



## Chronic urticaria in children: Etiologies, Clinical Manifestations, Diagnosis and Treatment

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### ABSTRACT

Chronic urticaria is defined as a skin disease with central induration (wheal) and erythema formation around it (flare) that appears at least twice a week and remains at least for 6 weeks continually. The incidence of urticaria in children is about 0.1-3%. Most cases of chronic urticaria occur in children between 6-11 years. Autoimmune and allergy immaturity is one of the reasons of lower incidence of chronic urticaria in younger children.

Quality of life impairment in children with urticaria has been known to be similar to diseases with severe atopic dermatitis, epilepsy, diabetes mellitus and asthma.

There are several causes for chronic urticaria in children in different reports. In most of cases the known etiologic agents are varies from 21 to 83%. Overall, infectious causes of chronic urticaria in children are more common and obvious than other in adults. In most cases, the cause of chronic urticaria are idiopathic or autoimmune. Urticaria severity divided to mild, moderate and severe was based on the number of wheals and severity of pruritus. Diagnosis of chronic urticaria is based on a good history and physical examination. The treatment of chronic urticaria is a patient education that is to remove the triggering and aggravating agents, resolving and treating of the known disease and the use of various medicines based on the history and clinical findings. The first medical therapeutics lines in children are anti-histamines, beta-blocker H1 and new generation of non-sedating agents.

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## Introduction

Chronic urticaria is defined as a skin disease with central induration (wheal) and erythema formation around it (flare) that appears at least twice a week and remains at least for 6 weeks continually. It may be associated with angioedema.<sup>1, 2</sup> The incidence of urticaria in children is about 0.1-3% and mainly being lower than in adults.<sup>3, 4</sup> Also, the incidences of both acute and chronic urticaria in the UK, Germany and Denmark are 3.4%, 4.4% and 5.5% , respectively.<sup>5-7</sup> The incidence of urticaria is 13% in Thailand.<sup>8</sup> In another report, urticaria merely was seen in 78.4%, angioedema 6.6% and angioedema associated with urticaria observed in 15% of children with chronic urticaria.<sup>9</sup> Most cases of chronic urticaria occur in children between 6-11 years. Autoimmune and allergy immaturity is one of the reasons of lower incidence of chronic urticaria in younger children. With increasing age, environmental factors stimulate the immune system more. Generally, chronic urticaria is more common among adult's women between ages 20-50 years old.

The relatively high cost of diagnosis and treatment of chronic urticaria has a considerable non-favourable effect on the patients' quality of life and their families. Quality of life impairment in children with urticaria has been known to be similar to diseases with severe atopic dermatitis, epilepsy, diabetes and asthma.<sup>10</sup> Since there are a few studies regarding chronic urticaria in children, in this study, we aimed to review the incidence, cause, symptoms and treatment of chronic urticaria in children.

## Etiologies

There are several causes for chronic urticaria in children in different reports. In most of cases the known etiologic agents are varies from 21 to 83%<sup>9, 11-13</sup> but in another study 65% of the etiology of chronic urticaria is found.<sup>13</sup> Overall,

infectious causes of chronic urticaria in children are more common and obvious than other in adults.<sup>12, 14</sup> In most cases, the cause of chronic urticaria are idiopathic or autoimmune (Tables 1 and 2).<sup>15, 16</sup>

## Infections

Acute infections can play a role in the production and exacerbation of the urticaria. Recurrent upper respiratory tract infections, pharyngitis, tonsillitis, sinusitis and otitis are often due to staphylococci and streptococci are associated with chronic urticaria that have been treated by proper therapeutic approach.<sup>17,18</sup> In another study, urinary tract infection (UTI), at the first rank and then Chlamydia pneumonia and Helicobacter pylori are associated with urticaria in children.<sup>12</sup> Also, infection has been reported to be associated with 7% cause of chronic urticaria and the symptoms are recovered through an appropriate treatment.<sup>13</sup> Further studies have shown that infection is the etiology of 13% disease.<sup>9</sup> Sackesen et al. reported that infections are the third common cause of chronic urticaria in children.<sup>12</sup> Du Toit et al. found a positive stool culture for *Ascaris lumbricoides*, but serum IgE specific against the parasite was positive in 29% of the cases.<sup>19</sup> In a study, parasite infections were reported to be a rare etiology of chronic urticaria in children and there was no significant difference between those patients who received metronidazole compared with untreated patients.<sup>20</sup> Many other researchers do not believe a relationship between chronic infections or parasites infections and chronic urticaria in children.<sup>5, 19, 21, 22</sup>

