Overview on chronic spontaneous urticaria in the pediatric age groups

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Introduction
Urticaria is a complex allergic skin disease, with considerable concern to allergists. The burden of such disease negatively impacts the quality of life, daily activities, practice of sport, and school/work performance of the affected child and his family. Patients with chronic urticaria, and their families showed higher prevalence of depression and anxiety, this may be attributed to lack of sleep with the unpredicted attacks of pruritis, the burden of treatment, and the frequent physician consultations. Furthermore, the mean time needed to reach the diagnosis may reach up to 2-4 years in some countries, adding more burden to the family. Studies concerned with the pathophysiology and etiology in the pediatric population are limited.

Chronic spontaneous urticaria (CSU) is defined as recurrent attacks of pruritic, migratory, urticarial wheals, with or without angioedema, on most days of the week for more than 6 weeks, without an identifiable trigger. After exclusion of the possible triggers of physical urticaria, the term "Chronic Spontaneous Urticaria" (CSU) is used, formerly was known as "Chronic Idiopathic Urticaria", but recently the possibility of autoimmune basis make the term idiopathic no longer used.

A recent systematic review stated that the lifetime prevalence of urticaria is 1.4%. CSU is reported more commonly in adults, with a prevalence rate ranging between 0.5% and 5%, more in females, and half of them showed remission within 1-3 years. However, in the pediatric population, acute urticaria is more common than chronic urticaria, and CSU is the commonest form of chronic urticaria, with a prevalence that seems to be lower than that in adults (0.1-0.3%).

Pathophysiology of CSU
Although the pathophysiology of CSU is not well-understood, mast cells and basophils are the primary effector cells, and their activation and degranulation are central to the process and occurs through various mechanisms in the superficial layers of skin. This is followed by the release of mediators such as histamine, platelet activating factor, arachidonic acid metabolites, and several cytokines leading to vasodilatation, stimulation of sensory nerves, and recruitment of other cells including macrophages, neutrophils, eosinophils, basophils and CD4+ T cells around vessels in a way similar to the late phase reaction to allergens. Interleukins 4 and 5 are elevated as well as the interferon-gamma messenger RNA expression. There is also elevation of TH2-initiating cytokines, including IL-33, IL-25, and thymic stromal lymphopoietin expressed as a mixed T helper 1 and 2 response. Regardless of the cause of mast cell activation, the sequelae are the same with vasodilatation and increased permeability of vessels and lymphatics leading to leakage of serum into upper and mid dermis inducing swelling and erythema seen in wheals. The affection is deeper in case of angioedema (deep dermis and subcutaneous tissue). Basopenia is observed in patients with CSU; this is explained by their migration to the site of wheals, and their numbers return to normal during remission.

Two possible mechanisms have been suggested to underlie the occurrence of CSU. The first involves dysregulation of intracellular signaling pathways within mast cells and basophils leading to defects in their trafficking and/or function and pathological activation. Activation of spleen tyrosine kinase (SYK) protein seems to be a major determinant of predilection toward spontaneous mast cell degranulation. Impaired negative regulation of mast cell activation owing to decreased levels of Src homology2 (SH2)-containing inositol phosphatases (SHIP) protein is also suggested to have pathogenic role in the development of CSU.
The second theory, which is more widely accepted, involves autoimmune mast cell activation, and probably explains the positivity of autologous serum skin testing (ASST) in around 50% of CSU patients (positive skin reaction 30 minutes after intradermal injection with the patient’s own serum). Autoantibodies against the low affinity IgE receptor FcεRII (CD23) have been demonstrated in a large percentage of CSU patients and were shown to activate eosinophils resulting in the release of major basic protein, triggering histamine release from mast cells, and basophils. IgG antibodies against the alpha subunit of the high-affinity FceRI on the surface of mast cells and basophils were found in a group of patients with CSU and were capable to induce histamine release in an IgE-independent fashion. However, IgG-anti IgE antibodies may also bind to and crosslink receptor-bound IgE on the surface of mast cells and basophils, leading to their activation.

