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MANAGEMENT OF PEDIATRIC CHRONIC SPONTANEOUS URTICARIA

Chronic urticaria (CU) occurs when pruritic wheals and/or angioedema manifests on most days of the week and persists for at least 6 weeks.[1] Recent evidence suggests that the point prevalence of pediatric CU is similar to adults, affecting ~ 0.5%-1.5% of children, with no sex predilection.[2-6] While ~ 20% of CU cases have an underlying physical/inducible trigger (chronic inducible urticaria, CIndU),[6] in most cases the hives occur spontaneously (chronic spontaneous urticaria, CSU).[7]

Update on pathogenesis

The exact etiopathogenesis of CSU remains unknown, however recent advances highlight mast cell activation through immune mechanisms. Half of adults with CSU are believed to have an autoimmune basis for their disease, where mast cell activating immunoglobulin IgG antibodies against the IgE molecule or its high affinity receptor FcεRI are implicated. Autoimmune CSU is suspected on the basis of either a positive *in vivo* autologous serum skin test (ASST) and/or a positive *in vitro* assay (*e.g.* basophil activation test).[1,8,9] Neither ASST nor *in vitro* tests, are currently recommended for routine use as their clinical utility remains unclear.[1,8,9] Furthermore, in the majority of adult CSU cases, IgE-type autoantibodies (*e.g.* IgE anti-interleukin(IL)-24 or anti-thyroid peroxidase) are capable of directly crosslinking and activating the FcεRI, a mechanism referred to as auto-allergy **(Figure 1)**.[10-13] These patients often have elevated serum IgE levels and may be better/faster responders to the anti-IgE monoclonal antibody, omalizumab.[14] Pathogenic IgM and IgA-type autoantibodies are also being discovered, but their role in CSU induction remains unclear and warrants further investigation.[15] While it is suspected that the immune pathogenesis of pediatric CSU is similar to that of adults, it has not yet be demonstrated.

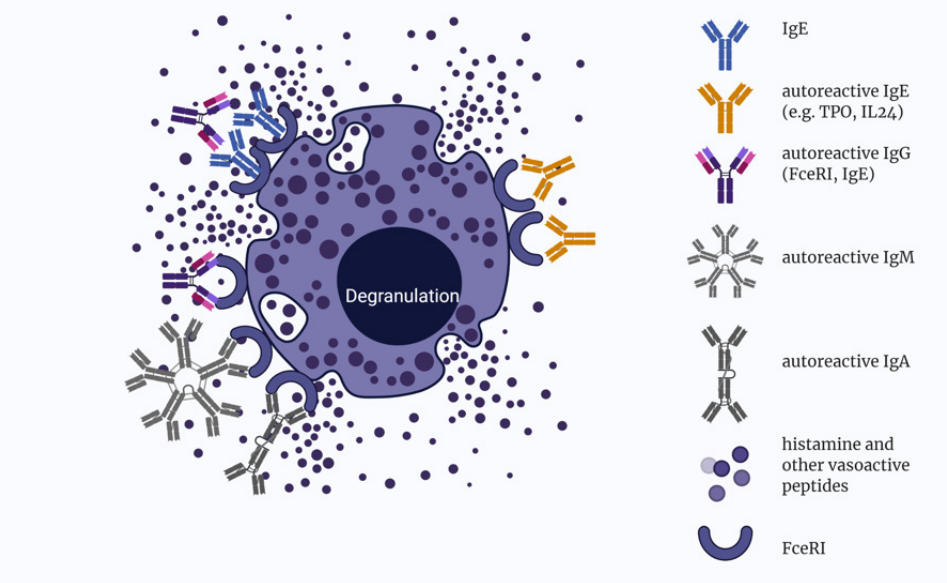

Figure 1. Pathogenesis of chronic spontaneous urticaria (CSU)

Legend. *It is believed that mast cell activation and degranulation is triggered by functionally active autoantibodies either of IgE-type (e.g. anti-IL-24 IgE, anti-TPO IgE, Autoreactive CSU) or IgG antibodies against the IgE molecule or its high affinity receptor, FcεRI (Autoimmune CSU). Self-reactive IgM and IgA antibodies are being described as well, but the role remains unclear. FcεRI, high affinity IgE receptor; IgE, Immunoglobulin E; IgG, immunoglobulin G; IgM, immunoglobulin M; IgA, immunoglobulin A; IL-24, interleukin-24; TPO, thyroid peroxidase. Created with Biorender®.*

Burden of disease

Due to intractable itch, secondary loss of sleep and impact on school/work productivity, CSU is associated with severe impairment in quality of life, often rated similar to other chronic diseases such as type I diabetes mellitus and epilepsy.[16,17] School performance is consequently affected and the prevalence of mood/anxiety disorders is increased in children with CSU.[17] Similar to adults, pediatric CSU is a chronic condition with an annual resolution rate of only 10 per 100-patient-years.[6] Hence, a safe and effective treatment is imperative for many years.

