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Chronic spontaneous urticaria in children - a systematic review on interventions and comorbidities

Hélène Cornillier[1] | Bruno Giraudeau[2] | Stéphane Munck[3] | Florence Hacard[4] | Annie-Pierre Jonville-Bera[2,5] | Gwenaëlle d'Acremont[6] | Bach-Nga Pham[7] | Annabel Maruani[1,2]

[1]Department of Dermatology, University François Rabelais Tours, CHRU Tours, Tours Cedex 9, France

[2]SPHERE - INSERM 1246, University of Tours and Nantes, Tours, France

[3]Department of Teaching and Research in General Practice, University Nice Sophia Antipolis, Nice, France

[4]Department of Allergology and Immunology, University Hospital Center of Lyon, Lyon, France

[5]Department of Clinical Pharmacology, CHRU Tours, Tours Cedex 9, France

[6]Pediatric office, Paris, France

[7]Laboratory of Immunology, University Hospital Centre of Reims, Reims, France

Correspondence
Hélène Cornillier, Department of Dermatology, CHRU Tours, Hospital Trousseau, Tours Cedex 9, Tours, France.
Email: drhcornillier@gmail.com

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Abstract

Background: Chronic spontaneous urticaria (CSU) is not frequent in children. Management guidelines have been developed for adults and randomized controlled trials (RCTs) included teenagers aged 12-18, but data for children under age 12 are limited. We performed a systematic review to assess comorbidities in children <12 years old with CSU and the efficacy and safety of treatments.

Methods: We searched for original articles of epidemiologic and treatment data in children <12 years old with CSU that were published from 2005 to July 2016 in MEDLINE, EMBASE, CENTRAL, and LILACS. Article selection and data extraction were performed in duplicate.

Results: Our systematic review included 9 reports on epidemiologic data (633 children). Five comorbidities and laboratory anomalies associated with CSU found were atopy (28.1%), positive autologous serum skin test (36.8%), thyroid biologic anomalies (6.4%) and detectable antinuclear antigen (10.4%), seroprevalence for *Helicobacter pylori* (21.1%), low vitamin D level (69.1%), and psychiatric disorders (70.4%). Only one study allowed for comparison with a control group. Our review included 10 studies (322 children), describing 5 different drug families, mostly H1-antihistamines (n = 297). One randomized controlled study compared single-dose rupatadine with single-dose desloratadine and placebo. Cyclosporine was effective and had no adverse effects in 18 children. Omalizumab, montelukast, and cefuroxime were reported in very small series (5, 1, and 1 patients).

Conclusions: H1-antihistamines are effective for CSU in children <12 years old, with reassuring safety data at licensed doses. Cyclosporine seems effective, but the level of evidence is low.

KEYWORDS

children, chronic urticaria, drugs, epidemiology, *Helicobacter pylori*, Treatment

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1 | INTRODUCTION

1.1 | Rationale

Urticaria is a common condition in the pediatric population. The cumulative incidence of all types of urticaria is estimated at 3.5%-8% in children, reaching 16%-24% in adolescents.[1] The most frequent type of urticaria is acute urticaria, which can be viral or allergic, linked to food or, more rarely, drugs in children.

Chronic urticaria is not frequent in children, with a prevalence close to 1.8%;[2] risk factors are not precisely known. According to various recommendations, the diagnosis is based on physical examination. It is defined as the occurrence of spontaneous wheals, angioedema, or both lasting for more than 6 weeks. Guidelines from the European Academy of Allergy and Clinical Immunology, Global Allergy and Asthma European Network, European Dermatology Forum, and World Allergy Organization divide chronic urticaria into 2 groups: chronic inducible urticaria and chronic spontaneous urticaria (CSU).[3] Chronic inducible urticaria includes symptomatic dermographism, cold urticaria, delayed-pressure urticaria, solar and heat urticaria, vibratory angioedema, cholinergic urticaria, contact urticaria, and aquagenic urticaria, whereas CSU is usually of unknown causes, even if triggers have been described.[4]

CSU results from mast-cell activation. Activated mast cells release histamine first, then other mediators such as platelet-activating factor, leukotrienes, and prostaglandins that induce sensory nerve activation, vasodilatation, and plasma extravasation. Treatment includes H1-antihistamines as first-line therapy; with refractory CSU, H2-antihistamines, antileukotriene, immunosuppressive drugs, and anti-IgE antibody (omalizumab) might be tried.[3,5,6]

Guidelines have been developed for managing chronic urticaria in adults,[3,7-10] and recent randomized controlled trials (RCTs) of omalizumab included teenagers from 12 to 18 years old.[11,12] However, there are no specific guidelines for children under age 12. Treatment algorithms are generally extrapolated from adult studies (Table S1). Lack of epidemiologic and therapeutic data led us to perform a systematic review of the epidemiology and interventions for CSU in children.

1.2 | Objective

We performed a systematic review to assess comorbidities and treatments for CSU in children <12 years old.

2 | METHODS

We systematically searched for original articles referring to the epidemiology of and treatment for CSU in children <12 years old. The PRISMA guidelines were followed up for reporting.

2.1 | Eligibility criteria

We included all original reports (for RCTs and observational reports) describing epidemiologic data and treatment for CSU with or without angioedema in children <12 years old. Reports of acute urticaria, inducible urticaria, and urticarial vasculitis were excluded.

2.2 | Information source and search

The search was performed by an information specialist (GF) on July 2016. We searched in the electronic databases MEDLINE via PubMed, EMBASE, CENTRAL, and LILACS for articles published in common European languages (English, French, Spanish, and German) from 2005 to July 2016. The search equations are in Data S1.

2.3 | Study selection strategy

According to the pre-defined criteria, 2 authors (HC, AM) independently selected reports on the basis of the title, then the abstracts. Then, the 2 authors examined the full texts of selected reports. Any discrepancies were resolved by consensus. In case of duplicate publications, we chose the most complete one.

2.4 | Data collection process and data items

For each selected report, 2 authors (HC, AM) independently extracted information on the first author, publication year, journal, country/site, study design, characteristics of patients, type of urticaria, severity and duration of urticaria, associated complications, and comorbidities. Collected data on treatment included study design, type of treatment, outcomes and efficacy, side effects, co-interventions, and follow-up. Any disagreements were resolved by consensus. If any RCT report was found, the risk of bias tool from the Cochrane Collaboration was used.[13]

2.5 | Statistical analysis

We planned to perform a meta-analysis if results of RCTs could be combined. Otherwise, the analysis was descriptive, reporting data as number (%).