During exacerbation of urticaria, activation of the coagulation pathway, raised fibrin degradation products, increased complement C5a anaphylatoxins are other observations in patients with CSU, that may enhance the stimulation of mast cells and release of mediators. Thrombin has been shown to directly increase mast cell degranulation, activate protease-activated receptors on mast cells, and enhance vascular permeability through actions on endothelial cells.

Although the significance of eosinophils in CSU is not clear yet they were found to be increased in skin biopsy specimens from lesional and non-lesional sites in patients with CSU. Together with mast cells and basophils, eosinophils may prime the skin for wheal formation in addition to a probable effect through eosinophils impact on the coagulation cascade.

An increased frequency of the HLA-DR4 allele has been found in patients with CSU as well as other autoimmune diseases including rheumatoid arthritis, type 1 diabetes mellitus. There is also increased frequencies of HLA-DR9 and HLADR12 among patients with CSU.

CSU patients were found to have significantly higher levels of anti-thyroid peroxidase (anti-TPO) antibodies, anti-thyroglobulin (i.e., antimicrosomal) antibodies (even in euthyroid subjects), anti-nuclear antibodies (ANA), rheumatoid factor, anti-transglutaminase IgA antibodies, and anti-parietal cell antibodies with anti-dsDNA, and anti-cardiolipin antibodies.

Histologically in CSU, there is dermal edema, enlarged capillaries, and perivascular non-necrotizing infiltration; predominantly by CD4+ lymphocytes, monocytes, neutrophils, eosinophils, and basophiles. An hour after the appearance of wheals, neutrophils come to dominate the infiltrated content. Worth to note that, 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.

Clinical presentation of CSU

CSU presents with recurrent fleeting wheals, with or without angioedema, observed daily for 6 weeks or more. Wheals are variable sized itchy swelling, involving only the superficial portions of the dermis, surrounded by erythema, with well-defined margins, and pallor in the center, associated with burning sensation and pruritis of variable severity. They are transient lasting 30 minutes or may persist up to 24 hours then resolve without hyperpigmentation. Angioedema is erythematous swelling of subcutaneous tissue or mucus membranes (back of hands or feet, eyelids, lips, tongue, and scrotum), painful more than itchy, and persist up to 72 hours until the triggering bradykinins are metabolized.

CSU is often associated with autoimmune thyroiditis and coeliac disease in children. However, the prevalence of hypothyroidism, often due to Hashimoto thyroiditis more than Graves’ disease, is below 1%. There is no clear evidence that treatment with thyroid supplementation therapy improves urticaria, while gluten free diet in celiac cases showed some benefit.

Classification of chronic urticaria

The updated EAACI/GA²LEN/EDF/WAO guidelines classified urticaria as either acute (lasting fewer than or 6 weeks) or chronic (lasting more than 6 weeks). If there is a physical stimulus or trigger for such skin lesions, the term chronic inducible urticaria (CIndU) is used, while no physical trigger is identified in CSU. The different triggers for CIndU are mentioned in table 1. CIndU may coexist with CSU, some cases may report some triggers as in cholinergic, cold urticaria, or dermographism. CIndU are transient lesions, lasting for brief hours, without accumulation of cells except the delayed pressure urticarial that can last for one day.
C:

Chronic Spontaneous Urticaria in Children

Activation of mast cells and basophils may occur due to several mechanisms: IgG autoantibodies against IgE antibodies and/or FcεRIs; IgE autoantibodies directed against dsDNA, tissue factor (TF), IL-24 and TPO; Neuropeptides, complement 5a component, proteases, prostaglandins, and Toll like receptors ligands, all these factors can induce the activation of mast cells and basophils, followed by the release of histamine and other mediators. Late-phase release of lipid mediators and cytokines may contribute to the process.

