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ORIGINAL ARTICLE

Taiwanese Dermatological Association consensus for the definition, classification, diagnosis, and management of urticaria

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Background/purpose: This report describes the 2014 consensus of the Taiwanese Dermatological Association regarding the definition, classification, diagnosis, and management of urticaria. This consensus is distributed to practices throughout Taiwan to provide recommendations for diagnostic and therapeutic approaches for common subtypes of urticaria, in order to improve the quality of life of urticaria patients. The consensus, thus, serves as an important reference for dermatologists throughout Taiwan.
Methods: All the consensus contents were voted on by the participating dermatologists, with approval by no less than 75% being required for inclusion. The consensus provides a comprehensive overview of urticaria, including recent advances in identifying its causes and the processes by which it develops.
Results: All the consensus meeting attendees agreed to a definition of urticaria, which states that it is characterized by the sudden appearance of wheals (also known as hives), angioedema, or both. Most of the experts (16 out of 19, or 84.2%) agreed that chronic urticaria is defined

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as the sudden occurrence of wheals and/or angioedema for a period of ≥ 6 weeks. In addition, the consensus attendees also approved the Urticaria Activity Score system or the Urticaria Activity Score for 7 days system as the recommended method for assessing disease activity in spontaneous urticaria.

Conclusion: It was also determined that the treatment goal for patients with any form of urticaria should be complete cessation of suffering from all urticaria symptoms. The recommended treatment algorithms for chronic spontaneous urticaria and acute urticaria were finally proposed and approved by 100% (19/19) and 84.2% (16/19) of the consensus attendees, respectively.

Introduction

This report provides a detailed description of the development process for the 2014 consensus of the Taiwanese Dermatological Association (TDA) regarding the definition, classification, diagnosis, and management of urticaria. The TDA consensus was based, in large part, upon the 2013 urticaria guidelines produced jointly by the European Academy of Allergy and Clinical Immunology (EAACI), the EU-funded Network of Excellence, the Global Allergy and Asthma European Network, the European Dermatology Forum, and the World Allergy Organization and the 2014 urticaria guidelines published by the American Academy of Allergy, Asthma & Immunology.[1,2] The TDA consensus is distinguished from those earlier guidelines primarily by its inclusion of a number of amendments made specifically for the sake of clinicians treating urticaria in Taiwan, and the consensus thus serves as an important reference for dermatologists throughout Taiwan.

A variety of original studies have investigated chronic urticaria (CU) among patients in Taiwan. A recent study by Lee et al,[3] for example, sought to characterize the clinical features of CU in Taiwan, and determined that although atopy does not affect the severity or duration of CU, it is associated with poor therapeutic responses to second-generation antihistamines. Accordingly, the authors suggest that taking a personal history of atopy, especially allergic rhinitis, is of particular importance in managing the symptoms of CU patients in Taiwan. In an earlier study comparing CU patients to controls with athletes foot, Yang et al[4] found stress and insomnia to be among the most important predisposing risk factors for CU among patients in Taiwan. Other studies involving CU patients in Taiwan have explored the efficacy of various treatments; for example, a multicenter study by Fang et al[5] confirmed the efficacy of levocetirizine for the management of urticaria in Taiwanese patients. In short, information from these and other Taiwan-based studies, as well as personal clinical experiences, was considered in addition to the aforementioned international guidelines in arriving at the TDA consensus.

The information in the consensus was agreed upon by a panel of national experts who convened at TDA urticaria consensus meetings held on March 30, 2014 and May 17, 2014, with all the specific aspects of the content requiring approval by at least 75% of the experts in attendance.

Methods

Consensus panel

A total of 19 dermatologists with extensive experience in urticaria management, recommended by their respective teaching hospitals in Taiwan and the TDA itself, were invited to and attended the TDA consensus meetings held in Taipei, Taiwan. The 2013 EAACI/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization and the 2014 American Academy of Allergy, Asthma & Immunology urticaria guidelines provided the foundations for the consensus that the panel approved in the meeting, although a variety of amendments made specifically for practitioners in Taiwan were also considered. For each of these amendments, discussions were conducted on the quality of scientific evidence (including transparency and clear criteria) supporting the given amendment, as well as on the risks and benefits of the recommended medications.[6–8]

Consensus voting system

The dermatologist experts attending the meeting cast their votes for individual content items by rating their approval of each item on a scale from 1 to 9, with 1 representing 0% approval and 9 representing 100% approval. When ratings of 7–9 accounted for ≥75% of the total votes cast, the item in question was deemed to have been approved. In the event that the original version of an item was not approved—i.e., when ratings of 7–9 accounted for < 75% of all the votes—potential amendments to the item were drafted and then voted upon. Votes on these amendments were conducted on a yes/no basis, with an agreement rating of > 50% being required for implementation. If an amendment to an item was approved, the amended item was then voted on again using the 1–9 scale, with approval again contingent upon ratings of 7–9 accounting for ≥ 75% of the votes. When ratings of 7–9 for an amended item accounted for < 75% of the votes, or when "no" votes for an amendment accounted for ≥ 50% of the votes, a different amendment to the item was voted upon. In this way, each item was approved either in its original form or in some amended form.

Results

Definition of urticaria

The following definition was approved by 100% (19 out of 19) of the consensus meeting attendees.

Urticaria is characterized by the sudden appearance of wheals (also known as hives), angioedema, or both.

