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The Turkish Guideline for the Diagnosis and Management of Urticaria-2016

Türkiye Ürtiker Tanı ve Tedavi Kılavuzu-2016

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Abstract

Background and Design: Albeit an easily recognized disease, urticaria features many diverse approaches which rationalize the need for an algorithm for the diagnosis, classification, etiopathogenesis, diagnostic evaluation and therapeutic approach. Therefore, authors from Dermatoallergy Working Group of the Turkish Society of Dermatology and the Turkish Dermatoimmunology and Allergy Association aimed to create an urticaria guideline for the diagnosis, treatment and follow-up of urticaria.

Materials and Methods: Each section of the guideline has been written by a different author. The prepared sections were evaluated in part by e-mail correspondence and have taken its final form after revision in the last meeting held by the participation of all authors.

Results: The guideline includes the description, classification, pathophysiology as well as diagnosis and treatment of urticaria. Urticaria is classified into two main types: acute urticaria (AU) and chronic urticaria (CU) while CU is further subdivided into spontaneous urticaria and inducible urticaria. The first step of treatment includes standard doses of second generation H1 antihistamines. In patients who do not respond to the first step, antihistamine dose is increased up to four times; if unsuccessful, another second-generation antihistamine is given in the same dose. In antihistamine-resistant cases, introduction of omalizumab is required. Omalizumab dose may be increased in patients failing to respond to the standard dose. In patients unresponsive to omalizumab, cyclosporine-A may be given. Routine diagnostic tests are not recommended in AU. In CU, erythrocyte sedimentation rate, differential blood count and C-reactive protein testing are the only investigations that are needed routinely.

Conclusion: CU is a disease that can be challenging for the physician in terms of treatment and follow-up. Depending on evidence-based data (and individual experiences), this guideline will have a leading role in the diagnosis and treatment of urticaria and help the physician to overcome the challenges in the management.

Keywords: Acute urticaria, algorithm, angioedema, chronic idiopathic urticaria, chronic spontaneous urticaria, guideline, physical urticaria, treatment urticaria, Turkey

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Öz

Amaç: Ürtikerin kolay tanı konulabilen ancak çok farklı yaklaşımların görülebildiği bir hastalık olması, son yıllarda hastalığın tanım, sınıflama, etiyopatogenez, tanısal testler ve tedavi yaklaşımları açısından bir algoritma içerisinde değerlendirilmesi gerekliliğini doğurmuştur. Bu amaçla Dermatoimmünoloji ve Allerji Derneği ile Türk Dermatoloji Derneği Dermatoallerji Çalışma Grubu içerisinde yer alan yazarlar, ürtikerin izleminde kanıta dayalı bir yol gösterici olması açısından bu ürtiker kılavuzunu oluşturmayı hedeflemiştir.
Gereç ve Yöntem: Bu kılavuz, her bölümü ayrı bir yazar tarafından yazılacak biçimde planlanmış; ürtikerle ilgili Medline verileri ve 2000-2016 yılları arasında yayımlanan tüm ürtiker tanı ve tedavi kılavuzları ve uzman görüşleri incelenmiş ve üç ayrı toplantıda tüm bu veriler ayrıntılı olarak tartışılmıştır. Dermatoloji uzmanlarına yönelik hazırlanan anket sonuçlarının değerlendirilmesinin ardından kılavuzun ana hatları belirlenmiş, hazırlanan bölümler e-posta yazışmaları ile diğer yazarlar tarafından da değerlendirilmiş ve tüm yazarlarla yapılan son toplantıda kılavuz tümüyle gözden geçirilerek hazır hale getirilmiştir.
Bulgular: Kılavuz, tanım, sınıflama, fizyopatoloji, etiyoloji ve tetikleyici faktörler ile tanı ve tedavi yaklaşımlarını içermektedir. Ürtiker, akut ve kronik olarak, kronik ürtiker (KÜ) ise "spontan" ve "uyarılabilir" olmak üzere sınıflanmıştır. Tedavinin ilk basamağını standart doz ikinci kuşak antihistaminler oluşturmaktadır. İlk basamakta yanıt alınamayan hastalarda antihistamin dozu dört katına kadar artırılır. Yanıt alınamayan durumlarda, başka bir ikinci kuşak antihistamin aynı dozda verilir. Yine yanıt alınamayan olgularda omalizumab tedavisine geçilir. Omalizumabın önerilen dozuna yanıt vermeyen olgularda doz artırılabilir. Omalizumaba yanıt alınamayan hastalarda ise siklosporin verilmesi önerilir. Rutin tanısal tetkikler AÜ'de önerilmezken, KÜ'de rutin tetkik olarak eritrosit sedimentasyon hızı, tam kan sayımı ve C-reaktif protein tetkiklerinin istenmesi yeterlidir.
Sonuç: Ürtiker özellikle kronikleştiğinde hekimler için tedavi ve izlem açısından güçlükler doğurabilen bir hastalıktır. Olabildiğince kanıta dayalı verilerden (ve kişisel deneyimlerden) yola çıkarak hazırlanan bu kılavuz, ürtikerli olgularda hem tanı ve tedavi yaklaşımlarının yönlendirilmesinde yol gösterici olacak, hem de hekimlerin bu süreçlerde yaşadıkları zorlukların aşılmasına katkı sunacaktır.
Anahtar Kelimeler: Akut ürtiker, algoritma, anjiyoödem, fiziksel ürtiker, kılavuz, kronik spontan ürtiker, kronik idiyopatik ürtiker, Türkiye, tedavi, ürtiker

Introduction

Urticaria is a common skin disease characterized by itchy and edematous plaques which abruptly arise and spontaneously disappear. Various causes and different mechanisms have been involved inthe pathogenesis and the disease which is classified heterogenously. Urticaria has chronic forms which last for years, types associated with angioedema (AE), rare inducible and syndromic forms beside acute forms which last shorter than six weeks. AE accompanies with approximately half of the cases. Chronic urticaria (CU) significantly impairs quality of life of the patients and may lead to socio-economic problems.

Urticaria is a disease which can be diagnosed easily however many different treatment approaches exist. Therefore, the disease recently needed to be addressed under a more precise and understandable algorithm with regard to definition, classification, etiopathogenesisi, diagnostic tests and treatment approaches. "Guideline for the Diagnosis and Management of Urticaria and Angioedema" was first published by English Society of Dematology in 2001 and "BSACI Guideline for Management of Chronic Urticaria and Angioedema" was published by British Society of Allergy and Clinical Immunology (BSAIC) in 2007 thereafter. Many countries created their own guidelines following the publication of "Guideline for Definition, Classification, Diagnosis and Management of Urticaria published by European Academy of Allergy and Clinical Immunology, European Global Allergy and Asthma Network, European Dermatology Forum and World Allergy Organization in 2008 and 2013.