3 | RESULTS

3.1 | Study selection

From 374 publications screened, 9 full texts were included for epidemiologic data involving 633 patients (1 case series, 5 cohorts, and 3 cross-sectional studies) and 10 full texts for intervention data involving 322 patients (6 case reports, 3 non-randomized prospective studies, and 1 RCT) (flowcharts of reports selected are in Figure 1A,B). The reasons for excluding full texts are in Table S2.

3.2 | Epidemiologic data

In our systematic review, we identified 5 comorbidities and laboratory anomalies: atopy (6 publications, n = 522 patients), positive

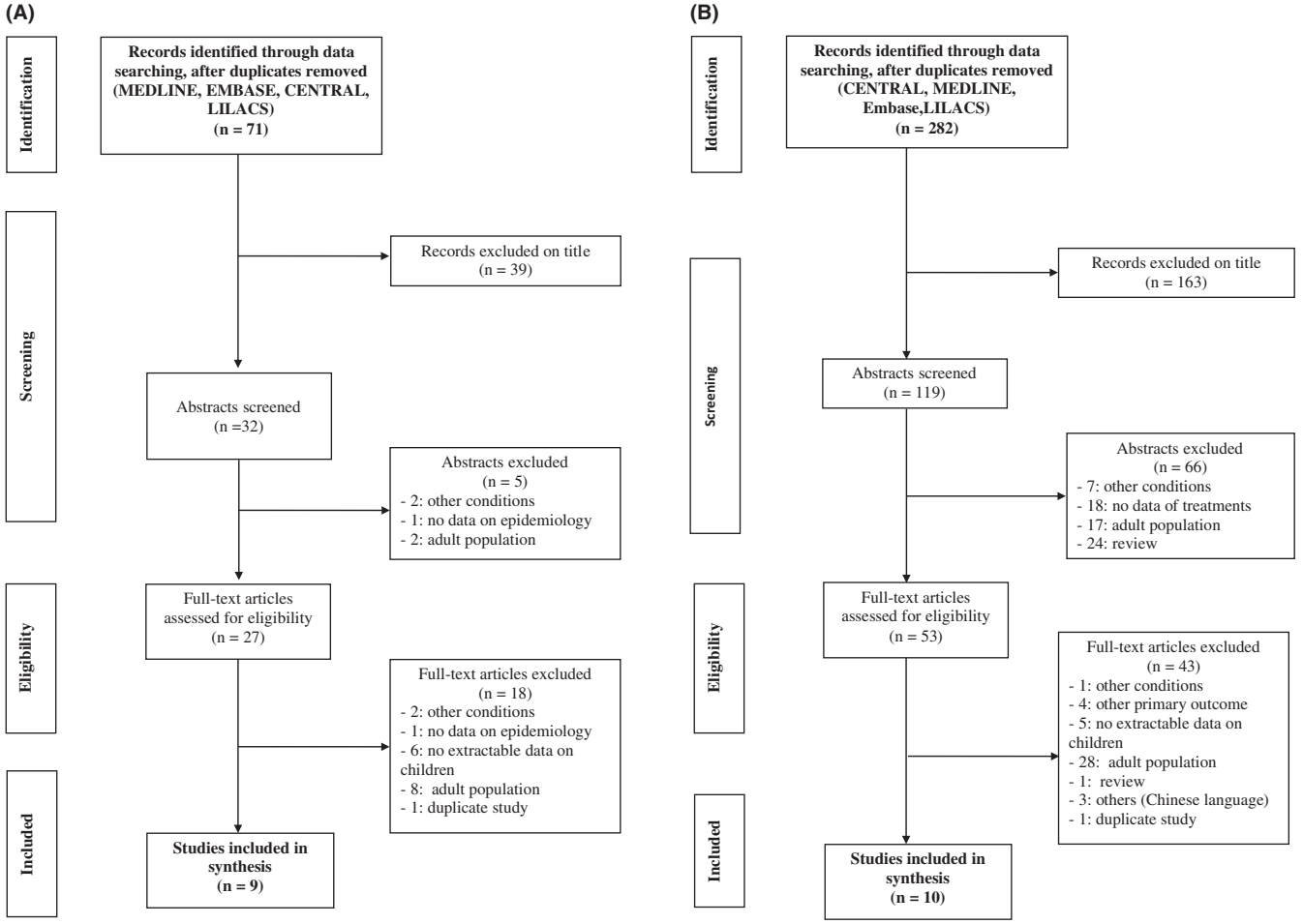


FIGURE 1 (A) Flowchart of publications reporting epidemiological data. (B) Flowchart on publications reporting interventions

autologous serum skin test (ASST; 5 publications, n = 304), autoimmunity laboratory anomalies (6 publications, n = 391), positive seroprevalence for *Helicobacter pylori* (3 publications, n = 90), 25-OH vitamin D deficiency (2 publications, n = 149), and psychiatric disorders (1 publication, n = 27) (Table 1). Only one study compared children with CSU to a control group, so we display descriptive data only.

The prevalence of global atopy was 28.1% in children with CSU (15.4% of asthma, 13.8% of allergic rhinitis, and 9.4% of atopic dermatitis), and 43.0% had a family history of atopy. Regarding the link between CSU and autoimmunity, 5 publications (n = 304 children) focused on the immunologic mechanism by performing the ASST. The ASST was positive in 36.8% of children with CSU (112/304). Antinuclear antibodies were detected in 10.4% of children (23/220 children), and thyroid antibodies (high titers of antithyroperoxidase and/or antithyroglobulin antibody) in 6.4% (20/314); one of these children had abnormal thyroid-stimulating hormone results.

The estimated seroprevalence of *H. pylori* in children with CSU was 21.1%; 2 patients had suggestive gastrointestinal symptoms associated with chronic urticaria. Vitamin D deficiency, defined by 25-OH vitamin D level <30 ng/mL, was found in 69.1% of children (2 publications, 103/149). One publication found psychiatric disorders in 70.4% (19/27), mainly anxiety disorders (13/27, 48.1%) and disruptive behavior disorders (7/26, 25.9%).

3.3 | Intervention data

In our systematic review, 322 children <12 years old with CSU received 5 different treatments: H1-antihistamines, cyclosporine, omalizumab, montelukast, and cefuroxime (Table 2). Overall, 230 children received H1-antihistamines for 6-8 weeks; 145 (63.0%) were in complete remission and 48 (20.9%) in partial remission after treatment. The only RCT included 199 patients randomly allocated to single-dose rupatadine (n = 63), single-dose desloratadine (n = 69), or placebo (n = 67); risk of bias assessment for this study is in Figure 2. The main outcome was percentage change in urticarial activity score 7 (UAS 7), and at 42 days, it differed with active treatment vs placebo (−30.3% placebo, −55.8% rupatadine, −48.4% desloratadine) ($P < .001$), with no significant difference between rupatadine and desloratadine. Ten minor adverse effects (AEs) were reported (1 with rupatadine, 4 with desloratadine, and 5 with placebo). In total, 46 patients had a double, triple, or quadruple dose of H1-antihistamines, with no reported side effects.

