

Review Series: Advances in Consensus, Pathogenesis and Treatment of Urticaria and Angioedema

Japanese Guidelines for Diagnosis and Treatment of Urticaria in Comparison with Other Countries

Michihiro Hide¹ and Takaaki Hiragun¹

ABSTRACT

Several guidelines for urticaria and angioedema have been published in Europe and United States since 1997. General principles for diagnosis and treatments of them are similar. However, each guideline has its own characteristics and shows differences in areas such as the coverage of urticaria subtypes, nomenclatures, and hierarchy of the medications. In Japan, the Japanese Dermatological Association (JDA) published its first guideline for urticaria and angioedema in 2005. It established a new classification of urticaria and angioedema together with the definition of each subtype. It emphasized the importance of discriminating idiopathic urticaria, consisting of acute urticaria and chronic urticaria from inducible urticaria, such as allergic urticaria, physical urticaria and cholinergic urticaria. It contains several unique algorithms for diagnosis and treatment of urticaria from a view point of clinical practices, and was further enforced by a style of EBM in 2011. Nevertheless, these guidelines have not been recognized outside of Japan, because of a language barrier. In this article, the outline of the newest guidelines by JDA are introduced and compared with the guidelines in other countries published in English.

KEY WORDS

angioedema, antihistamine, guideline, Japanese, urticaria

INTRODUCTION

Urticaria is one of the most common skin diseases and the management of this disease is an important issue in daily activities for many physicians. Urticaria is characterized by the appearance of itchy wheals and flare that usually disappear in hours. The diagnosis of urticaria itself is easy because of its characteristic clinical symptoms. Vascular dilatation, increase of vascular hyper-permeability and the activation of itch-sensory nerve system are the histopathological reactions that develop clinical symptoms observed in urticaria. It has been widely accepted that these reactions are induced by mast cell degranulation in the skin and antihistamines are the mainstay for the treatment of urticaria. However, the pathogenesis behind

mast cell degranulation is largely unknown and the treatment for urticaria refractory against antihistamine has been controversial. The European Academy of Allergy and Clinical Immunology (EAACI), Global Allergy and Asthma European Network (GA²LEN), and European Dermatology Forum (EDF) published their first guideline in 2006^{1,2} and revised it with World Allergy Organization (WAO) in 2009.^{3,4} On the other hand, Japanese Dermatological Association (JDA) published a comprehensive guideline for the treatment of urticaria and angioedema in Japanese in 2005.⁵ It was incorporated into two other Japanese guidelines, one for primary care in 2007⁶ and another for general physicians by Japanese Society of Allergology (JSA) in 2009.⁷ In this article, we introduce the contents of the newest version of the JDA guide-

¹Department of Dermatology, Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan.

Conflict of interest: MH received speaker's fee from Sanofi-Aventis, GlaxoSmithKline, and Mitsubishi Tanabe Pharma. TH has no conflict of interest.

Correspondence: Michihiro Hide, MD, PhD, Department of Derma-

tology, Institute of Biomedical and Health Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan.

Email: ed1h-w1de-road@hiroshima-u.ac.jp

Received 23 August 2012.

©2012 Japanese Society of Allergology

Table 1 Guidelines for urticaria and their authorizing organizations published in English or Japanese

1997	Physical urticaria: classification and diagnostic guidelines ⁹⁾ <i>European Academy of Allergology and Clinical Immunology (EAACI) Subcommittee on Allergic Skin Diseases</i>
2000	The diagnosis and management of urticaria ¹⁰⁾ <i>Joint Task Force on Practice Parameters (AAAAI, ACAAI, JCAAI)</i>
2001	Management and diagnostic guidelines for urticaria and angio-oedema ¹¹⁾ <i>British Association of Dermatologists (BAD)</i>
2005	Guidelines for the diagnosis and treatment of urticaria and angioedema ⁵⁾ <i>Japanese Dermatological Association</i>
2006	EAACI/GA ² LEN/EDF guidelines: definition, classification and diagnosis of urticaria ¹⁾ , and management of urticaria ²⁾ <i>EAACI/GA²LEN/EDF</i>
2007	AAITO Committee for Chronic Urticaria and Pruritus Guidelines ¹²⁾ <i>Associazione Allergologi Immunologi Territoriali Ospedalieri</i>
2007	BSACI guidelines for the management of chronic urticaria and angio-oedema ¹³⁾ <i>British Society for Allergy and Clinical Immunology (BSACI)</i>
2007	Guidelines for evaluation and management of urticaria in adults and children ¹⁴⁾ (revised) <i>British Association of Dermatologists (BAD)</i>
2007	Primary care version of guidelines for the diagnosis and treatment of urticaria and angioedema ⁶⁾ <i>Research group supported by Japanese Ministry of Health, Labour and Welfare</i>
2009	EAACI/GA ² LEN/EDF/WAO guidelines: definition, classification and diagnosis of urticaria, ³⁾ and management of urticaria ⁴⁾ (revised)
2010	Urticaria and angioedema in Japanese guidelines for the diagnosis and treatment of allergic diseases 2010 ⁷⁾ <i>Japanese Society of Allergology</i>
2011	JDA guidelines. Guidelines for the diagnosis and treatment of urticaria ⁸⁾ (revised) <i>Japanese Dermatological Association</i>

lines published in 2011,⁸ and compare it with other guidelines published in English.