The main goal for creating "Turkish Guideline for Diagnosis and Management of Urticaria" is being an evidence-based pioneer for dermatologists in our country for diagnosis, management and follow up of urticaria. Authors from Dermato-allergy Working Group of the Turkish Society of Dermatology and the Turkish Dermato-immunology and Allergy Association gathered three times, analyzed Medline data, urticaria diagnosis and treatment guidelines, expert opinions published between 2000-2015 and discussed in detail. Dermatologists who participated in a national dermatology symposium in October 2015 were applied a questionnaire composed of 10 questions. Main subjects of the guideline were specified after assessment of this questionnaire results, and each section of the guideline has been written by a different author. The prepared sections were evaluated in part by e-mail correspondence and have taken their final form after revision in the last meeting held by the participation of all authors.

Diagnosis, classification and epidemiology of urticaria

Definition

Urticaria is a disease characterized by itchy and edematous papule/plaques "urtica", AE secondary to deep dermis or subcutaneous involvement or both[1]. The clinical condition is defined as "acute urticaria" (AU) if lasts shorter than six weeks, CU if lasts for six weeks or longer. Definition of "episodic CU" may be used when episodes last for longer than six weeks however less than two episodes a week develop[2].

Classification

In recent years, definitions of "chronic idiopathic urticaria" and "chronic autoimmune urticaria" have been abandoned in order to emphasize the "endogenous" nature of the disease and provide a definitional unity and the term of "chronic spontaneous urticaria (CSU)" has been proposed in the light of the data obtained from the new studies on pathogenesis. Urticaria which develops in the presence of detectable physical or the other stimuli is defined as "inducible urticaria"[1].

Recommendation of Turkish Guideline for Diagnosis and Treatment of Urticaria for the classification of urticaria is shown in Table 1.

Epidemiology

Epidemiologic data about urticaria show insufficient and sometimes conflicting characteristics. These discrepancies arise not only from the properties andqualities of the scientific studies, but also fromdefinitions (idiopathic, physical, inducible urticaria etc.) and genetic, geographic and national differences. Approximately 15-20% of the individuals were detected to have experienced an AU episode during their lifetime[3,4].

Globally, CU is reported to be most common between ages 20-40, two fold more among females than males[3,5] and affects about 1% of the individuals (0.5-5%)[6]. CSU is reported in ½-3/4 (66-93% according to some references) and physical (inducible) urticarial,in approximately 1/3 of these individuals respectively[4,5,7-13].

Epidemiologic data about "chronic inducible urticaria" which consist 5-25% of CU cases and known to be seen among young adults are quite limited. Coexistence of CSU-physical urticaria (most commonly symptomatic dermographism and delayed pressure urticaria) is reported to vary between 10-50%[5].

Etiology of urticaria

An ample amount of factors are involved in the etiology of urticaria. While some of them are primary causes, some others are the factors which trigger lesion formation and lead to exacerbation. Etiologic factors vary according to the mechanism, duration of lesions and age groups, and etiologic screening also varies according to the type of urticaria While etiology remains unknownin 50% of CSU cases, the cause of inducible urticaria is usually detectable. The important point in these patients is to determine the threshold value which causes urticaria[3,14].

Etiology of spontaneous urticaria

Medications, foods, food additives, infections (bacterial, viral and fungal), parasitic infestations, allergens, internal diseases, malignities and the other dermatologic diseases are accused in the etiology of spontaneous urticaria[15].

Medications

While medications may cause AU either vis immunologic [immunoglobulin E-mediated (IgE)-mediated] or non-immunologic (non-allergic, pseudo-allergic) mechanisms, non-immunologic mechanism is involved in CU. Medications may be the primary cause in AU; however, they act as triggers or exacerbating factors in CU.

Urticaria is estimated to develop in 0.1%-0.3% of the patients who use non-steroid anti-inflammatory drugs (NSAIDs). NSAIDs may trigger acute episodes in CU or increase lesion severity. Prevalanceof Aspirin-induced AU or AE was reported as 1%. Aspirin may exacerbate CU in 30% of the cases. NSAID and Aspirin use is not recommended particularly in CU cases[16,17]. Angiotensin coverting enzyme (ACE) inhibitors may lead to AE independently from urticaria[18,19]. Therefore ACE inhibitors shouldn't be used in urticaria cases which are accompanied by AE. Urticaria-related medications are shown in Table 2.

Table 1. Classification of urticaria

Acute urticaria	Chronic urticaria	
<6 weeks	>6 weeks	
	Chronic spontaneous urticaria	Chronic inducible urticaria
		Symptomatic dermographism
		Cold urticaria
		Delayed pressure urticaria
		Solar urticaria
		Heat urticaria
		Vibration angioedema
		Cholinergic urticaria
		Aquagenic urticaria
		Contact urticaria

Food and food additives

Although there is a close relationship between AU and some foods, the role of foods in CU is still controversial. Studies indicate that food is responsible in 5.3% of AU cases. Eggs, milk, soy, peanut and wheat are the most commonly accused foods in little children; fish, shellfish and nuts, in older children. IgE-mediated food allergy is responsiblein approximately 10% of children with AU[20].

Table 2. Medications that most commonly cause urticaria[15]

Medications
Anti-inflammatory drugs Aspirin NSAIDs
Antimicrobial drugs Penicillins Cephalosporines Sulphonamides Aminoglycosides Tetracyclines
ACE inhibitors Enalapril, kaptopril
Radiocontrast media
Narcotic analgesics Opiads, codeine, morphine
Muscle relaxants
Antifungal drugs Fluconazole, ketoconazole
İntravenous fluids and blood products Dextran, sorbitol, mannitol Whole blood, erythrocyte suspension, plasma
Polypeptide hormones Insulin, corticotropin, vasopressine
Anesthetic drugs
Hypnotics
Contraceptives
Monoclonal antibodies
Vitamins
Vaccines
Others Kinin Hydralazine Pentamidine Atropine Polimyxin B Amphetamine

NSAIDs: Non-steroid anti-inflammatory drugs, ACE: Angiotensin converting enzyme

Most of food-related CSU cases in adults and children are regarded as pseudo-allergy[21]. The prevalence of pseudo-allergic reaction to food ingredients is quite variable in CU. It develops in genetically susceptible individuals and previous exposure is not needed. Pseudo-allergic reactions may develop against both natural food ingredients and additives[22,23].

Infections

Infections are responsible for half of the pediatric AU cases. Viral infections should be considered first in children who admit with AU. Group A beta-hemolytic streptococcus-related pharyngitis and mycoplasma pneumonia infections are the bacterial infections which play a role in AU etiology[24].

Infections are suggested to trigger and exacerbate the disease rather than being a primary cause in CU[25]. *Helicobacter pylori (H. pylori)* has been intensively investigated in CU and was suggested to be a potential risk factor for CU development[26,27]. Bacterial intensity and gastric inflammation were observed to be directly proportional with severity of urticaria[28].

