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Urticaria in Children and Adolescents: an updated review of the pathogenesis and management

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CONFLICT OF INTEREST

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Abstract. The present survey represents the latest data on diagnosis and management of childhood urticaria. It has been observed that urticaria occurs less often in children than adults, with symptoms rarely lasting for over 6 weeks. Triggers or aggravating factors can be found only in 21-55% of cases. Finding autoantibodies in children does not impact a disease prognosis, unlike in adult patients, where the presence of autoantibodies is associated with a more prolonged run of the disease, a more severe prognosis and more intensive treatment methods. The incidence of food allergy equals to 8-10% of cases. The incidence of H.Pylori infection in children is lower than in adults and comes to 10-18%. Medical experts recommend using the same treatment schemes for adults and children. This survey describes different urticaria management patterns suggested by experts from Europe, America and Russia in their recent guidelines. It has been noted that unlike the guidelines from 2014, the 2018 clinical practice guidelines for the diagnosis and management of urticarial once again suggest a 4-step treatment scheme with assigning Omalizumab for Step 3 and Cyclosporine A for Step 4 in the event of low therapeutic efficacy of the previous step or its impossibility. Leukotriene antagonists (LTRAs) are currently removed from basic management to alternative programs.

Key words: urticaria, chronic urticaria, children, etiology, pathogenesis, triggers, management, second generation antihistamines, anti-IgE therapy, cyclosporine, prognosis

Urticaria is one of the most common skin disorders. In recent decades, considerable progress in the study of disease etiology and pathogenesis has been achieved, modern classifications have been developed, and new treatment approaches have appeared. However, much still remains unexplained. This review describes the latest recommendations for the diagnosis and treatment of urticaria in children.

Urticaria presents itself with itching, wheals, and/or angioedema. [(1), (2)] According to international guidelines, urticaria should be differentiated into acute, with the duration of up to 6 weeks, and chronic urticaria (CU), if symptoms persist for more than 6 weeks. Depending on the trigger factor, it can also be divided into spontaneous and inducible variants. Inducible urticaria (CIndU) is due to physical triggers like cold, heat, pressure, vibration, ultraviolet rays. Other types of inducible urticaria include aquagenic, contact and cholinergic urticaria [(2)]. Nearly every fourth adult urticaria patient shows both, spontaneous and inducible.

About 15-25% of the population has experienced at least one episode of urticaria in their lifetime, mostly the acute variant[(3)]. Urticaria is rarely encountered in childhood (3.4% UK, 4.4% Germany, 5.4% Denmark), and its persistence is even less probable (0.1-0.3%). However, according to recent data, the prevalence of chronic urticaria among Korean children was 1.8% (chronic continuous urticaria, 0.7%; and chronic recurrent urticaria,

1.1%).[(4)] The cause or trigger of chronic urticaria in children (PcU) could be detected in 21-55% of cases [(5)]. The duration of chronic urticaria usually does not exceed 5-10 years. Although posing no threat to life, urticaria, nevertheless, has a great impact on patients' physical and psychological state [(6)]. Children with chronic urticaria more often have increased "bad school performance" as compared to healthy children [(7)].

Discussed pathomechanisms of chronic urticaria:

Activation of dermal mast cells plays the key role in pathogenesis of urticaria. Regardless of the cause of mast cell activation, the processes which evolve after that are similar: phosphorylation of tyrosine in beta and gamma chains of FcεRI with the production of tyrosine kinase (ITAM). ITAM activates intracellular mechanisms causing the release of granules with preexisting mediators (histamine, heparin, tryptase and TNF-α) and activation of synthesis of new anti-inflammatory cytokines/chemokines and eicosanoids [(8)]. Histamine determines the development of the immediate inflammation phase, inducing the release of neuropeptides (substance P, endorphins, enkephalines) by nerve endings. Mast cells are also able to produce vasoactive molecules (TNF-α, IL-6, thrombocyte activator, vascular endothelial growth factor) without degranulation. Vasoactive molecules aggravate symptoms of urticaria, and are responsible for the inefficiency of antihistamines and the effect of immunodepressants in some patients [(9)]. This phase of immediate inflammation evolves into a more complex process of interaction between cytokines, chemokines and adhesion molecules regulating vascular reaction and specific kinetics of cells. The newly involved cells secrete inflammatory mediators, intensifying and prolonging response. Even in visually intact skin, areas greater expression of chemokines and adhesion molecules with higher T-lymphocyte content can be detected, which reduces the threshold of mast cell sensitivity to trigger factors [(10)]. The signal of regulatory proteins (SIRPs) are responsible for limiting the release of mediators by mast cells and dephosphorizing ITAM tyrosine kinase. A defect in their function also affects the development of chronic urticaria. During exacerbations, the activation of the blood coagulation system can be detected. Thrombin increases the permeability of the vascular endothelium and enhances the release of inflammatory mediators by mast cells and production of C5a complement component. C5a (anaphylotoxin) is involved in the activation of mast cells and is a chemoattractant for neutrophils and eosinophils [(11), (12), (13)]. It has been noted that levels of prothrombin fragments 1+2 can be used for assessment of the activity of CSU in children [(14)]

Histological and clinical characterization

Histological changes in urticaria are characterized by dermal edema, enlarged capillaries, perivascular non-necrotizing infiltration, predominantly by CD4+ lymphocytes as well as by monocytes, neutrophils, eosinophils and basophiles. An hour after the appearance of wheals, neutrophils come to dominate the infiltrated content [(3)]. The number of mast cells remains the same and does not differ from the number of mast cells in the intact areas of the skin or in healthy people [(10)].

Clinically, the wheal is a dense raised area of the skin, with a light-colored center surrounded by refractory erythema. Lesions may be different sizes, round or irregular, merging together, accompanied with itching and burning sensations. They are characterized by quick (in the course of 1-24 hours) complete disappearance. Angioedema is characterized by the inflammation of deeper layers of the dermis and subcutaneous tissue, which is more often accompanied with pain or burning rather than itching. Mucous membranes are often affected. Angioedema subsides more slowly, disappearing in the course of 24-72 hours. Isolated wheals appear in 78.4% of cases, angioedema – in 6.65%, while both symptoms are observed in 15% of cases [(15)]. In children, accompanying angioedema was reported in 48,2% cases [(16)].