Treatment objectives

The goal of treatment is to control CSU completely with as much or as little medication needed until spontaneous resolution occurs. Disease severity and control can be quickly assessed in clinic using the Urticaria Activity Score (UAS-7) and the Urticaria Control Test (UCT).[18,19] In general, good disease control/mild disease is defined by a UCT score ≥ 12 and an UAS-7 score ≤ 6. On the other hand, UAS-7 ≥ 28 and UCT ≤ 11 correspond to severe and poorly controlled disease.[19,20]

Treatment guidelines in children

So far, treatment guidelines dedicated to children with CSU are largely lacking and treatment decisions are either based on personal experience or extrapolated from general (adult) CSU guidelines. The EAACI/GA²LEN/EDF/WAO guidelines are the most widely-accepted CU/CSU guidelines worldwide and endorsed by many dermatologic societies including the Canadian Dermatology Association.[1] While they focus primarily on adult CU/CSU, children are included as a special population. The same management of pediatric CSU is recommended starting with second-generation (non-sedating) antihistamines (sgAHs) at the licensed dose for the patient's age. In the case of uncontrolled disease, clinicians should proceed with caution regarding further management, given the relative lack of studies in pediatric CSU **(Figure 2)**.[21] The SIP/SIAIP/SIDerP Italian guidelines are the only guidelines focusing on the pediatric population. Unlike other guidelines, the Italian guidelines divide the pediatric group into ≥12 and <12-years-old and recommend omalizumab prior to the titration of sg-AHs in teenagers (≥12 years-old) given omalizumab's indication for CSU in this age group **(Figure 2)**.[22,23] Of note, systemic glucocorticoids are only recommended for the short-term treatment of acute exacerbations of CSU, due to their poor safety profile[1,8,9], whereas the use of first-generation antihistamines (fgAHs) is strongly discouraged due to their anticholinergic side effects and hence, neither of these modalities is included in the step-wise treatment algorithm.[24-28] Other potential treatments that may be considered on a case-by-case basis in resistant cases include: leukotriene receptor antagonists (LTRA), phototherapy, hydroxychloroquine and more.[1]

What is the evidence behind treatment recommendations for pediatric CSU?

H1-antihistamines (H1-AH)

H1-AHs prevent H1 receptor activation by histamine.[26] They are the first and usually the second line treatment of CSU regardless of the patient's age. AHs are classified as older fgAHs (e.g. hydroxyzine, diphenhydramine) and newer sgAHs. First-generation antihistamines cross the blood-brain barrier and have potent dose-dependant anti-cholinergic adverse effects (e.g. sedation, reduced cognitive activities).[24-31]