Kilic, in a study on 200 children with idiopathic chronic urticaria showed that IgG antibody was positive against *Helicobacter pylori* (HP) in 6 (30%) of the patients. The correlation between HP and urticaria remains unknown but it may play a role by inducing IgE production or

developing gastrointestinal inflammation and more absorption of antigen that cause severity of urticaria.<sup>23</sup> Although, other studies have shown that there might be a relation between parasite and chronic urticaria, divesting of the urticaria by parasite is a controversy.<sup>24</sup> For this reason, the involvement of parasitic infections is necessary following eosinophilia or traveling to endemic regions.<sup>15</sup> In another investigation, all symptoms of urticaria disappeared following proper treatment of HP, but in conclusion, further studies are needed to clarify the relationship between urticaria and HP.<sup>25</sup> However, some studies confirmed the association between HP and children with chronic urticaria.<sup>26-28</sup> Furthermore, HP can cause severe chronic urticaria such as physical urticaria.<sup>29</sup> Other studies have rejected the relationship between chronic urticaria and HP.<sup>12, 30, 31</sup> Urinary tract infection (UTI) may play a role in the development and severity of chronic urticaria. In a study by Sackesen, 5.6% of boys and 7.4% of girls had UTI, but 71% were asymptomatic. Nevertheless, there are no strong reasons to prove that treatment of UTI can improve urticaria.<sup>12, 32, 33</sup> It seems the parasites seldom play a role in the development and severity of chronic urticaria. Other parasitic infections such as *Giardia lamblia*, *Blastocystis hominis*, *Dientamoeba fragilis*, *Toxocara canis*, and *Strongyloides stercoralis* could induce chronic urticaria. As a final point, the role of parasites in the development and prognosis of the disease is unclear.<sup>9, 20, 34, 35</sup> Oral infections, sinus abscesses, vaginal candidiasis and gastrointestinal candidiasis are seldom effective in chronic urticaria.<sup>15</sup>

### **Malignancy**

There are controversies data regarding the correlation between chronic urticaria and malignancy and their association is not clear.<sup>36-38</sup> The assessment of the relationship between the disease and malignancy is important based

on history and clinical examination, but there is no reason to perform a routine examination or screening for malignancy.

### **Food allergy and supplements**

Basically most of the physicians and families believed that food agents have an important role in the development and severity of chronic urticaria. Although the relationship between acute urticaria and food is known, however, the relation between chronic urticaria and food it remained unclear. Most of the patients have food intolerance than is an exact allergy. Food additives and preservatives have a further role in the severity of chronic urticaria symptoms (pseudo allergy).

In a report of 3-17 years old children, 75% of the causes of urticaria severity were due to food additives such as coloring agents, preservatives, monosodium glutamate and sweetener agents such as saccharine / cyclamate.<sup>39</sup>

Sometimes urticaria reaction occurs following consumption of food products (allergy), aeroallergens like birch tree sensitivity, because there is a cross-reactivity between foods especially fruits and vegetables and aeroallergens.<sup>40</sup> In a report by Kauppinen, food additives (21%), and food allergy (9%) are considered as the etiologic factors after physical urticaria (29%) in children.<sup>13</sup> In Volonakis's study, the known causes of chronic urticaria were reported in food allergy 28% and food additives 26%.<sup>9</sup> In another study on patients with chronic urticaria who did skin prick test, 35.1% were positive. History of food allergy was positive in 39.4% of these patients.<sup>20</sup> In Ghaffari et al.'s study, 15% had a positive skin prick test and mites were the most common allergen.<sup>41</sup>

