by CU, symptoms resolve in about 25% of cases within three years of presentation.

For the "classic" phenotype of urticaria (excluding papular urticaria, urticaria pigmentosa, urticarial vasculitis as in anaphylactoid purpura, and rare genetic forms of urticaria/angioedema including complement abnormalities and chronic infantile neurological cutaneous and articular syndrome), it is hard to delineate a special semeiotic peculiar to childhood.

Etiopathogenesis

Table VII summarizes the main causes of childhood urticaria.¹⁰ As observed, food and infection in general can be responsible for the majority of cases, because children usually take fewer drugs than adults and drug administration can also be more easily controlled. Current data from Europe and the United States indicate that IgE-mediated food allergies affect between 6% and 8% of children. As for the presence of infestations (intestinal worms), the major bias is geographical and cultural characteristics. In other words, anisakis urticaria can be suspected in the Japanese population, even in childhood, while it is very difficult to encounter amoebiasis in European or North-American children.

While acute forms can be different from chronic forms in that a cause is more frequently established in the former (*e.g.*, acute infection, allergen ingestion), the presence of urticaria in both cases may significantly impair QoL. Children commonly miss significant periods of school because of a lay perception that the condition is infectious or allergic and a fear

TABLE VII.—*Main causes of childhood urticaria.*

<i>Infections</i>
— Viral (HBV, EBV, influenza, adeno- and enterovirus infection, etc.)
— Bacterial (Streptococci)
— Fungal
— Parasitic (<i>Toxocara canis</i>)
<i>Drugs</i>
— Penicillin and cephalosporins
— Non-steroidal inflammatory drugs (e.g., aspirin, ibuprofen)
— Histamine liberator drugs: codeine, radiocontrast products
<i>Food</i>
— Cow's milk proteins
— Eggs ¹
— Peanuts, sesame seeds, nuts
— Fish and seafood
— Exotic fruits
— Food additives
<i>Insect bites</i>
— Hymenopteras and arachnida
<i>Physical agents (chronic urticaria)</i>
— Cholinergic urticaria, cold urticaria and dermatographism
— Idiopathic
<i>Associated diseases</i>
— Autoimmune diseases

Modified from: Labrèze C *et al.*¹⁰. ¹Especially uncooked egg white.

that the child is unwell. When it is possible to exclude a drug with certainty and to reasonably rule out a food (e.g., after following an elementary diet for one week) as the possible culprit for urticaria, infections should be considered. In these cases, when a bacterial or fungal cause cannot be reasonably suspected (e.g., lack of specific signs, lack of pus, negative cultures, normal blood white blood cells, etc.), a viral etiology should then be taken into consideration. Urticaria due to an infective origin usually lasts a few days, while urticaria due to a food lasts only a few hours.

It should be noted that most food allergies common in childhood (cow's milk, hen's egg, wheat, peanuts) occur between 6 and 24 months of age and disappear in almost three quarters of cases before five years of age. Therefore, urticarial or eczematous episodes due to foods are much less common in schoolchildren.^{11, 12} Although almost all the forms of urticaria that have been described in adults can also be observed in children, papular urticaria and urticaria pigmentosa occur almost exclusively in children.

In children, as well as adults, the development of urticaria can be an isolated event without systemic

reaction or it can be a prelude to the development of an anaphylactic reaction. In children, physical factors such as pressure or cold exposure are the most commonly diagnosed precipitating factors for chronic urticaria; other factors account for less than 1% of cases. Interestingly, one study reported that 30% or more of children with CU have an autoimmune etiology with positive autologous serum skin test (ASST) findings.¹³ Additionally, approximately 4% of children with CU have positive antithyroid antibodies, although most patients with positive antithyroid antibodies remain euthyroid. Therefore, the association has not been established because most children present with hyperthyroid symptoms or hypothyroid symptoms before or after the onset of CU and the urticarial symptoms do not always improve with thyroxine-replacement therapy. Nonetheless, thyroid monitoring is encouraged in children with CU.¹⁴

Pathogenesis

Activation of cutaneous mast cells is of pivotal importance in the pathogenesis of urticaria. The traditional concept of mast cell hyper-releasability, indicating the great susceptibility of these cells to activation signals in urticaria patients, was proposed a long time ago but has not been formally proven.¹⁵ Mast cell activation causes degranulation and release of histamine and other preformed mediators stored in specialized granules (serotonin, neutral proteases, proteoglycans), as well as the *de novo* synthesis and secretion of cytokines, chemokines, eicosanoids, and growth factors. This mediator "storm" ultimately leads to the clinical picture of hives, through the induction of vasodilation, increased microvascular permeability, and stimulation of the recruitment and activation of leukocytes. Histamine, which is capable of inducing itching, erythema and edema, is recognized as the most important mediator of urticaria, although several proinflammatory mediators released by both mast cells and other cell types may play a direct or indirect pathogenic role.

