



Predicting inadequate treatment response in children with chronic spontaneous urticaria

Yu-mi Park¹ | Min-su Oh² | Ji-won Kwon¹

¹Department of Pediatrics, Seoul National University Bundang Hospital, Seongnam, South Korea

²Department of Pediatrics, Jeju National University Hospital, Jeju, South Korea

Correspondence

Ji-won Kwon, Department of Pediatrics, Seoul National University Bundang Hospital, Seongnam, 13620, South Korea.
Email: pedas@snubh.org

Editor: Motohiro Ebisawa

Abstract

Background: We aimed to investigate the treatment response and associated factors for loss of control in children with chronic spontaneous urticaria (CSU).

Methods: A total of 240 CSU patients (aged 0-17 years) were enrolled in a single-center study in Korea from May 2014 to May 2019. We retrospectively reviewed the medical records and compared the duration of treatment and step of medications using the urticaria control test (UCT, range 0-16 points). Serum total immunoglobulin levels, eosinophil count, allergic sensitization, autologous serum skin test, antinuclear antibody, thyroid function test, erythrocyte sedimentation rate, and C-reactive protein were measured. The patients were divided into well-controlled (sustained UCT ≥ 12), partly controlled (fluctuating UCT around 12), and poorly controlled (sustained UCT < 12) groups.

Results: Of the 240 children, 150 (62.5%) achieved well-controlled status; 74 (30.8%), partly controlled; and 16 (6.7%), poorly controlled. Longer duration (adjusted odds ratio: 1.09, 95% confidence interval: 1.05-1.13, $P < .001$) and higher treatment steps (5.61, 2.82-11.14, $P < .001$) for reaching the initial 12 points or more of UCT score, initial urticaria activity score (UAS) score (1.06, 1.03-1.09, $P < .001$), and food sensitization (1.88, 1.03-3.46, $P = .041$) were associated with inadequate treatment response. The mean duration to symptom free for 1 month without medication was 14.6 months in the well-controlled group and 22.1 months in the partly controlled group ($P = .002$).

Conclusion: Children with CSU have a good treatment response. Longer duration and higher treatment step until the initial disease control, higher initial UAS7 score, and food sensitization can predict inadequate treatment response.

KEYWORDS

allergen sensitization, child, chronic spontaneous urticaria, treatment outcome

1 | INTRODUCTION

Chronic urticaria (CU) is defined as urticaria accompanied by wheal and itching lasting for at least 6 weeks. A study from the Korean Health Insurance database reported that the annual prevalence of

CU in Korea was 2.64%-3.52%. The prevalence of chronic spontaneous urticaria (CSU) reached 1.13 ~ 1.67%, which accounts for 42.9-47.5% of all cases of CU.¹ In children, a previous Korean study reported a prevalence of 0.7%, while an Italian study reported a prevalence of 0.38%-0.84%,^{2,3} which was lower than that in adults.

The natural course of CSU in children is generally favorable. About 10%-32% of patients showed remission at 1 year from disease onset, 31%-54% at 3 years, and 38%-72% at 5 years.⁴⁻⁶ Since the CSU characteristics differ between pediatric and adult patients,^{7,8} application of the results of adult studies among children is limited.

Several studies have evaluated the factors associated with the characteristics of CU, control status, and remission in children. Children with CU have a higher prevalence of allergic disease⁹ and allergic sensitization¹⁰ than healthy children. A history of atopic dermatitis is a risk factor for subsequent CSU.¹¹ However, the association between CU remission and allergic diseases or sensitization remains controversial.⁶ CSU generally persists for more than 3-5 years, and most patients show good response to medications. Nevertheless, not all patients with CU are able to maintain their well-controlled status during the follow-up, and pediatric patients may show emotional and behavioral impairments, which have a negative impact on their quality of life.^{12,13} Therefore, it is crucial to determine the associated factors for loss of control.

Some instruments, including urticaria activity score (UAS), urticaria control test (UCT), and CU quality of life (CU-QOL) score, have been validated for the measurement of severity, disease control, and QOL in CU.^{6,14,15} Although UAS7 has been validated for CU patients of all ages^{4,16}, UCT has only been validated in adults.^{17,18} In children, only a few studies have investigated the factors associated with

Key Message

Children of chronic urticaria showed favorable response to medications. Tests for allergic sensitization are not routinely recommended in the practical guidelines. But this study showed that food sensitization is associated with loss of control in children with chronic urticaria. The evaluation of allergic sensitization may help predict the urticaria control status in the clinical setting.

disease control status. In the present study, we aimed to investigate the clinical features according to CU control status and to identify the factors associated with loss of CU control.