A wheal typically exhibits the following three characteristics: (1) initial presentation of a swelling of variable size that is sometimes surrounded by a reflex erythema, without epidermal change; (2) itching or, sometimes, a tingling or burning sensation; and (3) a fleeting nature, with the skin usually returning to its normal appearance within 24 hours.

Angioedema is characterized by the following features: (1) a sudden, pronounced erythematous swelling or skin-colored swelling of the lower dermis and subcutis, with frequent involvement of the submucosa and (2) pain rather than itching in some cases; the resolution of an angioedema is slower than that of a wheal, and may take up to 72 hours.

Classification of urticaria according to its frequency, duration, and causes

A given case of urticaria can be classified as acute or chronic on the basis of its duration, with acute urticaria defined as the spontaneous occurrence of wheals, angioedema, or both for a period of $<$ 6 weeks, while CU is defined as the sudden occurrence of wheals and/or angioedema for a period of $\geq$ 6 weeks. Figure 1 presents an algorithm for the clinical classification of the acute and chronic forms, as well as for the various CU subtypes, and includes footnotes providing additional information regarding causes and alternative names for several subtypes.

Assessment of disease activity using the Urticaria Activity Score

In both clinical care and medical trials, the Urticaria Activity Score (UAS) system, a simple scoring system proposed in previous guidelines and since validated in a study by Młynek et al,[9] is the recommended method for assessing disease activity in spontaneous urticaria. More specifically, the Urticaria Activity Score for 7 days (UAS7) is the standard used by the EAACI for such evaluations (Figure 2). The UAS provides two distinct advantages: (1) due to widespread adaptation, the use of the UAS allows for a direct comparison of study and results from various researchers worldwide, and (2) the UAS is based on the patient's own assessment of the key symptoms such as wheals and pruritus, and this self-assessment is particularly valuable because the intensity of urticaria symptoms changes often, such that 24-hour self-evaluation scores taken once daily by the patient for several days provide the best picture of overall disease activity.

Diagnosis

In recent years, substantial progress has been achieved in identifying the causes of different types and subtypes of urticaria. For example, Zuberbier and Maurer[10] have

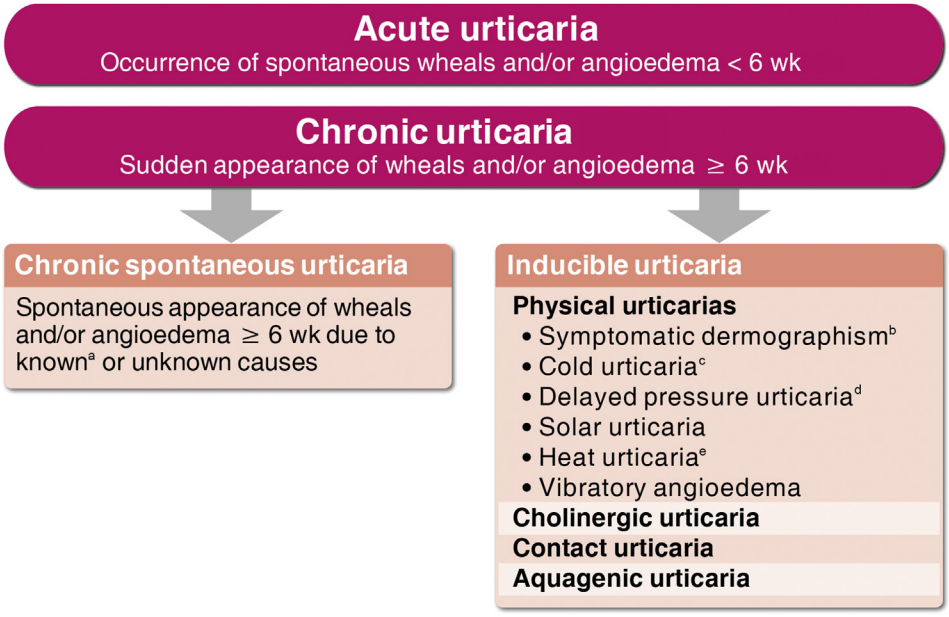

Figure 1 Classification of subtypes of chronic urticaria (presenting with wheals, angioedema, or both). Of the consensus attendees, 84.2% (16/19) approved this figure. [a] For example, autoreactivity, i.e., the presence of mast cell-activating autoantibodies. [b] Also called urticaria factitia and dermographic urticaria. [c] Also called cold contact urticaria. [d] Also called pressure urticaria. [e] Also called heat contact urticaria. *Note*. From "The EAACI/GA^{2}LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update," by Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, et al, 2014, *Allergy, 69*, p. 868—87. Copyright 2014. John Wiley & Sons A/S. Adapted with permission.

Score	Wheals	Itch
0 None	None	None
1 Mild	<20 wheals/24 h	Mild (present, but not annoying or troublesome)
2 Moderate	20–50 wheals/24 h	Moderate (troublesome, but does not interfere with normal daily activity or sleep)
3 Intense	>50 wheals/24 h or large confluent areas of wheals	Intense (severe itching, which is sufficiently troublesome to interfere with normal daily activity or sleep)

