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CONSENSUS GUIDELINES

MANAGEMENT OF CHRONIC URTICARIA IN ASIA (ACGCU) **2010**

PREPARED BY THE AADV STUDY GROUP



League of Asean Dermatological Societies



Asian Academy of Dermatology and Venereology

AADV Asian Consensus Guidelines for Management of Chronic Urticaria

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Dear Colleagues,

On behalf of the Organising Committee, it is my pleasure to present the work of the AADV Study Group for the Asian Consensus Guidelines for the Management of Chronic Urticaria.

This work was completed at the 19th Regional Congress of Dermatology (Asian-Australasian) out in the city of Kota Kinabalu, Sabah, East Malaysia 2010. This work embraces elements of the International Clinical Practice Guidelines from Europe.

We thank the Members of the panel from across Asia who offered their expertise and input by adding their input for the formulation of this consensus.

It is the objective of this document to provide a more structured approach to the management of chronic urticaria for the patients in the Asian region.

Dr. Steven K.W. Chow Organising Chairman 19th RCD 2010 Convening Chairman AADV Study Group ACGMCU

1. 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. For a majority of patients, symptoms differ by the extensiveness of the areas affected. The severity and clinical presentation can differ substantially from patient to patient.
- Symptoms of chronic urticaria persist for over six (6) weeks and is a frustrating condition for both patients and caregivers.
- The aim of treatment to achieve complete symptom relief. This takes quite a long time to achieve 100% 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). Treating the cause is the most desirable option, but it is, unfortunately, not applicable in the majority of patients, especially in cases of inducible urticarias which are mainly idiopathic.
- Secondly, treatment is aimed at providing symptomatic relief. In all cases, symptomatic relief should be offered while searching for causes. Symptomatic treatment is currently the most frequent form of management. It aims to ameliorate or suppress symptoms by inhibiting the release and/or the effect of mast cell mediators and possibly other inflammatory mediators.
- Health Related Quality of Life (HRQL) is increasingly recognized as a primary outcome in clinical trials, population studies and public health. The patients' well-being should be central to the treatment regiment keeping in mind that chronic urticaria often recurs over an extended duration from six weeks to over twenty years.
- The treatment options available were evaluated from the various guidelines using the following methods.

2. METHODS

- These consensus guidelines for the management of urticaria were sourced from the European and International guidelines for management of chronic urticaria and various other literature sourced from Asian journals available from online databases.
- These guidelines were then discussed in detail by the study group members. 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 thirteen (13) countries around Asia including two (2) world renowned specialists in urticaria from Europe.
- As there is an existing international consensus on "Definition, Classification, and Routine Diagnosis of Urticaria" [2] the following website can be referred to for further information: <u>http://www.nature.com/jidsp/journal/v6/n2/full/5640037a.html - note1</u>.

3. MANAGEMENT OF CHRONIC URTICARIA

- The general measures concerning management of chronic urticaria is firstly, the identification and elimination of the underlying cause(s) and/or eliciting trigger(s).
- Next is the provision of available information to the patient(s) concerning the symptoms and advice regarding avoidance of potential triggers such as: alcohol overuse, excessive physical tiredness, mental distress, prolonged pressure on the skin (ie. tight clothing & bag straps), and overheated surroundings.
- Following the above is the provision of symptomatic relief which should always be offered while searching for causes.
- Avoidance of the eliciting trigger or stimulus, 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 to prognosticate and manage adequately.
- For physical urticaria the impact of physical stimuli can be diminished and symptoms improved by appropriate measures (e.g., cushioning in pressure urticaria).
- In spontaneous acute and chronic urticaria, treatment of associated infectious and/or inflammatory processes, including *Helicobacter pylori*-associated gastritis, parasitic diseases, or food and drug intolerance may be helpful in selected cases.
- 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.

- Chronic urticaria is also recognized as a stress-vulnerable disease in which psychological stress can trigger or increase itching. It is suggested that effective management processes could take into account psychological factors in some of the patients.
- 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.

3.1 Identification and elimination of the underlying cause / potential trigger

- One of the major approaches for treating a patient is to find out the cause of the symptoms and devise means for protecting the patient from further exposure.
- Known triggers include: drugs, food, food additives, infections (bacterial, viral, fungal), parasitic infestations and dermatological disorders.
- Following elimination of the suspected agent, only recurrence of symptoms in a double-blind provocation test will provide definitive proof.

