Asia Pacific allergy

pISSN 2233-8276 · eISSN 2233-8268

Current Review

Asia Pac Allergy 2012;2:149-160

Management of chronic urticaria in Asia: 2010 AADV consensus guidelines

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This guideline is a result of a consensus reached during the 19th Asian-Australasian Regional Conference of Dermatology by the Asian Academy of Dermatology and Venereology Study Group in collaboration with the League of Asian Dermatological Societies in 2010. Urticaria has a profound impact on the quality of life in Asia and the need for effective treatment is required. In line with the EAACI/GA^{2}LEN/EDF/WAO guideline for the management of urticaria the recommended first-line treatment is new generation, non-sedating H1-antihistamines. If standard dosing is ineffective, increasing the dosage up to four-fold is recommended. For patients who do not respond to a four-fold increase in dosage of non-sedating H1-antihistamines, it is recommended that therapies such as H2-antihistamine, leukotriene antagonist, and cyclosporine A should be added to the antihistamine treatment. In the choice of second-line treatment, both their costs and risk/benefit profiles are the most important considerations.

Key words: Asia; Consensus; Guideline; Wheal; Treatment; Urticaria

INTRODUCTION

Urticaria is a heterogeneous group of diseases that result from a large variety of underlying and potential causes, elicited by a great diversity of factors [1, 2]. For a majority of patients, symptoms can differ by the extent of the areas affected as well as the severity and clinical presentation [1]. Symptoms of chronic urticaria can persist for 6 weeks or more and are frustrating for both patients and caregivers. The aim of treatment is to achieve complete symptom relief. Although the severity of urticaria may fluctuate, spontaneous remission may occur at any time [1, 2]. However, it can take quite a long time to achieve complete remission. Management of chronic urticaria consists of two important approaches. Firstly, the identification and elimination of the underlying cause(s) and/or eliciting trigger(s) [1, 2]. Treating the cause is the most desirable option, but it is, unfortunately, not applicable in the majority of patients, in which urticaria is idiopathic [1]. Secondly, treatment is aimed at providing symptomatic relief [1]. In all cases, unless contraindicated, symptomatic relief should be offered while searching for the underlying cause [1]. Symptomatic treatment is currently the most frequent form of management. It aims to ameliorate or

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Received: February 20, 2012
Accepted: April 4, 2012

suppress symptoms by inhibiting the release and/or the effect of mast cell mediators and possibly other inflammatory mediators [1, 2].

Health related quality of life is increasingly being recognized as a primary outcome in clinical trials, population studies and public health [1]. In treatment the patient's well-being should be a central focus as chronic urticaria can persist over an extended duration from six weeks to over twenty years.

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METHODS

The treatment options available were evaluated by the following methods. Information was sourced from the European and International guidelines for management of chronic urticaria and from Asian journals available from online databases such as MEDLINE from 2000-2010. These guidelines were then discussed in detail by the study group members with review of primary references where applicable. At a final meeting a consensus was obtained by means of a simple voting system. The study group consisted of more than 30 dermatology specialists from 13 countries around Asia including 2 world renowned specialists in urticaria from Europe who are among the authors of the referenced European consensus [1-3]. As there is an existing international consensus on the definition, classification, and routine diagnosis of urticaria [3] which have been generally adopted in Asia, it was not discussed. For reference the recommended diagnostic tests in common urticaria types are shown in Table 1.

Management of chronic urticaria: causes and triggers

In general the management of chronic urticaria begins with the identification and elimination of the underlying cause(s) and/or eliciting trigger(s) [1, 2].

During consultation the information to the patient(s) concerning the symptoms and advice regarding avoidance of potential triggers should be made available such as: alcohol overuse, excessive physical tiredness, mental distress, prolonged pressure on the skin (i.e. tight clothing & bag straps), and hot environments. The provision of symptomatic relief which should always be offered while searching for causes [1]. Avoidance of the eliciting trigger can be instituted for patients with IgE-mediated urticaria. A substantial subset of patients can have a combination of both, e.g. chronic and physical urticaria. These have to be identified in order for adequate prognosis and management. For physical urticaria the impact of physical stimuli can be diminished and symptoms improved by appropriate measures (e.g. cushioning in pressure urticaria) [1, 2]. In spontaneous acute and chronic urticaria, treatment of associated infectious and/or inflammatory processes, including *Helicobacter pylori*-associated gastritis [4], parasitic diseases [5], or food [6] and drug intolerance may be helpful in selected cases [1, 2]. In addition, it must be noted that some factors, e.g. analgesic drugs, can elicit new wheal formation as well as augment pre-existing urticaria [1, 7].

Chronic urticaria is also recognized as a stress-vulnerable disease in which psychological stress can trigger or increase itching [1]. It is suggested that effective management processes could take into account psychological factors in some of the patients [1]. Many pharmacological and non-pharmacological interventions are available but clinical practice guidelines have created a more unified approach. For these reasons, the treatment regimen should be tailored to the individual patient.

Identification and elimination of the underlying cause / potential trigger

Determining the cause of the symptoms and devising means of protecting the patient from further exposure will help to facilitate recovery. Known triggers include: drugs, food, food additives, infections (bacterial, viral, fungal), parasitic infestations and dermatological disorders [1, 6, 8]. Following elimination of the suspected agent, only recurrence of symptoms in a double-blind provocation test will provide definitive proof [1, 7].