Possible causes/triggers of chronic urticaria

A lot of relevant causes and/or triggers are discussed. The development of PcsU is associated with persistent viral, bacterial, by parasitic or helminthic infection, consumption of food and food additives, drugs, but approximately in 40% of cases, chronic spontaneous urticaria is an autoimmune/autoallergic/autoreactive process, depending on the countries.

Autoreactive urticaria In 2013, the European Academy of Allergy and Clinical Immunology (EAACI) published the criteria for the diagnosis of autoimmune urticaria: (a) positive biological tests in vitro demonstrating functional activities of autoantibodies (basophile histamine-release test or detection of CD63 and CD203 activation markers on the basophile surface with the method of flow cytometry), (b) positive autologous serum skin test, (c) detection of autoantibodies to FcεRIα [(17)]. In rare cases, anti-IgE antibodies are produced [(18)].

The autologous serum skin test is the only available diagnostic tool in everyday practice. The sensitivity and the specificity of this method is 70% and 80% respectively [(15)]. A positive autologous serum skin test was observed with similar frequency in the population of both children and adults (40-45%). The presence of autoantibodies in adults is associated with longer treatment, a worse prognosis and a need for more intensive therapy. The detection of autoantibodies in children does not affect the prognosis [(5), (19)]. Recently it was found that positive CD63 basophil activation test is common in PcsU and is associated with high disease activity[(20)]. Low blood basophil counts on the contrary were linked to earlier symptoms resolution.[(21)]

Patients suffering from cU can simultaneously have another autoimmune pathology [(22)]. Thus, antithyroid antibodies can be found in 4.3%-17.3% of children and 27% of adults diagnosed with CSU [(23)] (24)]. In a retrospective study of 852 pediatric patients in Brazil, a higher prevalence of PcsU in patients with systemic lupus erythematosus (SLE) was shown [(25)]. SLE disease activity index in patient with urticaria was also higher. The majority of patients presented with urticaria symptoms before or at the onset of SLE [(26)]. The prevalence of antithyroid antibodies in this group of patients was 20%, compared with 7% in overall SLE population [(25) (27)].

The link between chronic urticaria and celiac disease is also interesting. The comparison of 79 children suffering from urticaria with a control group revealed that the group of children with urticaria had a greater frequency of celiac disease than the control group (5 and 0.67% respectively). Two weeks on a gluten-free diet helped to achieve remission of urticaria in most patients [(28)].

Intolerance Urticaria

Parents often believe that food allergy is the cause of urticaria. It is true, that ingestion of many foods, including eggs, milk, soy, peanuts, wheat, seafood, nuts in sensitized infants/children may cause acute urticaria (more frequently, than in adults). In these cases, acute generalized urticaria may warn of future anaphylaxis. Such children should be properly examined in order to reveal their specific food trigger [(2)]. The association with food in chronic urticaria is less clear. According to research data, the frequency of food allergies confirmed by anamnesis data, the detection of IgE specific antibodies in the blood and in provocative tests fluctuates between 8% and 10% [(19)]. The recent research by Korean authors also underlines that food allergy is an uncommon cause of CSU. [(29)]

Disease recurrence may be caused by histamine intolerance associated with the superfluous presence of histamines in foods and/or with metabolism disorders (deficiency of diamine oxidase enzyme). Diamine oxidase is the main enzyme responsible for histamine degradation. This enzyme is produced by enterocytes of intestinal mucosa. Certain drugs suppress the activity of diamine oxidase, lowering the sensitivity threshold to foods rich in histamine or stimulating its production [(30)]. Such foods include certain types of fish (tuna, sardines, anchovies), cheese (Emmental, Gouda), salami, sausages, fruit and vegetables, especially tomatoes, wine and beer. Drugs inhibiting diaminoxidase cover: imipenem, dobutamine, pancuronium, pentamidine, verapamil, isoniaside, clavulanic acid, dihydralazine, chloroquine, cyclocerine, acetylcysteine, metoclopramide, cefuroxime [(31)]. No data in children are available.

Food additives (preservatives, dyes and sweetener: sodium benzoate (E211), sodium metabisulphite, monosodium glutamate (E620), sodium nitrate, tartrazine (E102), erythrosine (E127), sorbic acid, butylated hydroxyl anisole, saccharin/cyclamate) and natural salicylates (raspberry, black currant, cherries, apricots, plums, oranges, tomatoes and others) may trigger manifestations of chronic urticaria or intensify its symptoms, but they are rarely the only cause of the disease. In 2005, Di Lorenzo et al. studied 838 adult patients with chronic urticaria. Higher sensitivity to food additives was detected in just 1-3% of the cases [(32)]. In pediatric population reported frequency of intolerance to additives confirmed by oral challenge ranges from 21% to 2.6% [(33) (34)]. In order to exclude hypersensitivity to food additives it is possible to prescribe an elimination diet for at least 3 weeks, followed by provocation.

The efficiency of three week low-pseudoallergen diet was studied in a small cohort of children more than 15 years ago. The diet was beneficial to 12/16 (75%) children with chronic urticaria. All the children responded to reintroduction of prohibited food [(35)]. These data correlate with adult studies, showing that 31-70% of patients with chronic spontaneous urticaria may benefit from a pseudoallergen-free diet [(36) (37)]. The influence

of histamine-low diets has never been examined in children. However, in the cohort of adult patients with concomitant gastrointestinal symptoms, up to 75% had clinical improvement after the third week of low-histamine diet. In these patients, a higher quality of life and a reduction of antihistamine intake were achieved. The authors postulated that low-histamine diet is 'a therapeutically useful and cost-free tool' and that this diet is easier to perform for patients, than a low-pseudoallergen diet with equal efficiency [(38)]. It is interesting, that it is impossible to predict whether a patient will benefit from avoiding histamine in his diet based on clinical history (daily symptoms, previous experience of tolerating or not tolerating histamine-rich foods) or the initial level of diamine oxidase activity [(39) (38)].Because of the differing diets and eating habits across the world, it is important to remember that success rates may vary greatly. More research is needed to determine the effect of of natural and artificial ingredients of food on urticaria.

Among drugs that are able to provoke urticaria exacerbations are non-steroidal anti-inflammatory drugs and antibiotics, predominantly penicillins, cephalosporins [(40)].