TABLE 1 Comorbidities in children <12 y old with chronic spontaneous urticaria

				Comorbidities						Laboratory results				
Reference (author, year)	Country	Study design	Population (N)	Atopy (%)	Asthma (%)	Rhinitis (%)	Atopic dermatitis (%)	Food allergy (%)	Psychiatric disorders (%)	Positivity for ASST[a] (%)	Abnormal thyroid results (%)	Abnormal antinuclear antibodies (%)	Low 25-OH vitamin D level (%)	Positivity for Helicobacter pylori (N/total)
Seung Jin Lee, 2016	Korea	Cross-sectional	57	19.3	–	–	–	0	–	–	–	–	100	–
Mahadevan, 2015	United Kingdom	Retrospective cohort	158	–	20	18	17	14	–	–	–	–	50	–
Cavkaytar, 2014	Turkey	Cohort	81	24.7	–	–	–	–	–	22.2	8.6[b]	–	–	–
Akelma, 2013	Turkey	Cross-sectional	32	21.8	15.6	12.5	15.6	–	–	–	–	26.7	–	10/32[e]
Geschwandtner, 2013	Brazil	Retrospective cohort	57	–	–	–	–	–	–	53	20[b]	–	–	–
Sahiner, 2011	Turkey	Retrospective historical cohort	100	32.7	10.1	7.1	2	1	–	46.7	3.7[c]	13.8	–	3/31[f]
Hergüner, 2011	Turkey	Cross-sectional	27	–	–	–	–	–	70.4	–	–	–	–	–
Jirapongsananuruk, 2010	Thailand	Cohort	94	34	12.8	14.9	2.1	16	–	38.3	0[d]	2.1	–	–
Kilic, 2010	Turkey	Case series	27	–	–	–	–	–	–	25.9	14.8[b]	0	–	6/27[f]

[a]ASST = autologous serum skin test.
[b]High titers of antithyroperoxidase or high titers of antithyroglobulin antibody.
[c]High titers of antithyroperoxidase antibody.
[d]Abnormal thyroid-stimulating hormone or high titers of antithyroperoxidase or high titers of antithyroglobulin antibody.
[e]*Helicobacter pylori* rapid strip test.
[f]*Helicobacter pylori* IgG antibodies.

Cyclosporine treatment was reported in 18 cases and was efficient in all, with complete remission between 2 days and 3 months. No AE was noted. The efficacy of omalizumab was described in 5 case reports and was efficient, with complete remission (80%) and partial remission (20%) between 1 day and 20 months (median 7 days); no AE was noted. Montelukast, in addition to H1-antihistamines, was efficient, with partial remission in one case reported but no mention of AEs. In addition to H1-antihistamines, cefuroxime treatment was reported in 1 case and was efficient.

4 | DISCUSSION

4.1 | Epidemiologic data

Our systematic review found 5 comorbidities and laboratory anomalies associated with CSU in children <12 years old: Atopy was found in 28.1%; 36.8% had a positive ASST result; 6.4% had thyroid biologic anomalies and 10.4% detectable antinuclear antigen; seroprevalence for *H. pylori* was 21.1%; low 25-OH vitamin D level was found in 69.1%; finally, 70.4% of cases featured psychiatric disorders. None of these studies included a control group.

CSU in children is less common than in adults, and we have little information on the natural course of the disease. Sahiner et al showed that 50% children were symptom free within 5 years.[14] Previous studies showed that the disease severity seems to be a risk factor for CSU persistence, and the recovery rate seems to be better for boys than girls and for children <10 years old.[14,15] The prevalence of atopy in children with CSU (28.1% in our review) seems greater than in the general pediatric population. However, previous epidemiologic observations were controversial.[4,16] The very recent study from Lee et al, involving 4076 children in Korea, showed atopy significantly associated with acute allergic urticaria but not chronic urticaria.[2]

The prevalence of a thyroid pathology in children with CSU (6.4%) is less than that in reports of adults with CSU. Indeed, autoimmune pathologies are an evolving process, which can manifest several years after the appearance of CSU. The mechanism of thyroid autoimmunity associated with urticaria is not understood. The presence of antithyroid IgG antibodies seems an indicator of autoimmunity. Kim et al showed an increase risk of CSU in a large adult population with autoimmune thyroid diseases.[17] Some authors suggest that children with chronic urticaria and a positive ASST result should be screened for thyroxin, thyroid-stimulating hormone, and antithyroid antibodies.[15,18] In our review, the ASST was positive in 36.8% of children with CSU (range 22.2%-52.6%), which is similar to previous data in adults.[19] This autoreactivity has been attributable to an IgG autoantibody directed against the alpha-chain of the high-affinity receptor for IgE (FcERIalpha) of mast cells and basophils or against IgE itself.[20] Although ASST is not a diagnostic test, some authors suggest that children with a positive result should be followed up for the development of new autoimmune disease.[14]

We found an *H. pylori* seroprevalence of 21.1% in children with CSU, but no conclusion can be established because of no controls. Data regarding a possible association between *H. pylori* and CSU are controversial in the adult population.[21] In the same way, no conclusion can be raised about the high prevalence of 25-OH vitamin D deficiency in children with CSU because such a deficiency is highly prevalent in the general population. Indeed, the study from Lee et al found no significant difference in deficiency between children with CSU and healthy controls.[2]

Finally, 1 publication revealed psychologic comorbidities in children with CSU. Whether this association, if confirmed, results from urticarial lesions or pruritus or is a causative factor of activated immunologic pathway is unclear.[22]

4.2 | Treatments

Among 5 interventions found in children <12 years old with CSU, only studies of H1-antihistamines included a sufficient number of patients to conclude on efficiency. Second-generation non-sedating antihistamines are the mainstay of treatment for children with CSU. Treatments used were cetirizine, levocetirizine, desloratadine, fexofenadine, or rupatadine. Complete remission was noted in 50%-60% of children with a single dose and 97.5% with a quadruple dose. Unlike in adults, no RCT has been performed in children to demonstrate the efficacy of increasing the dose of H1-antihistamines by up to fourfold, with no improvement with the standard dose of antihistamine vs a switch to another treatment.[4,23] H1-antihistamines were well tolerated in these studies, but we cannot exclude a lack of power to detect rare adverse effects, particularly QT elongation, which has been described with fexofenadine and ebastine in adults. These data are consistent with previous studies showing that H1-antihistamines were well tolerated in children with urticaria or allergic rhinitis.[24]