### **Autoimmune**

The association between autoimmunity disorders and chronic urticaria is less common in children than adults. Chronic urticaria is associated with the diseases such as celiac

disease, diabetes type II, IBD, JRA and SLE.<sup>42</sup> The prevalence of autoimmune thyroiditis in children with chronic urticaria comparing with normal person has been reported to be 15-24% and 7-8%, respectively.<sup>42-45</sup> Mainly, the prevalence of thyroid autoimmune disease in children with chronic urticaria is less common than in adults. In a study<sup>46</sup>, 4.3% of children with chronic urticaria had positive anti- thyroid antibody that all of them were females and they suggested periodic evaluation of TSH and anti-thyroid antibody. Kilic et al. showed that anti-thyroid antibody was positive in 14.8% of children with chronic urticaria. The incidence of autoimmunity is increasing with age.<sup>47</sup> They also found angioedema and autologous serum skin test (ASST) was positive in 85.7% and 25.9% , respectively. As a whole, previous studies have shown that the antibody against FCεR1α was positive in 30-50% of children with chronic urticaria.<sup>19, 48, 49</sup> In Brunetti et al.'s study, children with chronic urticaria had positive serum autologous skin test in 44% and basophil histamine release test was positive in 40% of the subjects. The sensitivity and specificity of ASST test are 70% and 80%, respectively. These tests were positive in idiopathic cases or in known cases such as physical urticaria, infection urticaria or allergic urticaria.<sup>49</sup> In Du Toit's study, FCε R1α antibody tests were positive in 47% of cases. There was no relationship between serum autologous skin test and the disease improved.<sup>19</sup> The ASST test was positive in 41% of cases in Du Toit's study, 45% in Brunettei's and 38% of cases were positive in Godse's and Jirapengsanaruk's studies.<sup>19-20,49-50</sup> However, the sensitivity of histamine release test is lower than the sensitivity of the ASST test. There are several reports regarding the correlation between celiac disease and chronic urticaria. In Camiuti et al.'s research, celiac disease was shown in 5% of cases and 67% of

the control in children with chronic urticaria.<sup>51</sup> Since chronic urticaria has been improved following the removal of gluten from the diet, which suggests this association. Hyman reported a child with chronic urticaria who was afflicted with autoimmune thyroiditis and diabetes type 1.<sup>52</sup>

### **Vasculitis Urticaria**

Vasculitis urticaria constitutes less than 5% of all patients with urticaria.<sup>21</sup> In these cases, the patients are suffering from fever, arthralgia and increased ESR which is associated with urticaria lesions similar to petechial and pain more than itchiness. These lesions remained for more than 24 hours and improved by color changes.<sup>15</sup> The causes of the disease remain unknown. Systemic Lupus Erythematosus (SLE), juvenile rheumatoid arthritis (JRA), hepatitis B and C, paraproteinemia, non-steroid anti-inflammatory drugs (NSAIDs), penicillin, sulfonamides, EBV, sjogren disease, monoclonal gam apathy IgA and IgM, mixed cryoglobulinemia and malignancies suggest causes of chronic urticaria in children.<sup>53, 54</sup>

### **Periodical syndromes associated with cryoptrin**

Auto inflammatory diseases are due to CIAS-1 gene mutation. They are rare causes of chronic urticaria in children including: cold familial auto inflammatory syndrome, Meckel- Wels syndrome and multi-system inflammatory disorders with neonatal onset. There is dermal neutrophils infiltration in the skin biopsy of these patients.<sup>55</sup>

Aspirin and other NSAIDs inhibit cyclooxygenases and decrease prostaglandin D2 (PGD2), and prostaglandin E2 (PGE2) which play a role in the inhibition of mast cells release and increasing leukotriene C4 (Ltc4), leukotriene D4 (LtD4) and leukotriene E4 (LtE4) production that lead to inflammation and urticaria formation with effect on microvascular system.<sup>56</sup> Volonakis found that medicines are

included, 17% of etiologic factors of chronic urticaria.<sup>49</sup>

### Idiopathic chronic Urticaria

There are different reports about the chronic idiopathic urticaria in children. Brunitti has reported that 29% of chronic urticaria is due to idiopathic cause.<sup>49</sup> Sockesen et al. reported that 47% of chronic urticaria cases were idiopathic.<sup>12</sup> In another study, the most common cause of chronic urticaria was reported idiopathic.<sup>20</sup> Also, in a study by Harris, from 94 children with chronic urticaria, only 15 children had been known of the cause of the disease and the others had idiopathic etiology and the incidence of the disease was equal in both genders.<sup>57</sup> Volonakis found no etiologic factors in 75% of the studied children with idiopathic chronic urticaria.<sup>9</sup>