Apart from mast cells, which are key effector cells in urticaria pathogenesis, other cells may contribute to the amplification and maintenance of the inflammatory network. Most of these cells (lymphocytes, macrophages, eosinophils, neutrophils, and basophils) make up the inflammatory infiltrate seen upon

histopathological examination of wheals, and particularly CU lesions,¹⁶ which were those most extensively studied. Basophils are another important source of histamine and are repeatedly implicated in urticaria development; however, their role in the pathogenesis of the disease, and particularly of CU, remains unclear.¹⁴ The available evidence for the role of basophils and lymphocytes in CU is summarized in Table VIII.¹⁶⁻²⁴

Mast cell activation is a complex phenomenon triggered by numerous stimuli and mediated by various mechanisms, which could be either immunological or non-immunological^{15,25} (Figure 1). The interaction of allergens with the IgE/IgE receptor at the cell surface (FcεRI), which is regarded as the most important immunologic type of activation, is actually involved in a minority of urticaria patients and even more rarely in those with CU. Evidence supports the role of many other immunological as well as extrinsic/pseudoallergic mechanisms, which are likely to be more common than true allergic IgE-mediated reactions in ordinary urticaria. It is also possible that a multifactorial pathogenesis involving multiple cofactors and mechanisms might be operative in more cases than expected, particularly in those defined as “idiopathic”. However, IgE-dependent mechanisms can play an important role in a relevant proportion of patients with food-dependent exercise-induced urticaria/anaphylaxis,¹⁴ and although only substantiated on very few occasions, they may contribute to other forms such as acquired cold, solar, and cholinergic urticarias.²⁶⁻²⁹

Circulating immune complexes may activate mast cells by interacting with the membrane-bound receptor for IgG (FcγR). Nevertheless, despite the absence of definite data, a marginal role of immune complexes may be hypothesized in CU, or in cases exhibiting features intermediate between vasculitis and “ordinary” CU.³⁰ The interaction of mast cells with specific T cells is very complex. As components of innate immunity and due to the expression of major histocompatibility complexes (class molecules and Toll-like receptors) as well as adhesion and costimulatory molecules (including ICAM-1, CD40, CD80, and CD86), mast cells can act as antigen presenting cells capable of causing the activation and proliferation of T cells. In turn, the close and symbiotic contact with activated T cells results in enhanced mast cell activation and degranulation.^{15,31}

An autoimmune mechanism has been characterized in a subgroup of patients suffering from CU, who

TABLE VIII. — *Novel findings concerning basophils and lymphocytes in CU.*

Cell types	Available evidence
Basophils (4-7)	— Trend towards basopenia possibly due to recruitment of basophils into the skin lesions and/or degranulation. — Hyporesponsiveness to several stimuli, including anti-IgE antibodies and C5a (possibly due to desensitization), but hyper-responsiveness to the serum. — Enhanced expression of activation markers and hyper-responsiveness to IL-3. — Recent detection of a bimodal distribution of basophil phenotypes: 1) responders, with a response to anti-IgE activation to FcεRI similar to healthy subjects (in nearly 50% of CU patients); 2) non-responders, which were insensitive to optimal anti-IgE stimulation (in the remaining 50% of cases) because of abnormalities in FcεRI signalling pathway (elevated levels of SHIP-1 and SHIP-2).
Lymphocytes (2, 8-10)	— Prominent presence in skin lesions of CD3+, CD4+, and CD8+ cells showing signs of activation (CD25). — Secretion of both Th2 and Th1 cytokines (Th0 profile). — Aberrant signalling through the p21Ras pathway. — Defective functions of circulating CD4+ CD25+ and CD4+CD25- T cells

CU: chronic urticaria; IL: interleukin; FcεRI: high affinity IgE receptor; SHIP: Src-homology 2-containing-5'-inositol phosphatase; Th: T helper.

reacted positively to the ASST, a screening test helpful for detecting the presence of histamine releasing factors (HRFs) in the serum.³²⁻³⁴ In so-called autoimmune urticaria, the HRFs were identified as functional IgG1 and IgG3 autoantibodies against IgE or the alpha-subunit of the FcεRI receptor (present in 5-10% and 35-40% of patients with CU, respectively). The histamine releasing activity of these autoantibodies that is able to cause mast cell and basophil activation was found to be augmented in the presence of components of the classical complement cascade, especially C5a. The suggestion that CU may have an autoimmune basis also came from the recognition of its association with thyroid autoimmunity, as well as with T-cell signalling abnormalities and HLA alleles (DR4 and DQ8) described for other autoimmune diseases.^{23,33} However, the autoimmune hypothesis still presents some inconsistencies, such as the presence of autoantibodies in other skin disorders and positive reactions to ASST in healthy controls. This test does not exclude the possibility that non-immunoglobulin factors found