Focal bacterial infections (urogenital, dental, etc), parasitic infestations, onychomycosis, tinea pedis and mucocutaneous candidiasis may trigger CU episodes[25].

Autoimmune and chronic inflammatory diseases

Thyroid diseases are seen 2-3 fold higher among CSU patients compared to normal population. Present studies stress a relationship between autoimmune urticaria and autoimmune thyroiditis. Non-infectious chronic inflammatory processes were reported to be a potential cause of urticaria. Gastritis, reflux oesophagitis, cholecystitis or cholangitis and rarely connective tissue diseases are the non-infectious inflammatory diseases detected as a cause of urticaria[29].

Malignity

Many cancer-related CU cases were reported in literature. Leukemia, lymphoma, myeloma, thyroid, testis, ovarian, bladder, colon and lung cancer are the neoplasms which were reported to coexist with CU. Etiologic role of malignity could not be proven in urticaria[30].

Others

Grass pollens, yeast spores, house dust mites, smoking, orthopedic /dental implant and protheses and amalgam dental fillings were reported to trigger and/or exacerbate CSU[31,32]. Psychological stress, depression and anxiety may play a role in the etiology of urticaria, particularly in precipitation and exacerbation of acute episodes[31].

Medications, infectious foci and foods should be questioned in the etiology of AU. In CSU, there are many etiologic factors which may precipitate or exacerbate urticarial lesions.

Pathophysiology of urticaria

Urticaria is a mast cell-mediated disease however signals which lead to mast cell activation are variable and not clearly revealed. Mediators which are released from mast cells like histamine and platelet activating factor lead to urticarial lesions through sensorial nerve activation, vasodilation and plasma extravasation[1,33]. Up-regulation in endothelial cell adhesion molecules, mild-moderate increase in mast cell count and varying degrees of mixed inflammatory perivascular infiltrate are seen in urticarial plaques. These changes are also seen in non-lesional skin in some urticaria types[34].

Systemic inflammatory findings also accompany with local cutaneous infiltrate in attacks and inflammatory markers such as C-reactive protein, interleukin-6 (IL-6) and matrix metalloproteinase 9 may increase[35,36]. Th17 cells and IL-17 cytokine family and Treg cells have been investigated in auto-immune etiology in recent years[37].

Immunopathogenesis of CU may be summarized as follows: High affinity IgE receptor (FcεRI) or anti-IgE functional antibodies lead to histamine release from blood basophils and tissue mast cells. Activated mast cells and basophils release many inflammatory mediators, chemokines and cytokines. Eosinophils which are activated through antibodies bound to low affinity receptor (FcεRI) initiate tissue factor-mediated coagulation pathway. Thrombin leads to vasodilation, increased vascular permeability and direct mast cell degranulation. Activated T cell-mast cell contact contributes to mast cell activation through multifunctional cytokine and chemokine release.

Clinical features

Urticarial lesions are composed of varying diameters of papules (urtica) and plaques characterized by central swelling and perpheralreflex erythema. Plaques which are usually itchy, sometimes with burning sensation, disappear without leaving any mark or scar in shorter than 24 hours. Mucosa is frequently involved in AE; burning, tenseness and pain are felt rather than itching. Findings disappear later than urticaria (up to 72 hours)[38]. While only urticaria is seen in half of the patients; urticaria and AE coexist in 40% and AE is seen alone in 10%[39].

Physical urticaria, coexists with CSU in approximately 20% of the patients40, is characterized by urticarial lesions and/or AE triggered by external physical factors like mechanic (friction, pressure and vibration), thermal (cold, hot) stimuli, electromagnetic radiation (solar radiation)[41]. Physical urticaria is classified as symptomatic dermographism, late pressure urticaria, vibratory AE, cold urticaria, heat urticaria and solar urticaria according to the precipitating factor. Since it arises as response to increased body temperature, cholinergic urticaria is not classified as physical urticaria and is included in the other inducible urticarias; symptoms are typically precipitated with hot bath or exercise[42]. Urticarial lesions typically last short in inducible urticaria (a few min-hours) and arises a few minutes after contact with the stimulus. Lesions develop 4-8 hours after contact in late pressure urticaria, differently from the other inducible urticarias. It should be known that inducible urticarias could be accompanied by common urticaria, AE and anaphylaxis[43].

Plaques disappear in shorter than 24 hours without leaving a mark in CSU.

Assessment of quality of life

CSU is a disease which affects social lifeand leads to sleep disturbance and labor loss[44,45]. Its negative effect on quality of life was found similar tothose of the patients who are waiting for coronary by-pass surgery[46,47]. International guidelines recommend the use of health-related quality of life scales[1,48]. Chronic Urticaria Quality of Life Questionnaire (CUQoL) was developed for the assessment of the effect of urticaria on physical, psycho-social functions and daily life, its Turkish reliability and validity has been performed (Appendix 1)[49,50]. Angioedema Quality of Life Questionnaire is available for assessment of AE[51].

Assessment of disease severity

Urticaria Activity Score (UAS) is widely used for the assessment of disease severity[52]. UAS is filled out by the patient every day, it includes wheal count and itching severity. Use of UAS7 which evaluates the symptoms within the recent 7 days is recommended for evaluating the patients between visits. Maximum score of UAS7 is 42 (Table 3)[1]. Disadvantage of UAS is that it is not useful for inducible urticaria and AE. Angioedema Activity Score was developed for the assessment of AE severity[51]. Overall daily score is between 0-15 and addressing this score for 4 weeks enables better assessment of AE severity.

Assessment of disease control

UAS7 is mainly used for the assessment of disease severity. However "Urticaria Control Test (UCT)" which is composed of four simple questions was developed for improving patient compliance and it is a practical tool in the clinical setting (Appendix 2)[53].

CUQoL is recommended for the assessment of the influence of the disease on quality of life, UAS7 is recommended for the assessment of disease severity, UCT is recommended for evaluating whether the disease is under control.

Diagnostic tests in acute, chronic and physical urticaria

Table 3. Urticaria activity score

Score	Weals	Score	Itch
0	No	0	No
1	Mild (<20/24 hours)	1	Mild (present but not disturbing)
2	Moderate (20-50/24 hours)	2	Moderate (disturbing but not interfere with daily activities or sleep)
3	Severe	3	Severe(severe itching, interferes with daily activities or sleep)

UAS7: Urticaria activity score for 7 days; total (minimum 0-maximum 42) (UAS7≤6 may be evaluated as well controlled, 7-15 as mild, 16-27 moderate and 28-42 severe urticaria)[54]

Main goal of diagnostic approach in urticaria is to determine the type and subtype of urticaria, and reveal the underlying causes particularly in long standing or severe CSU patients. All tests are not required for every urticaria patient[1,14,55-61]. The first step is a thoroughhistory (Appendix 3). The second step is dermatologic and systemic examination. No routine diagnostic tests are required for AU.