Infect-Urticaria

Infections are considered to be the most frequent cause of acute spontaneous urticaria in children. A figure of 48.4% incidence in 953 acute urticaria cases has been reported [(41)]. It is also very common in children that new episodes of infection are accompanied by reappearance or aggravation of urticaria symptoms, causing chronic spontaneous urticaria[(5)]. With age the prevalence of infection as the cause of urticaria decreased [(41)]. The most frequent etiologies were upper respiratory tract infections. A variety of viruses are suspected, including adenovirus, enterovirus, rotavirus, respiratory syncytial virus and others [(42)]. However, only the role of herpesvirus infections as triggers of acute urticaria in children was confirmed in clinical studies [(43)]. The link of chronic urticaria to herpes virus infection is less evident. There are case reports, describing the disappearance of urticaria lesions after antiviral therapy in adult patients [(44)]. Recent data also suggest that HHV-6 and other human herpesviruses could play a role as cofactors in chronic urticaria. [(45)] The link between hepatitis virus infections and episodes of acute and chronic urticaria has been confirmed and is the most frequently reported association in adults, but not in children [(46) (47)].

The association with Mycoplasma pneumoniae is frequent, especially in children with acute urticaria [(48) (49)]. Chlamydia pneumonia is less often reported as cause of acute, recurrent and chronic urticaria [(50)].

Streptococcus spp. upper respiratory tract and urinary infections are associated with different types of urticaria [(46)]. In a study in 1980, beta-hemolytic streptococcal infection was determined in 13 of 32 children with acute urticaria. Infection was not always clinically apparent. All the patients recovered from urticaria after antibiotic therapy [(51)].

Prevalence of nasal S.aureus carriage in children with chronic urticaria is higher than in healthy controls [(52)]. Only in one third of cases, antibiotic therapy leads to complete resolution of skin symptoms. A small amount of patients showed only partial improvement, indicating that S.aureus can be a trigger and aggravating factor [(46)].

The association of different types of urticaria with parasitic infections (Blastocystis hominis, Giardia lamblia, Fasciola hepatica, Toxocara canis, Echinococcus granulosus, Strongyloides Stercoralis, Hymenolepis nana, Ascaris lumbricoides, Anisakis simplex, Cimexlectularis, Argas reflexus) has been determined for many decades. Reports of frequency among children with chronic urticaria range from 1% to 3,5% [(40)]. This cause is not believed to be of great significance in Western countries but may play a role in endemic regions. Parasitic infection (strongyloides, toxocara, and filaria) can also be a cause of isolated angioedema [(53)]. Currently the most attention is paid to Anisakis simplex. People become infected with this nematode by consuming raw seafood.

Helicobacter pylori infection is the most frequently mentioned bacterial infection in the context of chronic urticaria, although its role still remains controversial [(54) (46)]. The frequency of active H. pylori infection in children with chronic urticaria is lower than in adults and varies, according to different references, from 2 to 18% [(50) (55)]. It is believed that H. pylori has an indirect effect on the course of chronic urticaria, reducing immunological tolerance and stimulating the production of autoantibodies, including autoantibodies to FcεRIα [(56)]. Nevertheless, successful eradication of H. pylori infection does not guarantee the recovery from chronic urticaria [(50) (55)].

The relationship of urticaria with oral cavity infections is not clearly understood. There are observations of a transient urticaria accompanied by fever after dental treatments, which is associated with bacteriaemia and/or toxinemia, inducing the development of urticaria along immune and non-immune mechanisms. The release of histamine by mast cells in response to lipopolysaccharides of gram-negative oral flora (Veilonella sp.) is the main factor of urticaria exacerbations in patients with odontogenic infections. In addition, bacterial anaphylotoxins have direct vasodilatory effect [(57)]. It is recommended to assess the condition of the oral cavity in patients with chronic urticaria.

Inducible urticaria (CindU)

This is a subgroup with 2 different subtypes:

physical urticaria is a heterogeneous group of disorders where wheals are induced by physical stimuli: cold, heat, pressure, vibration, ultraviolet rays. It is one of the leading causes of chronic urticaria both in children and adults [(40)]. Patients may suffer from several subtypes of urticaria simultaneously. Cold-induced urticaria deserves particular attention in view of its potential danger. According to some report, at the time of diagnosis, half of the patients have had a history of severe anaphylactic reactions [(58)]. Trigger factors include cold objects, air and fluids. A figure of 8.5% incidence in 226 children has been reported [(34)]. Cold-induced urticaria is classified as primary (of unknown etiology) and secondary, associated with viruses, helminthic or bacterial infections, cryoglobulinemia and autoimmune disorders. In pediatric populations, secondary forms of cold-induced urticaria associated with herpesvirus infections prevail [(59)]. Delayed pressure urticaria is uncommon in children. Solar urticaria can also be rarely seen [(40)].

Diagnosis of physical urticaria should be confirmed by special tests [(60)]. When the diagnosis is confirmed, contact with triggers should be avoided: in case of symptomatic dermographism, patients should not wear tight clothes, in case of cold-induced urticaria it is contraindicated to drink cold liquids, eat ice-cream, dive and swim in water.

Nonphysical types of urticaria include cholinergic, aquagenic and contact urticaria. Cholinergic urticaria is rarely observed in small children, but becomes more common in adolescents. The frequency of cholinergic urticaria among 226 children with chronic urticaria was 2.7% [(34)]. It is characterized by the appearance of small pruritic wheals, less than 5 mm in diameter. These emerge a few minutes after core body temperature elevation, which can be passive (hot baths or showers, emotional stress) or active (physical exercise) [(5), (54)]. Aquagenic urticaria, where the appearance of wheals does not depend on water temperature, is very rare in children. Immunologic contact urticaria is a manifestation of immediate type reaction to proteins and chemical agents, often to latex. The appearance of wheals in the perioral area is a common manifestation of food allergies and cross-reactivity (pollen-fruit syndrome). Contact urticaria may cause systemic, life-threatening reactions [(61)].

Differential diagnoses

Exercise induced urticaria is now classified as a subgroup of anaphylaxis. The reaction develops mostly within the first 30 minutes of physical exercise. It is manifested as skin lesions, which rapidly progress to systemic symptoms, such as headache, dizziness, abdominal cramps, wheezing, decrease of blood pressure and syncope. Young adults and teenagers are at greater risk for systemic manifestations. In some cases, anaphylaxis develops only when certain foods are consumed up to 6 hours before exercise. The most common culprit is wheat, less frequently caused by seafood, fish, nuts, milk, eggs, vegetables, and fresh fruits, especially peaches It has been reported that a frequent detection of IgE to peach lipid transfer protein is found in such patients. [(62)]. IgE-dependent hypersensitivity underlies systemic reactions, however, isolated food consumption, which is not followed by physical exercise, does not lead to allergic reactions. Diagnostic algorithms include performing provocative tests individually with suspected food products, with physical exercises and together – when the food is consumed before exercises. Sensitivity of the test is only 70%, while the risk of adverse effects is high. Detection of specific IgE to omega-5-gliadin allows the avoidance of provocative tests if the trigger factor is wheat [(63)]. Patients are recommended not to consume causative foods up to 6 hours prior to physical activity. The patients should not be allowed to eat 3-5 hours before sport activities.