Table 1. Main characteristics of chronic urticaria

<table>
<thead>
<tr>
<th>Chronic Spontaneous Urticaria</th>
<th>Spontaneously occurring wheals, angioedema, or both &gt; six weeks with no known trigger</th>
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</thead>
<tbody>
<tr>
<td>Chronic Inducible Urticaria</td>
<td>Wheals that appear after exposure to a specific physical stimulus.</td>
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<tr>
<td>Cholinergic Urticaria</td>
<td>Wheals with raising body temperature as after hot bath or exercise with sweating.</td>
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<tr>
<td>Heat Urticaria</td>
<td>Wheals with exposure to high local heat.</td>
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<tr>
<td>Solar Urticaria</td>
<td>Wheals with exposure to ultraviolet sunrays.</td>
</tr>
<tr>
<td>Aquagenic Urticaria</td>
<td>Wheals with exposure to water.</td>
</tr>
<tr>
<td>Contact Urticaria</td>
<td>Wheals after contact with specific substance.</td>
</tr>
<tr>
<td>Vibratory Urticaria</td>
<td>Wheals within 1-2 hour of exposure to vibratory source.</td>
</tr>
<tr>
<td>Delayed pressure Urticaria</td>
<td>Delayed appearance of wheals (12 hour) after application of vertical pressure on skin.</td>
</tr>
<tr>
<td>Cold Urticaria</td>
<td>Wheals with exposure to cold substances as cold water or ice.</td>
</tr>
<tr>
<td>Dermatographism</td>
<td>Rapid appearance of wheals within few minutes of scratching or shearing force.</td>
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</table>

Diagnostic workup of CSU
Diagnosis of CSU is based on comprehensive history taking and physical examination. Extensive work up, and investigations are not recommended unless alternative diagnosis is suspected, or in long standing unresponsive cases.

History should focus on age at onset, duration, how frequent are the attacks, the clinical presentation during the attack, including description of size, shape, distribution of wheals, presence of angioedema, periodic fever, joint or muscle affection, eye symptoms, abdominal or chest pain, induction by physical triggers, drugs, food and stressful factors. History of gastrointestinal diseases, allergies, autoimmune disorders, and family history of similar condition is needed.

Complete blood count, and inflammatory markers as erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) are the only routine recommended investigation in cases with CSU. In some conditions, liver function tests, and tryptase level are requested.
Other diagnostic work up should be selected based on the clinical background to rule out underlying causes as Helicobacter-pylori (H-pylori) antigen test, and upper endoscopy, screening for infection, stool analysis, specific IgE, antinuclear antibody, thyroid profile and autoantibodies. Skin Prick testing can be used if relation to food is suspected, but in general it has a very limited role in CSU. Skin biopsies are seldomly needed for the diagnosis but might be needed in some cases to distinguish CSU from other inflammatory conditions such as urticarial vasculitis.

Basophil activation testing, D-dimer, and autologous serum skin testing (ASSST) were used to screen for autoantibodies against IgE receptors on mast cells, but are not recommended currently for CSU diagnosis in clinical practice. In basophil activation test, serum samples of patients with CSU cause in vitro histamine release from unaffected control basophils, however, this bioassay is time consuming and difficult to standardize as it requires fresh basophils from healthy donors making the test restricted to scientific research. In ASSST, autologous serum is intradermally injected with a subsequent positive wheal-and-flare reaction in individuals in CSU patients with variable positivity ranging between 35% and 58%. Positive results are not specific to CSU patients and may be seen in healthy controls. In addition, even when CSU is in remission, ASSST results remain positive, demonstrating a lack of clinical utility. Thus, a standardized assay to identify autoantibody mediated CSU in clinical practice is still lacking.

**Differential Diagnosis of CSU**

Clinical assessment is crucial to differentiate between CSU and disorders with urticaria like lesions in children (figure 2), Cryopyrin-associated periodic syndromes (CAPS), present with urticarial wheals, periodic fever, eye and joint manifestation, and present in 3 forms: familial cold auto-inflammatory syndromes (FCAS), Muckle-Wells syndrome (MWS) and neonatal-onset multisystem inflammatory disease (NOMID). Other rare inherited autoinflammatory syndromes that present with urticaria include hyper-IgD syndrome (HIDS) and tumor necrosis factor receptor alpha-associated periodic syndrome (TRAPS).

Acquired conditions presenting with urticaria needs to be differentiated from CSU as Schnitzler’s syndrome, that presents with attacks of mildly itchy urticaria, periodic fever, lymph node enlargement, joint, bone and muscle affection, as well as, Urticarial vasculitis that has urticarial like lesions, lasting more than 24 hours, painful not itchy, with residual pigmentation, and associated with systemic manifestation like fever, joint, and muscle manifestation.