### Physical Urticaria

Based on previous knowledge, idiopathic chronic urticaria is the most common types of chronic urticaria.<sup>15</sup> But in cases with known etiologies, chronic urticaria is the most common form of the disease and reported up to 53% of all cases.<sup>12</sup> In Kauppinen's study, physical urticaria was the most common cause of the disease.<sup>13</sup> But Volonakis reported physical urticaria in 6% of the cases.<sup>9</sup> Physical urticaria often included dermographism, aquagenic, cholinergic, delayed pressure, solar, vibration and exercise urticaria.<sup>3,15,58-60</sup> In Khakoo's study, from all kinds of reported physical urticaria, 38% were dermographism, 19% aquagenic, 77% cholinergic, 17% combined them, 9% pressure, 9% heat, 2% hyperthermic and 4% idiopathic.<sup>3</sup> In Sackesen's study, 53% of cases were physical urticaria that solar and cholinergic urticarias were their most common types.<sup>12</sup> A study showed that heat urticaria was associated with anaphylactic reaction in 30% of the cases and history of atopy was significantly positive in the subject or the family members.<sup>61</sup>

### Cholinergic urticaria

Cholinergic urticaria is developed due to central hyperthermia following activity, hot water, sweating or excitement. Cholinergic urticaria is characterized by central small edema with a large peripheral erythema associated with severe itchiness. The treatment of cholinergic urticaria with Omalizumab has been effective in cases with resistant to antihistaminic therapy.<sup>62, 63</sup>

### Pathogenesis

Urticaria is developed following the release of chemical mediators from mast cell and basophile which is an immune reaction by IgE mediator. Chemical mediators such as histamine and tryptase (performed) and prostaglandins and leukotriene (newly formed) are associated with cellular inflammatory process. Neutrophils and lymphocytes by releasing cytokines are involved in the disease. These cause vascular dilatation, central edema and peripheral erythema.<sup>64</sup> Narcotics, complements and substances-P are the agents that play a role in the development of urticaria without immune mediator and affect on mast cells directly and lead to clinical manifestations of the disease.<sup>56</sup>

Autoimmunity pathogenesis is due to hematologic factors that lead to the release of histamines from mast cells originating from the dermal not basophiles.<sup>65,66</sup> IgG3 (mainly), IgG1 (often) and IgG4 (occasionally) are IgG isotopes that play a role in the pathogenesis of urticaria.<sup>67</sup> The decrease of coagulation activation and thrombin production may play a role in the development of urticaria by increasing vascular permeability and activation of mast cells.<sup>68</sup> HLA is another factor which is associated with increased chronic urticaria. HLA DRB1 is the risk factor of chronic urticaria while HLA DQB1 is the protective factor of chronic urticaria.<sup>69</sup>

### Quality of life in children with chronic urticaria

Quality of life is often impaired in patients with chronic urticaria especially in children

and is associated with unpleasant side effects. There are several studies regarding the quality of life impairments as such absence from school. It had been reported that 7.4% of children with chronic urticaria were absent from school and 3.3% of their parents were absent

from work.<sup>70</sup> There was a significant difference in doing homework between these subjects with normal persons (4.8% versus 1.9%).

Urticaria severity divided to mild, moderate and severe was based on the number of wheals and pruritus (Table 3).

Sum of score: 0-6, Pruritus: none-no pruritus; mild-pruritus, not affecting daily life; moderate-pruritus affecting daily life; intense-pruritus modifying daily life and daily activities.

**Table1.** Features of included studies on the etiology of children with chronic urticaria

Author	Male	female	Idiopathic (%)	Autoimmune ASST (%)	Physical (%)	Infections (%)	Parasites (%)	Food allergy (%)	Aeroallergens (%)	Additives (%)	Drugs (%)	ANA positive (%)
Kauppinen	-	-	34	-	29	7	1	9	0	21	0	-
Volonaki	122	104	75	-	6	13	3	28	2.5	26	17	0
Brunetti	52	41	29	45	26	21	-	4	-	-	-	0
Sackesen	12	5	47	-	52	35	0	11	0	0	17	0
Du Toit	43	37	52	41	-	-	2	0	-	-	-	-
Jirapongsananuruk	42	52	52	38	-	-	5.3	4.2	-	-	-	2.1
Kilic	12	28	-	25.9	-	-	0	-	-	-	-	-