3.2 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 if its use is indispensable.
- The principle should be to avoid polypharmacy as far is possible, and to use as few drugs as possible concurrently, eliminating those which are not absolutely indispensable.
- Drugs causing pseudoallergic reactions (ie. *aspirin*) cannot only elicit but also aggravate pre-existing chronic urticaria. Elimination can be expected to improve symptoms. Aspirin may exacerbate chronic urticaria in 6.7 to 67% of patients although patients taking low dose aspirin for its anti-thrombotic properties can usually continue regular treatment.
- Avoidance of aspirin and other NSAIDs should usually be recommended because these drugs aggravate chronic urticaria in about 30% of patients.
- ACEIs (angiotensin converting enzyme inhibitors) are commonly associated with angioedema but they rarely cause chronic urticaria. However, ACE inhibitors should usually be avoided in chronic urticaria with or without angioedema.
- Other drugs implicated are alcohol, narcotics (codeine, morphine) and oral contraceptives.

3.3 Physical stimuli

- Avoidance of physical stimuli for the treatment of physical urticaria requires detailed information about the physical properties of the respective stimulus. However, in many patients the threshold for the individual eliciting stimulus is low and thus the total avoidance of symptoms is virtually impossible.
- For dermographicurticaria 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. When considering prevention in the case of cold urticaria, the impact of the chill factor in cold winds needs to be taken note of.
- 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; although it may be more difficult to prove in Asian countries subject to the availability of such facilities.

3.4 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.
- **Bacterial** infections such as dental sepsis, sinusitis, gall bladder, and urinary tract infection and even *Helicobacter pylori*.
- **Fungal** infections such as onychomycosis, tineapedis and candidosis were considered as relevant associated treatable conditions.
- **Parasitic** infestations such as strongyloidiasis, giardiasis and amoebiasis, are more prevalent particularly in developing and underdeveloped countries of Asia. 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. 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.

3.5 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.

3.6 Functional autoantibodies

- In some patients with chronic urticaria functional autoantibodies against the α-chain of the high-affinity receptor for IgE (Fc∈RI) have been found to be relevant. These auto-antibodies are termed conditional as they only recognize unoccupied Fc∈RI. The same conditional reactivity pattern has also been found in sera of atopic and normal healthy donors.
- Any condition resulting in accessibility of Fc∈RI will render these autoantibodies anaphylactogenic.
- 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 Fc∈RI allowing the conditional autoantibodies to induce urticaria symptoms.

3.7 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.

3.8 Dietary Management

- A practical approach would be removal or avoidance of suspected dietary "pseudoallergens". However, care should be taken with unnecessarily doing so, without any evident reasons. 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.
- 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 patients diet.
- 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 hours 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.
- 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.

3.9 Environmental and Miscellaneous triggers

- Grass pollens, mold, spores, animal dander, house dust mites and even tobacco smoke may provoke chronic urticaria.
- Urticaria may worsen during pregnancy and also pre-menstrually.
- Urticaria has been associated with a metal pin in femur, metal dental prostheses, and with dental amalgams.
- Depression may also cause or aggravate chronic urticaria.

3.10 Symptomatic therapy

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

3.11 Mast cell directed therapy

- At present, the most efficient drugs inhibiting mast cell mediator 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.
- Ciclosporin 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.

- PUVA reduces the numbers of mast cells in the upper dermis. It has been successfully used in mastocytosis and is helpful in treatmentresistant patients with this condition.
- 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.
- 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.

3.12 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.
- The development of second-generation nonsedating 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.
- This may be of additional benefit in controlling symptoms in urticaria if these effects occur at a clinically relevant dosage. There are some studies that show the benefit of a higher concentration of antihistamines in individual patients, but further investigations in this field are necessary.

- 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.
- Further progress with regard to drug safety was achieved by the development of the antihistamines cetirizine, fexofenadine, and descarboxyloratadine, which are cytochrome P450-independent metabolites of earlier antihistamines.
- The main drug interactions with sedating antihistamines are in association with drugs affecting the central nervous system like analgetics, hypnotics, sedatives, and mood elevating drugs, as well as alcohol.
- In addition, MAO 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.