Some conditions might present with recurrent angioedema but without wheals as Bradykinin-mediated angioedema including the hereditary angioedema (HAE) or angiotensin converting enzyme inhibitor induced angioedema. Anaphylaxis presents with both urticarial, and angioedema, but in association with other system involvement as respiratory (tightness, hoarseness of voice, difficult breathing), gastrointestinal tract and/or reduced blood pressure and collapse.

**Urticaria activity score (UAS)** is a good tool to assess severity of CSU and the response to treatment based on daily observation of wheals and associated pruritis.

- **Wheals:** none (score 0), mild with fewer than 20 wheal/day (score 1), moderate with 20-50 wheal/day (score 2), severe with more than 50 wheals or confluent areas of wheals/ day (score 3)
- **Pruritis or itching:** absent (score 0), mild but not irritating or troublesome (score 1), moderate (irritating but not interfere with sleep or daily activities)(score 2), severe (markedly irritating and interfere with daily activities and can not sleep) (score 3).

The sum of the daily scores over 7 consecutive days (minimum 0-maximum 42) comprise the total score. A total score less than 6 referred to as well controlled, 7-15 mild, 16-27 moderate, while a score 28-42 implies severe urticaria.

**Management of CSU**

Goal of treatment in CSU is to reduce symptoms that are annoying and affect school performance, sleep, and daily activities. Stepwise approach for the management of CSU patients with CSU is shown in figure 3.

- **Antihistamines** are the first line therapy used to reduce CSU symptoms. They block the stimulated H1 receptors in blood vessels and nerves. Continuous safe use of these drugs is supported by multiple studies, and result in stabilization of H1 receptors in inactive state. Antihistamines exist in 2 generations, the first generation are not recommended in CSU for their sedative, and anticholinergic action. Second generation H1-antihistaminics are the recommended group as they are long acting, non sedating medications, with less anticholinergic action.

The standard dose is started according to age and weight of the patient (table 2) but was found to be associated with response in less than 50% of cases. In case of lack of adequate control after 2 to 4
weeks, the dose is doubled, and then increased up to 4 folds the usual dose.\textsuperscript{41,42} A metaanalysis of H1-antihistamine up-dosing for CSU showed that 63.8\% of patients with CSU whose condition was not controlled with 1-fold dosing responded when the dose was increased 4-fold.\textsuperscript{43}

The choice of the antihistamines depend on the availability in suryp form or dispersable tablet, and the age approval in different countries.\textsuperscript{8}

Many of 2\textsuperscript{nd} generation antihistamines are well studied in children, and used in CSU as fexofenadine, desloratadine, cetirizine, levocetirizine, and loratadine with good safety profile in the pediatric population.\textsuperscript{8,44}

Doses are used once daily, but fexofenadine and cetirizine can be divided into 2 daily doses. Cetirizine is approved for use in CSU from 6 months.\textsuperscript{44}

The use of Leukotriene receptor anagonist (LTRA), was tried as add on therapy with antihistamines in non responders for 2 or 4 weeks.\textsuperscript{9,46} However, the EAACI/GA\textsuperscript{2}LEN/EDF/WAO guidelines did not recommened the use of montelukast in antihistamines resistant CSU cases.\textsuperscript{8} Their use remains off-label in CSU management. One double-blind RCT including 95 CSU patients over 12 years of age reported an additional improvement and better patient and physician-reported visual analogue scales in CSU patients receiving combined cetirizine therapy with zafirilukast compared to cetirizine monotherapy.\textsuperscript{47}

Combination of H1 and H2 antagontists has been given in patients uncontrolled on H1 antihistamines. Limponsanurak et al., 2016 stated that this combination is an alternative option in resistant cases with high safety profile and low cost.\textsuperscript{9} However, EAACI/GA\textsuperscript{2}LEN/EDF/WAO guidelines again did not recommend with or against this combination.\textsuperscript{8}

Oral corticosteroids might be added for 3 to 10 days in acute exacerbations or severe cases. However, their use is not preferable because of the chronicity of the disease, making repeated short corticosteroids courses challenging to track, with increasing side effects of systemic corticosteroids in both continual or intermittent use.\textsuperscript{9,41}