Drugs

Drugs frequently cause acute urticaria, but these can also be associated with chronic urticaria. When such agents are suspected in the course of diagnosis, they should be omitted entirely or substituted by another class of agents. The principle should be to avoid polypharmacy as far as possible, eliminating those which are not absolutely indispensable. Drugs causing non IgE mediated reactions [1] (e.g. aspirin) can not only elicit but also aggravate pre-existing chronic urticaria. Elimination can be expected to improve symptoms. Aspirin may exacerbate chronic urticaria in 30% of patients although patients taking low dose aspirin for its anti-thrombotic properties can usually continue regular treatment

Table 1. Recommended diagnostic tests in common urticaria subtypes

Types	Subtypes	Routine diagnostic tests (recommended)	Extended diagnostic programme* (suggested) For identification of eliciting factors and for ruling out possible differential diagnoses if indicated
Spontaneous urticaria	Acute spontaneous urticaria	None	None
	Chronic spontaneous urticaria	Differential blood count and ESR or CRP omission of suspected drugs (e.g. NSAID)	Test (i) infectious diseases (e.g. *Helicobacter pylori*); (ii) type I allergy; (iii) functional autoantibodies; (iv) thyroid hormones and autoantibodies; (v) skin tests including physical tests; (vi) pseudoallergen-free diet for 3 weeks and tryptase; (vii) autologous serum skin test, lesional skin biopsy
Physical urticaria	Cold contact urticaria	Cold provocation and threshold test (ice cube, cold water, cold wind)	Differential blood count and ESR/CRP cryoproteins rule out other diseases, especially infections
	Delayed pressure urticaria	Pressure test (0.2-1.5 kg/cm^2 for 10 and 20 min)	None
	Heat contact urticaria	Heat provocation and threshold test (warm water)	None
	Solar urticaria	UV and visible light of different wave lengths	Rule out other light-induced dermatoses
	Dermographic urticaria/ urticaria factitia	Elicit dermographism	Differential blood count, ESR/CRP
Other urticaria types	Aquagenic urticaria	Wet cloth at body temperature applied for 20 min	None
	Cholinergic urticaria	Exercise and hot bath provocation	None
	Contact urticaria	Prick/patch test read after 20 min	None
	Exercise-induced anaphylaxis/urticaria	According to history exercise test with/without food but not after a hot bath	None

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; NSAID, nonsteroidal anti-inflammatory drugs. *Depending on suspected cause. Unless strongly suggested by patient history, e.g. allergy. As indication of severe systemic disease. Taken from Table 5: Definition, classification, and routine diagnosis of urticaria: a consensus report [3].

[6]. It is advised that in the presence of chronic urticaria, aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) should not be recommended because the potential for aggravation of symptoms [6, 9, 10]. Angiotensin converting enzyme inhibitors (ACEIs) are commonly associated with angioedema but they rarely cause chronic urticaria. However, ACEIs should usually be avoided in chronic urticaria with or without angioedema. Other drugs implicated include alcohol, narcotics (codeine, morphine) and oral contraceptives [6, 11-13].

Physical stimuli

Avoidance of physical stimuli for the treatment of physical urticaria requires detailed information about the physical properties of the respective stimulus [1]. However, in many patients the threshold for the individual eliciting stimulus is low and thus the total avoidance of symptoms is virtually impossible [1, 6]. For dermographic urticaria as well as in delayed pressure urticaria, simple devices (such as broadening of the handle of heavy bags) may be helpful in the prevention of symptoms [1]. When considering prevention in the case of cold urticaria, the impact of the chill factor in cold winds needs to be taken note of [1]. For solar urticaria, the exact identification of the range of eliciting wavelengths may be important for the appropriate selection of sunscreens or for the selection of light bulbs with a UVA filter [1]; although it may be more difficult to prove in Asian countries subject to the availability of such facilities.

Infections and infestations

Among the causal factors associated with chronic urticaria, the following fit into this particular category. Viral infections are known to frequently trigger or aggravate the condition [6]. Bacterial infections such as dental sepsis, sinusitis, gall bladder, urinary tract infections and *Helicobacter pylori* infection have been implicated in chronic urticaria. Fungal infections such as onychomycosis, tinea pedis and candidiasis were considered as relevant associated treatable conditions [6]. Parasitic infestations such as strongyloidiasis, giardiasis and amoebiasis, are more prevalent particularly in developing and underdeveloped countries of Asia [6]. Intestinal worm infestations, almost exclusively helminthic, elicit eosinophilia, although the absence of eosinophilia does not exclude the presence of a parasite. In tropical environments it is easier to de-worm in all cases [5]. House dust mites are ubiquitous allergens and common sensitizing agents and studies from Japan have implicated house dust mite sensitivity in chronic urticaria based on intradermal skin testing and *in- vitro* analysis [14].

Inflammatory processes

Apart from infectious diseases, chronic inflammatory processes due to other diverse diseases have been identified as causative for urticaria in the recent past. This holds particularly for gastritis, reflux esophagitis, or inflammation of the bile duct or bile gland [1].