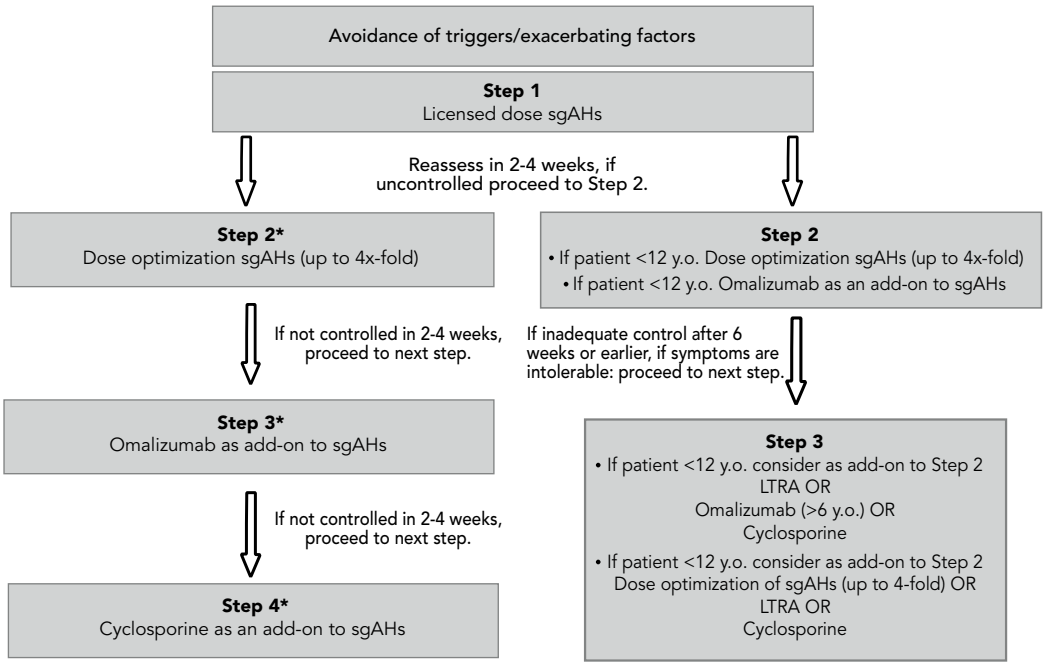

Figure 2. CSU treatment guidelines for children.

Well-designed published studies assessing the safety and efficacy of commonly used fgAHs for CSU in children are largely lacking and yet, these medications remain commonly used first-line, particularly in the primary care setting.[1,21] Second-generation antihistamines have a better safety profile and efficacy due to their H1 receptor selectivity and are more convenient to use due to their longer half-life.[31-35] The sgAHs licensed for pediatric use are summarized in **Table 1**. The only study that compared sgAH (cetirizine 5 mg daily) to a fgAH (oxatomide 25 mg daily) in children (2-6 years-old)[36] confirmed superiority of cetirizine in terms of itch, erythema and rapidity of clinical improvement ($p<0.05$). Complete CSU control was seen in 46% of children treated with cetirizine as opposed to 28% with oxatomide at 28 days.[36]

H1-antihistamines at licensed dosage

Six randomized controlled trials (RCTs) assessed the safety and efficacy of various sgAHs at their licensed dosage in children with CSU. Desloratadine and rupatadine in children aged 2-11, led to a 54% and 61% CSU improvement (defined as ≥ 50% decrease from baseline in a modified 7-day cumulative UAS-7 score), respectively.[37] Similar results were reproduced in two additional desloratadine double-blind RCTs in patients over 12 years of age (21 patients of pediatric age group).[38,39] Fexofenadine was also studied in adults and adolescents in a double-blind RCT, demonstrating satisfactory CSU control and a favorable safety profile.[40] Finally, levocetirizine hydrochloride was assessed in two RCTs for infants/children 6-11 months (study 1, n = 69) and children aged 1-5 years (study 2, n = 173) with allergic rhinitis and CSU showing a safety profile comparable to placebo.[41] Data from an allergic rhinoconjunctivitis study in children, further supports the safety of bilastine in this age group (**Table 1**).[42]

H1-antihistamines updosing

Only three studies have focused on the safety and efficacy of updosing sgAHs in children. Rupatadine 10 mg vs. 20 mg daily was found to be equally safe and effective for adults and adolescents with CSU.[43,44] Another RCT that included children ≥ 12 years old, demonstrated a dose-dependant urticaria control with an increasing fexofenadine dose up to 60 mg b.i.d. compared to the 20 mg fexofenadine group after which, the response plateaued for the 120 mg and 240 mg doses of fexofenadine.[45] Side-effects were similar to placebo regardless of the dose (maximal dose of fexofenadine used was 240 mg twice a day).[45] Unfortunately, robust studies in young children are limited. However, given the favorable safety profile of these drugs, many clinicians feel comfortable with sgAHs up-dosing (up to fourfold) in children.[46,47]

Omalizumab

Omalizumab, a monoclonal anti-IgE antibody, is approved by Health Canada for sgAH-resistant