Subtype of urticaria should be determined in CU. Despite there is no consensus for the diagnosis of CSU, limited number of tests are usually recommended depending on the history of the patient (Table 4)[1,14,55-61]. Skin tests for inducible urticaria are summarized in Table 5[1,41,43,56,58,59,61-63]. These tests should be performed in a setting where emergent intervention conditions are available. Test is terminated if it becomes positive before the expected time.

Routine diagnostic tests are not required in AU. Limited number of tests should be performed in CSU depending on the history of the patient.

Differential diagnosis

The other diseases presenting with urtica and AE should be considered in differential diagnosis (Table 6). Urticarial vacsulitis is among the diseases that should be considered first. Lesions last for longer than 24 hours and heal with purpura or pigmentation in urticarial vasculitis. Fever, arthralgia, increased sedimentation rate, hypocomplementemia, circulating immune complexes may be seen. Histopathology reveals leukocytoclastic vasculitis[64,65].

In cases of solitary AE accompanied by abdominal pain, hereditary or acquired AE must be excluded.

Auto-inflammatory diseases t should also be considered in the differential diagnosis of urticaria. Findings suggestive of auto-inflammatory diseases are as follows;

- Urticarial and/or maculo-papular rash lasting up to 24 hours (with or without itching),
- Starting before age of 20,
- Symptoms like fever, arthralgia, fatigue,

Table 4. Diagnostic tests for acute and chronic urticaria

	Routinediagnostic tests	History-based tests
Acute urticaria	**No**	**No**
Chronic urticaria	CBC, ESR, CRP Discontinuation of suspected drugs	- Infectious diseases *(H. pylori etc.)* - Thyroid hormones and auto-antibodies - Skin tests for inducible urticaria - Pseudo-allergen free diet for 3 weeks - Autologous serum skin test - Lesional skin biopsy

ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, *H. pylori: Helicobacter pylori*

Table 5. Skin tests in inducible urticaria	
Cold urticaria	An ice cube in plastic bag is applied onto volar side of forearm for 5 min and urtica development after 20 min is evaluated as positive
Late pressure urticaria	7 kg of weight is bound to a belt of 3 cm and hold on theshoulder, upper back, femur or volar side of forearm for 15 min. Erythema and edema development after 6 hours is evaluated as positive
Heat urticaria	Thermofor at 44 °C is applied onto volar side of the forearm for 5 min. Urtica development after 10 min is evaluated as positive
Solar urticaria	6 J/cm^2 UVA, 60 mJ/cm^2 UVB and visible light (projector) is applied at thigh. Urtica development after 10 min is evaluated as positive
Symptomatic dermographism	Volar side of forearm or skin of upper back is marked with a blunt object (closed tip of a pen, wooden spatula etc.). Urtica and itching development after 10 min is evaluated as positive
Vibration angioedema	Vibration device (1000 rpm) is applied onto volar side of forearm for 10 min. Angioedema development after 10 min is evaluated as positive
Aquagenicurticaria	A wet cloth at body temperature is worn for 20 min. Urticaria development within 30 min is evaluated as positive
Cholinergic urticaria	30 min of exercise (treadmill or biking) or 42 °C hot bath provocation is done. Urtica development after 10 min is evaluated as positive
Contact urticaria	Skin provocation test (open-closed patch test done with latex and food and evaluated at 20th min, skin prick test)
UVA: Ultraviolet A, UVB: Ultraviolet B, min: Minute	

- Neutrophil predominancy on histopathological examination[64-67].

Diagnostic algorithm for urticaria is shown in Figure 1.

General approach to urticaria treatment

Two main points of urticaria treatment include elimination of the cause and relieving symptoms. The precipitating cause is frequently known in AU. Detection and elimination of the causative factor (or factors) might be difficult in CU. The first step of treatment is providing support for the patient and establishing confidence between the physician and the patient[68]. In addition, the patient should be provided written and verbal information regarding the disease, warn about the factors that the patient should avoid from. Symptomatic treatment should be immediately started while etiology is being investigated.

Specific treatment can eliminate urticaria in only a small group of patients. Topical anti-pruritic medications, topical steroids and cold compress are not recommended because of inefficiency. All urticaria patients should be recommended to avoid from the factors that could precipitate or exacerbate urticaria.

Table 6. Differential diagnosis of urticaria
Dermatologic diseases - Urticarial vasculitis - Hereditary/acquired angioedema and other bradykinin-mediated angioedema conditions - Mastocytosis - Hypereosinophillic syndrome - Figurate erythema - Bullous pemphigoid/herpes gestationes - Erythemamultiforme - Anaphylaxis - Cutaneous and systemic lupus erythematosus - Dermatitis herpetiformis - Insect bite - Polimorphic light eruption - Wells syndrome - Autoimmune progesterone dermatitis - PUPPP
Urticarial syndromes in auto-inflammatory diseases **Hereditary** - Familial mediterranean fever - Hyper IgD syndrome - TRAPS - Cryopirinopathies - FCAS - Muckle-Wells syndrome - NOMID Acquired - Schnitzler syndrome
Cytokine-mediated angioedema syndromes - Eosinophillic episodic angioedema (Gleichsyndrome) - Eosinophillic non-episodic angioedema - NERDS - Idiopathic capillary leak syndrome(Clarkson syndrome)
IgD: Immunoglobulin D, PUPPP: Polymorphic eruption of pregnancy, TRAPS: Tumor necrosis factor receptor-related period syndrome, FCAS: Familial cold auto-inflammatory syndrome, NOMID: Newborn onset multi-system inflammatory disease, NERDS: Nodular, eosinophillic, rheumatism, dermatitis, swelling

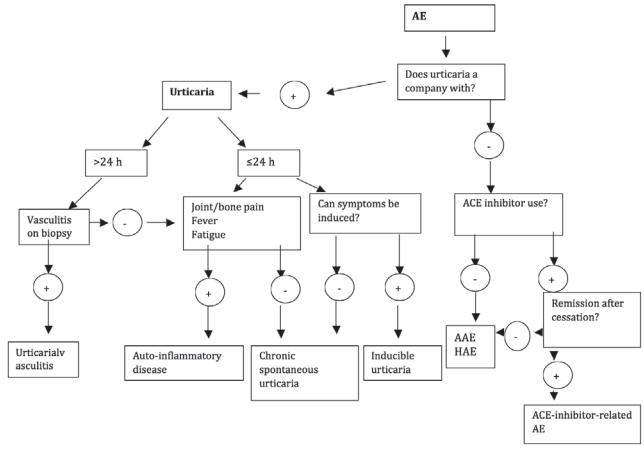

Figure 1. Diagnostic algorithm for urticaria
*AE: Angioedema, ACE: Angiotensin converting enzyme, **"Maurer M, Magerl M, Metz M, et al. Practical algorithm for diagnosing patients with recurrent wheals or angioedema. Allergy 2013;68:816-9"*

1. Physical triggers: Strenuous physical exercise and high environment temperature should be avoided as elevated body temperatures could induce urticaria. Light clothes should be worn, rubbing and strong drying should be avoided in dermographic urticaria. Tolerance development methods are not recommended in inducible urticaria because they are not practical and carry the risk of anaphylaxis.