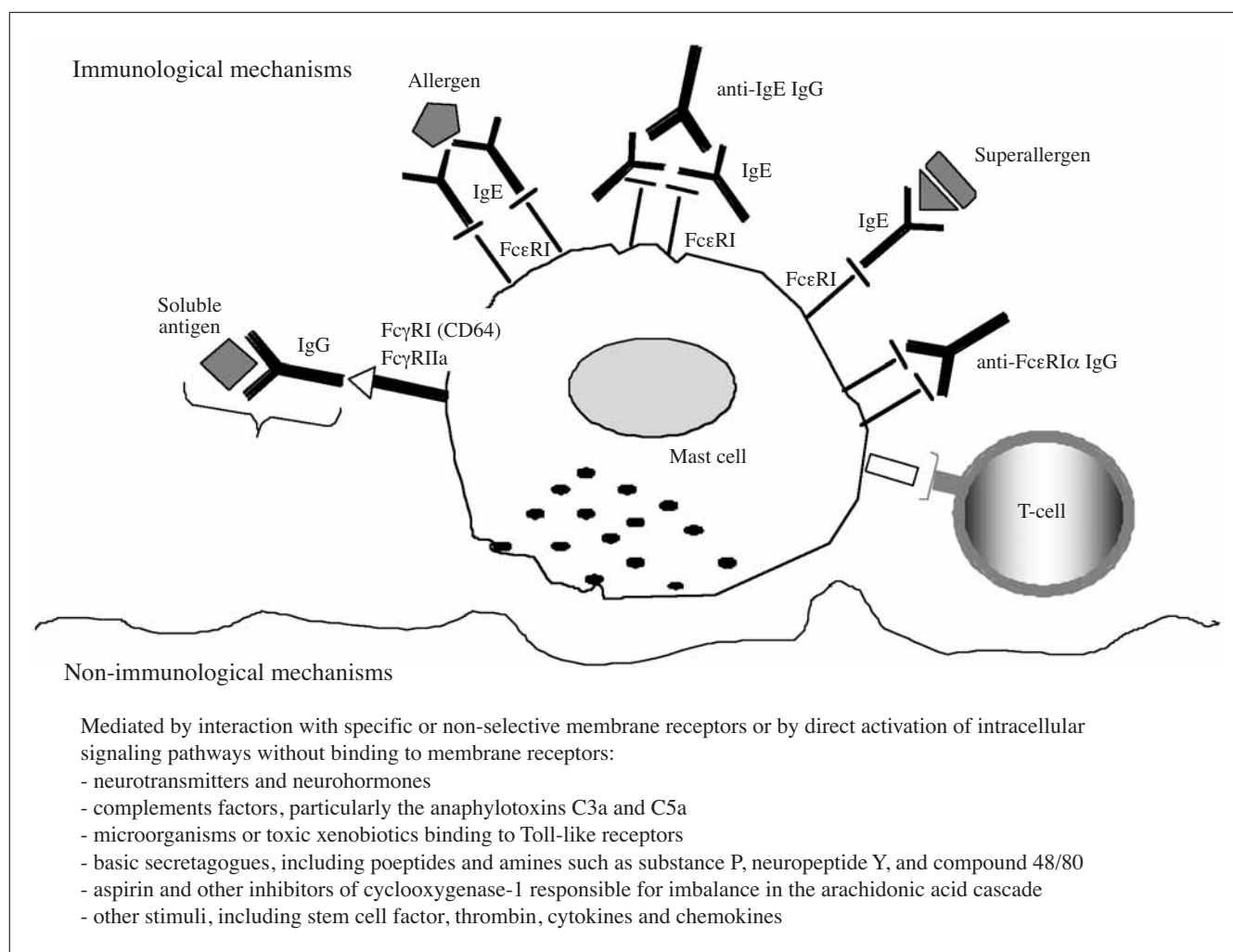


Figure 1.—Immunological and non-immunological mechanisms of mast cell activation.

in serum may be the actual HRFs. Of note, IgG-depleted serum still maintains the ability to induce a positive ASST.³⁵ Some investigators have evaluated CU patients using an autologous plasma skin test (APST) instead of the ASST, and observed that positive APST results were more frequent than positive ASST results. A functional role of platelet-derived factors present in the plasma and not in the serum was hypothesized.³⁶ The same authors provided hints supporting the activation of the extrinsic pathway of the coagulation cascade in CU.

In summary, little is known about pathomechanisms of physical urticarias,³⁷ a heterogeneous group of

urticarias triggered by physical and environmental stimuli, whose actual origin should be regarded as “idiopathic”.