sgAH	Licensed dose	Contraindications	Side Effects	Other
Loratadine	• 2-6 yo: 5 mg o.d. • ≥6 yo: 10 mg o.d.	Hypersensitivity	Headache	• Not metabolized by the CYP3A4.
Desloratadine	• 6-11 months: 1 mg o.d. • 1-5 yo: 1.25 mg o.d. • 6-11 yo: 2.5 mg o.d. • ≥12 yo: 5 mg o.d.	Hypersensitivity	Headache, diarrhea	• Active metabolite of loratadine. • Safest in patient with renal failure.
Cetirizine	• 6-12 months: 2.5 mg o.d. • 1-2 yo: 2.5 mg o.d. • 2-5 yo: 2.5-5 mg o.d. • 6-11 yo: 5-10 mg o.d. • ≥12 yo: 10 mg o.d.	Hypersensitivity	Drowsiness, headache	
Levocetirizine	• 6 months to 5 yo: 1.25 mg o.d. • 6-11 yo: 2.5 mg o.d. • ≥12 yo: 5 mg o.d.	Hypersensitivity, end-stage renal disease, hemodialysis, patients ≤11 yo with renal impairment	Diarrhea, drowsiness	
Fexofenadine	• 6 months to 2 yo: 15 mg b.i.d. • 2-12 yo: 30 mg b.i.d. • ≥12 yo: 60 mg b.i.d.	Hypersensitivity	Headache, vomiting	• Safest in patient with renal failure. • Not metabolized by liver/the CYP3A4.
Rupatadine	• 2-12 yo: If 10-25 kg: 2.5 mg o.d. If >25 kg: 5 mg o.d. • ≥12 yo: 10 mg o.d.	Hypersensitivity, history of QTc prolongation and/or torsades de pointes, concurrent use of CYP3A4 inhibitors or other QTc-prolonging drugs	Drowsiness, headache	
Bilastine	• ≥12 yo: 20 mg o.d.	Hypersensitivity, history of QT prolongation and/or torsades de pointes	Drowsiness, headache	• No impact of CYP P450 metabolism.

Table 1: Second-generation antihistamines approved in pediatric patients

Legend. *CYP, cytochrome-P450 ; yo, years-old; o.d., daily; b.i.d., twice daily.*

CSU in patients ≥12 years-old and severe asthma in patients ≥6 years-old. Omalizumab's efficacy in CSU is thought to result from the inhibition of IgE-mediated FcεRI activation of mast cells and basophils[48], free serum IgE depletion and decreased FcεRI expression.[49] Additional mechanisms are being explored including normalization of basopenia.[50] While omalizumab's clinical program in CSU included 39 patients younger than 18 years of age[51-53], data regarding the potential use of omalizumab in younger children is only emerging. So far, case reports and case series include a total of 76 AH-resistant pediatric CU patients aged 4 to 17 years.[46,49,54-65] The most commonly used dosages were 150-300 mg subcutaneously every 4 weeks. Most patients (66 of 76) had a satisfactory response, whereas complete CSU control was seen in 44/76 patients. Importantly, no new safety signals were identified.

Cyclosporine

Cyclosporine inhibits T-cell activation and downstream production of IL-2, IL-3, IL-4, TNF-α and other inflammatory cytokines[66,67] as well as the suppression of histamine release.[68,69] Its use in CSU is off-label and studies assessing cyclosporine in pediatric CSU consist of one retrospective chart review, one case series and one case report including only 24 AH-resistant CSU patients in

total, aged from 9 to 18 years.[70-72] The starting dose of 3 mg/kg/day was usually used with slow adjustments depending on response. CSU was controlled completely in all 24 patients, although a publication bias (i.e. cases who failed treatment were not published) may have been present and cannot be excluded as potentially confounding these reported results. Patient response to treatment was fast—usually within 2 weeks.[70,72] In 23/24 patients, cyclosporine serum levels were monitored and kept below 200 ng/mL. No serious adverse events were reported, however total treatment duration varied from 10 weeks to 17 months.[70-72]

Oral glucocorticoids

The efficacy of systemic corticosteroids in improving disease severity of acute urticaria and CSU has been shown.[73] However, the inevitable serious side effects associated with their prolonged use and/or repeated short courses of treatment are the reason why clinical guidelines for the treatment and management of CSU strongly discourage the use of this class of medication in CSU, with the exception of short-term use (~10 days) for acute CSU exacerbations only.[1] Despite this, systemic corticosteroids remain commonly prescribed for both adults and children with CSU, especially in the primary care setting.[21,74]