2. Food: IgE-mediated food allergy is rare in urticaria. Lesions disappear within 24-48 hours if the responsible food is eliminated from diet in IgE-mediated urticaria. An elimination diet for 4 weeks is recommended in cases which pseudo-allergens are implicated (Appendix 2)[1,69,70]. Clinical signs begin to disappear 2-3 weeks after discontinuation of the food. Alcohol consumption is not recommended in urticaria patients[71].

3. Medications: Aspirin and NSAIDs are the main medications that should be avoided. ACE inhibitors, narcotics like morphin, codeine are not recommended as they may precipitate urticaria.

4. Fatigue, stress: The patients are recommended to avoid from stressful events as both lesions and pruritus may be exacerbated with physical and emotional stress. Some patients may benefit from psychological support[72,73].

5. Others: Less frequently reported triggers include smoke fume, house dust mites, pollens, spores and yeasts. There are cases of urticaria characterized bypremenstrual flares[61]. The patients should be informed about all these potential triggers.

Treatment of urticaria

Antihistamines

Chronic urticaria

Mechanism of action: Antihistamines have been introduced into the market in 1950. Many symptoms of urticaria develop through H1 receptors which are present on endothelial cells and nerves. So H1 receptor blockers are the mainstay of treatment[74,75].

Usage: Second generation H1 antihistamines are started at standard doses first. Studies indicate that second generation H1 antihistamines are more effective in high doses. Desloratadine, cetirizine, levocetirizine, bilastine, fexofenadine and rupatadine were shown to be more effective in higher than standard doses[1,76-80]. Recent guidelines recommend increasing the dose up to four-folds in patients in whom standard dose is insufficient[1]. Antihistamines should be used daily, not when needed[81].

Effectiveness: Well designed pharmacokinetic (absorption, distribution, metabolism and elimination) studies are not available for first generation H1 antihistamines. Pharmacodynamic studies which show the relationships between drug concentrations and activity are insufficient. Their antipruritic effect lasts for 4-6 hours[82,83].

Effect of second generation antihistamines lasts for 24 hours. Besides their antihistamine effects, they also suppress cytokines which play a role in the pathogenesis of urticaria through their anti-inflammatory effects.

Second generation H1 antihistamines cetirizine, levocetirizine, loratadine, desloratadine, acrivastine, rupatadine and ebastine are available in Turkey. However, azelastine, bepotastine, bilastine, epinastine, mequitazine, mizolastine and olopatadine are not available. Second line H1 antihistamines were shown to be safe and effective in randomized controlled studies[85,86].

Cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine, rupatadine and bilastin were studied in detail in urticaria[1,74]. When the results of comparative studies on second generation H1 antihistamines are evaluated, the available data were not sufficient to make a recommendation for the most effective antihistamine for CU treatment[6]. Response to treatment and potential side effects may vary between individuals.

Side effects and follow up: First generation H1 antihistamines may also block many cholinergic, alpha-adrenergic and serotonergic receptors, may lead to sedation, impaired sensory-motor and psycho-motor functions lasting for longer than 12 hours through easily passing blood-brain barrier and bounding to cerebral H1 receptors due to their low molecular weight and lipophillic nature. These medications were also reported to influence rapid eye movement period of sleep and learning performance[80,82,84,87]. First generation antihistamines may interact with analgesics, hypnotics, sedatives and alcohol[82,83].

Second generation antihistamines bind to cholinergic, alpha-adrenergic or serotonergic receptors less due to their high specificity for H1 receptors and low lipophillic nature and pass to central nervous system less. So they show less anti-cholinergic and sedative effects[81,82]. Fexofenadine shows minimum sedative effects while cetirizine and levocetirizine show maximum sedative effects[83]. Drug intercations are minimal[84]. Side effects of H1 antihistamines are shown in Table 7.

"Two main goals of urticaria treatment are elimination of the cause and abolition of symptoms. Detection or elimination of the cause may be difficult in CU. All patients are recommended to avoid from physical triggers, medications such as aspirin and NSAIDs, some foods and stress".

Use in children: Second generation H1 antihistamines should be preferred due to low side effect profile and high effectiveness[1].

Use in pregnancy and lactation: Loratadine, cetirizine and levocetizine should be preferred in pregnant and lactating women. These drugs are in category B in Europe and USA[1,6].

Acute urticaria

Antihistamines should be regularly used for 3-4 weeks. Second generation H1 antihistamines should be preferred[88]. Parenteral forms of some first generationantihistamines are used when rapid action is wanted or only under emergency conditions. Pheniramine maleate is the most commonly used antihistamine for this purpose in our country. 1/2-1 vial of drug is administered via slow intra-venous or intra-muscular route in an adult depending on body weight. Duration of action of a single dose is 4-8 hours[88].

Table 7. Side effects of H1 antihistamines[82]

System	First generation	Second generation
CNS	Impairment in learning, memory, sensory-motor functions, sedation, headache, confusion, agitation, dystonia, dyskinesia and hallucinations	Minimal or no side effect
Cardiovascular	Dose-dependent sinus tachycardia, reflextacchycardia, atrial refractory period prolongation and supraventricular arryhtmias	No side effect
Toxic high dose use	Severe CNS and cardiac side effects, may lead to death unless treated	No severe side effect or death was reported

CNS: Central nervous system

Standard doses of second generation H1 antihistamines are recommended in urticaria. Standard dose is increased up to four-fold if sufficient response cannot be obtained. Treatment is switched to another second generation H1 antihistamine at the final dose if symptoms cannot be controlled.

Antihistamines should be used daily, not when needed. Sufficient data are not available for recommending the most effective second generation antihistamine. First generation H1 antihistamines and H2 antihistamines are not recommended.

Leukotriene receptor antagonists (LTRA)

Mechanism of action: Anti-leukotriene agents suppress the effect of cysteinyl leukotrienes which are potent pro-inflammatory mediators and play a role in the pathophysiology of urticaria[89,90].

Usage: Recommended daily dose is 10 mg for montelukast and 20 mg bid for zafirluast. Despite the absence of a consensus on duration of treatment with LTRA in urticaria, longer than 2 years of use was reported in asthma and chronic obstructive pulmonary disease[89].

Effectiveness: LTRAs were found to be effective in urticaria, cold urticaria, solar urticaria and delayed pressure urticaria in combination with second line antihistamines[90,91].

Side effects and follow up: LTRAs are well tolerated and have low side effects. Reported side effects (headache, abdominal pain, dyspepsia, cough, nausea, diarrhea, elevated alanine amino-transferase/aspartate amino-transferase levels) are equal or close to placebo[89,92].