INTERNATIONAL GUIDELINES FOR URTICARIA

The first document that described of urticaria with the term “guideline” and was published in English was a position paper by EAACI in 1997.⁹ It dealt with classification and diagnosis of physical urticarias. In 2000, an American joint task force group published guidelines specific for acute and chronic urticaria and angioedema.¹⁰ These two documents did not cover the whole spectrum of clinical practices for urticaria, including spontaneously occurring type urticaria and inducible type urticaria. The first document that covered a wide spectrum of urticaria and angioedema observed in general practices was published by Grattan *et al.*, on behalf of British Association of Dermatologists (BAD).¹¹ Following these publications, various organizations in Europe published guidelines for the diagnosis and treatment of urticaria and angioedema (Table 1).^{1-4,11-14} The second version published by the EAACI group was approved by several organizations of allergy and dermatology, and was probably the most widely accepted in the world.^{3,4} Moreover, literatures for unmet clinical needs in chronic spontaneous urticaria were extensively reviewed with the best available information from the literature by GA²LEN task force group in 2011.¹⁵ However, many of the re-

cently published guidelines mainly dealt with the management of spontaneously occurring urticaria, the most common type of urticaria encountered in general medical practices. As a result, however, physicians may not obtain the full information for practices relating to other important types of urticaria, such as urticaria due to type I allergy, cholinergic urticaria, and physical urticarias.

The first Japanese guideline for the diagnosis and treatment of urticaria and angioedema was published in 2005 by JDA.⁵ This guideline has established the notion of “idiopathic urticaria”, which is same as “spontaneous urticaria” in recently published guidelines by EAACI and related organizations.¹⁻⁴ The secondary important characteristic of this guideline is the comprehensibility in terms of the classification of urticaria. It covers most of the clinical subtypes of urticaria and angioedema for diagnosis and treatments. Moreover, it was enforced with a chapter consisting of a first section of clinical questions and a second section of structured abstracts based on evidence-based-medicine by a revision in 2011.⁸

OUTLINES OF JAPANESE GUIDELINES FOR THE MANAGEMENT OF URTICARIA

The Japanese guideline for diagnosis and treatment of urticaria published by JDA in 2011 consists of two chapters: Chapter one comprehensively described the diagnosis and treatment of urticaria, and chapter

Table 2 Factors that may be associated with the pathogenesis of urticaria

1. Direct triggers (mainly exogenous and transient)	2. Background factors (mainly endogenous and continuous)
1) Exogenous antigens	1) Sensitization (specific IgE)
2) Physical stimuli	2) Infections
3) Sweating	3) Tiredness/stress
4) Foods [†]	4) Foods, except for antigens
Food antigens, food histamine, pseudo-allergens (pork, bamboo shoot, rice cake, spices, etc.), food additives (preservatives, artificial pigment), salicylic acids [†]	5) Drugs
5) Drugs	Aspirin [†] , other NSAIDs [†] (for FDEIA), angiotensin converting enzymes (ACE) inhibitors [†] (for angioedema), etc.
Antigens, contrast media, NSAIDs [†] , preservatives, succinic acid esters, vancomycin (red man syndrome), etc.	6) Autoantibodies against IgE or the high affinity IgE receptors
6) Exercises	7) Underplaying disease
	Collagen and related disease (SLE, Sjögren's syndrome, etc.), lympho-proliferating diseases, hereditary disorders (e.g. C1-INH deficiency), serum sickness, other organ dysfunctions, circadian rhythm (idiopathic urticaria tends to aggravate from evening toward morning)

[†]May act as either direct triggers or background factors.

Cited from reference 8.

two consists of 34 clinical questions and 179 structured abstracts with answers/comments for them. The outline of this guideline is described below.

DEFINITION AND DIAGNOSIS

Urticaria is a disease that pathologically develops wheal(s), a transient and localized edema accompanied by flare and, in most cases, itch. Deep and localized edema(s), which may appear by itself or together with superficial wheals, are particularly called as angioedema.

The diagnosis of urticaria is made mostly by detailed history taking and visual observations of the skin. It is important for physicians to correctly diagnose subtypes of urticaria, because treatments and/or patients' behavior vary among subtypes of urticaria. Moreover, two or more subtypes of urticaria may complicate a particular patient at the same time. Physicians should first make clear at the diagnosis of urticaria, if it occurs spontaneously or is induced by specific stimuli. In cases of anaphylactic shock and/or suffocation, actions such as adrenalin injection or airway management should be taken as necessary. Clinical examinations are not necessary for all cases, but may help to establish a solid diagnosis, especially for cases of inducible type urticaria.

FACTORS ASSOCIATED WITH THE PATHOGENESIS OF URTICARIA

Cause is a most frequently and strongly asked question in clinical practices for urticaria. The mechanism of urticaria developed by type I allergy is relatively simple and antigen should be identified as a cause in this type of urticaria. However, the involvement of exogenous and/or endogenous factors to develop urticaria, especially those with spontaneously occurring wheals, is not so straightforward. Moreover, any rela-

tion to factors, which have been known as potential causes of urticaria, may not be apparent in many cases of urticaria, especially those with spontaneously occurring wheals. On the other hand, individual patients may suffer from multiple types of urticaria and be simultaneously affected by various factors to induce or aggravate symptoms to variable degrees. Therefore, the question to find a cause itself may not be adequate in certain cases of urticaria. The 2011 JDA urticaria guideline has listed two groups of factors, which may be involved in the pathogenesis of urticaria, one that may directly act or trigger the development of urticaria, and another that indirectly acts to develop urticaria as underlying causes (Table 2).

CLASSIFICATIONS

The 2011 JDA urticaria guideline classified urticaria into four groups and 16 subtypes (Table 3). The "idiopathic urticarias" is a group of urticarias, that daily and spontaneously develop wheals. The group consists of acute urticaria and chronic urticaria, in which wheals occur for not less than 1 month or less than 1 month, respectively.