It is possible that autoinflammatory syndromes receive the differential diagnosis of urticaria. Conversely, in contrast to urticaria, urticarial syndromes may present with skin lesions other than wheals, such as papules, necrosis, vesicles, and hemorrhages. Lesions may be bilateral and symmetrical in appearance; individual lesions last longer, and their disappearance can leave marks, like hyperpigmentation or bruising. Other symptoms may also present such as fever, asthenia, and arthralgia. Systematic symptoms such as these are never seen in urticaria. [(64)]

Management of urticaria

The goal is: Treat the disease until it is gone. Treatment of urticaria is not very complicated as it is limited to prescription of second generation antihistamines in any type of subgroup. However, in some cases the use of standard doses of second generation AH does not control symptoms and more effective treatment options are needed.

Currently, physicians use the 2016 revision of WHO international guidelines for the diagnosis and treatment of urticaria [(2) (65)]. Also in use in Russia are clinical recommendations issued by the Russian Association of Allergologists and Clinical Immunologists (RAACI) and The Union of Pediatricians of Russia [(1), (66)]

Besides second generation antihistamines, elimination of revealed trigger factors is one of the main aspects of urticaria treatment. Sometimes individual pseudoallergen-reduced or low-histamin diets can be recommended for at least 3 weeks with a careful assessment of symptoms thereafter, and reintroduction of eliminated foods in case of inefficiency. It may also be necessary to discontinue regular or sporadic intake of NSAR. Paracetamol is allowed. In the case of dermographic and pressure-induced urticaria, tight clothing should be limited. To reduce itching and burning sensations it is discussed and sometimes helpful to prescribe topical creams and lotions with a cooling effect as a comedication with second generation antihistamines. The use of local anti-inflammatory drugs is not recommended.

In many countries there are no recommendations for urticaria treatments adapted to children. According to the latest international WHO guidelines, local expert committees are responsible for the prescription of increased weight-adapted doses second generation antihistamines in children.

In the 2017 documents regarding the treatment of chronic urticaria, experts recommend a four-step therapeutic approach. Standard doses of second generation antihistamines are used in the first line of treatment, and if they are not efficient during the first two weeks, a second line of treatment is attempted, upon which the dose of second generation antihistamines is increased 2-4 fold (weight adapted) in comparison to the therapeutic approach. Insufficient disease control during the first 2-4 weeks requires a third line of therapeutic treatment, which includes the add on prescription of anti-IgE therapy (approved therapy, ≥12 years age, otherwise off-label) in patients with CSU or combined CSU and CindU. A fourth line is attempted only if omalizumab does not work after 3-6 cycles,, other immunomodulating therapies like cyclosporine A (CsA) (off-label) should be considered. In severe cases short courses of corticosteroids can be used (0,5-1 mg/kg body weight (<1week) (fig.1) [(67)]

Prescription of high doses of second generation antihistamines and CsA requires patient-informed consent and approval by hospital administration, as these therapeutic approaches in children still remain off-label. Treatment of chronic urticaria with cyclosporin A should not last more than 3 months. Clinical effects develop early and should be noticed during the first week of therapy [(68), (69)].

The third step of treatment includes anti-IgE therapy in CU. The efficiency and safety of this method of chronic spontaneous and inducible urticaria treatment has been proven by numerous studies. It is permitted for children above the age of ≥ 12, and it follows the guidelines adopted for adults [(1)]. Latest data demonstrate a positive effect of anti-IgE therapy in children [(70), (71)]. In the previous RAACI and international WHO guidelines,

prescription of CsA or anti-IgE therapy was recommended as a third line of treatment. After increasing the dose of antihistamines, it was suggested to change second generation antihistamines at first or add LTRAs to the therapy. [(72; 60), (73)]. In a number of countries, the four-line urticaria guidelines are in use too [(74)]. It is also recommended to try anxiolytics and antidepressant medication in rare cases (but not in children) (Fig. 2) pointing out that stress factors may aggravate urticaria symptoms. Reduction of chronic stress with medication and psychoanalytic therapy may result in the improvement of the patient's health [(75), (76)].

The prognosis of urticaria is good. In most cases, acute urticaria is the only episode in a patient's life. It is considered that chronic urticaria in children has a more favorable outcome than in adults [(77)]. According to the results of the studies performed to identify the natural course of chronic urticaria in pediatric population, remission rates after one, three and five years from the onset of symptoms were 16.5-37%, 36-54% and 50-67,5%, respectively [(78) (79) (55) (77)]. After seven years, 96% of children were urticaria free, as compared to adults of whom at least 20% remain symptomatic after 10 years [(80)]. No clear predictors of disease remission were established based on demographic data and abnormal investigations [(77)]. [(81)]. Although, regression was more likely to occur quickly in children with low urticaria activity score values controlled by standard doses of antihistamines. [(16)] Therapeutic approaches are currently available which allow physicians to control the course of the disease and to improve quality of life.

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Literature:

1. **Federal Clinical Guidelines on the Diagnostics and Treatment of Urticaria, RAACI,2015. Russian Allergology Journal.2016; 1:10-21.**

2. **Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, et al. The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. Allergy.2014; 69:868-87.**

3. **Caproni M., Giomi B., Volpi W. et al. Chronic idiopathic urticaria: infiltrating cells and related cytokines in autologous serum-induced wheals. Clin Immunol.2005; 114 (3):284–292.**

4. **Lee SJ, Ha EK, Jee HM, et al. Prevalence and risk factors of urticaria with a focus on chronic urticaria in children. Allergy Asthma Immunol Res. 2017; 9(3):212-219.**

5. **Church M.K., Weller R., Stock P., Maurer M. Chronic spontaneous urticaria in children: itching for insight. Pediatr Allergy Immunol. 2011 ;22:1-8.**

6. **Maurer M, Church MK, Weller K. Chronic Urticaria in Children: Still Itching for Insight. JAMA Dermatol. 2017 Sep 27. doi: 10.1001/jamadermatol.2017.3183. [Epub ahead of print].**