Recent recommendations state omalizumab as a third-line treatment in adults with CSU resistant to a four-dose H1-antihistamine treatment.[3] In children <12 years old, only 5 cases were reported (with partial or complete remission in all), so the level of evidence of efficacy is very low. The safety profile is better known from extensive experience treating severe allergic asthma, and omalizumab is generally well tolerated in RCTs, although long-term follow-up data are not available.[25] The main severe risk is anaphylaxis.[26] Our review showed more data with cyclosporine (n = 18) than omalizumab (n = 5) in children. The main side effects linked to cyclosporine usually reported include elevated blood pressure and creatinine level, which are reversible at the end of treatment, as well as agitation and sleeplessness.[27,28] No side effects were described in the series included in our systematic review. In the current recommendations, leukotriene receptor antagonists can be used as second-line treatment, but these are no longer an integral part of the step-by-step management diagram. Few data are available and were not included in our review because they were recorded before the last 10 years. They are low cost and considered safe, but their psychiatric safety in the pediatric population needs to be elucidated.[29,30] Other treatments previously reported were H2-antihistamines and treatments based on the possible infectious etiology of CSU.[5]

TABLE 2 Interventions for chronic spontaneous urticaria in children <12 y old

Reference (author, year)	Study design	Intervention	Population (N)	Cointervention	Remission			Adverse event (N)
					Complete (%)	Partial (%)	No change (%)	
H1-antihistamines								
Hui, 2016	Prospective observational study (no funding)	Second-generation H1-antihistamines[a]	98	None	Step 1 (50) Step 2 (35.7) Step 3 (6.1) Step 4 (5.3)	None	None	—
Potter, 2015	RCT (sponsored by industry)	Randomization: -Rupatadine (R) -Desloratadine (D) -Placebo (P)	199 Group R (63) Group D (69) Group P (67)	None	Group R (60) Group D (54) Group P (36)	Group R (40) Group D (34) Group P (16)	—	10/199 R (1) D (4) P (5)
Cyclosporin								
Neverman, 2014	Interventional prospective study (no funding)	Cyclosporine 3 mg/kg/d	16	None	100	0	0	None
Doshi, 2009	Case report (no mentioned funding)	Cyclosporine 3 mg/kg/d	1[b]	Hydroxyzine ±prednisone	100	0	0	None
Giuliodori, 2009	Case report (no mentioned funding)	Cyclosporine 4 mg/kg/d for 2 mo then 0.3 mg/kg/d every 2 mo for 1 y	1	None	100	0	0	None
Omalizumab								
Netchiporouk, 2015	Case series (sponsored by FRSQ)	Omalizumab 150 mg/mo or 300 mg/mo	3[c]	None	100	0	0	None
Asero, 2014	Case report (no funding)	Omalizumab 300 mg/mo	1	None	100	0	0	—
Viswanathan, 2013	Case report (no mentioned funding)	Omalizumab 300 mg/mo	1[d]	None	0	100	0	—
Others								
Sanada, 2005	Interventional prospective study (no mentioned funding)	Montelukast 10 mg/d	1	Usual drug	0	100	0	—
Wieczorek, 2007	Case report (no mentioned funding)	Cefuroxime + Desloratadine	1	None	100	0	0	None

RCT, Randomized control trial.

[a]Cetirizine, desloratadine, levocetirizine, fexofenadine. posology: Step 1: <10 kg: cetirizine = 2.5 mg, levocetirizine = 1.25 mg, desloratadine = 1 mg, 10-19.99 kg: cetirizine = 5 mg, levocetirizine = 2.5 mg, desloratadine = 1.25 mg, 20-29.99 kg: cetirizine = 7.5 mg, levocetirizine = 3.75 mg, desloratadine = 2.5 mg, >30 kg: cetirizine = 10 mg, levocetirizine = 5 mg, desloratadine = 5 mg. For fexofenadine: <2 years old: 30 mg, 2-11 y old: 60 mg, >12 y old = 120 mg. All doses were multiplied by 2, at 2 wk, if the symptoms were not controlled (step 2), then by 3 from the initial dose at 4 wk (step 3) and then by 4 at 6 wk (step 4).

[b]1 case in children among 7 patients.

[c]3 cases in children among 4 patients.

[d]1 case in children among 19 patients.

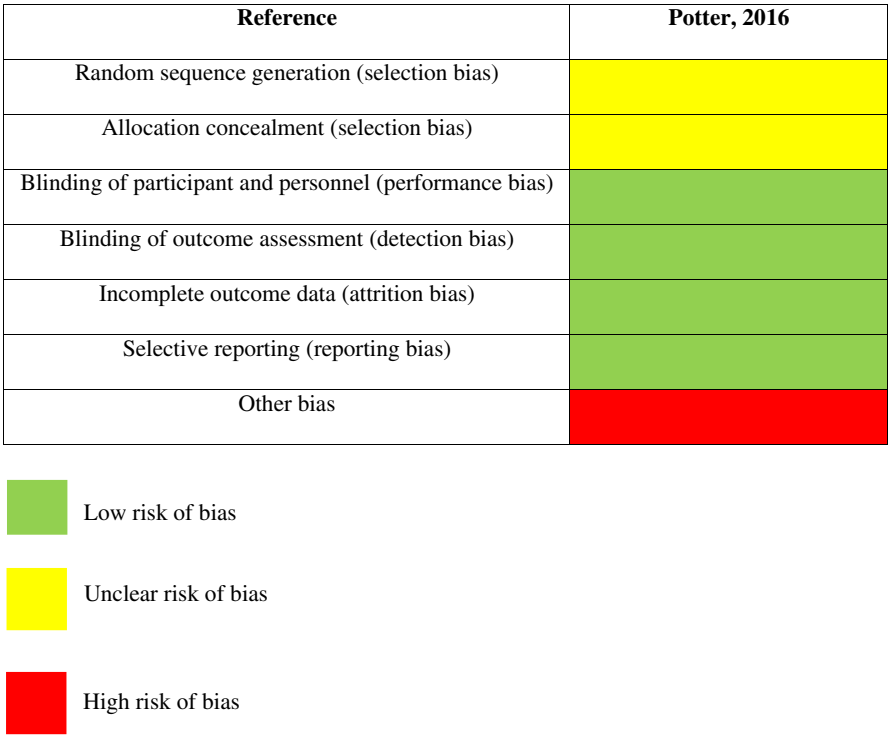


FIGURE 2 Risk of bias of the randomized controlled trial of Potter P et al, rupatadine is effective in the treatment of chronic spontaneous urticaria in children aged 2-11 y Pediatr Allergy Immunol. 2016 [Colour figure can be viewed at wileyonlinelibrary.com]

4.3 | Limitations

The main limitation of this review is that our research was limited to the last 10 years. Therefore, several reports on treatments such as leukotriene receptor antagonists, H2-antihistamines, and immunosuppressive drugs were not included, but this review intended to focus on new therapeutic options (ie, increased posology of H1-antihistamines and omalizumab). Similarly, we did not report epidemiologic factors previously described in children with CSU. The second limitation is linked to the publications included in the review. We found only a few articles, so data concern a limited number of patients. Epidemiologic studies involved no control groups, and interventional studies included only one RCT, funded by the industry. In this medical field, as in numerous others, too few RCTs involve pediatric subjects, except when there is a need for the drug to be licensed in children. Because of the heterogeneity of conditions, comorbidities, mode of outcomes, and follow-up in included studies, comparisons are difficult. In addition, a number of data were not mentioned, especially data on comorbidities and safety. Finally, our study features publication bias because only positive results were reported for the efficacy of interventions in observational reports.