2 | METHODS

2.1 | Participants

A total of 524 patients aged below 19 years were diagnosed with CU at Seoul National University Bundang Hospital from May 2014 to May

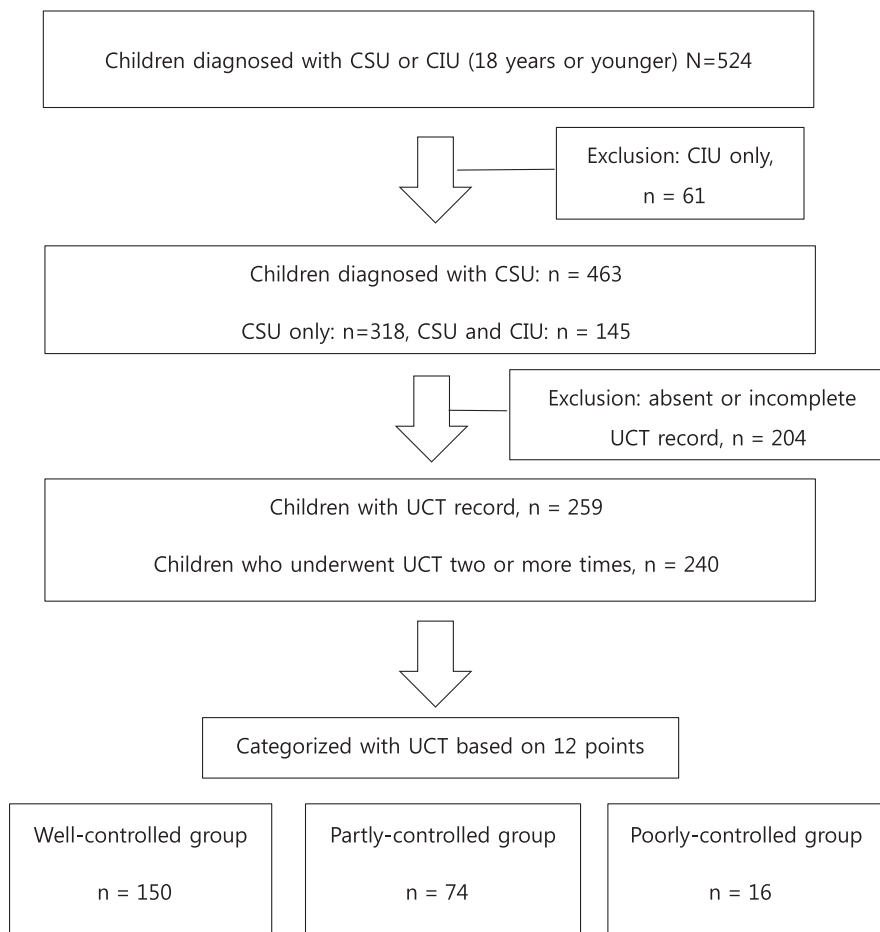


FIGURE 1 Flowchart of participant selection

2019. CSU was defined as spontaneous urticaria lasting for more than 6 weeks. We included patients who underwent UCT at least twice. A total of 240 patients were included in our study (Figure 1).

Children with chronic inducible urticaria (CIU) only, children without medication or with medication only as needed from the first visit, and children whose level of CU control cannot be determined due to incomplete check for UCT scores were excluded.

Patients' medical records were retrospectively reviewed. Demographic and clinical data, including age at onset, sex, history of allergic disease (asthma or recurrent wheezers, allergic rhinitis, atopic dermatitis, and food allergy), familial history of allergic disease, duration of urticaria, medication step, and duration of CU, were collected. After the initial visit, we evaluated the CU control for 2 or 3 weeks. And then if they were well-controlled status, follow-up duration was 2 or 3 months, but if not, follow-up duration was 2 or 4 weeks. Whenever possible, UCT and UAS7 scores were assessed for each visit.