Use in children: Pediatric oral granule (4 mg) and chewing tablet (4 mg daily for patients aged 2-5 years; 5 mg daily for patients aged 6-14 years) are available. They may be used beginning from 1 years of age in patients with asthma. Zafirlukast is used in adult doses in children above 12 years, data are not available about its use under 12 years[93].

Use in the elderly: Data are not available about safety of LTRA use in CU developing in the elderly[94].

Use in pregnancy: It is in category B for pregnancy. Available data indicate that LTRA use in pregnancy does not lead to a significant risk compared to general population. Only one study detected that the babies of whom mothers were treated with LTRA during pregnancy had lower birth weight. LTRAs should not be used for treatment of urticaria developing during pregnancy unless needed until larger and more comprehensive studies are done for safety and reliability[94,95].

Cyclosporine

LTRAs (particularly montelukast) may be used in combination with second line antihistamines both in CSU nor responsive to antihistamines and dermographic urticaria, cold urticaria, solar urticaria and delayed pressure urticaria due to low side effect profile and being safe.

Mechanism of action: It is a calcineurine inhibitor which suppresses T cell activation. Cyclosporine is known to suppress basophil and mast cell degranulation although T cell-mediated mechanism is proposed for its mechanism of action[96,97].

Usage: Recommended daily dose is 200 mg for adults (3-3.5 mg/kg/day). Dose is gradually decreased to 100 mg daily by decreasing 50 mg each month, then it is reduced 25 mg each month thereafter. It is used for 3-6 months.

Effectiveness: Four randomized- controlled double- blind studies, many case series and case reports published since 20 years support that combination of cyclosporine and antihistamines is effective in CU cases resistant to antihistamines[98-102]. Clinical response rates are between 64-95%. Symptoms may improve within the first two weeks of treatment. Remission lasting for 9 months may be achieved in 50% of the patients when treatment is completed. However relapses may be seen after discontinuation of therapy in some patients. In that case, maintenance therapy may be continued in the dose of 1.5-2 mg/kg/day[103]. It is used off-labelin the treatment of CSU.

Low dose (2.5 mg/kg(day) cyclosporine was shown to suppress symptoms when used for longer than 8 months in six patients with dermographic urticaria[104]. Cycloporine was also found to be effective in cold urticaria and solar urticaria[105,106].

Side effects and follow up: Risk of adverse events is correlated with duration of treatment. It may lead to hepatic and renal damage, hypertension, hirsutism and irreversible gingival hyperplasia. Urea, creatine, urinary examination and blood pressure control is recommended at the beginning of treatment and at every 4-6 weeks.

se in children: In a retrospective study of 7 patients with CU aged 9-16 years, remission was achieved in 1-4 weeks for six patients, and 8 weeks for one patient[100]. However pediatric usage should be limited for resistant cases and in experienced clinics.

Use in pregnancy: Category C in pregnancy (FDA).

Although cyclosporine is an effective agent for CSU treatment, due to long term side effects its use should be reserved for CU cases resistant to high dose of antihistaminesand omalizumab.

Omalizumab

Mechanism of action: It is a recombinant humanized monoclonal IgG antibody developed against IgE. It is bound to free IgE in plasma and interstitial space, reduces mast cell functions and triggers eosinophil apoptosis, reduces cytokine release from basophils and migration of immune cells to tissue[107].

Usage: It is used in the dose of 300 mg subcutaneously at every 28 days for 6 months. It is evaluated after intermittent doses, treatment is maintained as the same if symptoms continue.

Effectiveness: Approval and guideline recommendations are based on the results of a double blind placebo controlled study conducted with over 1.000 patients (XCUISITE, MYSTIQUE, ASTERIA I, ASTERIA II ve GLACIAL)[108-112]. These studies revealed a safety profile similar to placebo. Clinical recovery may develop one week after the first injection or up to four weeks. It is the only approved treatment option for CSU both in Europe and USA in patients above 12 years and resistant to antihistamines.Effectiveness of omalizumab was shown not only in autoimmune urticaria butalso in physical, cholinergic and the other urticaria forms. It is effective in more than 80% of the patients. It is not a curative treatment agent, relapse is frequent within 10 weeks after cessation of treatment. Therefore it should be administered as long as disease continues. Acute exacerbation is not encountered after discontinuation of treatment, return of clinical symptoms is slow. Control may be achieved within the first 4 weeks in 90% of the patients in whom omalizumab is started again[113].

Dose may beelevated to 450 mg or 600 mg if response cannot be obtained after 300 mg of omalizumab is given for 6 months. The patients who do not respond to 600 mg omalizumab for 3 months are accepted as resistant to omalizumab[114].

Side effects and follow up: Headache, upper abdominal pain, diarrhea and edema at injection site, erythema, pain and itching may be seen in 3% of the cases. No laboratory tests are required before and during treatment. Follow- up is recommended for 2 months at the first 3 injections and 30 mins thereafter.

Use in children: Evidence is accumulating on effectiveness and safety of omalizumab in patients 7 year old age and older. The drug is usedin the dose of 150-300 mg in pediatric cases and well tolerated[115]. However its use in children should be limited to experienced centers.

Use in pregnancy: Experience of omalizumab use for CSU in pregnancyis not available. However no increase was found in the prevalence of major anomalies in 169 pregnant cases (EXPECT study) for whom omalizumab was used for asthma treatment during pregnancy[116]. FDA classified omalizumab as a category B drug.

Omalizumab is the only effective and safe treatment option approved for CSU patients whose symptoms persist despite high dose antihistamine treatment. It may be used again without loss of effectiveness if recurrence occurs after 6 months of treatment.

Systemic steroids and other treatments

Systemic steroids

Although systemic steroids may provide symptom control in a short time both in acute and CU, level of evidence is low; and they should be used for maximum 10 days in acute exacerbations[1].

Other treatments

H2 blockers: Although a recent Cochrane analysis reported that adding a H2 antihistamine to a H1 antihistamine provides better improvement, its level of evidence low. So, H2 antihistamine use is not recommended in CU[117].

Anti-inflammatory drugs: Evidence level of the studies on effectiveness of dapson, sulfasalazine, hydroxychloroquine and colchicine is low[118-122].

Immune-suppressive drugs: Evidence level of the studies on effectiveness of methotrexate, mycophenolate mofetil, azathiopurine, tacrolimus, mizoribine and cyclophosphamide is low[123-128].

Other treatments

Intra-venous immunoglobulin: Publications are available reporting that it is effective in CSU, late pressure urticaria and solar urticaria. It may be tried in refractory cases[129,130].

Anticoagulant treatment (warfarine, low molecular weight heparin): In case series, It was reported to be an optionin patients whose D-dimer levels are high and refractory to standard treatments[131,132].

Phototherapy: It was found to be effective in inducible urticarias, mainly solar urticaria and symptomatic dermographism. There are limited studies reporting its effectiveness in CSU[133,134].