Diagnostic testing in CU

The most important diagnostic aid in evaluating patients with urticaria is a detailed history including all possible eliciting factors and the nature of the urticaria. In all published guidelines, intense and costly general *in vitro* screening procedures for urticaria are not recommended.³⁸⁻⁴³ Kozel *et al.*⁴¹ reviewed published stud-

ies with more than 50 patients that evaluated diagnostic laboratory tests in CU, for a total of 29 studies involving 6 462 patients. Overall, no relationship was found between the number of identified diagnoses and the number of laboratory tests performed. The range of identified diagnoses varied greatly between studies, and no relationship between the number of identified diagnoses and the number of performed laboratory tests was found. In acute or episodic ordinary urticaria, no investigations are required except where suggested by the history since allergenic triggers can be identified in 60-80% of acute urticarias. In cases of suspected allergy, IgE-mediated reactions can be confirmed *in vitro* by evaluating serum levels of allergen specific IgE (CAP fluoroimmunoassay). In CU, basic laboratory tests could be performed to rule out severe systemic disease. Complete blood count with differential analysis (eosinophilia can suggest bowel helminth infections in which case stools should be examined for ova and parasites; leucopenia can suggest systemic Lupus erythematosus), measurement of erythrocyte sedimentation rate (usually normal in CU but may be elevated in urticarial vasculitis) and, in cases of associated angioedema, serum complement C4 level should be carried out at the patient's first visit. A low level of complement C4 necessitates investigation of C1 esterase inhibitor levels to confirm hereditary angioedema. There is minimal evidence for the association between CU and other conditions such as *Helicobacter pylori* infection, candida infection, and malignancy, therefore, routine evaluation in the absence of a suggestive history is not recommended.³⁵ Blood tests for specific allergy (CAP fluoroimmunoassay) can be performed in case of suspected food allergy, although Type I allergy is rarely a cause of CU (pseudoallergic reactions to food or food additives may be more relevant). Bacterial, fungal, and parasitic infections are rare causes of CU. Beyond the baseline evaluation, the cost effectiveness of an extended *in vitro* procedure is very poor in patients with CU, the majority of patients being idiopathic.

Autoimmune urticaria

Thyroid autoimmunity in CU is more prevalent than in control populations so thyroid autoantibodies and thyroid function tests should be performed if an autoimmune etiology is suspected.⁴⁴ Where autoantibodies against FcεRI or IgE are thought to be involved, the *in*

vitro demonstration of release of histamine (or other reactant) from target basophils or dermal mast cells (histamine release assay [HRA]) remains the gold standard for confirming the presence of functional autoantibodies in CU patients' sera with a positive *in vivo* ASST.^{45,46} Other techniques to detect the autoantibody to FcεRI such as western blot and ELISA are time-consuming and unable to identify functional antibodies with histamine releasing properties.⁴⁷ New developments in *in vitro* diagnosis of autoimmune CU include measuring basophil activation markers such as CD63 and CD203c by means of flow cytometry,⁴⁸ and stimulating basophils of allergic or non-allergic donors with CU patients' serum in order to detect the presence of basophil-activating autoantibodies. CD63 is a tetraspan granule protein that appears *de novo* on cellular membrane after degranulation; in resting basophils, CD63 is anchored to basophilic intracytoplasmic granules and as a consequence of cell degranulation, is expressed with a high density on activated basophils and mirrors mediator release.⁴⁹ CD203c (E-NPP3) is a type II transmembrane molecule and belongs to a family of ecto-nucleotidetriphosphatase/phosphodiesterase enzymes; it is restrictedly expressed on basophils, mast cells, and precursors among hematopoietic cells, and upregulated upon degranulation of basophils.⁵⁰ CD63 expression has been shown to be significantly increased on basophils stimulated with sera from patients with CU and positive ASST *versus* patients with CU with negative ASST, in correlation with HRA.³¹⁻⁵³ In severe ASST+ CU patients, a serum-induced CD63 expression assay may also be used for monitoring the effectiveness of immunomodulatory drugs.⁵³ In addition, CD203c expression can be upregulated after incubation of donor basophils with sera from patients with CU and positive ASST, in correlation with both basophil histamine release and size of the ASST.⁵⁴ The serum-induced basophil activation test using flow cytometry to measure CD63 or CD203c expression can be used as a new *in vitro* screening test to identify patients with autoimmune urticaria, in which a second line therapy could be contemplated.

Differential diagnosis of urticaria

Although in most cases urticaria is an easily diagnosed condition, sometimes it must be differentiated from a number of disorders. The primary and sole