7. **Ferrer M. Epidemiology, healthcare, resources, use and clinical features of different types of urticaria. Alergologica 2005. J Investig Allergol Clin Immunol 2009; 19:21–6.**

8. **Grattan C. E. H., Autoimmune urticaria. Immunol Allergy Clin North Am.2004;24(2):163–81.**

9. **Frossi B., Gri G., Tripodo C., Pucillo C.. Exploring a regulatory role for mast cells: MCregs? Trends in Immunol.2010;31(3):97–102.**

10. **Smith C. H., Kepley C., Schwartz L. B., and Lee T.H.. Mast cell number and phenotype in chronic idiopathic urticaria. Journal of Allergy and Clin Immunol.1995; 96(3):360–4.**

11. **Cugno M, Marzano AV, Asero R, Tedeschi A. Activation of blood coagulation in chronic urticaria: pathophysiological and clinical implications.Intern Emerg Med. 2010; 5:97-101.**

12. **Asero R, Tedeschi A, Riboldi P, Griffini S, Bonanni E, Cugno M.Severe chronic urticaria is associated with elevated plasma levels of D-dimer. Allergy. 2008;63:176-80.**

13. **Takahagi S, Mihara S, Iwamoto K, Morioke S, Okabe T, Kameyoshi Y, et al. Coagulation/fibrinolysis and inflammation markers are associated with disease activity in patients with chronic urticaria. Allergy. 2010; 65:649-56.**

14. **Nishimura K, Kuzume K, Kagata Y. Arerugi. Coagulation in children with urticaria]. 2016 Mar;65(2):118-22. doi: 10.15036/arerugi.65.118.,**

15. **Criado P.R., Maruta C.W., Criado R.F.J., Silva dos Reis V.M. Chronic urticarial in adults: state-of-art in the new millennium. An Bras Dermatol. 2015;90 (1) :74-89.**

16. **Arik Yilmaz E, Karaatmaca B, Cetinkaya PG, Soyer O, Sekerel BE, Sahiner UM. The persistence of chronic spontaneous urticaria in childhood is associated with the urticaria activity score. Allergy Asthma Proc. 2017;38(2):136-42.**

17. **Konstantinou G. N., Asero R. , Ferrer M. , Knol E. F., Maurer M. ,Raap U. , Schmid-Grendelmeier P. , Skov P. S., . Grattan C. E. H. EAACI taskforce position paper: evidence for autoimmune urticaria and proposal for defining diagnostic criteria. Allergy.2013 Jan;68(1):27-36.**

18. **Jain S., Pathogenesis of chronic urticaria: an overview. Dermatol Res Pract. 2014; 2014:674-709.**

19. **Jirapongsananuruk O, Pongpreuksa S, Sangacharoenkit P, Visitsunthorn N, Vichyanond P. Identification of the etiologies of chronic urticaria in children: A prospective study of 94 patients. Pediatr. Allergy Immunol. 2010; 21:508–14.**

20. **Netchiporouk E, Moreau L, Rahme E, Maurer M, Lejtenyi D, Ben-Shoshan M. Positive CD63 basophil activation tests are common in children with chronic spontaneous urticaria and linked to high disease activity. Int Arch Allergy Immunol. 2016; 171(2):81-8.**

21. **Netchiporouk E, Sasseville D, Moreau L, Habel Y, Rahme E, Ben-Shoshan M. Evaluating comorbidities, natural history, and predictors of early resolution in a cohort of children with chronic urticaria. JAMA Dermatol.doi:10.1001/jamadermatol.2017.3182.**

22. **Fraser K, Robertson L. Chronic urticaria and autoimmunity. Skin Therapy Lett. 2013 Nov-Dec; 18(7):5-9.**

23. **Pedullà M, Fierro V, Marzuillo P, Capuano F, Miraglia Del Giudice E, Ruocco E. Skin disease and thyroid autoimmunity in atopic South Italian children. World J Clin Pediatr. 2016 Aug 8; 5(3):288-92.**

24. **Kilic G, Guler N, Suleyman A, Tamay Z. Chronic urticaria and autoimmunity in children. Pediatr Allergy Immunol. 2010 Aug;21(5):837-42.**

25. **Ferriani MP, Silva MF, Pereira RM, Terreri MT, Saad Magalhães C, Bonfá E, Pastorino AC, Carolina Dos Santos M, Appenzeller S, Ferriani VP, Len CA, Sallum AM, Libório J, Monteiro de Castro TC, Silva CA. Chronic Spontaneous Urticaria: A Survey of 852 Case. Int Arch Allergy Immunol. 2015;167:186–192.**

26. **Spadoni M, Jacob C, Aikawa N, Jesus A, Fomin A, Silva C: Chronic autoimmune urticaria as the first manifestation of juvenile systemic lupus erythematosus. Lupus 2011;20: 763–6.**

27. **Aikawa NE, Jesus AA, Liphaus BL, Silva CA, Carneiro-Sampaio M, Viana VS, Sallum AM. Organ-specific autoantibodies and autoimmuneautoimmune diseases in juvenile systemic lupus erythematosus and juvenile dermatomyositis patients. Clin Exp Rheumatol 2012;30(1):126-131.**

28. **Caminiti L., Passalacqua G., Magazzu G. Chronic urticaria and associated coeliac disease in children: a case control study. Pediatr Allergy Immunol 2005; 16: 428-32.**

29. **Chung BY, Cho YS, Kim HO, Park CW. Food Allergy in Korean Patients with Chronic Urticaria. Ann Dermatol. 2016 Oct;28(5):562-8.**

30. **Lessof MH, Gant V, Hinuma K, Murphy GM, Dowling RH. Recurrent urticaria and reduced diamine oxidase activity. Clin Exp Allergy. 1990;20:373-6.**

31. **Maintz L, Novak N. Histamine and histamine intolerance. Am J Clin Nutr.2007; 85:1185-96.**

32. **Di Lorenzo G, Pacor ML, Mansueto P, Martinelli N, Esposito-Pellitteri M, Lo Bianco C. Food-additive-induced urticaria: a survey of 838 patients with recurrent chronic idiopathic urticaria. Int Arch Allergy Immunol. 2005;138:235-42.**

33. **Kauppinen K, Juntunen K, Lanki H. Urticaria in children. Allergy 1984;39: 469–72.**

34. **Volonakis M, Katsarou-Katsari A, Stratigos J. Ethiologic factors in childhood chronic urticaria. Ann Allergy 1992;69: 61–5..**