Auto-hemotherapy: A randomized, placebo-controlled study from Turkey reported no significant difference among the effectiveness of autologous serum treatment, autologous whole blood treatment and placebo[135].

TNF-α blockers: Althoug data are available reporting the effectiveness of TNF-α blockers in CSU, the level of evidence is low[136].

Systemic steroids should be used for a maximum of 10 days in acute exacerbations.

Treatment algorithm recommended for CU by our guideline is shown in Figure 2.

Special conditions

Urticaria treatment in children

AU is more frequent in infants and children, and infections are proposed to play an important role in the etiology[137]. While streptococcus and staphylococcus-related upper respiratory tract infections, pharyngitis, sinusitis cause AU in children, they may rarely cause CU[138]. Despite insufficient data due to the limited number of studies onurticaria

in pediatric population, CU is reported to be seen less in children in prevalence studies. Thyroid auto-immunity is also lower in children with CSU, its ratio was found as 4.3%[139].

New generation H1 antihistamines are recommended as the first option as their long term safety profiles are better. First generation H1 antihistamines should not be used because of severe sedation andsychomotor skill impairment[140]. Recommendations about urticaria treatment in children are based on extrapolation of adult data (scientific data-based estimation). The study of Potter et al.[141] conducted inchildren with CSU aged between 2-11 years andinvestigated the effectiveness of rupatadine and desloratadine is the first placebo-controlled study in this age group. Both agents were found to be superior to placebo and rupatadine was found more effective at the end of 6 weeks of treatment. Levocetirizine was shown to reduce urticaria episodes by 60%[142]. The list of names and doses of the antihistamines which are recommended for children are given in Table 8.

Table 8. Pediatric antihistamines available in Turkey

Cetirizine	Syrup/drops	2-12 years: 5 mg/day	12 years and above: 10 mg/day
Loratadine	Syrup	2-12 years: 5 mg/day	12 years and above: 10 mg/day
Levocetirizine	Syrup/drops	2-6 years: 2x1.25 mg	6 years and above: 5 mg/day
Desloratadine	Syrup	6-11 months: 1 mg/day 6-11 months: 2.5 mg/day	1-5 years: 1.25 mg/day 12 years and above: 5 mg/day
Fexofenadine	Syrup	6 months-2 years: 2x15 mg/day 12 years and above: 120-180 mg/day	2-11 years: 2x30 mg/day
Rupatadine	Tablet	12 years and above: 10 mg/day	

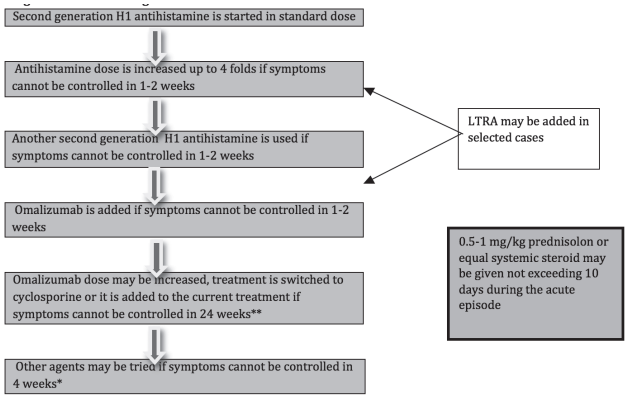

Figure 2. Treatment algorithm for urticaria
*LTRA: Leukotriene receptor antagonists, *Other treatments are addressed in "Other treatments" section of the guideline. **Although omalizumab is reported to be able to be used safely up to 600 mg in irresponsive cases, it is an out of indication application like cyclosporine*

Antihistamine doses may be elevated up to 2-4 folds depending on the age and weight of the patient if the patient is not responding to standard doses, as in the adults. This is recommended in some guidelines although safety studies are not available in children[1].

Sufficient data are not available about the use of LTRA, cyclosporine and omalizumab in children with CU. When extrapolation based on urticaria treatment in adults is done, these agents may be used in addition to antihistamines in third line. According to small number of case reports, LTRA is more effective than placebo in CU treatment in children however it should alwaysbe used in combination with antihistamines. Montelukast is used in the dose of 4 mg daily in asthma and allergic rhinitis treatment in children above 2 years of age in Turkey, however it is not approved for the treatment of urticaria. Omalizumab may be used in the dose of 150-300 mg monthly in children 12 years and older. Its administration and follow- up are as in adults. Cyclosporine was used in children unresponsive to antihistamine treatment as in adults and found quite effective. However it should be kept in mind that its use is off- label[94,100]. Systemic corticosteroids may be used for a maximum of 10 days in pediatric patients in the presence of AE episodes or widespread urticaria.

First generation H1-antihistamines should not be used in children as they may lead to psychomotor skill impairment. Dose of antihistamines may be elevated up to 2-4 folds depending on the age and weight of the children who are unresponsive to treatment. Omalizumab may be used in the dose of 150-300 mg/month in children 12 years or older in cases resistant to antihistamine treatment.

Urticaria management in pregnancy and lactation

Urticaria may develop as continuation of a previous CU or pregnancy urticaria (gestational urticaria). Gestational urticaria is quite rare and repeated in each pregnancy. It is considered to develop due to hypersensitivity to hormones although its etiology is not clear[57].

Avoidance of systemic drugs is the most preferred option in pregnancy, particularly in the first trimester. However treatment should be planned individually based on benefit and risk ratio. Recent guidelines recommend the conventional approach in pregnancy[1]. According to this, the first treatment option is systemic antihistamines. Chlorpheniramine is known to be safe in pregnancy and do not increase anomaly incidence[143]. Congenital anomalies were not foundin many pregnant women who used loratadine and in small number of patients who used cetirizine[144,145].

Pregnancy category was determined as B for chlorpheniramine, loratadine, cetirizine and levocetirizine. Pregnancy category is C for all other antihistamines. First generation antihistamines shouldn't be used just before delivery because of the risk of respiratory depression in fetus. Therefore all new guidelines stress that new (second) generation antihistamines are safer in management of pregnant women with urticaria.

All antihistamines are known to pass to breast milk in varying degrees. So they must be used in the minimum effective doses when required.

Loratadine and cetirizine may be preferred in urticaria treatment of lactating women as they are detected in scarce amount in breast milk[146,147].

Pregnancy category was determined as B for chlorpheniramine, loratadine, cetirizine and levocetirizine. Use of first generationantihistamines just before delivery is harmful because of therisk of respiratory depression in the fetus.
Conventional treatment algorithm may be used in pregnancy. However data are not available about dose escalation of antihistamines.
Loratadine and cetirizine may be preferred in urticaria treatment of lactating women.

Prognosis of urticaria

Urticaria may be acute, spontaneously recovering or chronic, may last for weeks, months or even years. There are no epidemiologic studies are available in the literature investigating the prognosis of AU in untreated patients. In only one study, 44 patients with AU were administered 10 mg daily loratadine until symptoms resolve and 65 patients were administered 50 mg of prednisolone for 3 days and then 10 mg/daily loratadine. No patients were reported to develop CU, and the disease was reported to be self-limited[148].