Functional autoantibodies

In some patients with chronic urticaria functional autoantibodies against the α-chain of the high-affinity receptor for IgE (FcεRI) have been found to be relevant. These auto-antibodies are termed conditional as they only recognize unoccupied FcεRI [15]. The same conditional reactivity pattern has also been found in sera of atopic and normal healthy donors. Any condition resulting in accessibility of FcεRI will render these autoantibodies anaphylactogenic [15]. This finding offers a unifying hypothesis for the manifestation of different forms of urticaria. Non-immunologic triggers may thereby influence directly or indirectly the number of accessible FcεRI allowing the conditional autoantibodies to induce urticaria symptoms [15].

Systemic diseases

Chronic urticaria can be a manifestation associated with hyperthyroidism and hypothyroidism (Hashimoto's thyroiditis). In some euthyroid patients with autoantibodies, treatment with thyroxine has been reported to alleviate the urticaria [6].

Dietary management

A practical approach would be removal or avoidance of suspected dietary "pseudoallergens". However, care should be taken to avoid unnecessary recommendation unless backed by reasonable evidence. Although the patient may have reactions to these substances, it is noted that they may not be causative.

In a subgroup of chronic urticaria patients, pseudoallergic reactions to naturally occurring food ingredients and in some cases to food additives are seen. If identified, the specific food allergens need to be omitted as far as possible but this should only be recommended if causality can be proven [1]. In these cases a diet containing only low levels of natural as well as artificial food pseudoallergens could be instituted and maintained for a prolonged period of at least 3-6 months. As they are aggravating factors during regular intervals of between 3-6 months these items can be re-introduced to the patient's diet [1]. During this time spontaneous remission is achieved in approximately 50% of patients. It should be underlined that avoidance of type I allergens clears urticaria symptoms within 24-48 h if relevant allergens are rapidly eliminated, whereas in pseudoallergy a diet has often to be maintained for 2-3 weeks before beneficial effects can be observed [1]. IgE-mediated food allergy is rare in urticaria. Dietary restrictions should only be recommended if allergens and psuedoallergens are proven to be causative by double-blind, provocation tests [1, 6-8].

Environmental and miscellaneous triggers

Grass pollen, mold, spores, animal dander, house dust mites and even tobacco smoke [16, 17] may aggravate chronic urticaria. Urticaria may worsen during pregnancy and also pre-menstrually. Urticaria has been observed in some instances to be associated with orthopaedic implants, dental prostheses, and with dental amalgams [18, 19]. Stress, depression and anxiety have been found to be associated as a potential causative or aggravating factor for urticaria [6, 20-22].

Management of chronic urticaria: treatment

Symptomatic therapy

These therapies aim at providing symptomatic relief to reduce the effect of mast cell mediators on the target organs.

Mast cell directed therapy

At present, the most efficient drugs inhibiting mast cell mediator

Box 1. Summary of causes and associated factors of chronic urticaria

Possible causes and associating factors	No. (%)
Idiopathic urticaria	337 (75)
Physical urticaria	43 (9.5)
Symptomatic dermographism	17 (3.8)
Cold urticaria	8 (1.8)
Delayed pressure urticaria	7 (1.6)
Adrenergic urticaria	6 (1.3)
Cholinergic urticaria	4 (0.9)
Solar urticaria	1 (0.2)
Infection	17 (3.8)
Dental caries	4 (0.8)
Parasitic infestation	3 (0.6)
Hepatitis	2 (0.4)
Sinusitis	2 (0.4)
Miscellaneous	6 (1.3)
Food	16 (3.6)
Thyroid diseases	15 (3.3)
Hyperthyroidism	12 (2.6)
Hypothyroidism	3 (0.6)
Dyspepsia	5 (1.1)
Atopy*	5 (1.1)
Drugs	5 (1.1)
Collagen Vascular diseases	5 (1.1)
Others	2 (0.4)

*Urticaria wheals were frequently accompanied by an exacerbation of asthma, allergic rhinitis or atopic dermatitis. Taken from Table 2: Chronic idiopathic urticaria: prevalence and clinical course [23].

release are corticosteroids. Therapies can be mast cell directed or at the receptor of the target organ. They should be avoided for long-term treatment of chronic urticaria, as dosages necessary to suppress symptoms are usually high with significant side-effects [2]. Cyclosporine also has a moderate, direct effect on mast cell mediator release, but this drug cannot be recommended as a standard treatment due to potentially severe adverse effects [2]. Phototherapy with ultraviolet light or photo chemotherapy (PUVA) reduces the numbers of mast cells in the upper dermis. It has been successfully used in mastocytosis and is helpful in treatment-resistant patients with this condition [2].

For the treatment of chronic urticaria, UVA and UVB treatment for 1-3 months can be added to the antihistamine treatment. Although there are limited controlled studies with NB-UVB phototherapy, findings have found to be an effective complementary treatment in combination with antihistamines [2]. Tolerance induction may also be considered and is sometimes used for cold urticaria and cholinergic urticaria therapy and as a standard treatment for solar urticaria where even a rush therapy with UVA has been proven to be effective [2].