Source: Caffarelli c. et al<sup>91</sup>

**Table 2.** Etiologic Features of chronic urticaria in children (Caffarelli c. et al<sup>91</sup>)

Diagnosis	No (%)
Idiopathic	316/565(55.9)
Autoimmune (positive autologous serum skin test)	76/267(28.4)
Physical triggers	59/391(15)
Allergy/intolerance	52/565(9)
Additives	18/95 (18.9)
Food allergy	22/565(3.8)
Drugs	7/298(2.3)
Inhalant allergy	5/268(1.8)
Parasites	14/394(3.5)
Infections	33/307(1)
Thyroid disease	0/220
Collagen vascular Disease	0/485

**Table3.** Chronic urticaria activation score

Score	Number of wheals	Pruritus
0	None	None
1	Mild (<20 wheals/24h)	Mild
2	Moderate (21-50 wheals/24h)	Moderate
3	Intense(>50 wheals/24h)	Intense

Source: Zitelli, K. B. et al<sup>88</sup>

## Diagnosis

Diagnosis of chronic urticaria is based on a good history and physical examination.<sup>86</sup> Laboratory tests are seldom helpful without them (Figure 1).<sup>15, 87</sup>

In severe cases with no response to appropriate dose of antihistamines, primary evaluation is necessary. In cases of leukocytosis, infection may be present. Increased neutrophil is suggested microvasculitis and eosinophil is recommended to be as the result of drug sensitivity of parasite infection. Urine analysis is done to detect urinary tract infection, BUN and ESR is important in inflammation, infection and autoimmune diseases. Although, thyroid function tests are normal in most of the patients, increased level of thyroid antibodies including anti-peroxidase and anti-thyroglobulin indicated autoimmunity. These patients should be controlled in the control of thyroid function (hypo or hyper thyroiditis). If correct diagnosis is not achieved, the next step will be performing cryoprotein test and the presence of celiac disease or hepatitis should be ruled out.

In cases with urticaria rash remaining more than 24/hrs., tenderness, petechial and/or purpura presenting vasculitis, febrile diseases, arthralgia and/ or arthritis, skin biopsy should be performed.<sup>15</sup>

The assessment of the effect of color is indicated in cases of eosinophilia, gastric symptoms or traveling to endemic regions.<sup>15</sup> ASST is positive in 4-76% of cases with chronic urticaria<sup>89</sup> with specificity of 70 % and sensitivity of 80%.

Although basophilic histamine releasing test (testing serum derived from the patient for IgE, FCεR1α) has not been approved in clinical practice, it can be helpful in diagnosing the disease.<sup>5, 83</sup>

Food allergy tests, concealed infections and malignancy tests are not routine in clinical practice for children and only used in specific cases.<sup>15, 36, 90</sup> The assessment of C1INH and

other related tests to hereditary angioedema are not recommended in chronic urticaria cases.

## Treatment of chronic urticaria in children

Similar to other allergic diseases, the treatment of chronic urticaria is a patient education that is to remove the triggering and aggravating agents, resolving and treating of the known disease and the use of various medicines based on the history and clinical findings (Table 4). Table 5 shows the different medicines which are used to control urticaria in children.

According to international guidelines<sup>71</sup>, like adults, the first medical therapeutics lines in children are anti-histamines, beta-blocker H1 and new generation of non-sedating agents. If therapeutic dose is not effective, it can be increased up to 4 folds of the standard dosage.

### First therapeutic line

**Antihistamines: First generation beta-blocker H1:** Antihistamines have anti-inflammatory effects and act as membrane stabilizers in mast cells and basophiles and decrease the release of mediators. All of these agents are applicable in children. Although antihistaminic agents are used most frequently in children, there is no strong evidence for their certain use due to their side effects that occur even in therapeutic dosage. Thus, it is better not to use the first generation of antihistamines such as chlorpheniramine, diphenhydramine and Promethazine in children.<sup>72,73</sup> The adverse effects of the first generation of antihistamines include: dry mouth, urinary retention and sinus tachycardia due to block of muscarine receptors and drowsiness, psychomotor and cognitive impairments due to the penetration of the drug into the central nervous system (CNS) and cause reducing sleep duration especially in REM sleep cycle.<sup>73</sup> In some cases, antihistamines stimulate the CNS in younger children; these medications are prohibited in

children younger than 6 years old around the world especially in the USA and the UK.<sup>74,75</sup>

**Antihistamines: Second generation beta-blockers H1:** The use of the second generation of antihistamines is preferred than the first generation. This group is used to treat chronic urticaria with different effects.