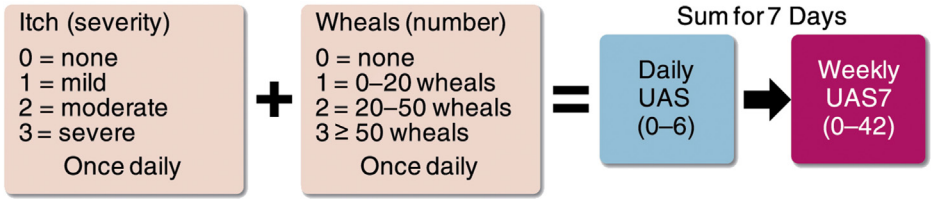

Figure 2 The UAS/UAS7 for assessing disease activity in CSU. Of the consensus attendees, 78.9% (15/19) approved this figure. Sum of scores: 0—6 for each day is summarized over 1 week (maximum 42). UAS is a diary-based, combined score of severity of itch and number of wheals (scale 0—6). CSU = chronic spontaneous urticaria; UAS = Urticaria Activity Score; UAS7 = Urticaria Activity Score for 7 days. *Note*. From "The EAACI/GA^{2}LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update," by Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, et al, 2014, *Allergy, 69*, p. 868—87. Copyright 2014. John Wiley & Sons A/S. Adapted with permission.

provided an extensive review of some of these advances pertaining to chronic spontaneous urticaria (CSU). The studies in question, however, have reported considerable variation in the frequency of the various underlying causes, differences that are likely to be the results, to some extent at least, of regional differences around the world, such as differences in the traditional diets of different regions and differing prevalence rates for various infections. As such, it is important for clinicians to bear in mind that it is not necessary to identify and investigate all the possible causative factors in all patients.

Patient history

Without necessarily aiming to identify all the potential causative factors, the first step in making an accurate diagnosis is taking a thorough patient history. Patients should be questioned regarding all the following points.

Characteristics. The following list of characteristics was approved by 100% (19/19) of the consensus meeting attendees: (1) time of onset of disease; (2) frequency/duration; (3) diurnal variation; (4) occurrence in relation to weekends, holidays, seasons, and foreign travels; (5) shape, size, and distribution of wheals; (6) associated angioedema; and (7) associated subjective symptoms of lesions, e.g., itch and pain.

History. The following list of relevant history items was approved by 100% (19/19) of the consensus meeting attendees: (1) family and personal history regarding urticaria and atopy; (2) previous or current allergies, infections, internal diseases, or other possible causes; (3) psychosomatic and psychiatric diseases; (4) relationship to the menstrual cycle; (5) smoking habits (especially, the use of perfumed tobacco products); (6) type of work; (7) hobbies; (8) stress (eustress and distress); (9) previous therapy and response to therapy; and (10) previous diagnostic procedures/results.

Possible factors for wheals. (1) Gastric/intestinal problems; (2) induction by physical agents or exercise; (3) use of drugs [e.g., nonsteroidal anti-inflammatory drugs, injections, immunizations, hormones, laxatives, suppositories, ear and eye drops and alternative remedies (Chinese herbs)], recreational drugs, and local anesthesia; (4) observed correlation to food and alcohol-containing beverages; and (5) surgical implantations and events during surgery.

Quality of life. Quality of life related to urticaria and emotional impact.

(*Note:* the abovementioned "possible factors for wheals" and "quality of life" items were approved by 78.9% (15/19) of the attendees.)

The second step of the diagnosis is a physical examination of the patient. When indicated by the patient history, this should include diagnostic provocation tests including drug, food, and physical tests. That being said, intensive and costly general screening programs for causes of urticaria are not recommended for most cases. Figure 3 shows the recommended diagnosis algorithm for urticaria, while Table 1 specifies the recommended diagnostic tests for frequent urticaria subtypes.

Clinical management of urticaria

Treatment goal. As noted above, the EAACI guidelines recommend using a patient's UAS7 score as a simple and