In Japan, the name of "chronic urticaria" is used to represent, on some occasions, urticaria that continues to occur for more than one month regardless of the presence of triggers. However, since the publication of the first guideline for urticaria by JDA in 2005, the use of "chronic urticaria" and "acute urticaria" has been confined to urticaria characterized by spontaneously occurring wheals. In this sense, chronic urticaria defined in the guidelines by JDA is identical to "chronic spontaneous urticaria" defined in the global guidelines.¹⁻⁴

Another characteristic of the JDA classification is that it also covers subtypes induced by the mecha-

Table 3 Subtypes of urticaria

-
1. Idiopathic urticaria
 - 1) Acute urticaria
 - 2) Chronic urticaria
 2. Inducible urticaria (Urticaria inducible by particular stimuli or conditions)
 - 3) Allergic urticaria
 - 4) Food-dependent exercise-induced anaphylaxis
 - 5) Non-allergic urticaria
 - 6) Aspirin urticaria (urticaria due to intolerance)
 - 7) Physical urticarias (Mechanical, cold, solar, heat, delayed pressure, aquagenic, and vibrative urticarias)
 - 8) Cholinergic urticaria
 - 9) Contact urticaria
 3. Angioedema
 - 10) Idiopathic angioedema
 - 11) Exogenous substances-induced angioedema
 - 12) Angioedema due to C1 esterase-inhibitor (C1-INH) impairments (Hereditary angioedema; HAE), autoimmune angioedema, etc.)
 4. Urticaria-related diseased
 - 13) Urticaria vasculitis
 - 14) Urticaria pigmentosa
 - 15) Schnitzler's syndrome
 - 16) Cryopirin-associated periodic fever (CAPS)
-

Cited from reference 8.

nism of type I allergy. Food-dependent exercise-induced anaphylaxis and contact urticaria are, or may be, induced by type I allergy, but categorized as independent subtypes in the guideline, because the treatments and managements for patients with these urticarias are substantially different from patients with other type I allergies.

EXAMINATIONS

There are two aims of clinical examinations for urticaria. One is to make a solid diagnosis, and the other one is to explore causes of the disease. They may vary according to subtypes of urticaria, suspected by clinical observations. In general, the former may be important for urticaria developed by type I allergy and physical urticarias. On the other hand, the latter may be more important for idiopathic urticaria. Clinical examinations that may be taken for urticaria subtypes are listed in Table 4.

TREATMENTS

General Principles

There are two principles for treating urticaria; the first one being to remove or avoid causes and/or aggravating factors of urticaria, and the second one being to use medications, including antihistamines. The former is more important than the latter in the management of inducible types of urticaria, whereas the latter is more important in spontaneously occurring

urticaria (Fig. 1).

Another important message of this algorithm is aims of the treatments for urticaria. Namely, the first one is to achieve a symptom-free condition by continuous use of medications as the first stage, and the second one is to achieve both symptom and drug-free condition, as the final stage.

The third point for the treatment is the balance of disease severity and burdens of the treatments. The guideline classified disease severities of urticaria into six levels with necessities of further treatments (Table 5).

Regarding medications for the treatment of urticaria, it is widely accepted that oral antihistamines may be used as a mainstay for virtually all subtypes of urticaria. However, the efficacies of medications including antihistamines on urticaria are largely variable among subtypes, or individuals. Therefore, the aims and nature of the treatment for urticaria should be planned, taking into the subtype and severity of urticaria as well as specific conditions of individual patients.

Medications

Many of the studies about pharmaceutical treatments for urticaria have been conducted for idiopathic urticaria and angioedema. Medications for idiopathic urticaria have been classified into four steps in the Japanese guidelines (Fig. 2). The first one is the use of standard dose of antihistamines among a list of non- or low-sedative antihistamines in Figure 4. If it is not sufficiently effective, change to other antihistamines or an increase up to twice the dose of non- or low sedative antihistamines are recommended (*recommendation level B-C1, evidence level II, V*). The medications grouped in the second step, as supplementary treatments, include histamine H₂-receptor antagonists, antileukotrienes, extracts of inflammatory rabbit skin inoculated with vaccinia virus, glycyrrhizinic acid, dapsone, anti-anxiety drugs, tranexamic acid, and Chinese herbs. The third step is the use of steroid equivalent to 5-15 mg/day prednisolone. The fourth step includes immunological treatments, such as ciclosporin, and prednisolone at 20 mg/day or more. The fourth step treatments are still experimental, and may be tried only if symptoms are very severe and refractory. Treatments to take after full suppression of symptoms are indicated in Figure 3.

Medications for other subtype of urticaria were described in the original guideline,⁸ but have not been included in the present article, because of the limited space. Most of them are, however, included in step 1 and 2 for idiopathic urticaria.

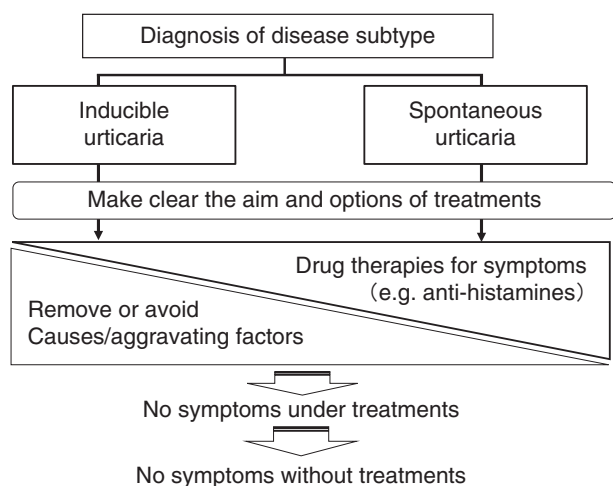
Cope with Causative and/or Aggravating Factors

Contributions of causative and/or aggravating factors to the pathogenesis of urticaria are largely variable.