TABLE IX.—*Cutaneous diseases that can manifest with urticarial lesions.*

Urticarial dermatitis
Contact dermatitis (irritant or allergic)
Insect bite reactions
Scabies
Exanthematous drug eruption
Mastocytosis (children)
Small vessel vasculitis (urticarial vasculitis)
Autoimmune bullous diseases:
— bullous pemphigoid
— gestational pemphigoid
— linear IgA dermatosis
— pemphigus herpetiformis
Pruritic urticarial papules and plaques of pregnancy (PUPPP)
Autoimmune progesterone/estrogen dermatitis
Interstitial granulomatous dermatitis
Eosinophilic cellulitis (Well's syndrome)
Neutrophilic eccrine hydroadenitis

lesion of urticaria is the wheal, which presents as a circumscribed cutaneous relief, with elastic consistency, a pink or pale color, and a variable erythematous surrounding flare. The lesions may have variable dimensions, with diameters ranging from a few millimeters to several centimeters, and be variable in number from a few to numerous lesions covering large areas. The distribution of the lesions is random and asymmetric on the body surface. In the case of a bilateral and symmetric urticarial eruption, the suspicion that it is not common urticaria should arise. Wheals are invariably pruritic, but no systemic symptoms are associated with common urticaria. Individual wheals last from minutes to hours, usually no longer than 24 hours, and disappear without leaving skin marks such as hyperpigmentation or bruising. In terms of histology, wheals of common urticaria show some dermal edema and a mixed perivascular infiltrate of variable intensity composed of macrophages, lymphocytes, and granulocytes, both eosinophils and neutrophils. No epidermal changes or endothelial cell damage is present.

The most important differential diagnosis of acute urticaria is anaphylaxis, which is characterized by skin urticaria or diffuse erythema plus systemic symptoms involving mainly, but not only, the gastrointestinal, respiratory, and cardiovascular systems. There are numerous conditions that may present with wheal-like or urticarial lesions and these can be divided into two categories. The first includes cutaneous diseases that may express with an urticarial component, such as insect bite reactions, exanthematous drug eruption, pre-bullous pemphigoid, cutaneous mastocytosis

(urticaria pigmentosa) in children, and urticarial dermatitis (Table IX). The term urticarial dermatitis was first adopted by pathologists, together with hypersensitivity urticarial reaction and hypersensitivity dermatitis, to describe a peculiar dermal hypersensitivity reaction pattern. Kossard *et al.* recently provided a more precise histological definition of urticarial dermatitis as the combination of upper dermal perivascular lymphocytic inflammation with eosinophils plus minimal epidermal spongiosis. Therefore, urticarial dermatitis should be interpreted as a predominantly dermal form of an eczematous process, clinically characterized by a persistent urticarial eruption with lesions symmetrically distributed on the trunk and extremities; eczematous lesions frequently coexist. Lesions are usually intensely pruritic. Exanthematous drug eruptions are the most common adverse drug reactions. Skin lesions usually begin 4 to 14 days after starting a new medication. Lesions are typically maculo-papular, with morbilliform or sometimes urticarial and purpuric aspects. The eruption first involves the trunk and upper extremities, often starting from axillae or groin, and becomes progressively confluent with a symmetric distribution. Pruritus or low-grade fever can be associated with the eruption. Histological examination exhibits mononuclear cell infiltrates around dermal vessels with eosinophils and interface dermatitis with apoptosis of few basal keratinocytes. In infants, urticarial lesions may be the presenting symptoms of cutaneous mastocytosis, but histology is needed to confirm this diagnosis.

The second category of disorders that may express with urticarial lesions includes systemic diseases or syndromes such as auto-inflammatory syndromes, connective tissue diseases, vasculitides, and hematological diseases (Table X). The most common disorder is urticarial vasculitis, which is a small vessel vasculitis with predominant skin involvement. It is characterized by urticarial lesions lasting more than 24 hours and accompanied by burning or painful sensations as well as pruritus; they resolve with residual hyperpigmentation or bruising. More rarely other skin lesions can be seen. Angioedema is present in fewer than half the patients. This diagnosis always requires histological confirmation on a skin biopsy, which reveals vasculitis of the small dermal vessels, usually leucocytoclastic. Urticarial vasculitis most commonly develops in association with autoimmune connective tissue diseases, and less commonly with inflammatory bowel diseases,

TABLE X.—Systemic diseases or syndromes that can manifest with urticarial lesions.

<i>Immunologic disorders</i>
— Systemic lupus erythematosus
— Sjögren syndrome
— Dermatomyositis
— Mixed connective tissue disease (Sharp's syndrome)
— Juvenile rheumatoid arthritis (Still's syndrome)
— Cogan's syndrome
— Relapsing polychondritis
— Hypocomplementemic urticarial vasculitis (McDuffy's syndrome)
— Acquired C1 inhibitor deficiency
— Cryoglobulinemia
— Serum sickness
<i>Vasculitides</i>
— Wegener's granulomatosis
— Churg and Strauss' disease
— Takayasu's arteritis
— Polyarteritis nodosa
<i>Genetic diseases</i>
— Muckle-Wells syndrome
— Wiskler-Fanconi disease
— Familial cold autoimmune syndrome
— Familial Mediterranean fever
— Familial hibernian fever
— Chronic multifocal recurrent osteomyelitis
— Hyper-IgD syndrome
— Chronic infantile neurological cutaneous and articular syndrome (CINCA)
<i>Hematologic diseases</i>
— Paroxysmic hemoglobinuria
— Polycythemia vera
— Hypereosinophilic syndrome
— Episodic angioedema with eosinophilia (Gleich's syndrome)
— Schnitzler's syndrome

viral hepatitis and paraproteinemia, renal diseases either as a paraneoplastic syndrome, or a drug reaction. Skin lesions may be associated with extracutaneous manifestations such as arthralgias (50% of patients), respiratory symptoms, fevers, and abdominal discomfort, particularly in hypocomplementemic patients. Urticarial vasculitis requires careful evaluation and follow-up of the patient. Therefore, many conditions can mimic urticaria, but a careful evaluation of skin lesion morphology, distribution, evolution, and duration allows an easy differential diagnosis.