2.2 | Assessment of disease activity and control

The disease activity in CSU patients was assessed by obtaining the UAS7 score. The UAS7 measures both pruritus (0, none; 1, mild; 2, moderate; and 3, intense) and the number of wheals (0, none; 1, mild [<20 wheals/24 h]; 2, moderate [20-50 wheals/24 h]; 3, intense [>50 wheals/24 h or large confluent areas of wheals]). The patients' scores over a 24-hour period for seven consecutive days were summed to yield a possible total score ranging from 0 to 42. Then, the UAS7 scores were used to categorize the severity of CSU in five steps (0, urticaria free; 1-6, well controlled; 7-15, mild; 16-27, moderate; and 28-42, severe).^{6,14,19}

Urticaria control test, a simple four-item instrument, is used to determine patients' disease status. Each question is ranked from 0 to 4 on the basis of severity, with a total possible score of 16. The cutoff value for a well-controlled disease was 12 points.^{14,17,18}

1. How much have you suffered from the physical symptoms of urticaria (itch, hives (welts), and/or swelling) in the last 4 weeks?
2. How much was your QOL affected by the urticaria in the last 4 weeks?
3. How often was the treatment for your urticaria in the last 4 weeks not enough to control your urticaria symptoms?
4. Overall, how well have you had your urticaria under control in the last 4 weeks?

The 12-point UCT scale was used to categorize the level of urticaria control as well-controlled (sustained UCT ≥ 2), partly controlled (fluctuating UCT around 12), or poorly controlled (sustained UCT <12). The CU control status was evaluated by assessing serial UCT scores. If the patient gained <12 points only once during follow-up when the medication step was down, he or she was considered to have a well-controlled status.

2.3 | Laboratory tests

Blood tests were performed to measure the total eosinophil count, serum total immunoglobulin E (IgE), erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP) level, liver function test (aspartate transaminase and alanine aminotransferase), thyroid-stimulating hormone (TSH), free thyroxine (T4), and antinuclear antibody (ANA).

Allergic sensitization was assessed by multiple allergen screening tests (MAST) (R-Biopharm) in children requiring continuous medication or skin prick tests (Allergopharma) for common allergens in those with a tolerable state of urticaria. Sensitization was defined as at least one positive MAST result, an allergen-induced wheal diameter of ≥ 3 mm and $\geq$ positive control (histamine 1 mg/mL) in SPTs. Types and number of allergen for MAST and SPT were described in Appendix S1. An autologous serum skin test (ASST) was performed in children older than 5 years, according to the European Academy of Allergology and Clinical Immunology (EAACI) and Global Allergy and Asthma European Network task force consensus report.²⁰ A positive result was defined as a serum-induced wheal diameter of at least 1.5 mm after 30 minutes, which is greater than that induced by saline.

2.4 | Treatment

The medication to control CU was used according to the CU guidelines suggested by the EAACI/World Allergy Organization¹⁴; the American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma and Immunology²¹; and the Korean Academy of Allergy, Asthma, and Clinical Immunology.²² If the patients failed to respond to a standard dose of second-generation non-sedating H1-antihistamine (2nd AH), the dose of the 2nd AH was increased 2-4 times, or the combined use of other medications, such as leukotriene receptor antagonist (LTRA), first-generation antihistamines, or H2-antagonist, was considered. In patients with severe CU exacerbation or severe urticaria, short-term treatment (3-7 days) of oral corticosteroid was indicated (Figure S1).

2.5 | Statistical analyses

Continuous variables were expressed as means and standard deviations (SDs), while the prevalence was expressed as percentage. Analysis of variance and Student's *t* test were used for between-group comparisons of continuous variables. Mann-Whitney *U* test was used in the comparison of total IgE that showed non-parametric distribution. Categorical variables were compared using Pearson's chi-square test. Univariate and multivariate logistic regression analyses were used to identify the risk factors for non-well-controlled urticaria. The multivariate regression test was adjusted for age, sex, allergy history, family history of allergic diseases, and total IgE levels.