Table 4 Subtypes of urticaria and aims of clinical examinations

Subtypes	Aims of clinical examinations
Idiopathic urticaria	Explore background and aggravating factors: Examinations should be done when involvement of factors are suspected by history, physical examination, etc.. No examinations are recommended if no apparent symptom except for urticaria was identified. Autologous serum skin test may prove the involvement of autoimmune mechanisms in a population of chronic urticaria.
Allergic urticaria Food-dependent exercise-induced anaphylaxis	Find causative antigen: Demonstration of specific IgE by prick test, serum test, such as immuno-Cap.
Non-allergic urticaria	No commonly recommended examination. Should be diagnosed according to the history of patients.
Aspirin urticaria	Identification of causative drug: Prick test with suspected drug to rule out the mechanism of type I allergy. Challenge with small amounts of suspected drug.
Physical urticarias	Examination for solid diagnosis: Challenge with physical stimuli suspected by history of patients, if necessary.
Angioedema	Decide subtype, explore cause and/or background factors: Examinations should be taken based on history of patients, as those for superficial urticaria (idiopathic and inducible). Measure C3, C4, CH50 and C1-INH activity when C1-INH deficiency was suspected without complication of superficial urticaria.
Urticaria vasculitis	Examination for solid diagnosis: Peripheral blood test (increase of CRP, WBC, and decrease of complements), skin biopsy to reveal pathological findings of vasculitis.
Urticaria pigmentosa	Examination for solid diagnosis: Scrub skin lesion (Darier's sign), skin biopsy to reveal accumulation of mast cells.
Schnitzler's syndrome	Examination for solid diagnosis: Peripheral blood test (increase of CRP, monoclonal IgM, WBC), skin biopsy to possibly reveal pathological findings of vasculitis (not in all cases).
Cryopirin-associated periodic fever (CAPS)	Examination for solid diagnosis: Peripheral blood test (increase of CRP, SAA, WBC) skin biopsy to reveal possibly reveal pathological findings of vasculitis (not in all cases), analysis of cryopirin gene, <i>CIAS1</i> .

Cited from reference 8.

**Fig. 1** Subtype classification and principles of the management of urticaria in the Japanese guideline by JDA in 2011. Cited from reference 8.

In general, pharmaceutical treatments are more important than extensive examinations to find a particular cause in the treatment of idiopathic urticaria. However, it is certainly important to find and avoid factors associated with urticaria, especially when medica-

tions are not effective. On the other hand, symptoms of urticaria induced by specific triggers, such as allergic urticaria induced by specific antigen, or non-allergic one in response to particular drug, cannot be suppressed in the presence of the stimuli.

Hardening and Tolerance

Although a principle to manage inducible type urticarias is to avoid stimuli and/or aggravating factors for symptoms, continuous loading of such factors may reduce the level of reaction. These effects, called as hardening or tolerance, may be induced in subtypes of urticaria with type I allergy, solar urticaria, cold urticaria, heat urticaria, and cholinergic urticaria, especially those with hypohidrosis, but may not be in mechanical urticaria.

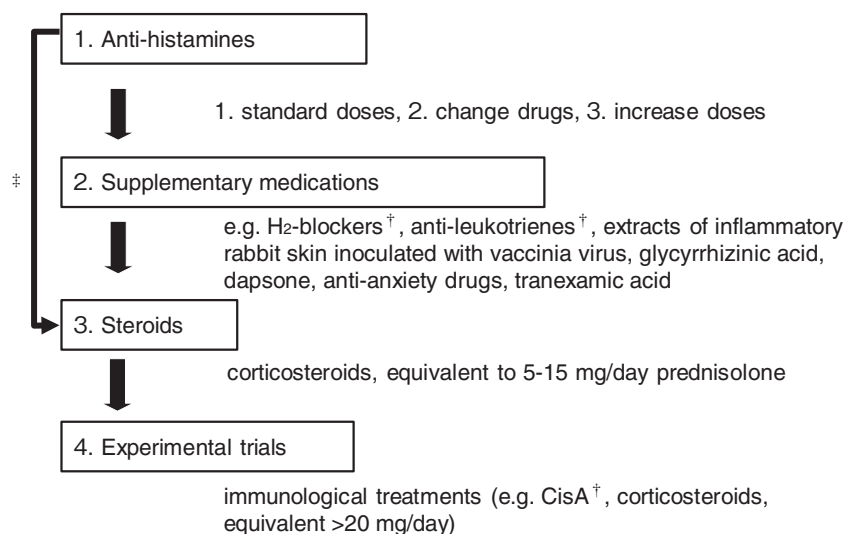
Algorithms for Acute and Chronic Urticaria

If the episode of urticaria symptoms appeared just once and was not very severe, it is not necessary to treat with medication. Urticaria that appeared for a few days or more should be treated with antihistamines for 4-5 days to prevent the appearance of further symptoms. If such treatments failed to suppress symptoms, patients should be treated according to

Table 5 Urticaria severities and necessities of the treatment for cases refractory to antihistamines

Level of severity	Symptoms	Necessity of adding and/or changing to other treatments	Aim of the treatment
6	Shock or similar to shock	Must	Regulation of the symptoms down to levels 4
5	Cannot manage a social life	High	
4	Manage to live with large difficulties	Depends on QOL, appearance or possibility of the side effects of treatments, cost and favorite of the patients, etc.	Remission of the symptoms by treatments
3	Tolerable but uncomfortable		
2	Mild symptoms		
1	Symptom is not recognized	Low	Gradual withdraw and stop medications

Cited from reference 8.

**Fig. 2** Treatment steps for idiopathic urticaria in the Japanese guideline by JDA in 2011. Cited from reference 8.

† Off label use.

‡ If prompt improvement is required.

the algorithm for chronic urticaria. Very severe cases with eruptions covering 30% or more of the body surface may be treated by a short use of systemic steroid (*recommendation level C1, evidence level IV*).

Treatment of chronic urticaria should be started with an antihistamine for two weeks following correct diagnosis and planning of the therapy. If symptoms disappeared or subsided, the same treatment should be continued (*recommendation level B, evidence level II*) for 1-2 months, and then doses of the antihistamine should be decreased gradually. The period of proactive treatment with an antihistamine after the complete disappearance of the symptoms are tentatively recommended as 4-7 days for urticaria with a history within 4 weeks, 1 month for urticaria lasted for 1-2 months, and 2 months for urticaria lasted for 2 months or longer (*recommendation level C1, evidence level VI*) (Fig. 3).