5 | CONCLUSION

Only a few data with no control group are available regarding comorbidities associated with CSU in children. H1-antihistamines are effective, with reassuring safety data. Cyclosporine seems effective but with low level of evidence. Additional studies are needed to better explore links between autoimmunity and CSU,[31] and randomized clinical trials are required to assess the efficacy and safety of escalading doses of H1-antihistamines, and immunosuppressive drugs and omalizumab in children.

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CONFLICT OF INTEREST

None.

ORCID

Hélène Cornillier http://orcid.org/0000-0001-5422-2459

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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Supplemental File 1. Data contained in the different international guidelines regarding management of CSU in the pediatric population

Guidelines	Management in Children
Europe	
Europe:	"The same first-line treatment and up-dosing (weight adjusted) is recommended as in adults. Only medications with proven efficacy and safety in the pediatric population should be used. All further steps should be based on individual considerations. " "We suggest the same treatment algorithm to be used in children with chronic urticaria (weak recommendation/clinical consensus)." "A strong recommendation was made by the panel to discourage the use of first-generation antihistamines in infants and children."
United Kingdom:	"Non-sedating antihistamines are the mainstay of treatment for children with chronic urticaria. Up to four times the recommended dose may be required to adequately control symptoms." "Evidence for the effectiveness of leukotriene receptor antagonists (LTRAs) as monotherapy is poor. Patients not responding to antihistamines alone should be offered a 1- to 4-week trial of the addition of a LTRA, e.g. montelukast 4–10 mg. Shortterm use of oral corticosteroids (3–5 days) may be required to gain control of symptoms." "Tranexamic acid can be effective in the treatment of isolated angioedema. " "Omalizumab is increasing evidence for the efficacy and safety of Omalizumab in children. Other therapies such as ciclosporin should be limited to use in difficult cases and only considered in specialist centres."
America	
USA:	None mentioned
Oceania	
Australia:	"Second generation H1-antihistamines remain the mainstay of CSU treatment in children. Up-dosing of second generation H1-antihistamines, to up to four can be use in second line treatments." "There are no controlled trials to support the use of cyclosporin or other second line agents, such as leukotriene receptor antagonists, H2 receptor antagonists, hydroxychloroquine, azathioprine or methotrexate, in treating children with CSU." "The strongest evidence exists for omalizumab, which has been shown to be safe and effective in treating CSU in patients from seven years of age."
Asia	
Asia:	"We suggest the same first line treatment and up-dosing as for children (weight adjusted) (weak recommendation, low-quality evidence): the first line treatment should be a non-sedating second generation H1-AH. If symptoms persist after 2 weeks, the treatment regimen should be adjusted and non-sedating second generation H1-AH can be up dosed up to 4 times. If symptoms persist after a further 1-4 weeks, the treatment regimen of the nsAH dosage can be changed to a 1st generation sedating antihistamine or an alternative 2nd generation nons edating antihistamine with the option of adding a leukotriene antagonist. Should exacerbation of symptoms occur, in addition the patient can be put on systemic corticosteroid for 3-7 days. If symptoms persist after a further 1-4 weeks, the treatment regimen of the nsAH dosage can be continued as a combination with the addition of a cyclosporine, second generation nonsedating H2-antihistamine, dapsone, or omalizumab. Should exacerbation of symptoms occur, in addition the patient should be put on systemic corticosteroid for another 3-7 days. Therapy with immunomodulating properties could be tried in patients with severe refractory autoimmune urticaria."
Japan:	None mentioned
Taiwan:	"First line treatment should be a non-sedating second generation H1-AH If symptoms persist after 2 weeks, the treatment regimen should be adjusted: switch for another non-sedating second generation H1-AH or add ketotifen or add first generation H1-AH or add another non-sedating second generation H1-AH" "Exacerbation of symptoms: patient can be put on systemic corticosteroid for 3-7 days within a month." "If symptoms persist after 4-6 week: add an alternative agent (Omalizumab or cyclosporine)."

Supplemental File 2. Search equations (MEDLINE)

2A. Search equations for chronic spontaneous urticaria in children and epidemiology

(MESH.EXACT("Urticaria") OR MJEMB.EXACT("chronic urticaria") OR TI(chronic spontaneous urticaria) OR AB(chronic spontaneous urticaria) OR (TI(chronic) OR TI(spontaneous)) AND TI(urticaria))
AND
(MJEMB.EXACT("adolescent") OR MJEMB.EXACT("baby") OR MJEMB.EXACT("school child") OR MJEMB.EXACT("infant") OR MJEMB.EXACT("newborn") OR MJEMB.EXACT("juvenile") OR MJEMB.EXACT("toddler") OR MJEMB.EXACT("preschool child") OR MJEMB.EXACT("child") OR MESH.EXACT("Child, Preschool") OR MESH.EXACT("Child") OR MESH.EXACT("Adolescent") OR MESH.EXACT("Infant") OR MESH.EXACT("Infant, Newborn") OR TI(Child) OR TI(children) OR TI(Kid) OR TI(kids))
AND
MESH.EXACT("Prevalence") OR MJEMB.EXACT("prevalence") OR MJEMB.EXACT("mortality") OR MJEMB.EXACT("incidence") OR MJEMB.EXACT("morbidity") OR MJEMB.EXACT("epidemiology") OR MESH.EXACT("Incidence") OR MESH.EXACT("Morbidity") OR MESH.EXACT("Epidemiology") OR MESH.EXACT("Data Collection") OR MJEMB.EXACT("information processing") OR MJEMB.EXACT("health survey") OR MESH.EXACT("Health Surveys") OR MESH.EXACT("Health Care Surveys") OR MJEMB.EXACT("health care survey") OR TI(epidemiology) OR TI(epidemiologic) OR TI(epidemiological) OR TI(prevalence) OR TI(incidence)
AND
TI(case PRE/0 control PRE/0 stud*) OR TI(cohort*) OR TI(follow PRE/0 up PRE/0 stud*) OR TI(longitudinal PRE/0 stud*) OR TI(prospective PRE/0 stud*) OR TI(retrospective PRE/0 stud*) OR MESH.EXACT(case-control studies) OR MESH.EXACT(cohort studies) OR MESH.EXACT(Cross-Sectional Studies) OR MESH.EXACT(Epidemiologic Studies) OR MESH.EXACT(Follow-Up Studies) OR MESH.EXACT(longitudinal studies) OR MESH.EXACT(prospective studies) OR MESH.EXACT(retrospective studies) OR EMB.EXACT(cohort analysis) OR EMB.EXACT(Cross-Sectional Study) OR EMB.EXACT(follow up) OR EMB.EXACT(longitudinal study) OR EMB.EXACT(prospective study) OR EMB.EXACT(retrospective study) OR EMB.EXACT.EXPLODE(case-control study)