Omalizumab, a monoclonal antibody against IgE, is the first drug approved for use in CSU patients who remain symptomatic on antihistamines.\textsuperscript{8,41} It is used as add on therapy to antihistamines in adolescents 12 years and older (figure 3). It reduces the level of IgE and the expression of its high affinity receptors on mast cells and basophils.\textsuperscript{8,48} The recommended dose is 150 mg injected subcutaneously every 4 weeks for 6 months, regardless the IgE level or the weight of the patient.\textsuperscript{8}

Patient assessment is done using UAS before treatment, and in the 4\textsuperscript{th} week after first dose. If no adequate response is achieved (reduction in UAS by at least 30\% from the starting score) the 2\textsuperscript{nd} dose can be increased to 300 mg monthly. If no adequate response perceived by the end of 2\textsuperscript{nd} month, discontinuation is advised. On the other hand, if adequate response is achieved, continued use omalizumab is recommended for at least 6 months with gradual stepping down of other medications.\textsuperscript{9}

After 6 months of treatment with adequate response on omalizumab, the dose can be reduced, or the interval between injections can be increased. Furthermore, discontinuation is considered whenever possible with assessment every 3-6 months, and upon physician opinion, Omalizumab can be readministered if needed.\textsuperscript{9,41}

Cyclosporine, is the fourth drug in cases unresponsive on omalizumab, with cautious use due to its nephrotoxic and hypertensive effect.\textsuperscript{8,41} The most common treatment regimen is at an initial dose of 3 mg/kg/day with slow adjustments depending on response to therapy up to 5 mg/kg/day and for a duration of 3-6 months.\textsuperscript{9,49}

There are no sufficient data supporting the use of hydroxy chloroquine, sulfasalazine, dapsone, vitamin D, H-pylori treatment and phototherapy in antihistamines resistant-CSU cases.

Emerging therapeutics for antihistamine-refractory CSU patients

Since the mast cells recruit eosinophils through the release of IL-5, so drugs as Mepolizumab and Reslizumab, anti-IL-5 monoclonal antibodies, as well as, benralizumab, an anti-IL-5 receptor monoclonal antibody have shown successful results in some patients with CSU; studies are ongoing to evaluate their efficacy.\textsuperscript{1,48}

Dupilumab is a monoclonal antibody that inhibits IL-4 and IL-13 signaling through blockade of their shared IL-4 alpha receptor subunit. Owing to their contribution to TH2-type immune response, inhibition of IL-4 and IL-13 is suggested as a possible therapeutic option in cases with CSU not responding to omalizumab with promising results.\textsuperscript{50}

Novel lines of treatment under research include the newer generation anti-IgE monoclonal antibody Ligelizumab (QGE031), a humanized monoclonal IgG antibody, with higher affinity to bind to Cε3 domain of IgE than omalizumab. Preliminary results show possible benefits with greater effect and longer duration compared to omalizumab.\textsuperscript{1,51} PEARL 1 and 2 are ongoing phase 3, multicenter, randomized,
double-blind, parallel group studies aimed to establish the efficacy and safety of ligelizumab in adolescents and adults subjects with antihistamine-refractory CSU (NCT03580369).

AZD1981 is an oral, selective, reversible antagonist for Chemoattractant rector-homologous molecule expressed on TH2 cells (CRTH2). It is now being assessed in a clinical trial for safety and efficacy of its use in antihistamine-resistant CSU with increasing interest.

AntieSiglec-8 (AK002) is a monoclonal antibody under investigation, binds to sialic acid immunoglobulin-like lectins (Siglec-8) that is uniquely expressed on eosinophils, mast cells, and basophils. The drug by inducing apoptosis of these cells and is believed to inhibit FceRI-dependent histamine and prostaglandin D2 (PGD2) release.\(^{16,53}\)

Topical use of Syk inhibitor (GSK2646264) to prevent spontaneous mast cell degranulation and release of histamine have been tried to decrease the urticarial wheals, owing to its selectivity and good skin penetration but results of phase 1/1b were not conclusive due to the small number of CSU patients included.\(^{16,54}\)