Therapy

In recent years some guidelines for urticaria treatment have been proposed by experts and scientific societies.

TABLE XI.—Hypoallergenic diet in urticaria patients.

<i>Foods to avoid</i>	<i>Foods rich in histamine and/or histamine releasers</i>
Exclude	Eggs (white in particular), fermented cheese, game, sausages and pork, liver, shellfish, tuna, anchovies, sardines, salmon, tomatoes, cucumbers, peppers, lentils, beans, fresh and dried fruit (less than below), chocolate, wine, beer, spirits, coffee
	<i>Foods with preservatives and/or dyes</i>
	All those canned and packaged, margarine, cakes, packaged drinks
<i>Foods permitted</i>	Cereals, starchy: bread, pasta, durum wheat, rice, meal, oats, barley, home-made cookies without yeast
	Dressings: butter, olive oil, salt
	Meat: turkey, lamb, beef, pork (grilled or steamed)
	Vegetables (those that are not prohibited) (see above)
	Fruit: pears and apples (peeled), bananas
	Drinks: fresh milk, water, black tea (not bags), camomile
	Dairy products: mozzarella, stracchino, ricotta, cottage cheese, yoghurt
	Sweeteners: sugar cane, honey

There is a close to unanimous consensus for the following steps:

1) patients should be given general advice such as explanations and written instructions.

2) patients should avoid triggering factors such as drugs known to worsen urticaria and/or angioedema (*i.e.* acetylsalicylic acid/non-steroidal anti-inflammatory drugs, codein, morphine, ACE inhibitors). In case of fever, paracetamol should be taken and in case of headache, joint and/or muscle pain, or other circumstances (when anti-inflammatory/antalgic treatments are required) nimesulide or other Cox-2 inhibitors should be administered. It is good clinical practice for patients with CU and with non-hereditary angioedema to stop any current therapy and shift to a different drug, whenever possible. In addition, it should be suggested that patients avoid excessive physical exercise, especially immediately after a meal or in hot environments. Patients should also avoid abrupt changes in temperature, prolonged exposure to the sun, emotional stress, and compression (from close-fitting clothes, work tools, etc.).

3) patients should follow an exclusion diet, namely without additives such as food dyes and preservatives. Alcohol and pseudoallergens can both elicit and worsen urticaria (Table XI).

4) in daily practice, regular antihistamine treatment for at least two months is highly recommended. Treatment for 3-12 months is advised for patients with a long history of urticaria/angioedema. Gradual with-

TABLE XII.—*Treatment in CIU.*

First line	sg ns H1-AH
Second line	sg ns H1-AH at quadruple dosage change sg ns H1-AH
Third line	corticosteroids short term use * sg ns H1-AH+H2-AH association of 2 different sg ns H1-AH
Fourth line	sg ns H1-AH +Cs A sg ns H1-AH+ antileukotriene receptors
Fifth line	Warfarin sg ns H1-AH+Dapsone or Nifedipine

*From the third line on a short-term use of corticosteroids during severe exacerbations can be useful.

Sg ns H1-AH: second generation non-sedative antihistamines; CsA: cyclosporin A.

drawal over a period of some weeks is recommended after achieving clinical remission.⁵⁴

Pharmacological treatments are stratified into several lines (Table XII). The first line is based on non-sedating second-generation H₁ antihistamines (ns2AH) (level of evidence 1++, grade of recommendation A) for at least one week. This class includes desloratadine, levocetirizine, and fexofenadine. The effectiveness and safety of desloratadine in the treatment of various forms of urticaria have been fully demonstrated.⁵⁵⁻⁶⁴ Numerous placebo-controlled, double-blind, randomized, multicentric studies have reported that the drug significantly reduces the signs and symptoms of urticaria as early as the first administration. The therapeutic effect continues for the duration of the treatment (Figure 2).

Moreover, desloratadine at 5 mg/die significantly improves QoL, pruritus and the number of hives in patients with chronic idiopathic urticaria, independently of the seriousness of the disease, with a rapid onset of action⁵⁸ (Figure 3). If the patient at first observation has already been given an adequate dosage of the previous antihistamines without any or with inadequate improvement, an alternative molecule belonging to the second-generation group can be chosen. In limited and selected cases a sedating agent should also be considered.