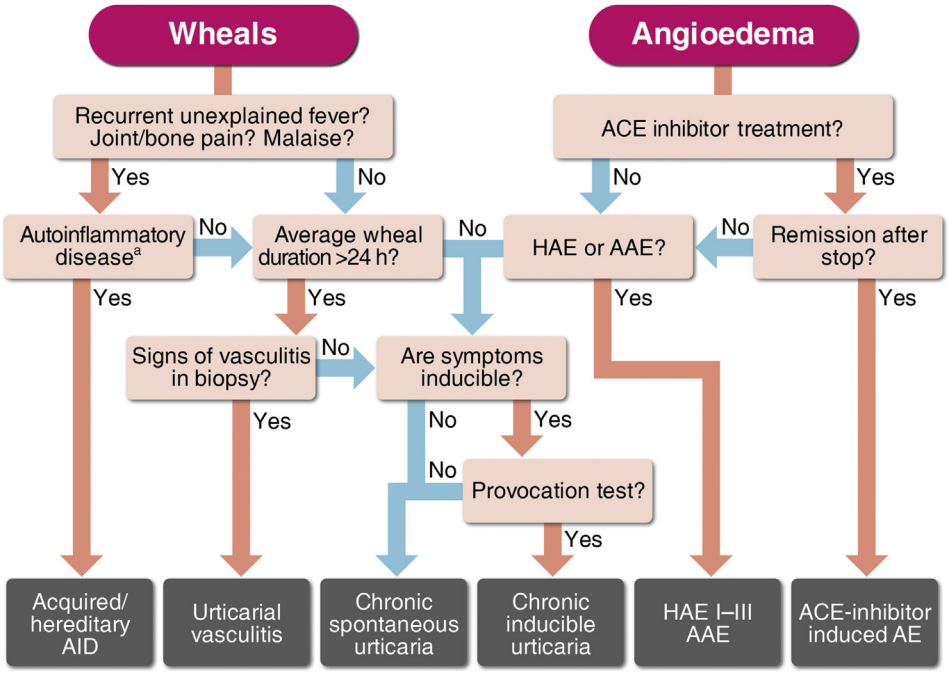

Figure 3 Recommended diagnosis algorithm for urticaria. Diagnostic algorithm for patients presenting with wheals, angioedema, or both. All the consensus attendees (100%; 19/19) approved this figure. [a] Autoinflammatory diseases are the result of uncontrolled activation of the innate immune system including Schnitzler syndrome, systemic juvenile idiopathic arthritis, cryopyrin-associated periodic syndromes, etc. [1] Other (new) drugs may also induce bradykinin-mediated angioedema. [2] Patients should be asked for a detailed family history and age of disease onset. [3] Test for elevated inflammation markers (C-reactive protein, erythrocyte sedimentation rate), test for paraproteinemia in adults, look for signs of neutrophil-rich infiltrates in skin biopsy; perform gene mutation analysis of hereditary periodic fever syndromes (e.g., cryopyrin-associated periodic syndrome), if strongly suspected. [4] Patients should be asked: 'How long do your wheals last?' [5] Test for Complement C4, C1-INH levels and function; in addition, test for C1q and C1-INH antibodies, if AAE is suspected; perform gene mutation analysis, if former tests are unremarkable but patient's history suggests hereditary angioedema. [6] Wait for up to 6 months for remission; additional diagnostics to test for C1-inhibitor deficiency should only be performed if the family history suggests hereditary angioedema. [7] Does the biopsy of lesional skin show damage of the small vessels in the papillary and reticular dermis and/or fibrinoid deposits in perivascular and interstitial locations suggestive of UV (urticarial vasculitis)? [8] Patients should be asked: 'Can you make your wheals come?' [9] In patients with a history suggestive of inducible urticaria, standardized provocation testing according to international consensus recommendations should be performed. [10] Acquired AIDs include Schnitzler's syndrome as well as systemic-onset juvenile idiopathic arthritis and adult-onset Still's disease; hereditary AIDs include cryopyrin-associated periodic syndromes such as familial cold autoinflammatory syndromes, Muckle—Wells syndrome, and neonatal-onset multisystem inflammatory disease, more rarely hyper-IgD syndrome and tumor necrosis factor receptor alpha-associated periodic syndrome. [11] In some rare cases, recurrent angioedema is neither mast cell mediator mediated nor bradykinin mediated, and the underlying pathomechanisms remain unknown. These rare cases are referred to as "idiopathic angioedema" by some authors. AAE = acquired angioedema due to C1 inhibitor deficiency; ACE-INH = angiotensin-converting enzyme inhibitor; AE = angioedema; AH = antihistamine; AID = autoinflammatory disease; HAE = hereditary angioedema; IL-1 = interleukin-1. *Note*. From "The EAACI/GA^{2}LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update," by Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, et al, 2014, *Allergy, 69*, p. 868—87. Copyright 2014. John Wiley & Sons A/S. Adapted with permission.

effective means for assessing the disease activity of CU. Moreover, the same guidelines also indicate that complete symptom relief should be the goal of treatment. In the TDA consensus meeting, this stated treatment goal of the EAACI guidelines was a topic of some discussion. Specifically, it was noted that only around 40% of patients can achieve a UAS7 score of 0, which would indicate complete symptom relief. In contrast, approximately 80% of patients can reach a UAS7 score of < 5, which is also a substantial improvement in most cases. Accordingly, attendees at the TDA consensus meetings raised the question of whether the treatment goal should be complete relief from all symptoms or whether a UAS7 score of ≤ 5 could be deemed sufficient as the goal of treatment. After some discussion, it was ultimately decided that complete symptom relief should be the treatment goal, but that the UAS7 score or response to a medication should also be used to determine whether the given treatment is effective. Along the same lines, it is worth noting that different patients, different illnesses, and different guidelines may have differing treatment goals (e.g., a patient may find it acceptable that symptoms are relieved simply to the extent that these are

Table 1 Recommended diagnostic tests in frequent urticaria subtypes.[a,11–22].

Types	Subtypes	Routine diagnostic tests (recommended)	Extended diagnostic program[b] (suggested based on history only) to identify eliciting factors & rule out possible differential diagnoses if indicated
Spontaneous urticaria	Acute spontaneous urticaria	None	None[c]
	Chronic spontaneous urticaria	Differential blood count & ESR or CRP Omission of suspected drugs (e.g., NSAIDs)	(1) Thyroid hormones & Copyright 2013. *Name of Copyright Holder*. Reprinted with permission. autoantibodies (2) Autologous serum skin test or basophil activation test (3) Type I allergy (IgE, MAST, CAP) (4) Functional autoantibodies (ANA, etc.) (5) Infectious diseases (e.g., *Helicobacter pylori*) (6) Lesional skin biopsy (7) Skin tests including physical tests (8) Tryptase[d] (9) Pseudoallergen-free diet for 3 wk
Inducible urticaria	Cold urticaria	Cold provocation & threshold test (ice cube, cold water, cold wind)	Differential blood count & ESR/CRP cryoproteins rule out other diseases, especially infections
	Delayed pressure urticaria	Pressure test	None
	Heat urticaria	Heat provocation & threshold test	None
	Solar urticaria	UV & visible light of different wavelengths & threshold test	Other light-induced dermatoses ruled out
	Symptomatic dermographism	Elicit dermographism & threshold test (dermographometer)	Differential blood count, ESR/CRP
	Vibratory angioedema	Test with vortex	None
	Aquagenic urticaria	Wet cloths at body temperature applied for 20 min	None
Inducible urticaria	Cholinergic urticaria	Exercise & hot bath provocation	None
	Contact urticaria	Cutaneous provocation test. Skin tests with immediate readings, e.g., prick test, prick-by-prick test, patch test	None

ANA = antinuclear antibodies; CAP = Phadia Immunocap (Phadia CAP) allergen-specific IgE test; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IgE = immunoglobulin E; MAST = Multiple-allergen simultaneous test; NSAID = nonsteroidal anti-inflammatory drug.