Owing to the role of Bruton tyrosine kinase (BTK) in the signal transduction downstream of FceRI and the B-cell receptor, Fenebrutinib (GDC-0853), a potent, selective, non-covalent BTK inhibitor, has been tried to inhibit IgE- and mast cell mediated responses and is now being studied in patients with antihistamine-resistant CSU (NCT03137069).\(^{55}\)

### Prognosis

CSU is a chronic disease with a long duration, and has high incidence of recurrence more in adult than in children.\(^{27}\) Among adult patients, it usually lasts for up to 11.5 years, remission after 1 year and 5 years are reported in 20-75% and 55% of patients respectively.\(^{2}\) In children, the median duration of CSU is 16 months,\(^{9}\) and remission rate is reported to range between 16 and 37% after one year.\(^{7,11}\)

Previous studies showed that 50% children were symptom free within 5 years, while disease severity seems to be a risk factor for CSU persistence. The recovery rate might be better for boys than girls in ages less than 10 years.\(^{15,56}\)

### Conclusion

Detailed history remains the main tool used for diagnosis of CSU, extensive work up is not recommended unless alternative diagnosis is suspected. Second generation antihistamines is the main line of treatment with stepping up of the dose up to 4 times the standard dose, taking into consideration the weight and age of the child. Omalizumab is an effective add on therapy to antihistamines, and is recommended in cases unresponsive or inadequately controlled on second generation antihistamines. Several studies are ongoing for providing safe and effective treatment options in refractory cases.

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**Table 2.** The recommended doses for some of the second generation antihistamines in infants and children

<table>
<thead>
<tr>
<th></th>
<th>Fexofenadine(^{9,45})</th>
<th>Desloratadine(^{9,43,45})</th>
<th>Cetirizine (^{9,44,45})</th>
<th>Loratadine(^{9,45})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td><strong>Step 2</strong></td>
<td><strong>Step 3</strong></td>
<td><strong>Step 4</strong></td>
<td></td>
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<tr>
<td>6mons-2yrs</td>
<td>30 mg</td>
<td>60 mg</td>
<td>90 mg</td>
<td>120 mg</td>
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<tr>
<td>2-11yrs</td>
<td>60 mg</td>
<td>120 mg</td>
<td>180 mg</td>
<td>240 mg</td>
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<tr>
<td>≥12yrs</td>
<td>120 mg(180 mg)</td>
<td>240 mg</td>
<td>360 mg</td>
<td>360 mg</td>
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<td><strong>Step 2</strong></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>6mons-1yrs (&lt;10kg)</td>
<td>1 mg</td>
<td>2 mg</td>
<td>3 mg</td>
<td>4 mg</td>
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<tr>
<td>1-5yrs (&lt;20kg)</td>
<td>1.25 mg</td>
<td>2.5 mg</td>
<td>3.75 mg</td>
<td>5 mg</td>
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<tr>
<td>6-11yrs (&lt;30kg)</td>
<td>2.5 mg</td>
<td>5 mg</td>
<td>7.5 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>≥1yrs (≥30kg)</td>
<td>5 mg</td>
<td>10 mg</td>
<td>15 mg</td>
<td>20 mg</td>
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<td><strong>Step 3</strong></td>
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<td>2-6yrs (&lt;10kg)</td>
<td>2.5 mg</td>
<td>5 mg</td>
<td>7.5 mg</td>
<td>10 mg</td>
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<td>5 mg</td>
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<td>20 mg</td>
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<td>&gt;6yrs (&lt;30kg)</td>
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<td><strong>Step 4</strong></td>
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<tr>
<td>2-12yrs</td>
<td>5 mg</td>
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<td>&gt;12yrs (&gt;30kg)</td>
<td>10 mg</td>
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</table>
Figure 2. Algorithmic approach to a case with chronic urticaria.\textsuperscript{9}

AAE: acquired angioedema; ACEI: angiotensin converting enzyme inhibitors; HAE: hereditary angioedema; NSAIDs: nonsteroidal anti-inflammatory drugs.
Figure 3. Therapeutic approach to patients with chronic spontaneous urticaria.\(^1,8,41\)

REFERENCES


Chronic spontaneous urticaria in children