Therapy at the target organ

Nearly all symptoms of urticaria are mediated by H1-receptors. H1-receptor antagonists are thus of eminent importance in the treatment of urticaria. With the increased availability of this group of substances since the 1950s, urticaria has become one of the diseases that can be treated effectively with a very low adverse effect profile [2]. The development of second-generation non-sedating or low-sedating antihistamines has improved the quality of life of urticaria patients. New generation antihistamines also exert anti-inflammatory effects by controlling that control reactions such as cytokine release from basophils and mast cells [2, 24]. This may be of additional benefit in controlling symptoms in urticaria if these effects occur at a clinically relevant dosage. The possibility of increased adverse cardiac effects of some second generation low-sedating antihistamines should be a consideration in the choice of the specific antihistamine, especially when using higher concentrations than those recommended by the manufacturers [2].

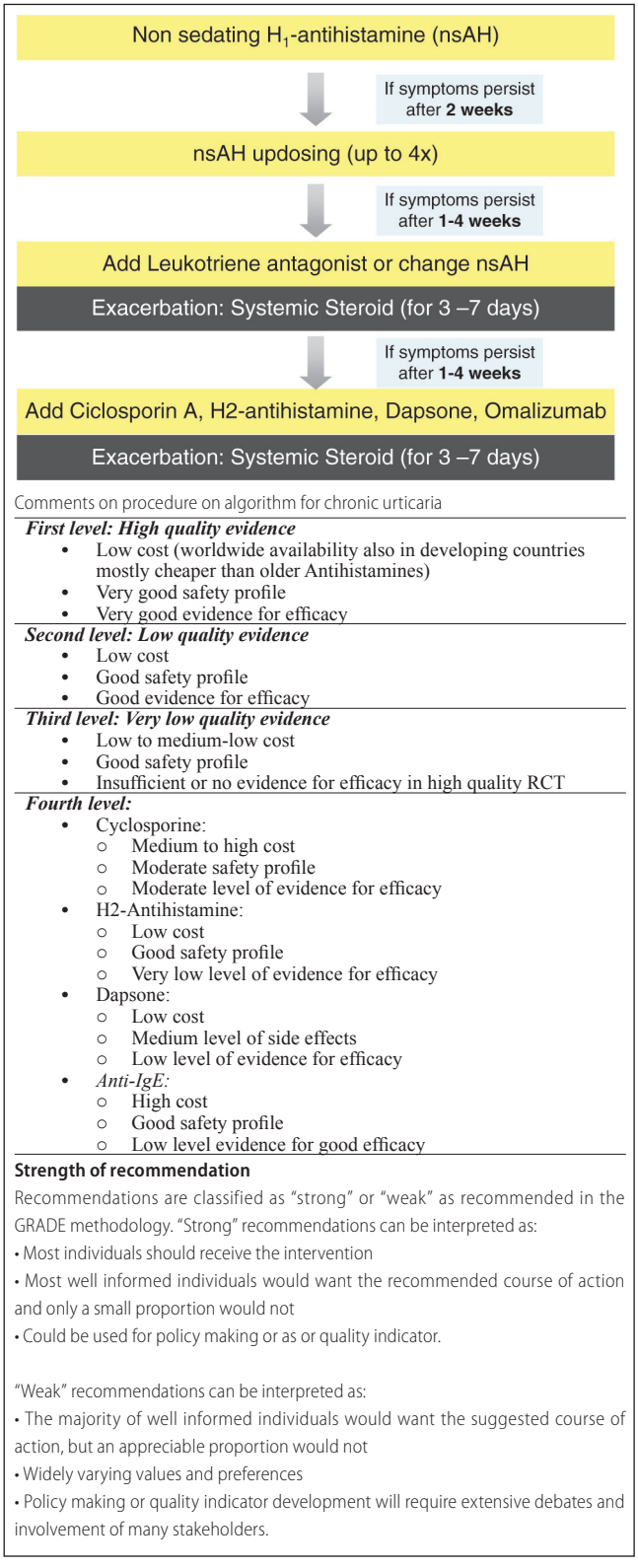
Newer antihistamines such as cetirizine, fexofenadine, and descarboxyloratadine, are cytochrome P450-independent metabolites of earlier antihistamines [2]. The main drug interactions with sedating antihistamines are in association with drugs affecting the central nervous system like analgesics, hypnotics, sedatives, and mood elevating drugs, as well as alcohol [2]. In addition, monoamine oxidase inhibitors can prolong and intensify anticholinergic effects. Some modern antihistamines are also metabolized by cytochrome P450 enzymes, and increased plasma levels are observed when there is concomitant treatment with drugs employing this enzyme system for metabolism such as ketoconazole or erythromycin [2].

Pharmacotherapy

Depending upon the severity of the disease and response to various medicines, drug therapy can be considered at various levels as defined by four levels of therapy as discussed below (Fig. 1).