Angioedema

The 2011 JDA urticaria guideline classified angioedema into three subtypes. Idiopathic angioedema and exogenous factor-induced angioedema should be treated according to the treatment for idiopathic urticarias and inducible type urticarias, respectively. Unlike the treatment of chronic urticaria, the effect of tranexamic acid has been endorsed for angioedema by several clinical studies (*recommendation level B, evidence level II*). Moreover, specific treatments are required for cases with deficiency of C1-inhibitor (C1-INH).¹⁶

Overall Algorithm for Urticaria

The overall practices for urticaria have been summarized in an algorithm shown in Figure 4. Since the importance of actions to take in each subtype is not same, but partially overlaps, it is important for physicians to comprehensively understand the whole pic-

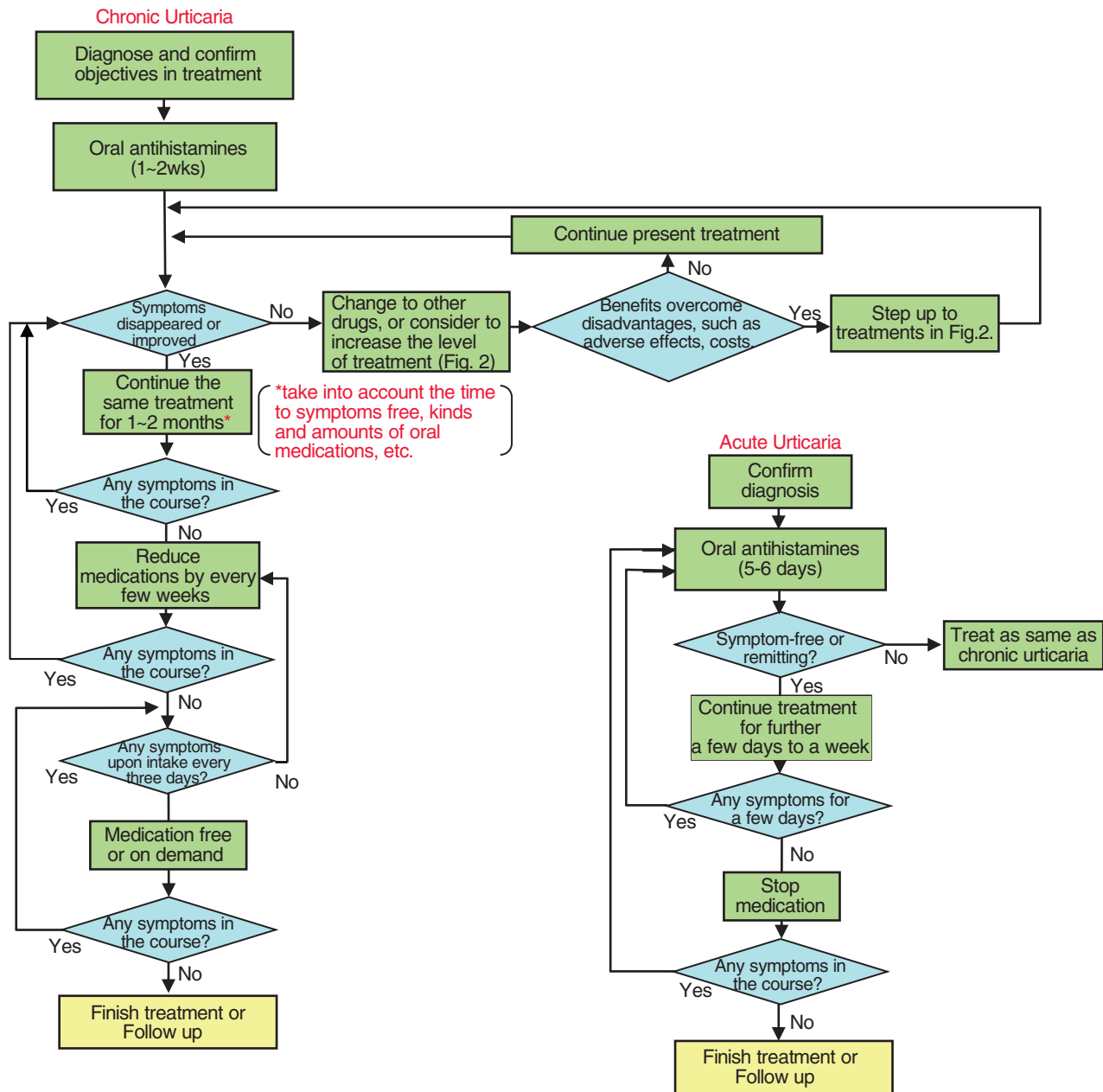


Fig. 3 Algorithm for idiopathic (spontaneous) urticaria in Japanese guideline by JDA in 2011. Cited from reference 8.

ture of urticaria and continue the treatment until a solution to all problems for each patient is achieved.

EBM FOR URTICARIA

The second chapter of the 2011 JDA urticaria guideline consists of two chapters; first for 34 clinical questions with levels of recommendation and evidence, and second for 179 structured abstracts. In this paper, questions and titles of the abstracts are listed in Table 6, 7, respectively.