Concerning the dosage, it has been verified in many studies that a higher dose of antihistamine can improve symptoms, so it is a common practice to increase the dose above the normal. Using antihistamines at quadruple dosages for one-four weeks makes it possible to control symptoms in the majority of patients with urticaria. This corresponds to the second line of treat-

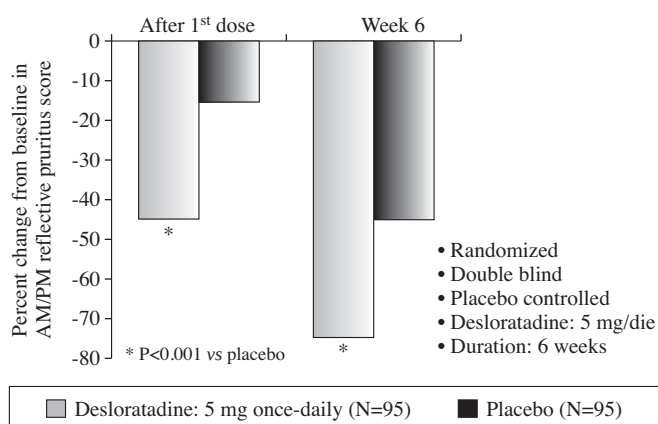


Figure 2.—Desloratadine provides rapid and durable pruritus relief to patients with CIU. From Ring *et al.*⁵⁵

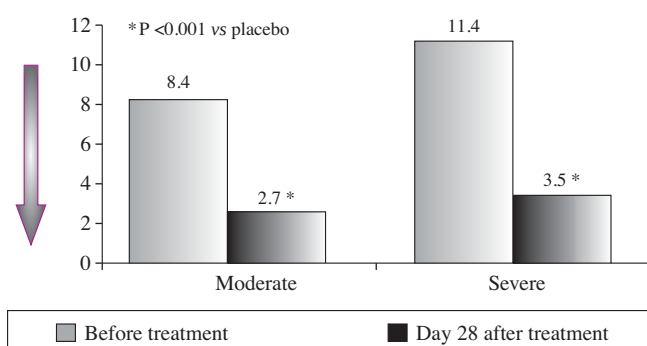


Figure 3.—Desloratadine in CIU: improved QoL in severe patients. From Seidenari *et al.*⁵⁸

ment. It should be noted that the increase in daily dosage to enhance efficacy should preserve the tolerability and safety profile of treatment, and this might happen only for some ns2AH.

In their study, Seibenhaar *et al.* showed that 5 mg/die desloratadine already reduced the critical temperature threshold (CTT); an increase in desloratadine dosage resulted in a further improvement both in terms of CTT reduction and hive diameter and pruritus reduction.⁶⁴

Among the new generation molecules, desloratadine has a significantly favorable safety profile in regards to the central nervous system and heart. In a clinical pharmacology study in which desloratadine was administered at doses of 45 mg/die (9 times the therapeutic dose) for 10 days, no change in the QTc interval was observed.⁵⁹ In case of low or no response