First line therapy

When symptoms present themselves, the first line treatment should be a non-sedating second generation H1-AH. Histamines are the main mediator of urticaria and non-sedating H1 antihistamines represent the initial and mainstay treatment of all



Comments on procedure on algorithm for chronic urticaria

First level: High quality evidence
- Low cost (worldwide availability also in developing countries mostly cheaper than older Antihistamines)
- Very good safety profile
- Very good evidence for efficacy

Second level: Low quality evidence
- Low cost
- Good safety profile
- Good evidence for efficacy

Third level: Very low quality evidence
- Low to medium-low cost
- Good safety profile
- Insufficient or no evidence for efficacy in high quality RCT

Fourth level:
- Cyclosporine:
  - Medium to high cost
  - Moderate safety profile
  - Moderate level of evidence for efficacy
- H2-Antihistamine:
  - Low cost
  - Good safety profile
  - Very low level of evidence for efficacy
- Dapsone:
  - Low cost
  - Medium level of side effects
  - Low level of evidence for efficacy
- *Anti-IgE:*
  - High cost
  - Good safety profile
  - Low level evidence for good efficacy

Strength of recommendation

Recommendations are classified as "strong" or "weak" as recommended in the GRADE methodology. "Strong" recommendations can be interpreted as:

• Most individuals should receive the intervention

• Most well informed individuals would want the recommended course of action and only a small proportion would not

• Could be used for policy making or as or quality indicator.

"Weak" recommendations can be interpreted as:

• The majority of well informed individuals would want the suggested course of action, but an appreciable proportion would not

• Widely varying values and preferences

• Policy making or quality indicator development will require extensive debates and involvement of many stakeholders.

Fig. 1. Recommended treatment algorithm for chronic urticaria. (Taken from Fig. 1: EAACI/GA^{2}LEN/EDF/WAO guideline: management of urticaria [1]).

urticarias. These agents are reasonably effective for many patients [1, 6]. The newer generation less sedating H1 antihistamines and less cholinergic effects are preferred over the older generation H1 antihistamines as the initial choice of therapy and different studies on role of antihistamines in chronic urticaria showed 44 to 91% response rate [6]. Antihistamines should be taken on regular basis, not as and when required to get consistent results [6]. Antihistamines should be given with due regard to age, pregnancy, state of health, and individual response. In summary, considering their good safety profile, second-generation antihistamines must be considered as first line symptomatic treatment for urticaria [6].

Second line therapy

If symptoms persist after 2 weeks, the treatment regimen should be adjusted and non-sedating second generation H1-AH can be up dosed up to 4 times [1]. Even though there is available evidence for increased dosing [25, 26] it should be noted that up dosing is not a part of current labelling for non-sedating second generation H1-AH in Asia.

The general consensus of the group is that Asians, being generally of smaller physical build, dosing of antihistamines can be continued in smaller increments and this was believed to be a successful approach. Other treatment options or combination therapy should be attempted for best response.

Table 2. Recommendations and suggestions for the management of urticaria

We recommend the use of the treatment algorithm as described in Fig. 1 for the symptomatic treatment of chronic spontaneous urticaria (strong, low quality evidence).
In patients with urticaria and no special indication, we recommend against the routine use of old sedating first generation antihistamines (strong recommendation, high quality evidence).
We recommend against the use of astemizole and terfenadine (strong recommendation, high-quality evidence).
We suggest the same first line treatment and up-dosing as described in Fig. 1 for children (weight adjusted) (weak recommendation, low-quality evidence).
We suggest the same first line treatment as described in Fig. 1 in pregnant or lactating women with chronic spontaneous urticaria but safety data in a large meta-analysis is limited to loratadine (weak recommendation, very low-quality evidence).
Remarks: higher doses may be required, but their safety profile needs to be carefully weighted against the potential additional benefit.

Taken from Table 2: EAACI/GA^{2}LEN/EDF/WAO guideline: management of urticaria [1].

Third line therapy

If symptoms persist after a further 1-4 weeks, the treatment regimen of the nsAH dosage can be changed to a 1st generation sedating antihistamine or an alternative 2nd generation non-sedating antihistamine with the option of adding a leukotriene antagonist. Should exacerbation of symptoms occur, in addition the patient can be put on systemic corticosteroid for 3-7 days [1]. The use of systemic corticosteroids in the treatment of urticaria is a controversial issue. Short courses of systemic steroids can be given in resistant cases of chronic urticaria that have not responded to H1 antihistamine [1, 6]. The efficacy of corticosteroid therapy is high, but long term therapy cannot be proposed because of known adverse effects, such as diabetes mellitus, hypertension, osteoporosis and gastrointestinal bleeding. Prolonged treatment of chronic urticaria with oral corticosteroids should usually be avoided except in disabling delayed or pressure urticaria and urticarial vasculitis, which are usually nonresponsive to antihistamines [1, 6]. Leukotriene receptor antagonists, zafirlukast (20 mg twice daily) and montelukast (10 mg once daily) have been shown to have beneficial effect in treatment of chronic urticaria especially in cases which were aggravated by the NSAIDs and food additives. Zileuton, a 5-lipooxygenase inhibitor, which inhibits leukotriene generation has been found to be effective in improving chronic urticaria [6].