Note. From "The EAACI/GA^{2}LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update" by Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, et al, 2014, *Allergy 69*, p. 868–87. Copyright 2014. John Wiley & Sons A/S. Adapted with permission.

[a] Of the consensus attendees, 89.5% (17/19) approved this table.

[b] Depending on the suspected cause.

[c] Unless strongly suggested by patient history, e.g., allergy.

[d] As an indication of severe systemic disease.

tolerable and quality of life, in turn, is improved). With respect to CU, however, it is believed that no patient would be willing to take medication every day and still suffer from urticaria symptoms. Therefore, with the aforementioned caveats in mind, it was decided that the treatment goal for patients with any form of urticaria should be complete cessation of suffering from all urticaria symptoms.

To the above end, Figure 4 shows the recommended treatment algorithm for CSU, including tracks for both nondrug and pharmacologic therapies. The figure also

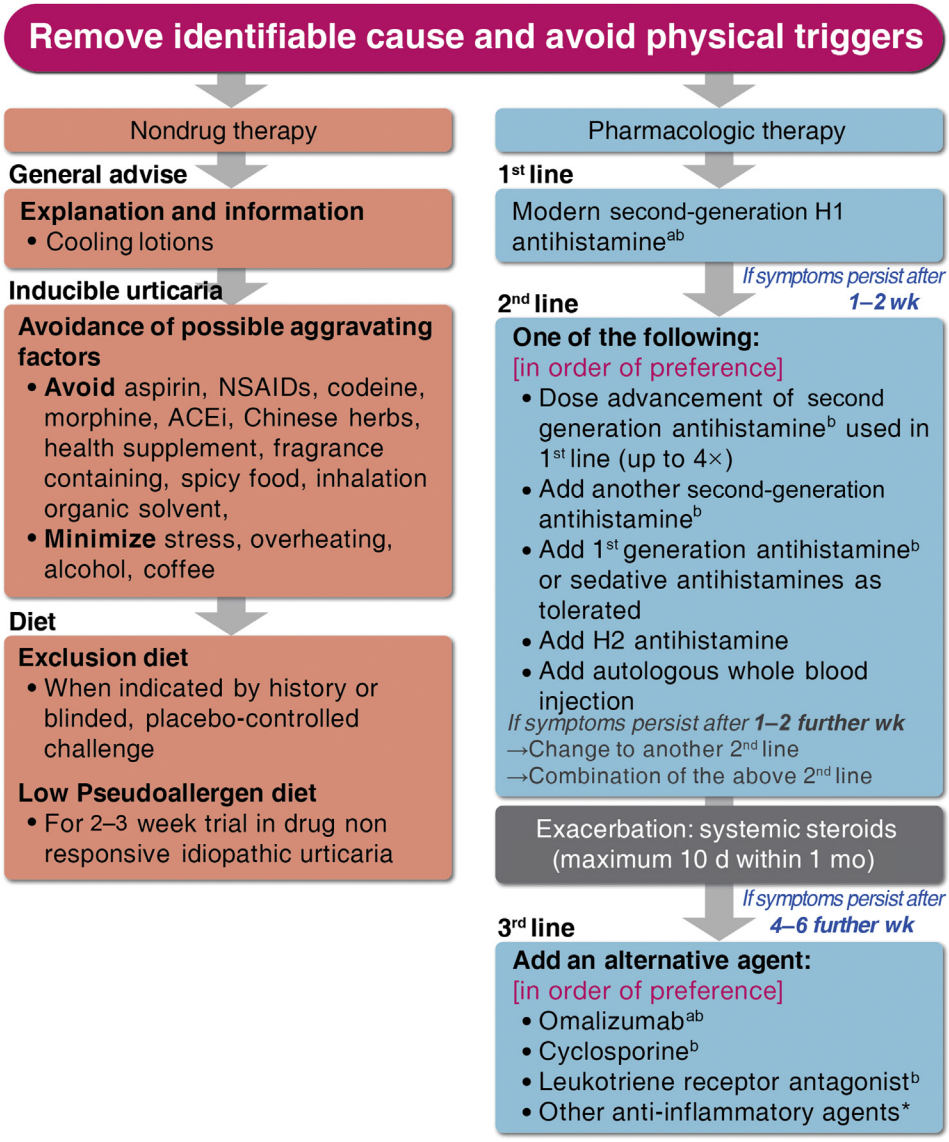

Figure 4 Recommended treatment algorithm for chronic spontaneous urticaria.[23–39] Please note that the listed order of the third-line treatments does not reflect preference. All the consensus attendees (100%; 19/19) approved this figure after discussions and amendments for each item. *First line = high-quality evidence*: low cost and worldwide availability (e.g., modern second-generation antihistamines also exist in developing countries, mostly cheaper than old sedating antihistamines), per daily dose as the half-life time is much longer, very good safety profile, good efficacy. *Second line = high-quality evidence*: low cost, good safety profile, good efficacy. *Third line as an add-on to AH. Cyclosporine A = high-quality evidence*: medium to high cost, moderate safety profile, good efficacy. *Omalizumab = high-quality evidence*: high cost, very good safety profile, very good efficacy. *Montelukast = low-quality evidence*: low cost, good safety, low efficacy. *Short course of corticosteroids = low-quality evidence*: low cost, worldwide availability, good safety profile (for short course only), good efficacy during intake, but very low for lasting efficacy. [a] H1 antihistamines and omalizumab are the licensed treatments for CSU (FDA/EMA). [b] Refer to Table S1 for approved age. ACEi = angiotensin-converting enzyme inhibitor; AH = antihistamine; CSU = chronic spontaneous urticaria; FDA = US Food and Drug Administration; MEA = European Medicines Agency; NSAID = nonsteroidal anti-inflammatory drug. *Note*. From "The EAACI/GA^{2}LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update," by Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, et al, 2014, *Allergy, 69*, p. 868–87. Copyright 2014. John Wiley & Sons A/S. Adapted with permission.

provides information on dietary and environmental factors that can potentially aggravate urticaria and should thus be minimized or avoided. Table 2 provides a list of alternative anti-inflammatory agents that can be considered for use in certain cases of CU, including information from the EAACI urticaria guideline regarding the degree of research evidence for each agent and the strength of the corresponding EAACI recommendation; British Society for Allergy and Clinical Immunology grades and indications for the agents are likewise included.

Table 2 Alternative anti-inflammatory agents for specific chronic urticaria indications.[a]

Alternative treatment	EAACI evidence	EAACI recommendation	BSACI grade	BSACI Specific indication/ comments	Side effects