QUESTIONS TO BE SOLVED

DEFINITION OF CHRONIC URTICARIA

Although a classification of urticaria has been published in the guideline by three European organizations, EAACI, GA²LEN, and EDF,¹ and later together with WAO,³ the definition of chronic urticaria remains vague. A “Joint Task Force on Practice Parameters” which represented several American societies¹⁰ and the “AAITO Committee for Chronic Urticaria and Pruritus Guidelines” in Italy¹² did not distinguish the subtype of urticaria with spontaneously occurring wheals from other types of urticaria that con-

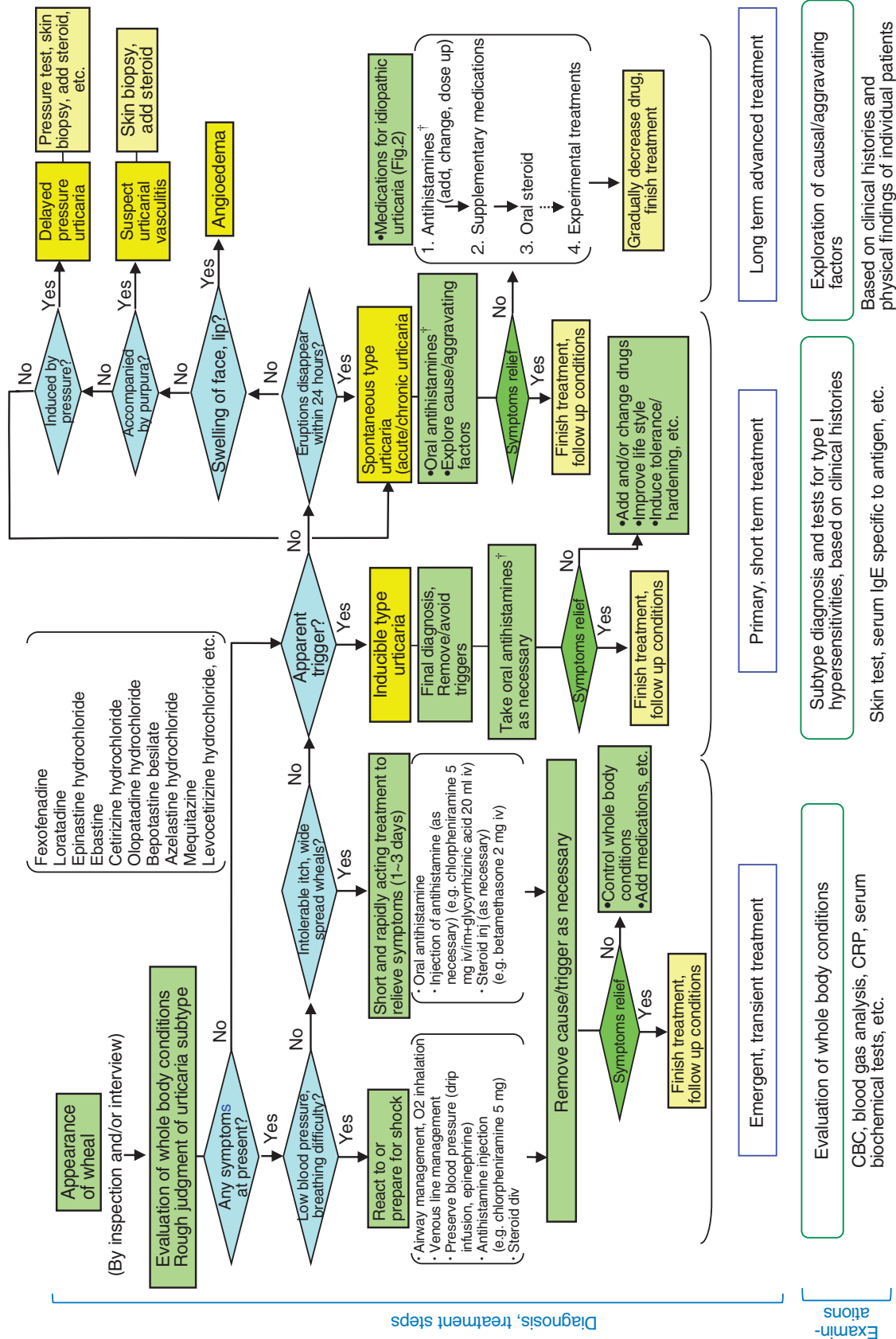


Fig. 4 Algorithm for over all practices for urticaria in Japanese guideline by JDA in 2011. Cited from reference 8.

† Non- or low-sedative second generation antihistamines.

Table 6 Clinical questions

-
- CQ1: Are examinations of type I allergy necessary for urticaria?
- CQ2: Are general biochemical examinations necessary for urticaria?
- CQ2-1: Are examinations necessary for acute urticaria?
- CQ2-2: Are examinations necessary for chronic urticaria?
- CQ3: Are topical steroids useful to suppress occurrence of urticaria symptoms?
- CQ4: Is local cooling, phenol and zinc oxide liniment, ointment containing antihistamines, or crotamiton useful to reduce already appeared symptoms of urticaria?
- CQ5: May antihistamines be used for pregnant/nursing women?
- CQ5-1: May antihistamines be used for pregnant women?
- CQ5-2: May antihistamines be used for nursing women?
- CQ6: Are steroids effective for acute urticaria?
- CQ7: Are antibiotics effective for acute urticaria?
- CQ8: Is it effective to increase a dose of antihistamine for chronic urticaria?
- CQ9: Are supplementary medications effective for chronic urticaria when administered concurrently with antihistamines?
- CQ9-1: Is the concurrent administration of H₂-receptor antagonists effective for chronic urticaria?
- CQ9-2: Is the concurrent administration of antileukotrienes effective for chronic urticaria?
- CQ9-3: Is the concurrent administration of dapsone effective for chronic urticaria?
- CQ9-4: Is the concurrent administration of glycyrrhizinic acid effective for chronic urticaria?
- CQ9-5: Is the concurrent administration of extracts of inflammatory rabbit skin inoculated by vaccinia virus effective for chronic urticaria?
- CQ9-6: Is the concurrent administration of tranexamic acid effective for chronic urticaria?
- CQ9-7: Is the concurrent administration of Chinese herbs effective for chronic urticaria?
- CQ9-8: Is the concurrent administration of anti-anxiety drugs effective for chronic urticaria?
- CQ10: May continue oral steroids, if it suppresses the appearance of chronic urticaria symptoms?
- CQ11: Are immunological treatments effective for chronic urticaria?
- CQ11-1: Is ciclosporin effective for chronic urticaria?
- CQ11-2: Are immunological treatments other than ciclosporin effective for chronic urticaria?
- CQ12: Should idiopathic urticaria be treated for a certain period continuously after the disappearance of symptoms?
- CQ13: Are adrenalin and steroids necessary for urticaria accompanied by anaphylactic shock?
- CQ14: Are antipyretics and analgesics without or with minimum COX1-inhibition safe for patients with aspirin-induced urticaria?
- CQ15: Is a change of antihistamines effective in the treatment of dermographic urticaria?
- CQ16: Are antihistamines effective for cold urticaria?
- CQ17: Is cold tolerance inducible for patients with cold urticaria?
- CQ18: Are antihistamines effective for solar urticaria?
- CQ19: Are immunological treatments effective for solar urticaria?
- CQ20: Are antihistamines effective for cholinergic urticaria?
- CQ21: Does making patients actively sweat improve the symptoms of cholinergic urticaria?
- CQ22: Are antihistamines effective for idiopathic angioedema?
- CQ23: Is tranexamic acid effective for idiopathic angioedema?
- CQ24: Is intravenous administration of C1-inhibitor effective for acute attacks of hereditary angioedema?
-