Fourth line therapy

If symptoms persist after a further 1-4 weeks, the treatment regimen of the nsAH dosage can be continued as a combination with the addition of a cyclosporine, second generation non-sedating H2-antihistamine, dapsone, or omalizumab. Should exacerbation of symptoms occur, in addition the patient should be put on systemic corticosteroid for another 3-7 days [1]. Therapy with immunomodulating properties could be tried in patients with severe refractory autoimmune urticaria. Cyclosporine has been shown to be effective in severe unremitting urticaria that had a poor response to conventional treatment with antihistamines [1, 6]. However, it cannot be recommended as standard therapy due to the high incidence of adverse events [1].

High dose of intravenous immunoglobulin (IVIG) has been found to be associated with some apparent benefits in the treatment of chronic urticaria. Plasmapheresis has been used to treat some patients with autoantibody positive severe chronic urticaria [6]. According to some case reports oral tacrolimus, low dose methotrexate, hydroxychloroquine, sulfasalazine, and dapsone, which also have immunomodulatory properties, have demonstrated some efficacy in the treatment of chronic urticaria. However in the case of oral tacrolimus, plasmapheresis and IVIG access may be an issue due to availability and costs and thus not readily as available throughout Asia. Warfarin therapy may be considered in a subgroup of patients with autologous serum skin test negative chronic urticaria and angioedema unresponsive to antihistamine [6, 27].

Prolonged corticosteroid treatment should generally not be given for chronic urticaria [1, 8]; it can, however, be used in urticarial vasculitis and then often in combination with colchicine or dapsone. Cyclosporine up to 5 mg per kg per day has been proven effective in patients with severe chronic urticaria.

The consensus recommendation for steroid therapy in Asian adults is in line with recommendations from the EAACI/GA^{2}LEN/EDF/WAO guideline for the management of urticaria [1] and outlined in Table 2.

Further therapeutic possibilities

Whereas antihistamines at higher concentrations will control symptoms in probably more than 95% of patients with urticaria, alternative treatments are needed for the remaining unresponsive patients (Table 3) [2]. Many of the alternatives are based on open trials or case reports. More recent approaches include leukotriene antagonists, interferon, or immunoglobulins [28]. On the other hand some treatment alternatives formerly proposed have been shown to be ineffective in double-blind, placebo-controlled studies and should no longer be used [2]. These include tranexamic acid and sodium cromoglycate in chronic urticaria, nifedipine in dermographicurticaria, and colchicine and indomethacin in delayed pressure urticaria [2, 29].

More selective immunotherapies are possibilities. The extracellular part of the subunit of FcεRIa or shorter peptide sequences containing the autoantibody epitopes could be used to bind to circulating FcεRIa auto antibodies, thereby inhibiting their attachment to receptors on mast cells or basophils [30].

First-generation H1-antihistamines: history & caveats

First-generation H1-antihistamines have been in clinical use since the 1940s and 1950s this class of drugs are still widely available and is the most frequent form of over-the-counter self-medication widely used for the treatment of allergic rhinitis, allergic conjunctivitis, urticaria, coughs, colds and insomnia.

Based on the European paper published by the GA^{2}LEN task force [31], their findings reveal that these drugs pose a considerable level of risk to the self-medicating general public and to special patient groups that are purchased over-the-counter in the absence of appropriate medical supervision.

The primary reason for their choice and usage by adults has been their availability for decades, patient's familiarity with them and their self-intuitive considerations that, "they must be both effective and safe". "In fact, patients believe them to be so safe that the warnings on the label that the drugs may cause drowsiness often go unheeded, or even unread even though they have potentially dangerous unwanted effects [31]."

Documented adverse effects associated with the sedating nature of first-generation H1-antihistamines include the following:

- Effects to rapid eye movement sleep [31],
- Impaired learning-cognitive impairment [31],
- Reduction in work efficiency - Within a small percentage they have been implicated in civil aviation, motor vehicle and boating accidents [31], and
- Suicide in teenagers and adults [31]

Special patient groups who are particularly at risk with first-generation H1-antihistamines are:

- Infants and young children [31]
- The elderly [31]

Table 3. Treatments in urticaria

Patient population	Intervention	Strength of recommendation for use of intervention	Alternative interventions (for patients who do not respond to other interventions)	Quality of evidence	Strength of recommend-ation for use of intervention
a. Acute spontaneous urticaria	Non-sedating second generation H_1-antihistamine	Strong	Prednisolone, 2 × 20 mg/day for 4 days	Low	Weak
			Prednisolone, 50 mg/day for 3 days	Very low	
			H_2-blocker, single dose for 5 days	Very low	
b. Chronic spontaneous urticaria	Non-sedating (ns) second generation (sg) H_1-antihistamine (AH) - Increase dosage if necessary up to four-fold	Strong	ns sg H_1-AH and cyclosporine	High	All weak
			ns sg H_1 and H_2-AH		
			Cimetidine	Very low	
			Monotherapy		
			Tricyclic antidepressants (doxepin)	Low	
		Weak	Ketotifen	Low	
			Hydroxychloroquine	Very low	
			Dapsone	Very low	
			Sulfasalazine	Very low	
			Methotrexate	Very low	
			Corticosteroids	Very low	
			Other treatment options		
			Combination therapy		
			ns sg H_1-AH and stanazolol	Low	
			ns sg H_1-AH and zafirlukast	Very low	
			ns sg H_1-AH and Mycophenolate mofetil	Very low	
			ns sg H_1-AH and narrowband UV-B	Very low	
			ns sg H_1-AH and omalizumab	Very low	
			Monotherapy		
			Oxatomide	Very low	
			Nifedipine	Very low	
			Warfarin	Very low	
			Interferon	Very low	
			Plasmapheresis	Very low	
			Immunoglobulins	Very low	
			Autologs whole blood Injection (ASST positive only)	Very low	