Consumption of des-loratadine, fexofenadine, levo-cetirizine in children older than 6 months and cetirizine and loratadine in children older than 2 years old has been also confirmed.<sup>76</sup>

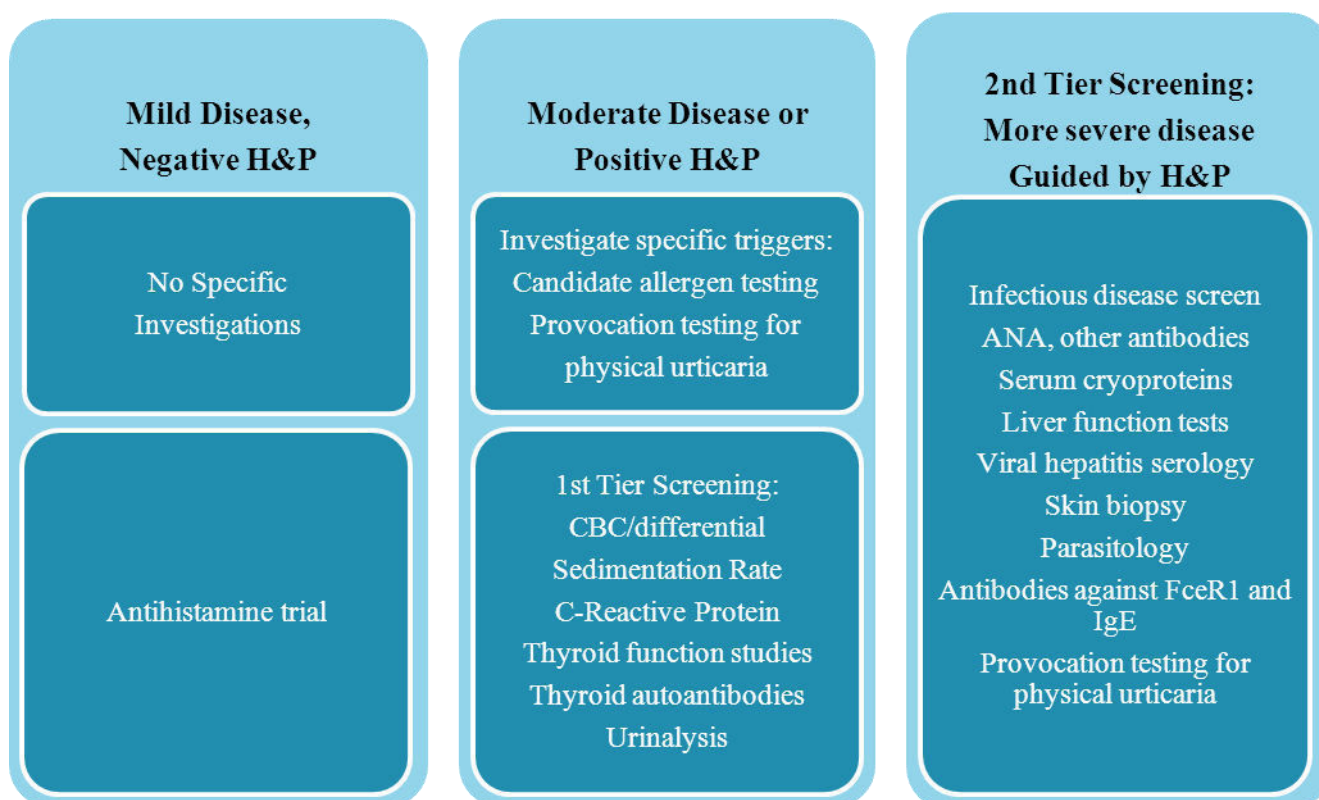
Generally, there is no evidence of tolerance or known adverse effects related to the antihistamine. But daily consumption of the drugs is associated with adverse effects due to drowsiness without CNS effect.<sup>77</sup>

In nonresponsive cases to the usual dose, increasing the dosage up to 4 folds has been recommended. Combination therapy with other therapeutic agents is used in cases with no response to the treatment with antihistamines.<sup>78, 79</sup>

### Second line therapies

Combining of antihistamines with leukotriene antagonist or H2-blocker is used for second line therapy. These compounds are able to control the chronic urticaria better than the first line therapy.

In the next stage, if there is no response to treatment, other medications such as cyclosporine, dapsone, omalizumab and or steroids are used.