2B. Search equations for chronic spontaneous urticaria in children and interventions

(MESH.EXACT("Urticaria") OR MJEMB.EXACT("chronic urticaria") OR TI(chronic spontaneous urticaria) OR AB(chronic spontaneous urticaria) OR (TI(chronic) OR TI(spontaneous)) AND TI(urticaria))
AND
(MJEMB.EXACT("adolescent") OR MJEMB.EXACT("baby") OR MJEMB.EXACT("school child") OR MJEMB.EXACT("infant") OR MJEMB.EXACT("newborn") OR MJEMB.EXACT("juvenile") OR MJEMB.EXACT("toddler") OR MJEMB.EXACT("preschool child") OR MJEMB.EXACT("child") OR MESH.EXACT("Child, Preschool") OR MESH.EXACT("Child") OR MESH.EXACT("Adolescent") OR MESH.EXACT("Infant") OR MESH.EXACT("Infant, Newborn") OR TI(Child) OR TI(children) OR TI(Kid) OR TI(kids))
AND
(MESH.EXACT.EXPLODE("Therapeutics") OR MESH.EXACT.EXPLODE("Drug Therapy") OR MJEMB.EXACT("nonsurgical invasive therapy") OR MJEMB.EXACT("salvage therapy") OR MJEMB.EXACT("homeopathy") OR MJEMB.EXACT("biological therapy") OR MJEMB.EXACT("therapy") OR MJEMB.EXACT("conservative treatment") OR MJEMB.EXACT("treatment withdrawal") OR MJEMB.EXACT("emergency treatment") OR MJEMB.EXACT("patient care") OR MJEMB.EXACT("prophylaxis") OR MJEMB.EXACT("treatment indication") OR MJEMB.EXACT("treatment response") OR MJEMB.EXACT("disease control") OR MJEMB.EXACT("therapeutic error") OR MJEMB.EXACT("device therapy") OR MJEMB.EXACT("treatment duration") OR MJEMB.EXACT("drug therapy") OR MJEMB.EXACT("substitution therapy") OR MJEMB.EXACT("supplementation") OR MJEMB.EXACT("maintenance therapy") OR MJEMB.EXACT("retreatment") OR MJEMB.EXACT("systemic therapy") OR MJEMB.EXACT("physical medicine") OR MJEMB.EXACT("counseling") OR MJEMB.EXACT("intensive care") OR MJEMB.EXACT("time to treatment") OR MJEMB.EXACT("rehabilitation") OR MJEMB.EXACT("early intervention") OR MJEMB.EXACT("leeching") OR MJEMB.EXACT("stereotactic treatment") OR MJEMB.EXACT("therapy delay") OR MJEMB.EXACT("personalized medicine") OR MJEMB.EXACT("computer assisted therapy") OR MJEMB.EXACT("radiotherapy") OR MJEMB.EXACT("local therapy") OR MJEMB.EXACT("lavage") OR MJEMB.EXACT("therapy effect") OR TI(treatment) OR TI(therapeutic) OR MJEMB.EXACT("histamine H2 receptor antagonist") OR MJEMB.EXACT("histaminergic receptor affecting agent") OR MJEMB.EXACT("histamine H1 receptor antagonist") OR MJEMB.EXACT("histamine H3 receptor antagonist") OR MJEMB.EXACT("antihistaminic agent") OR MJEMB.EXACT("histamine H4 receptor antagonist") OR MESH.EXACT("Histamine Agents") OR MESH.EXACT("Histamine H2 Antagonists") OR MESH.EXACT("Histamine H1 Antagonists") OR MESH.EXACT("Histamine Antagonists") OR MESH.EXACT("Omalizumab") OR MJEMB.EXACT("omalizumab") OR MJEMB.EXACT("methotrexate") OR MESH.EXACT("Methotrexate") OR MESH.EXACT("Anti-Allergic Agents") OR MESH.EXACT("Cyclosporine") OR MJEMB.EXACT("cyclosporin") OR MJEMB.EXACT("montelukast") OR TI(Montekulast) OR TI(cyclosporine) OR TI(methotrexate) OR TI(singulair) OR TI(xolair) OR TI(omalizumab) OR AB(Montekulast) OR AB(cyclosporine) OR AB(methotrexate) OR AB(singulair) OR AB(xolair) OR AB(omalizumab) OR TI(histamine))