Table 3 (cont'd)

Patient population	Intervention	Strength of recommendation for use of intervention	Alternative interventions (for patients who do not respond to other interventions)	Quality of evidence	Strength of recommend-ation for use of intervention
c. Physical urticaria	Avoidance of stimuli	Strong			
c1. Symptomatic dermographism/ Urticaria factitia	Non-sedating second generation H_1-antihistamine	Weak	Ketotifen (see also chronic urticaria) Narrowband UV-B therapy	Very low Very low	All weak
c2. Delayed pressure urticaria	Non-sedating second generation H1-antihistamine	All weak	Combination therapy Montelukast and ns H_1-AH (loratadine) Monotherapy Prednisolone 40–20 mg *Other treatment options* Combination therapy Ketotifen and nimesulide Monotherapy Topical clobetasol propionate Sulfasalazine	 Very low Very low Very low Very low Very low	All weak
c3. Cold urticaria	Non-sedating second generation H_1-antihistamine Increase dose up to four-fold	Strong	Trial with penicillin i.m./p.o. Trial with doxycyline p.o. Induction of physical tolerance. *Other treatment options* Cyproheptadine Ketotifen Montelukast	Very low Very low Very low Low Very low	All weak
c4. Solar urticaria	Non-sedating H_1-antihistamine	Weak	Induction of physical tolerance *Other treatment options* Plasmapheresis + PUVA Photopheresis Plasma exchange IVIGs Omalizumab	Very low Very low Very low Very low Very low Very low	All weak
d. Cholinergic urticaria	Non-sedating H_1-antihistamine – Increase dosage if necessary	Weak	'Exercise tolerance' *Other treatment options* Ketotifen Danazol Omalizumab	Very low Very low Very low Very low	All weak

ASST, autologous serum skin test; PUVA, phototherapy with ultraviolet light or photo chemotherapy. Taken from Table 3: EAACI/GA^{2}LEN/EDF/WAO guideline: management of urticaria [1].

• Pregnant women [31]

It is in the opinion of the Asian Academy of Dermatology and Venereology Study Group that second generation non-sedating antihistamines should be prescribed as first-line treatment. But based on extenuating circumstances where availability, costing, coupled with proper medical advice providing warnings about the adverse effects of sedation or somnolence in environments where the patient may be subject to harm or may be causal in harming others, prescription of first-generation H1-antihistamines can be carried out (Table 4).

Non-pharmacological and alternative approaches

Similar with many other therapeutically challenging disorders, chronic idiopathic urticaria has seen an abundance of fad therapies, including ayurvedic and homeopathic medications and naturopathy. Frequent tepid showers and application of soothing lotions can be prescribed as cooling agents when wheals erupt and are pruritic. These include 0.5-1% menthol or calamine in aqueous cream/lotion and 10% crotamiton lotion [32].

PUVA has been used for treating chronic urticaria, but the reported results have been inconclusive. A complementary psychological treatment of patients suffering from chronic idiopathic urticaria seems necessary, because of the high prevalence of

Table 4. Available drug choices in Asia for treatment of chronic urticaria

Drug name	Brand or trade names in Asia	Drug class
Desloratadine	Aerius	Second generation non sedating H_1-antihistamine (nsAH)
Ebastine	Aleva	
Fexofenadine	Allegra	
Loratadine	Clarityne	
Mizolastine	Mizollen	
Cetirizine	Zyrtec	Second generation mild sedating H_1-antihistamine (nsAH)
Levocetirizine	Xyzal	
Cyclosporine	Sandimmun	Immunosuppressant
Cimetidine	Tagamet	H_2-receptor antagonist antihistamines
Dapsone	Dapsone	Antibacterial, Anti-inflammatory
Doxepin	Sinequan	Tricyclic antidepressants
Famotidine	Famotin	H_2-receptor antagonist antihistamines
Hydroxychloroquine	Plaquenil	Anti-malarial
Indomethacin	Indocin IV vial,	Non-steroidal anti-inflammatory
Interferon	Betaferon vial, Intron-A Multidose pen, Peg-Intron Pre-filled Redi pen, Rebif Ready-to-use pre-filled syringe, Roferon-A Pre-filled syringe	Antivirals immunological chemotherapy
Ketotifen	Zaditen	Piperidine
Methotrexate	Methotrexate Pfizer vial & Methotrexate tab	Antimetabolite
Methylprednisolone	Depo-Medrol vial, Medrol tab	Corticosteroids
Montelukast	Singulair	Leukotriene receptor antagonist
Mycophenolatemofetil	Cellcept, Myfortic	Immunosuppresant
Nifedipine	Adalat	Calcium channel blocker
Omalizumab	Xolair	Anti-IgE antibody
Oxatomide	Tinset tab	Phenylpiperazine
Pentoxifyllin	Trenlin SR tab, Trental 400,	Anti vascular (or arterial) claudication
Prednisolone	Deltacortril, Hostacortin H, Wysolone	Corticosteroids
Ranitidine	Zantac	H_2-receptor antagonist antihistamines
Stanazolol	Winstrol	Anabolic steroid
Sulfasalazine	Salazopyrin	Anti-inflammatory
Terbutaline	Bricanyl, Dhatalin, Bricasma	Antiasthmatic
Warfarin	Coumadin	Anticoagulant
Zafirlukast	Accolate	Leukotriene receptor antagonist, Antiasthmatic
Zileuton	Zyflo	Leukotriene receptor antagonist