35. **Ehlers I, Niggemann B, Binder C, Zuberbier T. Role of nonallergic hypersensitivity reactions in children with chronic urticaria. Allergy 1998 ; 53;1074–1077.**

36. **Zuberbier T, Chantraine-Hess S, Hartmann K, Czarnetzki BM. Pseudoallergen-free diet in the treatment of chronic urticaria. A prospective study. Acta Derm Venereol 1995;75: 484-7**

37. **Magerl M, Pisarevskaja D, Scheufele R, Zuberbier T, Maurer M. Effects of a pseudoallergen-free diet on chronic spontaneous urticaria: a prospective trial. Allergy 2010; 65:78-83.**

38. **Wagner N, Dirk D, Peveling-Oberhag A, Reese I, Rady-Pizarro U, Mitzel H, Staubach P. A Popular myth - low-histamine diet improves chronic spontaneous urticaria - fact or fiction? J Eur Acad Dermatol Venereol. 2016 Sep 13. doi: 10.1111/jdv.13966.**

39. **Siebenhaar F, Melde A, Magerl M, Zuberbier T, Church MK, Maurer M. Histamine intolerance in patients with chronic spontaneous urticaria. J Eur Acad Dermatol Venereol. 2016 Oct;30(10):1774-7.**

40. **Caffarelli C, Cuomo B, Cardinale F, Barberi S, Dascola CP, Agostinis F, Franceschini F, Bernardini R. Aetiological factors associated with chronic urticaria in children: a systematic review. Acta Derm Venereol. 2013 May;93(3):268-72.**

41. **Liu TH, Lin YR, Yang KC, Chou CC, Chang YJ, Wu HP: First attack of acute urticaria in pediatric emergency department. Pediatr neonatol 2008; 49:58-64.**

42. **Wedi B, Raap U, Wieczorek D, Kapp A. Urticaria and infections. Allergy Asthma Clin Immunol 2009; 5(1);10.10.doi:10.1186/1710-1492-5-10.**

43. **Mareri A, Adler SP, and Nigro G. Herpesvirus-associated acute urticaria: An age matched case-control study. PLoS One 2013: 8(12):e85378.doi:10.1371/jornal.pone.0085378.eCollection. 2013.**

44. **Imbalzano E, Casciaro M, Quartuccio S, Minciullo PL, Cascio A, Calapai G, Gangemi S. Association between urticaria and virus infections: A systematic review. Allergy Asthma Proc. 2016 Jan-Feb; 37(1):18-22.**

45. **Feb, Dreyfus DH. Serological evidence that activation of ubiquitous human herpesvirus-6 (HHV-6) plays a role in chronic idiopathic/spontaneous urticaria (CIU). Clin Exp Immunol. 2016;183(2):230-8.**

46. **Minciullo PL, Cascio A, Barberi G, and Gangemi S. Urticaria and bacterial infections. Allergy Asthma Proc 2014;35:295–302.**

47. **Vaida GA, Goldman MA, Bloch KJ. Testing for hepatitis B virus in patients with chronic urticaria and angioedema. J Allergy Clin Immunol. 1983;72:193-8.**

48. **Wu CC, Kuo HC, Yu HR, et al. Association of acute urticaria with Mycoplasma pneumoniae infection in hospitalized children. Ann Allergy Asthma Immunol , 2009;103:134 –9.**

49. **Timitilli A, Di Rocco M, Nattero G, et al. Unusual manifestations of infections due to Mycoplasma pneumoniae in children. Infez Med 2004;12:113–7,.**

50. **Sackesen C, Sekerel BE, Orhan F, et al. The etiology of different forms of urticaria in childhood. Pediatr Dermatol, 2004; 21:102–8**.

51. **Schuller DE, and Elvey SM. Acute urticaria associated with streptococcal infection. Pediatrics 1980;65:592–6.**

52. **Ertam I, Biyikli SE, Yazkan FA, et al. The frequency of nasal carriage in chronic urticaria patients. J Eur Acad Dermatol Venereol 2007;21:777–80.**

53. **Krishnamurthy A, Naguwa SM, Gershwin ME: Pediatric angioedema. Clin Rev Allergy Immunol 2008;34:250-9.**

54. **Pite H., Wedi B., Borrego L.M., Kapp A., Raap U. Management of childhood urticaria: current knowledge and practical recommendations. Acta Derm Venereol. 2013;93: 500-8.**

55. **Sahiner UM, Civelek E, Tuncer A, Yavuz ST, Karabulut E, Sackesen C. Chronic urticaria: etiology and natural course in children. Int Arch Allergy Immunol 2011;156: 224–30.**

56. **Greaves MW., Chronic idiopathic urticaria and H pylori: not directly causative but could there be a link? ACI Int. 2001;13:23-6.**

57. **Goga D, Vaillant L, Pandraud L, Mateu J, Ballon G, Beutter P. The elimination of dental and sinusal infectious foci in dermatologic pathology. A double-blind study in 27 cases confined to chronic urticaria. Rev Stomatol Chir Maxillofac.1988; 89:273-5.**

58. **Siebenhaar F, Weller K, Mlynek A, et al. Acquired cold urticaria: clinical picture and update on diagnosis and treatment. Clin Exp Dermatol 2007; 32(3):241-5.**

59. **Morais-Almeida M, Marinho S, Gaspar A, Arêde C, Loureiro V, Rosado-Pinto J. Cold urticaria and infectious mononucleosis in children. Allergol Immunopathol (Madr). 2004 Nov-Dec;32(6):368-71.**

60. **Magerl M, Altrichter S, Borzova E, Giménez-Arnau A, Grattan CE, Lawlor F, Mathelier-Fusade P, Meshkova RY, Zuberbier T, Metz M, Maurer M. The definition, diagnostic testing, and management of chronic inducible urticarias - The EAACI/GA(2) LEN/EDF/UNEV. Consensus recommendations 2016 update and revision. Allergy. 2016 Jun;71(6):780-802.**

61. **Gimenez-Arnau A, Maurer M, De La Cuadra J, Maibach H. Immediate contact skin reactions, an update of Contact Urticaria, Contact Urticaria Syndrome and Protein Contact Dermatitis -- "A Never Ending Story". Eur J Dermatol. 2010 Sep-Oct;20(5):552-62.**