CQ, clinical question. Cited from reference 8.

tinued to appear for 6 weeks or longer. Recently, Maurer and his international colleagues proposed to use the name “chronic spontaneous urticaria”, rather than “chronic urticaria”, and not to use “chronic idiopathic urticaria”.¹⁷ In Japan, the first guideline by JDA in 2005 clearly defined “chronic urticaria” and “acute urticaria” as subtypes of spontaneously occurring urticaria.⁵ A minor difference between “chronic urticaria” in the JDA guideline and “chronic spontaneous urticaria” in the EAACI guideline is the duration of disease. Around the world, the term “chronic”

for urticaria has been used mostly for urticaria that continues to appear for six weeks or longer. On the other hand, it has been widely and historically used in Japan for urticaria appearing for not less than one month. However the distinction between acute and chronic urticaria was made arbitrarily and there is no fundamental distinction between acute and chronic.¹⁸ Moreover, even one month may be too long as a period to categorize urticarias that spontaneously occur for days or weeks and are mostly self-remitting, apart from those occur for months or longer and are often

Table 7 Structured abstracts

1. Examinations for urticaria
 - 1-1) Infectious diseases
 - 1-2) General clinical examinations/thyroid autoimmunity
2. Antihistamines
 - 2-1) Treatment of acute urticaria with antihistamines
 - 2-2) Antihistamines for pregnant women
 - 2-3) Antihistamines for nursing women
 - 2-4) Increase in dose of antihistamines for chronic urticaria
3. Supplementary medications for chronic urticaria
 - 3-1) H₂-receptor antagonists
 - 3-2) Antileukotrienes
 - 3-3) Dapsone
 - 3-4) Glycyrrhizinic acid
 - 3-5) Extracts of inflammatory rabbit skin inoculated by vaccinia virus
 - 3-6) Tranexamic acid
 - 3-7) Anti-anxiety drugs
4. Experimental treatments for chronic urticaria
 - 4-1) Ciclosporin
 - 4-2) Intravenous immunoglobulin
 - 4-3) Plasmapheresis
 - 4-4) Warfarin
 - 4-5) Methotrexate
 - 4-6) Cyclophosphamide
 - 4-7) Tacrolimus
 - 4-8) Mycophenolate mofetil
 - 4-9) Omalizumab
5. Aspirin-induced urticaria
 - 5-1) Safety of antipyretic analgesics with minimum COX1-inhibition for patients with aspirin-induced urticaria
6. Treatments of physical urticaria
 - 6-1) Antihistamines for dermographic urticaria
 - 6-2) Antihistamines for cold urticaria
 - 6-3) Induction of cold tolerance in cold urticaria
 - 6-4) Antihistamines for solar urticaria
 - 6-5) Immunosuppressants for solar urticaria
7. Treatments of cholinergic urticaria
8. Treatments of angioedema
 - 8-1) Antihistamines
 - 8-2) Antileukotrienes
 - 8-3) Tranexamic acid
 - 8-4) Intravenous C1-inhibitor therapy for acute attacks of hereditary angioedema

Cited from reference 8.

refractory. In any case, nomenclature of urticaria subtypes is still an important issue for both better practice and investigations of urticaria.¹⁹

STEROIDS

Systemic steroids are most likely used on many occasions in medical practices for urticaria. They may suppress late reactions of severe anaphylactic reactions and symptoms of spontaneously occurring urti-

caria. However, the evidence for treatment with systemic steroids for idiopathic (spontaneous) urticaria is scant, especially that for long term prognosis is poor. The 2011 JDA urticaria guideline allows for the short term use of steroids for severe acute urticaria with wheals covering not less than 30% of the body surface (*recommendation level C1, evidence level IV*). It also recommends not using steroids for a long time even if some symptoms do not disappear (*recommendation level C2, evidence level VI*). Thus, the eligibility of steroids for urticaria is variable and should be decided based on the conditions of patients, including subtype, severity, and time course of urticaria, and potential side effects for individual patients. Further evidence and guidelines for more detailed usage of steroids are expected.

OMALIZUMAB

Omalizumab is a monoclonal antibody against IgE and currently licensed for severe asthma in a number of countries including Japan. The effectiveness of omalizumab for urticaria has been proven not only for autoimmune urticaria²⁰ in which the high affinity IgE receptor is activated by autoantibodies, but also for a wide range of urticarias, including physical urticarias, cholinergic urticaria, and non-autoimmune chronic spontaneous urticaria.²¹⁻²⁵ An option of the treatment with omalizumab has been included in the fourth step of treatment for chronic urticaria in the 2009 EAACI guideline.⁴ In the United States, a Phase III multicenter study for chronic spontaneous urticaria resistant to antihistamines was in progress as of 2012.²¹ Further study of omalizumab may allow the expansion of its use to severe and refractory cases of urticaria in Japan.