Natural course of CU cannot be predicted. Patients usually recover spontaneously. Recovery rates are variable in the literature. Remission occurs in 30%-50% of adult CU patients within 1-3 years after beginning of symptoms[10,149,150]. CU symptoms continue for longer than 5 years in 11% of the patients. Factors which determine response to therapy and disease severity are limited in CU. The disease may lasts longer in severe cases[151]. Disease severity and duration were found to be associated with AE, coexistence with physical urticaria, advanced age and positive thyroid antibodies. There are some studiesindicating that autologous serum skin test (ASST) positivity is also related with severe symptoms. It is suggested that patients who have predominantly neutrophillic tissue infiltration poorly respond to antihistamines. However no marker is available to determine the response to therapy[151-158].

Most of the studies about prognosis of CU are retrospective and age of onset of the disease, disease duration, treatments before being enrolled in the study and ethnicity of the patients are different[151]. Ratio of the patients who benefited from step treatment in 6 months was found as 39% in a very new prospective treatment[159]. In a recent systematic review, no relationship was found between ASST positivity and disease activity and longstanding disease in patients with CU[160].

Remission rates were found as 18.5%, 54% and 67.7%, respectively; 1,3 and 5 years after disease onset in 92 patients aged between 4-15 years in a prospective study. No association betweenthe presence of autoimmunity and remission rates were found and also any factor wasn't demonstarated determining the remission[161].

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Appendix 1. Chronic Urticaria Quality of Life Questionnaire

Name: .....

Date: .....

Gender: ☐ Male ☐ Female

Date of birth: .....

You will see a table composed of questions. Please read each question carefully and mark the most appropriate item for you among five. Please select only one item and answer all questions.

	No	Little	Moderate	Much	Excessive
How much discomfort did you feel during recent 15 days?					
1.Itching					
2. Wheals					
3. Swelling of the eyes					
4. Swelling of the lips					
Please state the degree of urticaria it it had limited your life during recent 15 days.					
5. Work life					
6. Physical activities					
7. Sleep					
8. Spare time					
9. Social relationships					
10. Nutrition					

We aim to obtain details about the urticaria-related problems and difficulties through the following questions (please consider recent 15 days).

	No	Little	Moderate	Much	Excessive
11. Do you have difficulty to sleep?					
12. Do you awaken during night?					
13. Do you feel tired at daytime as you cannot sleep well at night?					
14.Do you have difficulty to concentrate?					
15. Do you feel nervous?					
16. Do you feel dispiritedness?					
17. Do you need to put limits for food selection?					
18. Are you ashamed due to the signs on your body developing due to urticaria?					
19. Do you hesitate to go general places?					
20. Do you have problems to use cosmetic products? (parfumes, creams, lotions, shower gels, make up materials etc.)					
21. Do you need to make limitations about your clothes?					
22. Did you need to limit your sports activities due to urticaria?					
23. Did you feel discomfort about the side effects of the medications used for treating urticaria?					

Appendix 2. Urticaria control test

1. How severe did you feel urticaria-related physical signs during recent 4 weeks (itching, wheals and/or swelling)?

☐ Vey much ☐ Much ☐ Moderate ☐ Little ☐ No

2. How was your quality of life affected due to urticaria during recent 4 weeks?

☐ Vey much ☐ Much ☐ Moderate ☐ Little ☐ No

3. How successful was urticaria treatment for suppressing your discomfort during recent 4 weeks?

☐ No ☐ Little ☐ Some ☐ Good ☐ Very good

4. How well was your urticaria suppressed during the recent 4 weeks?

☐ No ☐ Little ☐ Some ☐ Good ☐ Completely

***Each response is scored between 0 and 4; minimum score is 0; score of ≥12 indicate well controlled disease; ≤11 indicates that the disease is not under control.**

Appendix 3. Urticaria patient history form*

1. Since when do you have urticaria?

Please write a date.....

2. How frequent do your wheals appear?

☐ Continuously ☐ Daily ☐ Weekly ☐ Monthly ☐ Other (please specify) .....

3. When do your wheals diappear?

☐ <1 hour ☐ 1-24 ☐ >24

4. Do you have marks or spots when the wheals disappear?

☐ Yes ☐ No

5. Sites where your wheals occur.....

☐ Itchy ☐ Painful

6. Do you have swelling in your lips, eyelids, palms and soles?

☐ Yes ☐ No

7. Do you have fever, abdominal pain and arthralgia accompanying your rashes?

☐ Yes ☐ No

8. Where and when do your rashes/swellings become frequent?

☐ In house ☐ Out of house ☐ At work ☐ On weekdays ☐ On weekend ☐ On holiday

9. Did your complains begin after the following?

☐ Infection ☐ Contrast medium exposure ☐ Drug use ☐ Vaccination ☐ Injection ☐ Other (please specify) .....

.....

10. Do you think that your complaints are associated with any of the following?

☐ Itching ☐ Tight clothes ☐ Rubbing ☐ Leaning against somewhere ☐ Sitting for a long time

☐ Walking for a long time ☐ Biking ☐ Carrying weight ☐ Vibration

☐ Cold exposure (snow, wind, rain, water, shower, sea, pool, icecream, icy drinks)

☐ Hot exposure (bath, sauna, Turkish bath etc.)

☐ Contact with water (independently from temperature)

☐ Physical exercise, sports, sexual intercourse, spicy or hot drink/food

☐ Excitement, fear, stress ☐ Sweating ☐ Sun exposure

☐ Contact ☐ with ☐ latex materials (handgloves, condom etc.) ☐ Alcohol ☐ Cigarette

11. Do you have a family history of the following?

☐ Allergic rhinitis ☐ Allergic asthma ☐ Allergic eczema ☐ Allergic conjunctivitis

12. Do your complaints increase upon consumption of particularfoods?

☐ Yes ☐ No

(Fish, strawberry, banana, peanuts, nuts, shell fish, soy, cheese, alcohol, chocolate, eggs dairy, ice cream, canned, frozen food, delicadessen products, meat products, prepared foods, drinks, artificial sweeteners)

13. Your job?

.....

14. Do you have hobbies?

.....

.....

15. Please write the medications which you used for urticaria in the recentyear?

.....

.....

16. Please write all the medications which you used in the recent year and vaccinations if you had (antihypertensive, aspirin, antibiotic, vitamin, oral contraseptive, pschiatry drugs, herbal mediactions and teas, hypnotics, rheumatid drugs, analgesics, gastrointestinal medications, influenza medications)

.....

.....

17. Do you have any other diseases?

☐ Yes ☐ No

Please state if yes .....

18. Do you suspect from potential causes for your urticaria? What can be the causes? Do you find any relationship?

.....

.....

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