62. **Romano A, Scala E, Rumi G, Gaeta F, Caruso C et all. Lipid transfer proteins: the most frequent sensitizer in Italian subjects with food-dependent exercise-induced anaphylaxis. Clin Exp Allergy. 2012 Nov;42(11):1643-53. doi:10.1111/cea.12011.**

63. **Matsuo H, Dahlstrom J, Tanaka A, Kohno K, Takahashi H, Furumura M, et al. Sensitivity and specificity of recombinant omega–5 gliadin-specific IgE measurement for the diagnosis of wheat-dependent exercise-induced anaphylaxis. Allergy 2008;63:233–236.**

64. **Peroni A, Colato C, Zanoni G, Girolomoni G.Urticarial lesions: if not urticaria, what else? The differential diagnosis of urticaria: part II. Systemic diseases. J Am Acad Dermatol. 2010 Apr;62(4):557-70.doi: 10.1016/j.jaad.2009.11.687., quiz 571-2.**

65. **Maurer M., Magerl M., Metz M., Zuberbier T. Revisions of the international guidelines on the diagnosis and therapy of chronic urticarial J.Dtsch.Dermatol.Ges.2013:11(10): 971-7.**

66. **Federal Clinical Guidelines on the medical assistance to children with urticaria, RAACI, The Union of Pediatricians of Russia, 2016. http://www.pediatr-russia.ru/sites/default/files/file/kr_krap.pdf**

67. **Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B et al. The EAACI/GA²LEN/EDF/WAO Guideline for the Definition, Classification, Diagnosis and Management of Urticaria. The 2017Revision and Update., Allergy. 2018 Jan 15: doi: 10.111/. Vol. all.13397.**

68. **Doshi DR, Weinberger MM. Experience with cyclosporine in children with chronic idiopathic urticaria. Pediatr Dermatol. 2009;26:409–13.**

69. **Neverman L, Weinberger M. Treatment of chronic urticaria in children with antihistamines and cyclosporine. J Allergy Clin Immunol Pract. 2014 Jul-Aug; 2(4):434-8.**

70. **Maurer M., Church M.K., Gonçalo M., Sussman G., Sánchez-Borges M.. Management and treatment of chronic urticarial.J.Eur.Acad.Dermatol.Venereol. 2015;29 (3):16–32.**

71. **Maurer M, Metz M, Brehler R, Hillen U, Jakob T, Mahler V, Pföhler C, Staubach P, Treudler R, Wedi B, Magerl M. Omalizumab treatment in patients with chronic inducible urticaria: A systematic review of published evidence. J Allergy Clin Immunol. 2017 Jul 2. Vols. pii: S0091-6749(17)31163-6. doi: 10.1016/j.jaci.2017.06.032. .**

72. **Zuberbier T, Asero R, Bindslev-Jensen C, Walter Canonica G, Church MK et all.Dermatology Section of the European Academy of Allergology and Clinical Immunology, et al. Organization. EAACI/GA(2)LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. Allergy. 2009;64(10):1417-26.**

73. **Federal Clinical Guidelines on the Diagnostics and Treatment of Urticaria. Russia, Moscow. RAACI, 2018. http://nrcii.ru/docs/5.urticaria.pdf**

74. **Ferrante G, Scavone V, Muscia MC, Adrignola E, Corsello G, Passalacqua G, La Grutta S. The care pathway for children with urticaria, angioedema, mastocytosis. World Allergy Organ J. 2015 Feb 2 ; 8(1):5.**

75. **Bernstein JA, Lang DM, Khan DA, Craig T, Dreyfus D et all. The diagnosis and management of acute and chronic urticaria: 2014 update. J Allergy Clin Immunol. 2014 May;133(5):1270-7.**

76. **Choi SH, Baek HS. Approaches to the diagnosis and management of chronic urticaria in children. Korean J Pediatr. 2015 May; 58(5):159-64.**

77. **Chansakulporn S, Pongpreuksa S, Sangacharoenkit P, PacharnP, Visitsunthorn N, Vichyanond P, et al. The natural history ofchronic urticaria in childhood: a prospective study. J Am AcadDermatol. 2014 ;71:663-8.**

78. **Harris A, Twarog FJ, Geha RS. Chronic urticaria in childhood: natural course and etiology. Ann Allergy 1983;51:161-5.**

79. **Du Toit G, Prescott R, Lawrence P, Johar A, Brown G, Weinberg EG, et al. Autoantibodies to the high-affinity IgE receptor in children with chronic urticaria. Ann Allergy Asthma Immunol 2006;96:341-4.**

80. **Powell RJ, Leech SC, Till S, Huber PA, Nasser SM, Clark AT, Mar, British Society for Allergy and Clinical Immunology. BSACI guideline for the management of chronic urticaria and angioedema. Clin Exp Allergy. 2015;45(3):547-65.**

81. **Yologlu N, Baydemir C, Aydogan Eser I M. The predictive factors for remission of chronic spontaneous urticaria in childhood: Outcome from a prospective study. Allergol Immunopathol (Madr). 2016 Jul 28. pii: S0301-0546(16)30073-8. doi: 10.1016/j.aller.2016.**