Methotrexate	Very low	Weak	D (rare)	Beneficial for corticosteroid-dependent chronic idiopathic urticaria (2 patients); efficacy in urticarial vasculitis (1 patient)	Loss of appetite; nausea; vomiting; abdominal pain; impaired digestion; dyspepsia; inflammation & ulceration in mouth & throat; increase in level of liver enzyme; herpes zoster; effects on the blood, e.g., anemia, leukopenia, & thrombocytopenia; diarrhea; dry cough; shortness of breath; chest pain; fever; rashes; redness & itching; headache; tiredness; drowsiness
Hydroxychloroquine	Very low	Weak	Not specified	Improvement of QoL, but no reduction in urticaria scores or medication requirements	Feeling or being sick, loss of appetite, dizziness, ringing in the ears, headache, mood swings, fits, spasm of airways, muscle weakness, decreased reflexes, low platelets, bone marrow depression, abnormal nerve conduction, abnormal liver function, seen on blood tests, lowering of the blood glucose level, diarrhea, stomach pain, visual disturbances, vertigo, hearing loss, nervousness, psychosis, liver failure, itchy & raised rashes, muscle wasting, anemia, low white blood cells, general tissue swelling, problems with heart, conduction system, bleaching of hair/hair loss
Dapsone	Very low	Weak	D (rare)	Several single case reports of successful treatment of urticarial vasculitis in resistant cases; helped 1 patient with autoimmune thyroiditis to stop oral steroid treatment	Back, leg, or stomach pain; bluish fingernails, lips, or skin; difficult breathing; fever; loss of appetite; pale skin; skin rash; unusual tiredness or weakness
Colchicine	Ineffective	—	D (rare)	One patient showed total clearance of urticarial vasculitic rashes & chronic vasculitic ulceration after previously being unresponsive to steroids in combination with dapsone & HCQ	Diarrhea, nausea or vomiting, stomach pain
Azathioprine	Less evidence available	—	—	—	Black, tarry stools; bleeding gums; blood in urine or stools; chest pain; cough or hoarseness; fever or chills; lower back or side pain; painful or difficult urination; pinpoint red spots on the skin; shortness of breath; sore throat; sores,

(*continued on next page*)

Table 2 (*continued*)

Alternative treatment	EAACI evidence	EAACI recommendation	BSACI grade	BSACI Specific indication/ comments	Side effects
					ulcers, or white spots on the lips or in the mouth; swollen glands; unusual bleeding or bruising; unusual tiredness or weakness
Ketotifen	Low	Weak	—	—	Chills, cough, diarrhea, fever, general feeling of discomfort or illness, headache, joint pain, loss of appetite, muscle aches & pains, nausea, runny nose, shivering, sore throat, sweating, trouble sleeping, unusual tiredness or weakness, vomiting

BSACI = British Society for Allergy and Clinical Immunology; EAACI = European Academy of Allergy and Clinical Immunology; HCQ = hydroxychloroquine; QoL = quality of life.
[a] Of the consensus attendees, 89.5% (17/19) approved this table.

Meanwhile, it is important to note that the 2013 EAACI urticaria guideline addresses acute urticaria and CU simultaneously, always recommending the use of H1 antihistamines. In order to provide additional information, therefore, the TDA consensus meetings sought to establish a recommended treatment algorithm specifically designed for acute urticaria. The resulting treatment algorithm is shown in Figure 5, and includes specific information on when to prescribe epinephrine, systemic steroids, and H1 and H2 antihistamines. For example, it is recommended that epinephrine should be used as the third-line treatment (after H1 and H2 antihistamines and systemic steroids) for severe angioedema or as the first-line treatment should the patient present with serious respiratory, cardiac, or gastrointestinal symptoms.