**Figure 1.** Approach to evaluation of chronic urticaria in children (Source: Zitelli, K. B. et al<sup>88</sup>)



**Table 4.** Management strategies for Pediatric Chronic Urticaria<sup>88</sup>**Education and Counselling: The first step of CU management**

What is Urticaria? What is chronic urticaria?

What we know about potential causes and their relevance to the patient

Reassurance and support for patient and caregivers

Suggest a symptom diary to aid with treatment and identification of potential triggers.

**Antihistamines: First line treatment. Give in Scheduled doses (not as needed)**

H1 First- generation (more sedating, best for night time use):

Diphenhydramine, hydroxyzine

H1 Second- generation (Less sedating):

Cetirizine, Levocetirizine, Fexofenadine, Loratadine, Desloratadine

H2 Antihistamines:

Cimetidine, Ranitidine

**Other therapeutic options (in carefully selected or refractory cases)**

Leukotriene receptor antagonist (in combination with anti-H1):

Montelukast, zafirlukast

Tricyclic antidepressant with strong anti-H1 and H2 properties:

Doxepin

Oral corticosteroids

Cyclosporine

Dapsone

Anti-IgE antibodies:

Omalizumab

Intravenous immunoglobulin

Plasmapheresis

**Table 5.** Various therapeutic agents using to control urticaria in children

Therapeutic agents	Characteristics	Examples
Antihistamines First generation H1 blocker	Sedating , use at night	Diphenhydramine Hydroxyzine
Antihistamines second generation H1 blocker	Lower sedating effect	Cetirizine, Levocetirizine, Loratadine, Desloratadine, Fexofenadine
Antihistamines H2 blocker	-	Cimetidine, Ranitidine
Other therapeutic agents using in resistant or in special cases		a. Leukotriene receptor antagonists such as: montelukast, zafirlukast(combined with beta- blocker) b. Tricyclic anti-depressants (H1, H2 blocker): doxepine c. Oral steroids d. Cyclosporine e. Dopsone f. IVIG g. Anti IgE: omalizumab h. Plasmapheresis

There are a few studies regarding the use of these drugs in children. Doxepin is a drug that is used overnight. Cyclosporine is a calcineurin inhibitor that has been used in autoimmune disorders and declines histamine release by inhibition of leukocyte function. The usual dose of the drug is 2-5 mg/kg/day. In several studies, the use of cyclosporine in children was safe and effective. However in some studies, it has been less recommended due to possible complications and less experience in children. When cyclosporine is prescribed, renal function (BUN, Cr), blood pressure and cholesterol level should be monitored.<sup>80, 81</sup>

Intravenous immunoglobulin with 400 mg/kg/day for 5 days has been effective in some patients.<sup>6</sup> Omalizumab has been effective in patients with chronic urticaria especially in autoimmune cases that have resistance to antihistamine therapy. But it has not been used routinely in a wide range yet.<sup>82</sup>

### Prognosis

Although, there are a few literatures about chronic urticaria improvement and prognosis of the disease, the results of the studies are controversial. The prognosis of chronic urticaria is not benign actually like before. It has been reported that chronic urticaria improved completely in 11.6% of cases after one year and 38.4% after 5 years.<sup>72</sup> Generally, the positive history of allergy diseases and frequent urticaria attacks are associated with poor prognosis. Harris et al. in a study found that the moderate duration of urticaria was about 16 months and in 58% of cases, the disease improved completely after one year.<sup>57</sup> Patients with autoimmune urticaria have experienced more severe, longer and more frequent urticaria attacks.<sup>83,84</sup> In Kauppinen's study, 50% of patients who were followed up

for 3 to 8 years had shown complete recovery.<sup>13</sup>

In a prolonged process, prognosis of periodical syndrome associated with cryoprotein is not suitable and leads to end organ damage.<sup>55</sup> In cases with positive ASST, urticaria is more severe and quality of life becomes worse.<sup>66, 83, 85</sup> But there was not any similarity in other reports.<sup>20</sup>

### Conclusion

Although chronic urticaria in children is less prevalent than adults, the disease has unpleasant effects on children and their parents. In spite of several studies, idiopathic urticaria is the most common form of chronic urticaria in children and other causes such as food, medicine, infection, autoimmunity and parasites play roles in developing and aggravating the disease. In most cases, the disease is treated with antihistamine but in rare cases, other therapeutic agents may be necessary. Further studies are recommended to identify the etiologic factors and appropriate treatment in children with chronic urticaria.

### Conflict of Interest

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