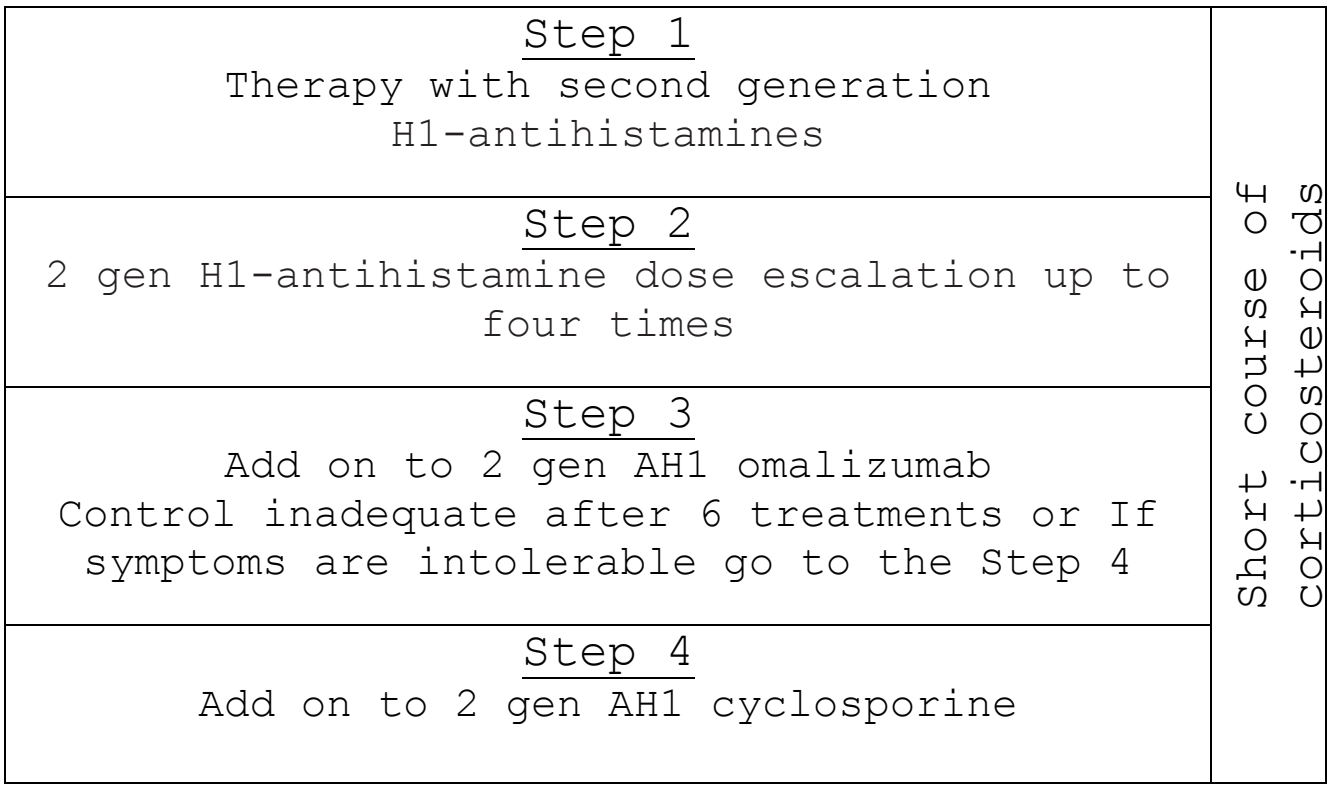

Figure 1. Latest recommended chronic urticaria therapy approach (Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B et al. The EAACI/GA^{2}LEN/EDF/WAO Guideline for the Definition, Classification, Diagnosis and Management of Urticaria. The 2017Revision and Update., Allergy. 2018 Jan 15: doi: 10.111/. Vol. all.13397.)

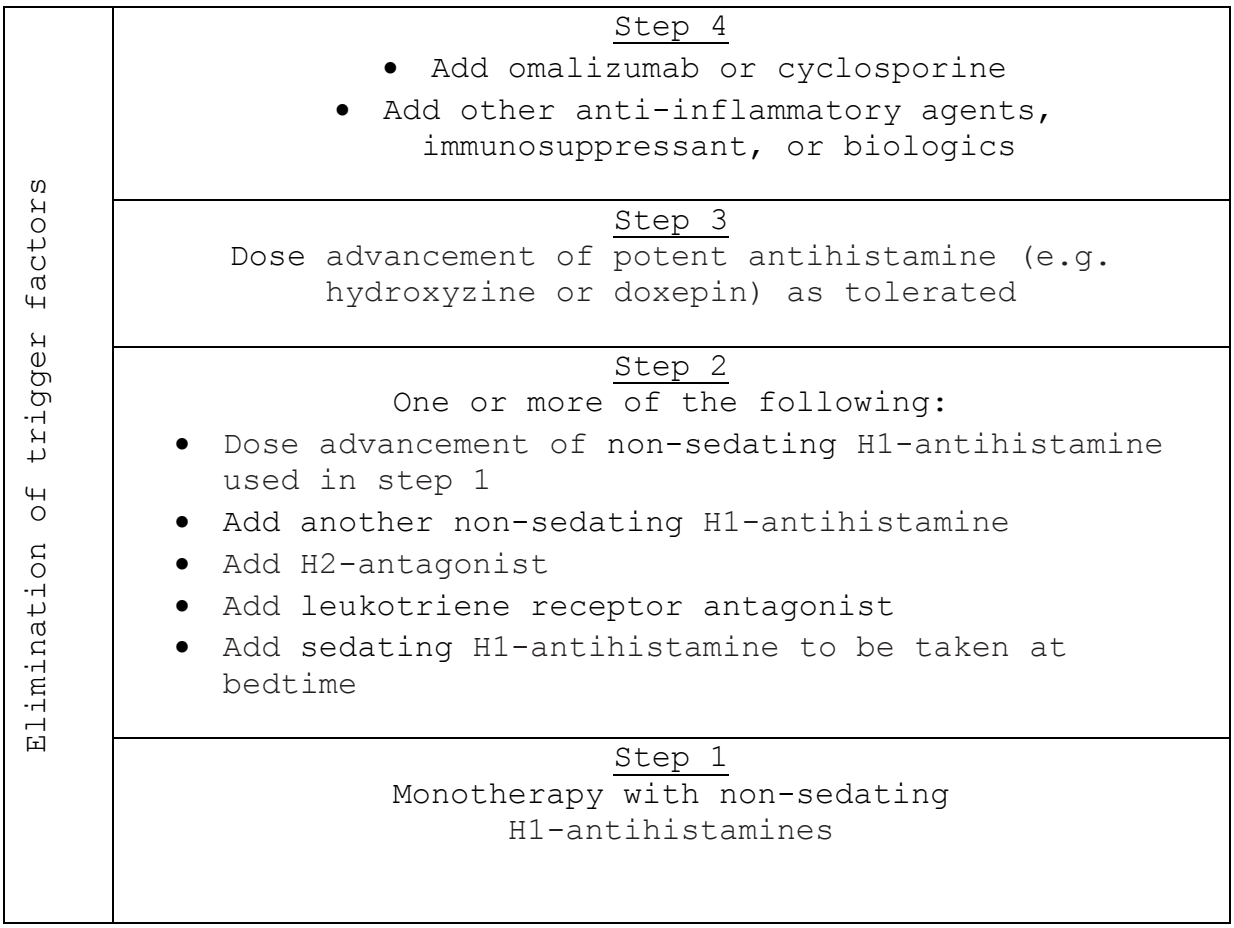

Figure 2. Recommended chronic urticaria therapy approach
(Adapted from Bernstein JA, Lang DM, Khan DA, Craig T et all. The diagnosis and management of acute and chronic urticaria: 2014 update. J Allergy Clin Immunol. 2014;133(5):1270-1277.)