Due to the vast number of available drugs from each drug type across Asia, the alphabetical list provided covers proprietary, non-generic trade name drugs.

psychological symptoms. Relaxation under hypnosis has produced a decrease in itching, but not in the number of hives [33].

Limitations

Data regarding the racial differences of chronic urticaria in Asia, its epidemiology, socio-economic impact and outcomes of management was not covered as part of this consensus. However it is recognized as an important area for further investigation. Future editions of this consensus will endeavour to address this knowledge gaps where possible.

CONCLUSION

The quality of life with chronic urticaria is severely affected and management of the disease should therefore be prompt and with close cooperation between patient and physician. Due to the high variability of disease severity, an individual approach is necessary for each patient. As a first line, triggering factors should be avoided as far as possible and any associated diseases should be treated. In the majority of patients, symptomatic pharmacologic treatment is possible with new generation antihistamines, with a very low adverse effect profile and good patient compliance.

In rare, non-responding patients higher dosages and alternative medication should be tried. Most of these, such as corticosteroids or cyclosporine, should be reserved for severely affected patients because of their unfavourable adverse effect profile. These treatment options exist and are discussed in detail in the text: second generation antihistamines (including up to four-fold higher; corticosteroids in severely affected patients; cyclosporine for patients refractory to other modalities).

First generation sedating antihistamines should no longer be used as initial therapy except in those few countries where second generation antihistamines are not available or where their use outweigh their risks. Since the severity of urticaria may fluctuate and spontaneous remission may occur at any time, it is also important that the necessity for continued or alternative drug treatment is re-evaluated every 3-6 months.

ACKNOWLEDGEMENTS

The production of these guidelines is made possible through an unrestricted educational grant from MSD. The authors would also like to thankfully acknowledge the contributing Members of the AADV Study Group for the Asian Consensus Guidelines for Management of Chronic Urticaria (ACGCU): Dr. Ma. Teresita Gabriel, Institute for Tropical Medicine, Philippines; Associate Prof. Nopadon Noppakun, Chulalongkorn University, Thailand; Dr. Kanokvalai Kulthanan, Siriraj Hospital, Mahidol University, Thailand; Dr. Choon Siew Eng, Hospital Sultanah Aminah, Malaysia; Dr. Koh Chuan Keng, Koh Skin Clinic, Malaysia; Dr. Sabeera Begum, Institut Pediatrik, Hospital Kuala Lumpur, Malaysia; Dr. M. Pubalan Columbia Asia Hospital, Miri, East Malaysia; Dr. Roshidah Baba, Hospital Kuala Lumpur, Malaysia; Dr. Mardziah Alias, Damansara Specialist Hospital, Malaysia; Dr. Loh Liew Cheng, Subang Jaya Medical Centre, Malaysia; Dr. Henry Boon Bee Foong, Hospital Pantai Putri, Malaysia; Datin Dr. Asmah Bt. Johar, Hospital Kuala Lumpur, Malaysia; Dr. Rona E. Nadela, Consultant Dermatologist, Philippines; Dr. Kusmarinah Bromono, Consultant Dermatologist, Indonesia; Dr. Titi Lestari, Consultant Dermatologist, Indonesia; Prof. Dr. Benny Effendi Wiryadi, University School of Medicine, Indonesia; Dr. Seow Chew Swee, National University Hospital, Singapore; Dr. Tan KianTeo, National Skin Centre, Singapore; Dr. Lim Yen Loo, National Skin Centre, Singapore; Dr. Vichet Chan, National Centre for HIV/Aids, Dermatology and STI Control, Cambodia; Dr. Koushik Lahiri, Consulting Dermatologist and Dermatosurgeon, India; Prof. HachiroTagami, Tohoku University School of Medicine, Japan; Associate Prof. Dr. Soyun Cho, Seoul National University Hospital, Korea; Prof. Dr. Li-He Zhang, Peking University, Beijing, China; Prof. Lai Wei, Peking University People's Hospital, Beijing; Prof. Chrang-Shi Lin, National Yang-Ming University, Taiwan; Prof. Dr. Azer Rashid, Khyber Teaching Hospital, Pakistan; Dr. William KK Fung, The University of Hong Kong, Hong Kong; Prof. Dr. med. Torsten Zuberbier, Charité – Universitätsmedizin, Germany; Professor Malcolm W. Greaves, St John's Institute of Diseases of the Skin, London, United Kingdom; Dr. Saumya Panda, KPC Medical College, India.

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