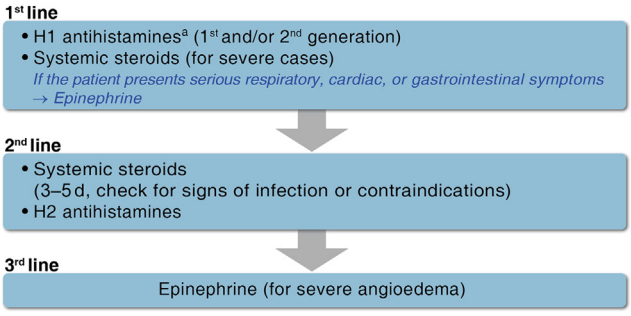

Figure 5 Recommended treatment algorithm for acute urticaria. Of the consensus attendees, 84.2% (16/19) approved this figure. [a] Refer to Table S1 for approved age. *Note*. From "The EAACI/GA^{2}LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update," by Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, et al, 2014, *Allergy, 69*, p. 868—87. Copyright 2014. John Wiley & Sons A/S. Adapted with permission.

With regard to the algorithm recommended in Figure 4, it should be noted that the time between each line of defense was shortened from the original EAACI guidelines upon which the TDA consensus is based. It may thus take longer than the time intervals listed for any medication's effectiveness to become evident. As such, it is recommended that physicians move to the next line only when a given medication or a combination of medications has no effect. It is also worth noting that not all dermatologists will agree on the placement of certain drugs in these lines of defense; however, all options must be made available. Drugs listed in these guidelines are listed in order of preference, but it is still considered permissible within these guidelines for physicians to skip certain drugs. Please also be aware that some of the drugs have been added to the guidelines on the basis of clinical evidences or experiences provided by Taiwanese dermatologists, rather than on the basis of published evidence from clinical trials. In addition, please bear in mind that when adding first or second antihistamines in the second line of defense, it is also common to increase the dosage, and for this reason, the qualifier "as tolerated" has been added in these guidelines. Clinicians should also be aware that H1 antihistamines and omalizumab are the only medications licensed for treating CU by the US Food and Drug Administration and European Medicines Agency. It was also determined that the treatment goal for patients with any form of urticaria should be complete cessation of suffering from all urticaria symptoms. However, titration of H1 antihistamines was not included in this consensus.

As made clear by the above discussion, although the TDA consensus was largely based on the EAACI guidelines and other previously published guidelines, this consensus differs from those guidelines with regard to a number of details. These differences, a number of which are listed in Table 3, were based, to varying degrees, on research studies conducted in Taiwan as well as on the clinical experiences of the consensus experts in treating patients in Taiwan.

Table 3 Treatment algorithms of the AAAAI, EAACI, and TDA guidelines.

Treatment algorithm	Guidelines		
	AAAAI	EAACI	TDA[a]
1st line	• Second-generation H1 antihistamine • Avoidance of triggers (e.g., NSAIDs) & relevant physical factors if physical urticaria/angioedema syndrome is present	Second-generation H1 antihistamine	Second-generation H1 antihistamine
2nd line	1 or more of the following: • Dose advancement of 2nd-generation antihistamine used in the 1st line • Addition of another 2nd-generation antihistamine • Addition of an H2-antagonist • Addition of a leukotriene receptor antagonist • Addition of the 1st-generation antihistamine to be taken at bedtime	Up to 4× licensed dose of H1 antihistamine	1 or more of the following: • Up to 4× licensed dose of 2nd-generation H1 used in the 1st line • Addition of another 2nd-generation antihistamine • Addition of a 1st-generation antihistamine or sedative antihistamines as tolerated • **Addition of an H2 antihistamine** • **Addition of autologous whole blood injection** **If symptoms persist after further 1–2 wk, change to another 2nd line/combination of the above 2nd line** • **Exacerbation: systemic steroid (maximum 10 d within 1 mo)**
3rd line	Dose advancement of potent antihistamine as tolerated	• Addition of omalizumab, cyclosporine A or montelukast • Exacerbation: systemic steroid (3–7 d)	Addition of an alternative agent: • Omalizumab • Cyclosporine • **Leukotriene receptor antagonist** • Other anti-inflammatory agents
4th line	Addition of an alternative agent: • Omalizumab or cyclosporine Other anti-inflammatory agents, immunosuppressants, or biologics	N/A	N/A
Symptom persistence	N/A	• Between 1st & 2nd lines: 2 wk • Between 2nd & 3rd lines: 1–4 wk	• **Between 1st & 2nd lines: 1–2 wk** • **Between 2nd & 3rd lines: 4–6 wk**
Renal & hepatic impairment	N/A	N/A	**Dose adjustment may be needed for patients with impaired renal or hepatic function**

AAAAI = American Academy of Allergy, Asthma & Immunology; EAACI = European Academy of Allergy and Clinical Immunology; NSAID = nonsteroidal anti-inflammatory drug; N/A = not available; TDA = Taiwanese Dermatological Association.
[a] Unique aspects of the TDA guidelines are highlighted in bold type.

Management in special populations

Elderly patients. In general, dose selection for elderly patients should be considered carefully due to possible drug interactions or adverse effects, such as urinary retention, dry mouth, glaucoma, and central nervous system effects. In addition, the risk of patient falls or traffic accidents should be taken into consideration when prescribing antihistamines. On balance, the use of medications for CSU in elderly patients may be considered when the potential benefits outweigh the potential risks to the patient.

Patients with renal or hepatic impairment. Dose adjustment may be needed for patients with impaired renal or hepatic function. Dose adjustment should also be considered for patients receiving dialysis (whether hemodialysis or peritoneal dialysis). Please refer to Table S1 for specific recommendations regarding the use of individual medications for patients with renal or hepatic impairment.