Supplemental File 3. Reasons for excluding full texts

3A. Epidemiology

Article references	Cause of exclusion
Brüske I, Standl M, Weidinger S, Klümper C, Hoffmann B, et al. Epidemiology of urticaria in infants and young children in Germany--results from the German LISAplus and GINIplus Birth Cohort Studies, Pediatric allergy and immunology: official publication of the European Society of Pediatric Allergy and Immunology 2014; 25	Other conditions (acute urticaria)
Mogica-Mogica JD, Gómez-López VM, Association between Helicobacter pylori and allergic and non-allergic chronic urticaria, Revista alergia Mexico (Tecamachalco, Puebla, Mexico: 1993) 2013; 60	No extractable data on children
Kennedy JL, Stallings AP, Platts-Mills TAE, Oliveira WM, Workman L, et al Galactose-α-1,3-galactose and delayed anaphylaxis, angioedema, and urticaria in children, Pediatrics 2013; 131	Other conditions (acute urticaria)
Zuel-Fakkar NM, Abdel Hameed DM, Hassanin OM, Study of Blastocystis hominis isolates in urticaria: a case-control study, Clinical and experimental dermatology 2011; 36	No detailed extractable data on chronic urticaria No extractable data on children
Zaraa I, Sliti N, Ben Kheder Z, El Euch D, Trojjet S, et al.Chronic urticaria: a report of 233 cases, La Tunisie médicale 2010; 88	No extractable data on children
Katsikas G, Karageorgaki ZT, Bertsias GK, Spanakis E, Kritikos HD, et al. An underlying systemic disease is common among patients with chronic, treatment resistant urticaria, referred to a tertiary referral centre for autoimmune diseases, Clinical and experimental rheumatology 2010; 28	Population > 13 years old
Kulthanan K, Jiamton S, Rutnin N-o, Insawang M, Pinkaew S, Prevalence and relevance of the positivity of skin prick testing in patients with chronic urticaria, The Journal of dermatology 2008; 35	Adult population
Sianturi GN, Soebaryo RW, Zubier F, Syam AF, Helicobacter pylori infection: prevalence in chronic urticaria patients and incidence of autoimmune urticaria (study in Dr. Cipto Mangunkusumo Hospital, Jakarta), Acta medica Indonesiana 2007; 39	Population > 15 years old
Kulthanan K, Jiamton S, Thumpimukvatana N, Pinkaew S, Chronic idiopathic urticaria: prevalence and clinical course, The Journal of dermatology 2007; 34(5)	Population > 15 years old
Feibelmann TCM, Gonçalves FT, Daud MS, Jorge AdS, Mantese SAO, et al. Assessment of association between autoimmune thyroid disease and chronic urticaria, Arquivos brasileiros de endocrinologia e metabologia 2007; 51	Adult population
Kulthanan K, Jiamton S, Gorvanich T, Pinkaew S, Autologous serum skin test in chronic idiopathic urticaria: prevalence, correlation and clinical implications, Asian Pacific journal of allergy and immunology / launched by the Allergy and Immunology Society of Thailand 2006; 24	Adult population
Song Z, Zhai Z, Zhong H, Zhou Z, Chen W, et al., Evaluation of autologous serum skin test and skin prick test reactivity to house dust mite in patients with chronic spontaneous urticaria, PloS one 2013; 8	No extractable data on children
Asero R, D-dimer: a biomarker for antihistamine-resistant chronic urticaria, The Journal of allergy and clinical immunology 2013; 132(4)	Intervention studies
Persechino S, Annibale B, Caperchi C, Persechino F, Narcisi A, et al., Chronic idiophatic urticaria and Helicobacter pylori: a specific pattern of gastritis and urticaria remission after Helicobacter pylori eradication, International journal of immunopathology and pharmacology 2012; 25	Adult population
Guerra L, Rogkakou A, Massacane P, Gamalero C, Compalati E, et al., Role of contact sensitization in chronic urticaria, Journal of the American Academy of Dermatology 2007; 56	Adult population
Amsler E, Soria A, Vial-Dupuy A, What do we learn from a cohort of 219 French patients with chronic urticaria?, European journal of dermatology : EJD 2014; 24	No extractable data on children
Chansakulporn S, Pongpreuksa S, Sangacharoenkit P, Pacharn P, Visitsunthorn N, et al., The natural history of chronic urticaria in childhood: a prospective study, Journal of the American Academy of Dermatology 2014; 71, Pages: 663-668	Duplicate study
Zuberbier T, Balke M, Worm M, Edenharter G, Maurer M, Epidemiology of urticaria: a representative cross-sectional population survey, Clinical and experimental dermatology 2010; 35, Pages: 869-873	No extractable data on children

3B. Interventions

Article references	Cause of exclusion
Ulrich W, Anti-IgE for chronic urticaria - are children little adults after all? Pediatric Allergy and Immunology 2015; 26	No extractable data
Lee J, Aspirin desensitization as a treatment for aspirin-sensitive chronic spontaneous urticaria, Dermatologic therapy 2015; 28	Population> 12 years old
Johnson M, Kwatra G, Badyal DK, Thomas EA, Levocetirizine and rupatadine in chronic idiopathic urticaria, International journal of dermatology 2015; 54	Population > 12 years old
Sussman G, Hébert J, Barron C, Bian J, Caron-Guay R-M, et al., Real-life experiences with omalizumab for the treatment of chronic urticaria, Annals of allergy, asthma & immunology: official publication of the American College of Allergy, Asthma, & Immunology 2014; 112	No extractable data
Cavkaytar O, Arik Yilmaz E, Buyuktiryaki B, Sekerel BE, Sackesen C, et al., Challenge-proven aspirin hypersensitivity in children with chronic spontaneous urticaria, Allergy 2015; 70	Other primary outcome
Sharma VK, Singh S, Ramam M, Kumawat M, Kumar R, A randomized placebo-controlled double-blind pilot study of methotrexate in the treatment of H1 antihistamine-resistant chronic spontaneous urticaria, Indian journal of dermatology, venereology and leprology 2014; 80	Population > 12 years old
Košnik M, Kopač P, Eržen R, Bajrović N, Adamič K, et al., Omalizumab in chronic urticaria: our experience and literature review, Acta dermatovenerologica Alpina, Pannonica, et Adriatica 2014; 23	Population > 12 years old
Okubo Y, Shigoka Y, Yamazaki M, Tsuboi R, Double dose of cetirizine hydrochloride is effective for patients with urticaria resistant: a prospective, randomized, non-blinded, comparative clinical study and assessment of quality of life, The Journal of dermatological treatment 2013; 24	Population > 12 years old
Amsler E, Soria A, Vial-Dupuy A, What do we learn from a cohort of 219 French patients with chronic urticaria?, European journal of dermatology: EJD 2014; 24	No extractable data
Tao S, Acupuncture treatment for 35 cases of urticaria, Journal of traditional Chinese medicine, Academy of Traditional Chinese Medicine 2009; 29	No extractable data
Labrador-Horrillo M, Valero A, Velasco M, Jáuregui I, Sastre J, et al., Efficacy of omalizumab in chronic spontaneous urticaria refractory to conventional therapy: analysis of 110 patients in real-life practice, Expert opinion on biological therapy 2013; 13	Population > 12 years old
Khafagy NH, Salem SAM, Ghaly EG, Comparative study of systemic psoralen and ultraviolet A and narrowband ultraviolet B in treatment of chronic urticaria, Photodermatology, photoimmunology & photomedicine 2013; 29	Population > 12 years old
Kaplan A, Ledford D, Ashby M, Canvin J, Zazzali JL, et al., Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy, The Journal of allergy and clinical immunology 2013; 132	Population aged > 12 years old
Zimmerman AB, Berger EM, Elmariah SB, Soter NA, The use of mycophenolate mofetil for the treatment of autoimmune and chronic idiopathic urticaria: experience in 19 patients, Journal of the American Academy of Dermatology 2012; 66	Population > 12 years old
Geschwandtner DT, Chong Neto HJ, Riedi CA, Rosário NA, Autologous serum skin test (ASST) and response to treatment in children with chronic idiopathic urticaria, Allergy: European Journal of Allergy and Clinical Immunology 2013; 68	Other primary outcome
Britto-Williams P, Pansare M, Management of chronic idiopathic urticaria in childhood: are we on the same page?, The journal of allergy and clinical immunology. In practice 2013; 1	Other primary outcome
De Vos C, Mitchev K, Pinelli M-E, Derde M-P, Boev R, Non-interventional study comparing treatment satisfaction in patients treated with antihistamines, Clinical drug investigation 2008; 28	No extractable data