CONCLUSION

Principles of the treatment and hierarchy of medications for urticaria in guidelines in Japan and those in Europe appear in general to be the same. However, there are still some differences between these guidelines, especially in terms of nomenclature and coverage of urticaria. It is expected that experts and organizations in this field will further cooperate, both regionally and internationally, to find the best platform for dealing with urticaria and to relieve patients of the burdens of urticaria.

REFERENCES

1. Zuberbier T, Bindslev-Jensen C, Canonica W *et al*. EAACI/GA₂LEN/EDF guideline: definition, classification and diagnosis of urticaria. *Allergy* 2006;**61**:316-20.
2. Zuberbier T, Bindslev-Jensen C, Canonica W *et al*. EAACI/GA₂LEN/EDF guideline: management of urticaria. *Allergy* 2006;**61**:321-31.
3. Zuberbier T, Asero R, Bindslev-Jensen C *et al*. EAACI/GA₂LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. *Allergy* 2009;**64**:1417-26.

4. Zuberbier T, Asero R, Bindslev-Jensen C *et al*. EAACI/GA²LEN/EDF/WAO guideline: Management of urticaria. *Allergy* 2009;**64**:1427-43.
5. Hide M, Furue M, Ikezawa Z *et al*. [Guidelines for the diagnosis and treatment of urticaria and angioedema]. *Nihon Hifukagakkai Zasshi [Jpn J Dermatol]* 2005;**115**:703-15 (in Japanese).
6. Hide M, Furue M, Oji M *et al*. [Primary care version of guidelines for the diagnosis and treatment of urticaria and angioedema]. 2007. Available at: http://www.jaanet.org/pdf/guideline_skin04.pdf (in Japanese).
7. Hide M. [Urticaria and angioedema]. In: Japanese Society of Allergology, Nishima S (eds). [*Japanese Guideline for the Diagnosis and Treatment of Allergic Diseases 2010*]. Tokyo: Kyowa Kikaku, 2010;317-29 (in Japanese).
8. Hide M, Morita E, Furukawa F *et al*. [JDA guidelines. Guidelines for the diagnosis and treatment of urticaria]. *Nihon Hifukagakkai Zasshi [Jpn J Dermatol]* 2011;**121**:1339-88 (in Japanese).
9. Kontou-Fili K, Borici-Mazi R, Kapp A, Matjevic LJ, Mitchel FB. Physical urticaria: classification and diagnostic guidelines. An EAACI position paper. *Allergy* 1997;**52**:504-13.
10. Joint Task Force on Practice Parameters. The diagnosis and management of urticaria: a practice parameter part I: acute urticaria/angioedema part II: chronic urticaria/angioedema. Joint Task Force on Practice Parameters. *Ann Allergy Asthma Immunol* 2000;**85**:521-44.
11. Grattan C, Powell S, Humphreys F; British Association of Dermatologists. Management and diagnostic guidelines for urticaria and angio-oedema. *Br J Dermatol* 2001;**144**:708-14.
12. Tedeschi A, Girolomoni G, Asero R; AAITO Committee for Chronic Urticaria and Pruritus Guidelines. AAITO Position paper. Chronic urticaria: diagnostic workup and treatment. *Eur Ann Allergy Clin Immunol* 2007;**39**:225-31.
13. Powell RJ, Du Toit GL, Siddique N *et al*. BSACI guidelines for the management of chronic urticaria and angio-oedema. *Clin Exp Allergy* 2007;**37**:631-50.
14. Grattan CE, Humphreys F; British Association of Dermatologists Therapy Guidelines and Audit Subcommittee. Guidelines for evaluation and management of urticaria in adults and children. *Br J Dermatol* 2007;**157**:1116-23.
15. Maurer M, Weller K, Bindslev-Jensen C *et al*. Unmet clinical needs in chronic spontaneous urticaria. A GA²LEN task force report. *Allergy* 2011;**66**:317-30.
16. Horiuchi T, Ohi H, Ohsawa I *et al*. Guideline for hereditary angioedema (HAE) 2010 by the Japanese Association for Complement Research. *Allergol Int* 2012. In press.
17. Maurer M, Bindslev-Jensen C, Gimenez-Arnau A *et al*. Chronic Idiopathic Urticaria (CIU) is no longer idiopathic: time for an update! *Br J Dermatol*. Epub 2012 Jul 27.
18. Champion RH, Pye RJ. Urticaria—clinical aspects. In: Champion RH, Greaves MW, Kobza Black A, Pye RJ (eds). *The Urticarias*. Edinburgh, London, Melbourne, New York: Churchill Livingstone, 1985;135-40.
19. Grattan CE. Towards rationalizing the nomenclature and classification of urticaria: some guidance on guidelines. *Clin Exp Allergy* 2007;**37**:625-6.
20. Kaplan A, Joseph K, Maykut RJ, Geba GP, Zeldin RK. Treatment of chronic autoimmune urticaria with omalizumab. *J Allergy Clin Immunol* 2008;**122**:569-73.
21. Kaplan AP. Biologic agents in the treatment of urticaria. *Curr Allergy Asthma Rep* 2012;**12**:288-91.
22. Metz M, Altrichter S, Ardelean E *et al*. Anti-immunoglobulin E treatment of patients with recalcitrant physical urticaria. *Int Arch Allergy Immunol* 2011;**154**:177-80.
23. Metz M, Bergmann P, Zuberbier T, Maurer M. Successful treatment of cholinergic urticaria with anti-immunoglobulin E therapy. *Allergy* 2008;**63**:247-9.
24. Otto HF, Calabria CW. A case of severe refractory chronic urticaria: a novel method for evaluation and treatment. *Allergy Asthma Proc* 2009;**30**:333-7.
25. Saini S, Rosen KE, Hsieh HJ *et al*. A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with H1-antihistamine-refractory chronic idiopathic urticaria. *J Allergy Clin Immunol* 2011;**128**:567-73.