3.13 Pharmacotherapy

 Depending upon theseverity 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.

Figure 1. Recommended treatment algorithm for chronic urticaria

(Adapted from Figure 1 - EAACI/GA²LEN/EDF/WAO guideline: management of urticaria)



Comments on procedure on algorithm for chronic urticaria

First level: High quality evidence	Third level: Very low quality
 Low cost (worldwide availability 	evidence
also in developing countries	 Low to medium-low cost
mostly cheaper than old	 Good safety profile
Antihistamines)	 Insufficient or no evidence for
 Very good safety profile 	efficacy in high quality RCT
 Very good evidence for efficacy 	
Second level: Low quality evidence	
Low cost	
 Good safety profile 	
Good evidence for efficacy	

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

Table 1. Box of recommendations and suggestions for the management of urticaria(Taken from EAACI/GA²LEN/EDF/WAO guideline: management of urticaria)

- We recommend the use of the treatment algorithm as described in Fig. 1 for the symptomatic treatment of chronic spontaneous urticaria (both high and 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, lowquality 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.

3.14 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 urticarias. These agents are reasonably effective for many patients.
- The newer generation less sedating H1 antihistaminesand 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.
- Antihistamines should be taken on regular basis, not as and when required to get consistent results. 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.

3.15 Second line therapy

- If symptoms persist after two (2) weeks, the treatment regimen should be adjusted and non-sedating second generation H1-AH should be updosed up to four (4) times.
- General consensus from this study states that as Asians are generally of smaller physical builds, dosing can be continued in smaller increments as this approach has been found to be successful.
- Other treatment options different types or combination therapy should be tried for best response.

3.16 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.
- The use of systemic corticosteroids in the treatment of urticaria is a controversial issue. Short courses of systemic steroids can utilize a wider dosing range for asian application (10-30 mg of prednisolone) can be given in resistant cases of chronic urticaria that have not responded to H1 antihistamine. 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.
- 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 5lipooxygenase inhibitor, which inhibits Leukotriene generation has been found to be effective in improving chronic urticaria.

3.17 Fourth line therapy

- If symptoms persist after an even further 1 4 weeks, the treatment regimen of the nsAH dosage can be continued as a combination with the addition of a Ciclosporin, second generation non-sedating H2antihistamine, Dapsone, Omalizumab.
- Should exacerbation of symptoms occur, in addition the patient should be put on systemic corticosteroid for another 3 – 7 days.
- Immunotherapy could be tried in patients with severe refractory autoimmune urticaria. Ciclosporin has been shown to be effective in severe unremitting urticaria that had a poor response to conventional treatment with antihistamines. Long term treatment with ciclosporine over the short term therapy has not been found to be associated with more benefit in the clinical improvement.
- High dose of intravenous immunoglobulin 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.
- According to some reports oral tacrolimus, low dose methotrexate, hydroxychloroquine, sulfasalazine, and dapsone, which have immunomodulatory properties, are effective in the treatment of chronic urticaria.
- Warfarin therapy may be considered in a subgroup of patients with ASST negative chronic urticaria and angioedema unresponsive to antihistamine.
- Prolonged corticosteroid treatment should generally not be given for chronic urticaria; it can, however, be used in urticarial vasculitis and then often in combination with colchicine or dapsone.

- Ciclosporin up to 5 mg per kg per day has been proven effective in patients with severe chronic urticaria.
- This recommendation for Asian adults, is to start with 40 mg prednisolone per day for 2 days, subject to bodyweight and to decrease the dose by 10 mg daily for 3 days and subsequently use an alternate-day regimen for another 2 weeks.
- Recurrence is common but if the response is dramatic, 5–10 mg of prednisolone per day can be reinstituted for a week during severe exacerbations.

3.18 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.
- Many of the alternatives are based on open trials or case reports. More recent approaches include leukotriene antagonists, interferon, or immunoglobulins.
- 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. These include tranexamic acid and sodium cromoglycate in chronic urticaria, nifedipine in dermographicurticaria, and colchicine and indomethacin in delayed pressure urticaria.
- More selective immunotherapies are possibilities. The extracellular part
 of the subunit of FceRla or shorter peptide sequences containing the
 autoantibody epitopes could be used to bind to circulating FceRla auto
 antibodies, thereby inhibiting their attachment to receptors on mast cells
 or basophils.