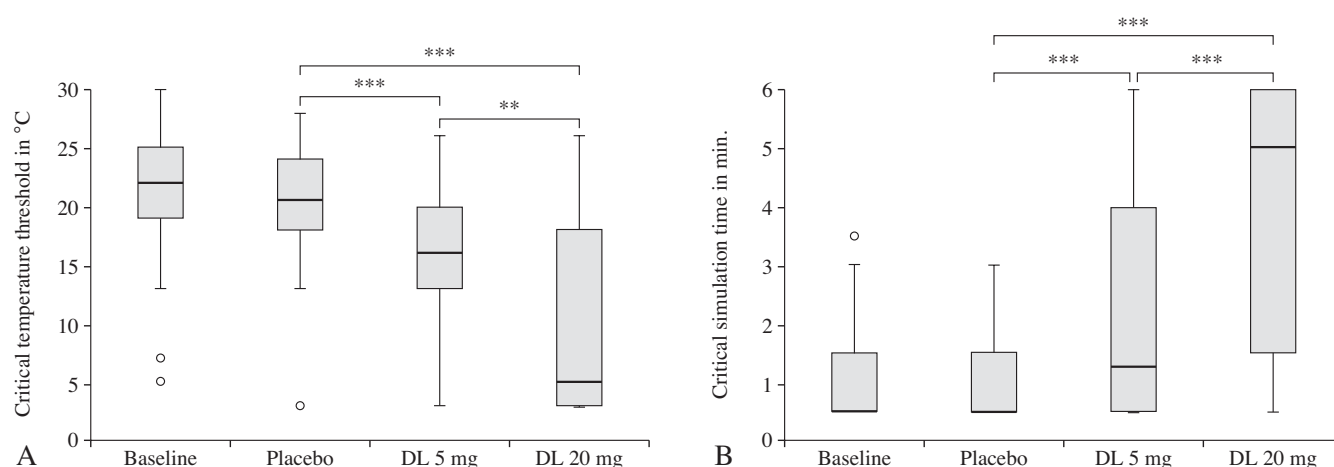


Figure 4.—A) Box and whisker plots showing the CTTs elicited by using cold provocation at baseline and after treatment with placebo, 5 mg of desloratadine, and 20 mg of desloratadine every day for 7 days (assessed 10 minutes after provocation); B) CSTTs elicited by using cold provocation at baseline and after treatment with placebo, 5 mg of desloratadine, and 20 mg of desloratadine every day for 7 days. Circles within the figures represent outliers, and triangles illustrate extreme values. DL: desloratadine; ** $P \leq 0.01$; *** $P \leq 0.001$ (assessed 10 minutes after provocation).

to this latter regimen, the prescription of a different antihistamine is recommended.

The third line of pharmacological treatment provides for the combination of two antihistamines, including a sedating antihistamine at night as needed. As an alternative, a leukotriene receptor antagonist (*e.g.*, montelukast) in combination with antihistamines can be considered. A short-term use of corticosteroids (*e.g.*, 40 mg/day prednisolone for up to one week), especially during severe exacerbations, cannot be excluded. In patients with severe unremitting disease uncontrolled by different antihistamines, a fourth-line approach may be considered: this includes cyclosporin in a “step-down” approach (5 mg/kg > 2.5 mg/kg). In a double-blind study, the clearance of this drug was obtained in two thirds of the patients with a remission of four-five months in 25% of the patients after discontinuing therapy. Warfarin as single therapy and dapsone or nifedipine in combination with antihistamines have been occasionally reported as effective. Drugs with C or D grades of recommendation such as colchicine, methotrexate, stanozolol, sulphasalazine, or intravenous immunoglobulin infusion are of rare and marginal usefulness and their use is unsubstantiated by adequate evidence. Other alternatives such as tranexamic acid and sodium cromoglycate have been shown to be ineffective and should no longer be used.

Physical urticarias

It is not always simple to avoid physical stimuli by behavioral prevention. Physical urticarias can be more resistant to therapy than ordinary CU. In physical urticarias, the therapies recommended are the same as those suggested for ordinary CU. The first-line treatment is represented by ns2AH, although in delayed pressure urticaria and cold and solar urticaria, the response may be disappointing (Figure 4). In non-responsive cases, a combination therapy with leukotriene inhibitors has been carried out successfully in some cases, namely in small series of patients with delayed pressure urticaria. In a study carried out by Nettis *et al.* desloratadine in daily monotherapy or in association with montelukast in patients with delayed pressure urticaria proved effective in reducing pruritus and diameter of hives.⁶¹

People with cold urticaria should carry an injectable form of epinephrine for use in the event of a serious reaction. Up-dosing of non-sedating antihistamines can improve the therapeutic response in ACU patients who do not respond satisfactorily to treatment with standard doses. Some patients affected with heat contact urticaria or solar urticaria have been treated with desensitization. The hypothesis that TNF- α could play a crucial role in some cases of delayed pressure urticaria seems to have been recently confirmed by the success of anti-TNF- α treatment in this form of

urticaria. Recently, a patient with idiopathic cold urticaria was successfully treated with omalizumab, a monoclonal antibody that selectively binds to human IgE; this report suggests a pivotal role of IgE in this form of urticaria.⁵⁴ In solar and cholinergic urticarias, induction of tolerance is sometimes successful and should be tried in non-responsive patients. In particular, desensitization with ultraviolet A or ultraviolet B lights could be of particular help in patients with solar urticaria.

Riassunto

Documento del gruppo italiano di ricerca sulla orticaria

Il gruppo di ricerca italiano sulla orticaria ha elaborato un documento incentrato sulla definizione e la classificazione dell'orticaria, tenendo conto dei recenti progressi nella individuazione delle cause, dei fattori scatenanti e del meccanismo patogenetico di questa malattia. Data l'evidenza del fatto che l'orticaria ha un profondo impatto sulla qualità della vita dei pazienti, è necessario disporre di trattamenti efficaci. Pertanto, sulla base della recente letteratura, sono state valutate le specifiche alternative terapeutiche nella gestione dell'orticaria. Gli antistaminici non-sedativi sono raccomandati come prima linea di trattamento. Essi si sono dimostrati efficaci in diversi studi randomizzati in doppio cieco. In alcuni casi possono essere necessari dosaggi più elevati rispetto a quelli raccomandati. Tuttavia, terapie complementari o alternative possono essere somministrate nelle varie forme di orticaria e aggiustate in base al corso della malattia e alla risposta individuale al trattamento. Farmaci immunosoppressori come i corticosteroidi non sono raccomandati per il trattamento a lungo termine, a causa di inevitabili e gravi effetti avversi.

PAROLE CHIAVE: Orticaria - Agenti immunosoppressivi - Corticosteroidi.

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