Other treatments studied in childhood CSU

In rare cases, CSU remains uncontrolled despite dose optimization of sgAHs and/or adjunctive use of omalizumab/cyclosporine. In these cases, a case-by-case decision for the next adjunctive therapy may include LTRAs. LTRAs (montelukast and zafirlukast) inhibit leukotriene signaling providing an anti-inflammatory effect.[75-77] They have an excellent safety profile and the only contraindications to their use are hypersensitivity to the formulation (montelukast and zafirlukast) and hepatic failure (zafirlukast).[78-81]The rationale for LTRAs in CSU is demonstrated by their efficacy in other Th2-mediated diseases such as asthma and hay fever. *In vitro* studies validated their role in wheal suppression.[75-77] However, LTRAs did not live up to their promise in the clinic,[82-84] hence their use remains off-label in CSU. The only RCT including a pediatric cohort (95 patients > 12 years of age) showed a modest advantage of the combination of cetirizine 10 mg and zafirlukast 40 mg o.d. vs. cetirizine 10 mg as monotherapy.[77] The estimated efficacy benefit of adding zafirlukast 40 mg to cetirizine 10 mg was approximately 10%.

Hydroxychloroquine, an antimalarial agent, has demonstrated anti-inflammatory properties through the modulation of antigen presentation, inhibition of DNA synthesis and pro-inflammatory cytokines.[85] The recommended maximal daily dose of 5mg/kg of real weight is recommended to minimize the risk of retinopathy, associated with long-term therapy.[86,87] While, the overall safety profile is reassuring, regular ophthalmologic follow-up after five years of use (or based on individual risk factors) and episodic monitoring of biochemical/hematologic parameters is warranted.[88] Promising efficacy of hydroxychloroquine (400 mg daily) in sgAH-resistant adult CSU was demonstrated in a small RCT (vs. placebo) of 48 patients,[89] data in children however, is limited to only 1 successful case report (9-month-old infant).[90]

A prospective case-control study involving 58 patients (≥ 14 years-old) treated with high-dose vitamin D supplementation (at 300 000 IU/month)[91] and a case report of a 14-year-old patient treated with vitamin D (50,000 IU weekly for 5 doses then 2000 IU daily)[92] demonstrated that high-dose vitamin D supplementation in patients with proven vitamin D deficiency may lead to better control of CSU. However, given the observational nature of the study, the potential for confounding is present. Additionally, the safety of using such high doses of vitamin D in children is not well established.[93]

Phototherapy is sometimes used off-label in CSU patients given the long-term experience in using this treatment modality for a wide variety of pruritic dermatoses. Two phototherapy regimens (psoralen and ultraviolet A [PUVA] vs. narrowband ultraviolet B [NB UVB]) were compared in an observational study involving adolescents (aged >14). Similar reductions in CSU symptoms was demonstrated in both treatment groups.[94]

Allergen-specific immunotherapy in children with CSU and a proven IgE-mediated allergy was evaluated in two studies supporting a potential benefit in these patients.[95] Further, while children were excluded from the recently published RCT employing ligelizumab (a newer generation anti-IgE monoclonal antibody) in moderate-to-severe sgAH-resistant CSU, one active RCT that includes adolescents is ongoing.[96] Finally, data in pediatric CSU on ketotifen, cromolyn sodium, doxepin, sulfones, H2-AHs, a pseudo allergen free-diet and conventional immunosuppressants (e.g. methotrexate) is even more limited.

Conclusion

While more research in pediatric CSU is ongoing, important questions remain, including whether 1) the pathogenesis of pediatric CSU is similar to adult CSU, 2) treatment options currently approved for use in adults and adolescents can be extrapolated for use in younger patients, 3) all sg-AHs are as effective as each other, and 4) up-dosing of sgAHs can be recommended in children. Unfortunately, there is a paucity of literature regarding the efficacy and safety of many drugs used in CSU in pediatric patients of all ages.

For now, the use of sgAHs as a first-line treatment for pediatric CSU is widely-accepted and supported by the international guidelines and several well-designed RCTs.[36-45] While, no specific sgAH is recommended over another, age-specific recommendations should be taken into consideration **(Table 1)**.[1,8,9] We and others, have safely up-dosed sgAHs in children. In fact, our recent data suggest that approximately 90% of children with CSU can be well- and safely- controlled with sgAHs at the licensed and/or increased dosage (up to fourfold).[46] In cases of disease refractory to AHs, omalizumab is approved for children >12 years for CSU and >6 years for asthma.[51-53] However, there is also likely to be a benefit in younger age groups.[49,54,57-65] LTRAs and cyclosporine may be considered on a case-by-case basis. However, given the superiority and better safety profile of sgAHs over the sedative fgAHs in pediatric (and adult) CSU, clinicians should refrain from using fgAHs on a regular basis.

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