3.19 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 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 **GA2 LEN** task force [34], 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, patients 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."

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

- Effects to REM sleep [34]
- Impaired learning cognitive impairment [34]
- Reduction in work efficiency Within a small percentage they have been implicated in civil aviation, motor vehicle and boating accidents [34]
- Suicide in teenagers and adults [34]

Special Patient Groups who run the highest risks with first-generation *H1-antihistamines* are:

- Infants and young children [34]
- The Elderly [34]
- Pregnant Women [34]

It is in the opinion of the Study Group (for the Asian Consensus Guidelines for the Management of Chronic Urticaria) that second generation nonsedating 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.

3.20 Non-pharmacological and Alternative approaches

- Similar to 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 most pruritic. These include 0.5-1% menthol or calamine in aqueous cream/lotion and 10% crotamiton lotion.
- Phototherapy with ultraviolet light or photo chemotherapy (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 psychological symptoms. Relaxation under hypnosis has produced a decrease in itching, but not in the number of hives.

Table 2: Treatments in Urticaria

(Taken from Table 3: EAACI/GA²LEN/EDF/WAO guideline: management of urticaria)

Patient population	Intervention	Strength of recommendat ion 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	Non-sedating	Strong	Prednisolone, 2 × 20 mg/dav* for 4 davs	Low	Weak
urticaria	generation		Prednisolone, 50 mg/day* for 3 days	Very low	
	H1- antihistamine		H ₂ -blocker, single dose for 5 days	Very low	
b. Chronic spontaneous urticaria	Non-sedating second generation	Strong Weak	ns sg H1-AH and ciclosporin ns sg H1 and H2-AH Cimetidine	High Very low	All weak
	H1- antihistamine - Increase		Monotherapy Tricyclic antidepressants (doxepin)	Low	
	if necessary up to four-		Ketotifen Hydroxychloroquine Dapsone	Low Very low Very low	
	fold		Methotrexate Corticosteroids	Very low Very low Very low	
			Other treatment options Combination therapy ns sg H1-AH and		
			stanazolol ns sg H1-AH and	Low	
			ns sg H1-AH and Mycophenolate mofetil	Very low	
			ns sg H1-AH and narrowband UV-B ns sg H1-AH and	Very low	
			omalizumab	Very low	
			Monotherapy Oxatomide Nifedipine Warfarin Interferon Plasmapheresis Immunoglobulins Autologs whole blood Injection (ASST positive only)	Very low Very low Very low Very low Very low Very low Very low	

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Patient population	Intervention	Strength of recommendat ion 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 dermographis m/Urticaria factitia	Non-sedating second generation H1- 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	All weak	Combination therapy Montelukast and ns H1- AH (loratadine)	Very low	All weak
	H1- antihistamine		Monotherapy Prednisolone 40–20 mg*	Very low	
			Other treatment options Combination therapy Ketotifen and nimesulide	Very low	
			Monotherapy Topical clobetasol propionate Sulfasalazine	Very low Very low	
c3. Cold urticaria	Non-sedating second generation H1- 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 H1- 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
c5. Cholinergic urticaria	Non-sedating H1- antihistamine – Increase dosage if necessary	Weak	'Exercise tolerance' Other treatment options Ketotifen Danazol Omalizumab	Very low Very low Very low Very low	All weak

Table 3. Treatments in urticaria (Summary)

This table summarizes the current standard drug treatment and alternatives in several subtypes of urticaria. (Taken from Table 4: EAACI/GA²LEN/EDF/WAO guideline: management of urticaria)