Children under the age of 12 years and pregnant women. Figures 6 and 7 present the recommended treatment algorithms for children under the age of 12 years and pregnant women, respectively. With regard to children, a general recommendation is that only those medications that have been proved by past researches to be safe and effective in the pediatric population should be used. For this reason, cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine are among the recommended medications for treating patients under the age of 12 years, as all these medications have been well studied in pediatric populations, with the long-term safety of each having been well established.[40,41]

In principle, the same considerations should apply to the treatment of pregnant women. As a general rule, considering the potential risks and benefits, prescribing clinicians should avoid the use of any systemic treatment in pregnant women, especially during the first trimester. At the same time, pregnant women also have a right to receive the best therapy possible, and although systematic studies regarding the safety of treatments for pregnant women with urticaria have yet to be carried out, it is also worth noting that no studies have been conducted regarding the possible negative effects of increased levels of histamine occurring in urticaria treatment during pregnancy. Furthermore, because a number of the modern second-generation antihistamines are now available for purchase without a prescription and have thus been used widely in treating both allergic rhinitis and urticaria, it can be assumed that many pregnant women have used these drugs, especially during the earliest stages of pregnancy (i.e., before they were aware that they were pregnant); however, there have been no widespread reports of problems occurring as a result of this widespread usage. Nonetheless, maintaining the highest safety is of paramount importance during pregnancy, and prescribing clinicians should carefully adhere to the consensus guidelines accordingly.

Breastfeeding women: If used by a nursing mother, low concentrations of all H1 antihistamines will be excreted in the mother's breast milk. Furthermore, nursing infants have been known to occasionally become sedated after ingesting old first-generation H1 antihistamines transmitted in breast milk. For this reason, the use of second-generation H1 antihistamines is typically considered preferable for nursing mothers. As a general rule, the risk-to-benefit ratio for use of these drugs in breastfeeding women should be considered on a case-by-case basis, and when a satisfactory balance is indicated between the risks and benefits—i.e., when the potential benefits to the mother in terms of urticaria relief outweigh any possible

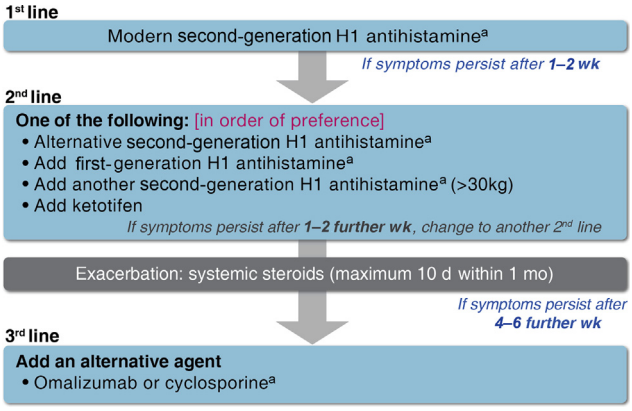

Figure 6 Recommended treatment algorithm for CSU in children under the age of 12 years. All the consensus attendees (100%; 19/19) approved this figure. [a] Refer to Table S1 for approved age. CSU = chronic spontaneous urticaria. *Note*. From "The EAACI/GA^{2}LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update," by Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, et al, 2014, *Allergy, 69*, p. 868—87. Copyright 2014. John Wiley & Sons A/S. Adapted with permission.

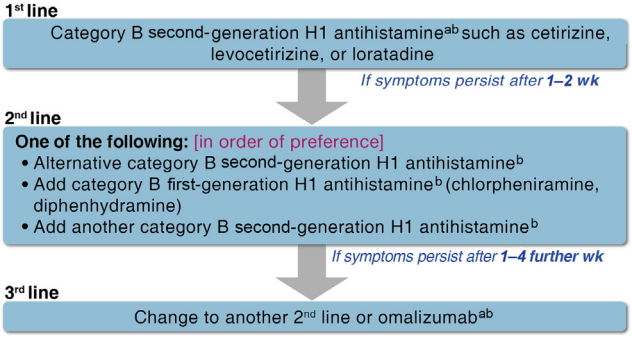

Figure 7 Recommended treatment algorithm for CSU in pregnant women. All the consensus attendees (100%; 19/19) approved this figure. [a] H1 antihistamines and omalizumab are the licensed treatments for CSU (FDA/EMA). [b] Refer to Table S1 for approved age and use in special populations. CSU = chronic spontaneous urticaria; FDA = US Food and Drug Administration; MEA = European Medicines Agency. *Note*. From "The EAACI/GA^{2}LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update," by Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, et al, 2014, *Allergy, 69*, p. 868—87. Copyright 2014. John Wiley & Sons A/S. Adapted with permission.

risks to the infant that may result from transmission of the drug in the mother's milk—then the use of the medication under consideration will generally be considered acceptable. That being said, all prescribing decisions should be re-evaluated, as necessary, according to the most current recommendations provided by the relevant regulatory authorities. Please refer to Table S1 for specific recommendations regarding the use of individual medications in breastfeeding women.

Conclusion

By means of the current consensus, the TDA has updated the most recent information on urticaria, with a special emphasis on Taiwan, in order to provide doctors and patients with an optimal care model and to increase the quality of urticaria care. Moreover, future research efforts into a variety of relevant topics, including, but not limited to, the global epidemiology of urticaria in adults and children, social and economic consequences of urticaria, and identification of new biological markers for urticaria, should allow for further refinement of treatment guidelines and, in turn, increased care quality in the future.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jfma.2015.09.009.

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