TABLE 1 Comparison of demographics according to each group (N = 240)

	Well-controlled N = 150	Partly controlled N = 74	Poorly controlled N = 16	P-value
Sex (M:F) (%)	78:72 (52.0:48.0)	34:40 (45.9:54.1)	10:6 (62.5:37.5)	.436
Age (years)	6.42 ± 4.04	6.49 ± 4.41	7.59 ± 4.15	.565
CSU only vs CSU + CIU (%)	104:46 (69.3:30.7)	47:27 (63.5:36.5)	12:4 (75.0:25.0)	.559
Duration from disease onset to last follow-up (wks)	65.16 ± 67.76 (7.86-647.4)	91.92 ± 59.43 (9.00-280.4)	64.10 ± 57.43 (10.71-198.6)	.001
Symptom free for 1 mo without medication (n = 82)	63 (42.0%)	19 (25.7%)	0	<.001
Duration to symptom free for 1 mo without medication (wks)	62.40 ± 37.35 (7.86-175.0)	94.51 ± 42.27 (29.00-187.29)		.002
Allergic history	71 (47.3%)	44 (59.5%)	8 (50.0%)	.231
Asthma	16 (10.7%)	16 (17.6%)	0	.101
Allergic rhinitis	47 (31.3%)	25 (33.8%)	4 (25.0%)	.783
Atopic dermatitis	32 (21.3%)	22 (29.7%)	5 (31.3%)	.317
Family history of allergic disease	81 (54.0%)	42 (56.8%)	6 (37.5%)	.373
Duration of symptoms at diagnosis (month)	8.02 ± 14.65	7.00 ± 10.02	11.98 ± 14.08	.400
Initial medication				
2 nd AH usual dose	120 (80.0%)	52 (70.3%)	8 (53.3%)	.018
Updosing 2 nd AH (x2-4) and/or other medication	30 (20.0%)	21 (28.4%)	6 (40.0%)	
Others		1 (1.3%)	1 (6.7%)	
Oral corticosteroid	7 (4.7%)	6 (8.1%)	2 (12.5%)	.248
Treatment response for the first-step medication (%)	119:31 (79.3:20.7)	49:25 (66.2:33.8)	8:8 (50.0:50.0)	.010
Initial UAS7 (n = 205)	12.53 ± 9.13	17.20 ± 9.59	21.13 ± 14.32	<.001
Initial UCT (n = 188)	8.01 ± 2.97	7.05 ± 3.46	5.93 ± 3.00	.023
Sensitization, any	109 (72.7%)	59 (79.7%)	11 (68.8%)	.447
Inhalation	77 (51.3%)	36 (48.6%)	7 (43.8%)	.814
Food	67 (44.7%)	46 (62.2%)	9 (56.3%)	.043
Positive ASST (n = 76)	16 (36.4%)	8 (30.8%)	1 (16.7%)	.604
Positive ANA (n = 118)	27 (37.5%)	10 (27.8%)	4 (40.0%)	.567
TEC (mm ³)	234.04 ± 173.57	267.37 ± 169.37	244.46 ± 225.95	.429
ESR (mm/hr)	9.87 ± 8.11	10.41 ± 7.74	11.25 ± 10.17	.770
Total IgE, geometric mean (IU/mL)	91.10 ± 3.35	112.5n1 ± 3.34	163.04 ± 3.57	.123 ^a

Values are presented as number (percentage) or mean ± standard deviation.

Abbreviations: AH, antihistamine; ANA, antinuclear antibody; ASST, autologous serum skin test; CIU, chronic inducible urticaria; CSU, chronic spontaneous urticaria; ESR, erythrocyte sedimentation rate; IgE, immunoglobulin E; TEC, total eosinophilic count; UAS, urticaria activity score; UCT, urticaria control test.

^aMann-Whitney U test was used in the comparison of total IgE that showed non-parametric distribution.

Results from logistic regression analyses were expressed as odds ratios (ORs) and 95% confidence intervals (CIs).

A *P*-value of $<.05$ was considered significant. All analyses were performed using SPSS for Windows version 25.0 (IBM Corp.).

2.6 | Ethical Approval

This study was approved by the institutional review board of Seoul National University Bundang Hospital (B-1909/567-109). This study was retrospective, proceeded on waiver of informed consent.

3 | RESULTS

3.1 | Demographic characteristics of each controlled group

The mean age of 463 patients with CU was 6.8 years at the initial visit, and 51.6% were men. A total of 318 (68.7%) patients were diagnosed with CSU only (mean age of 6.49 years), while 145 were diagnosed with both CSU and CIU (median age, 7.40 years) (Table S1).