Type of urticaria	Standard treatment	Alternative treatment
a. acute urticaria	nonsedating H ₁ - antihistamines	initially prednisolone, 50 mg per d for 3 d
b. chronic urticaria	nonsedating H ₁ - antihistamines – increase dosage if necessary	Combination: dapsone and pentoxifyllin Combination: H ₁ and H ₂ -blocker Combination: H ₁ -blocker and B -sympathomimetics (e.g., terbutaline) Combination: H ₁ -blocker and psychotropic drugs Tricyclic antidepressants (doxepin) Danazol (stanozolol) Leukotriene antagonists Sulfazalazine Corticosteroids Ciclosporin Interferon PUVA lasmapheresis Immunoglobulins
 c. physical urticaria 1. dermographic urticaria – increase concentration if necessary 	always consider avoidance of stimuli nonsedating H ₁ - antihistamines	
2. delayed pressure urticaria	high-concentration nonsedating H ₁ -antihistamines	short-term corticosteroids trial with penicillin, 3 ×1.2 Mil IU per d p.o., or
3. cold urticaria	H ₁ -antihistamines	physical tolerance (cold bath)
4. solar urticaria	induction of physical tolerance (hardening with UV light)	nonsedating H ₁ -antihistamines
 d. special types of urticaria 1. cholinergic urticaria 	nonsedating H ₁ -AH – increase concentrate-i on if necessary	Danazol, stanzolol (only severe cases)

Table 4: Available drug choices for treatment of chronic urticaria

With reference to the treatment algorithm as described in Figure 1 and further referenced to Table 2 & 3, the following is a list of recommended available drugs used for the treatment of urticaria.

- **Note 1:** 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.
- Note 2: * (Reflects references)

Second generation Non sedating H1-antihistamine (nsAH)					
		Phar	Pharmacologic Properties		
		at clinica	at clinically recommended dosages		
			Interaction potential		
Drug Name	Brand or Trade names	e Sedation	Drug	Food	
Desloratadine	Aerius *[129]	- *[97][98][102]	- *[97][99][102]	- *[97][102]	
Ebastine	Aleva *[130]	- *[105][110]	- *[108][110]	- *[108][110]	
Fexofenadine	Allegra *[131]	- *[113][132]	+ *[114][132]	+ *[114]	
Loratadine	Clarityne *[138][140]	- *[142][143]	+ *[144]	- *[143]	
Mizolastine	Mizollen	- *[116][122]	- + *[116] *[122][133]	- *[116][122]	
Second generation Mild sedating H1-antihistamine (nsAH)					
Cetirizine	Zyrtec *[134]	- *[125]	- *[126]	+ *[126]	
Levocetirizine	Xyzal *[135]	- *[119]	+ *[119]	*[119]	

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Drug name	Brand or Trade names	Drug class
Ciclosporin	Sandimmun	Immunosuppressant
Cimetidine	Tagamet	H ₂ -Receptor antagonist
		Antihistamines
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	Antivirals Immunological
	Multidose pen, Peg-	Chemotherapy
	Intron Pre-filled Redi	
	pen, Rebif Ready-to-use	
	pre-filled syringe,	
	Roferon-A Pre-filled	
	syringe	
Drug name	Brand or Trade names	Drug class
Ketotifen	Zaditen	Piperidine
Methotrexate	Methotrexate Pfizer vial	Antimetabolite
	& Methotrexate Wyeth	
	tab	
Methylprednisolone	Depo-Medrol vial,	Corticosteroids
	Medrol Tab	
Montelukast	Singulair	Leukotriene receptor
		antagonist
Mycophenolatemofetil	Cellcept, Myfortic	Immunosuppresant
Nifedipine	Adalat	
Omalizumab	Xolair	Anti-IgE Antibody
Oxatomide	Tinset tab	Phenylpiperazine
Pentoxifyllin	Trenlin SR tab, Trental	Anti vascular (or
	400,	arterial) claudication
Prednisolone	Deltacortril, Hostacortin	Corticosteroids
	H, Wysolone	

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Ranitidine	Zantac	H ₂ -Receptor antagonist
		Antihistamines
Stanazolol	Winstrol	Anabolic steroid
Sulfasalazine	Salazopyrin	Anti-inflammatory
Terbutaline	Bricanyl, Dhatalin,	Antiasthmatic
	Bricasma	
Warfarin	Coumadin	Anticoagulant
Drug name	Brand or Trade names	Drug class
Zafirlukast	Accolate	Leukotriene receptor
		antagonist,
		Antiasthmatic
Zileuton	Zyflo	Leukotriene receptor
		antagonist

4. 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 concentrations and alternative medication should be tried. Most of these, such as corticosteroids or ciclosporin, 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; ciclosporin 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.

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