Kocatürk E, Aktaş S, Türkoğlu Z, Kavala M, Zindanci I, et al., Autologous whole blood and autologous serum injections are equally effective as placebo injections in reducing disease activity in patients with chronic spontaneous urticaria: a placebo controlled, randomized, single-blind study, The Journal of dermatological treatment 2012; 23	Population > 12 years old
Arik Yilmaz E, Cavkaytar O, Uysal Soyer O, Tuncer A, Sackesen C, Successful treatment of an infant with chronic urticaria caused by Blastocystis spp, Allergy: European Journal of Allergy and Clinical Immunology 2012; 67	Article in Chinese language
Shi L-H, Fang C-Y, Li X-M, Therapeutic effect of anti-anaphylaxis granule on chronic urticaria and its impact on serum levels of RANTES, Chinese journal of integrated traditional and Western medicine 2009; 29	Article in Chinese language
Jin C-Y, Wang D-L, Fang Z-D, Effect of integrative Chinese and Western medicine in treating chronic urticaria and its impact on interleukin-10 and interleukin-8 in peripheral blood, Chinese journal of integrated traditional and Western medicine, 2008; 28	Article in Chinese language
Simons FER, H1-antihistamine treatment in young atopic children: effect on urticaria, Annals of allergy, asthma & immunology: official publication of the American College of Allergy, Asthma, & Immunology 2007; 99	Others conditions (acute urticaria)
Lara-Corrales I, Balma-Mena A, Pope E, Chronic urticaria in children, Clinical pediatrics 2009; 48(4)	Other primary outcome
Augustin M, Ehrle S, Safety and efficacy of desloratadine in chronic idiopathic urticaria in clinical practice: an observational study of 9246 patients, Journal of the European Academy of Dermatology and Venereology : JEADV 2009; 23	Population > 12 years old
Yadav MK, Rishi JP, Nijawan S, Chronic urticaria and Helicobacter pylori, Indian journal of medical sciences 2008; 62	Population > 12 years old
Serhat Inaloz H, Ozturk S, Akcali C, Kirtak N, Tarakcioglu M, Low-dose and short-term cyclosporine treatment in patients with chronic idiopathic urticaria: a clinical and immunological evaluation, The Journal of dermatology 2008; 35	Population > 12 years old
Khalaf AT, Liu XM, Sheng WX, Tan JQ, Abdalla AN, Efficacy and safety of desloratadine combined with dipyridamole in the treatment of chronic urticaria, Journal of the European Academy of Dermatology and Venereology : JEADV 2008; 22	Population aged > 12 years
Engin B, Ozdemir M, Prospective randomized non-blinded clinical trial on the use of dapsone plus antihistamine vs. antihistamine in patients with chronic idiopathic urticaria, Journal of the European Academy of Dermatology and Venereology : JEADV 2008; 22	Population > 12 years old
Bajaj AK, Saraswat A, Upadhyay A, Damisetty R, Dhar S, Autologous serum therapy in chronic urticaria: old wine in a new bottle, Indian journal of dermatology, venereology and leprology 2008; 74(2)	Population > 12 years old
Gimenez-Arnau A, Pujol RM, Ianosi S, Kaszuba A, Malbran A, et al., Rupatadine in the treatment of chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled multicentre study, Allergy 2007; 62	Population > 12 years old
Zhao Y, Acupuncture plus point-injection for 32 cases of obstinate urticaria, Journal of traditional Chinese medicine Academy of Traditional Chinese Medicine 2006; 26	Population > 12 years old
Shahar E, Bergman R, Guttman-Yassky E, Pollack S, Treatment of severe chronic idiopathic urticaria with oral mycophenolate mofetil in patients not responding to antihistamines and/or corticosteroids, International journal of dermatology 2006; 45	Population > 12 years old
McGirt LY, Vasagar K, Gober LM, Saini SS, Beck LA, Successful treatment of recalcitrant chronic idiopathic urticaria with sulfasalazine, Archives of dermatology 2006; 142(10)	Population > 12 years old
Kalogeromitros D, Kempuraj D, Katsarou-Katsari A, Makris M, Gregoriou S, et al., Theophylline as 'add-on' therapy to cetirizine in patients with chronic idiopathic urticaria. A randomized, double-blind, placebo-controlled pilot study, International archives of allergy and immunology 2006; 139	Population > 12 years old
Jianli C, The effect of acupuncture on serum IgE level in patients with chronic urticaria, Journal of traditional Chinese medicine Academy of Traditional Chinese Medicine 2006; 26	Population > 12 years old

Najib U, Bajwa ZH, Ostro MG, Sheikh J, A retrospective review of clinical presentation, thyroid autoimmunity, laboratory characteristics, and therapies used in patients with chronic idiopathic urticaria, Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 2009; 103	Population > 12 years old
Slowik SM, Slavin RG, Aspirin desensitization in a patient with aspirin sensitivity and chronic idiopathic urticaria, Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 2009; 102	Population > 12 years old
Pons-Guiraud A, Nekam K, Lahovsky J, Costa A, Piacentini A, Emedastine difumarate versus loratadine in chronic idiopathic urticaria: a randomized, double-blind, controlled European multicentre clinical trial, European journal of dermatology: EJD 2006; 16	Population > 12 years old
Blaiss MS, Clinical safety and efficacy of antihistamines in children 6 months to 12 years for treatment of allergic rhinitis and chronic idiopathic urticaria, International Pediatrics 2009; 24	Review
Ogawa Y, Ichinokawa Y, Hiruma M, Machida Y, Funakushi N, et al., Retrospective cohort study on combination therapy with the histamine H2-receptor antagonist lafutidine for antihistamine-resistant chronic urticaria, The Journal of dermatological treatment 2013; 24	Population > 12 years old
Maurer M, Rosén K, Hsieh H-J, Saini S, Grattan C, et al., Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria, The New England journal of medicine 2013; 368	Population > 12 years old
Magen E, Mishal J, Possible benefit from treatment of Helicobacter pylori in antihistamine-resistant chronic urticaria, Clinical and experimental dermatology 2013; 38	Population > 12 years old
Neverman L, Weinberger M, Relationship of clinical characteristics of chronic urticaria in children to treatment outcome, Journal of Allergy and Clinical Immunology 2014; 133	Duplicate study