According to the level of CSU control, 150 (62.5%) patients had a well-controlled status, 74 (30.8%) had a partly controlled status, and 16 (6.7%) had a poorly controlled status. No significant differences were observed in the level of CSU control by age or sex ($P = .436$ and $P = .565$, respectively).

Approximately 34.1% (82/240) of the patients showed symptom free for 1 month without medication during the follow-up period, 63 (42.0%) had a well-controlled status, and 19 (25.7%) had a partly controlled status. The mean duration to symptom free for 1 month without medication was longer in the partly controlled group (22.1 months) than in the well-controlled group (14.6 months) ($P = .002$).

No difference was observed in the history of allergic diseases (asthma, AR, and AD) among the different control groups, even though it was slightly higher in the non-well-controlled group (57.8% vs 47.3%, $P = .231$). For the first-step medication, 79.3% in the well-controlled group, 66.2% in the partly controlled group, and 50% in the poorly controlled group showed good treatment response ($P = .010$). There was no difference in the sensitization rate between groups. However, patients in the well-controlled group had lower sensitization rates to foods than those in other groups. A usual dose of 2nd AH for initial treatment was used in 80.0% of well-controlled, 70.3% of the partly controlled, and 53.3% of the poorly controlled group ($P = 0.018$) (Table 1).

3.2 | Disease severity and duration of and medications for initial disease control

The mean UAS7 scores at the first visit were 12.53, 17.20, and 21.1 points in the well, partly, and poorly controlled groups, respectively

($P < .001$). The severity of UAS7 in each group is shown in Figure S2. The mean UCT scores at the first visit were 8.01, 7.05, and 5.93 points in the well, partly, and poorly controlled groups, respectively ($P = .023$). The well-controlled group and the partly controlled group achieved 12 points in the UCT within a mean duration of 7.57 weeks and 13.41 weeks, respectively. Approximately 87.1% of the patients from the well-controlled group and 61.4% from the partly controlled group achieved 12 points within 3 months (Figure S3A).

At 12 points of UCT, 68.9% of the patients from the well-controlled group used a usual dose of 2nd AH, while the rest used higher doses of 2nd AH (3.4%), the usual dose of 2nd AH with other medications (12.8%), or a higher dose of 2nd AH with other medications (14.9%). In the partly controlled group, the usual dose of 2nd AH (34.3%), increased dose of 2nd AH (4.3%), the usual dose of 2nd AH with other medications (21.4%), or increased dose of 2nd AH with other medications was used (Figure S3-B).

3.3 | Factors associated with not-well-controlled urticaria

To evaluate the factors associated with CSU control, we re-categorized the patients into well-controlled and not-well-controlled groups (partly and poorly controlled groups). Univariate logistic regression showed the results in terms of the initial UAS7 score (1.06; 1.03-1.09; $P < .001$), duration (1.09; 1.05-1.13; $P < .001$), and medication (4.74; 2.55-8.82; $P < .001$) until the initial disease control (reaching 12 or more UCT score) and food sensitization (1.95; 1.14-3.32; $P = .014$), initial UCT score (0.89; 0.80-0.98; $P = .015$), and response to the first-step medication (0.45; 2.55-8.82; $P < .001$).

Similarly, the results of multivariate logistic regression showed that a higher initial UAS7 score (OR, 1.06; 95% CI: 1.03-1.09; $P < .001$), longer duration (1.09; 1.05-1.13; $P < .001$) and higher medication step (5.61; 2.82-11.14; $P < .001$) until initial the disease control, and food sensitization (1.88; 1.03-3.46; $P = .041$) were the risk factors for a not-well-controlled CSU. Higher initial UCT score (0.87; 0.79-0.97; $P = .008$) and treatment response for the first-step medication (0.42; 0.23-0.79; $P = .007$) were favorable factors for controlling CSU.

There was no difference in CU control according to age, sex, allergic history, family history of allergic disease, duration of symptoms at diagnosis, and CIU, ASST, or laboratory findings such as total eosinophilic count, IgE, liver function test, thyroid function test, or ANA status (Table 2).

4 | DISCUSSION

In our study, children with CSU generally showed good responses to medications. However, a longer duration and higher treatment step for the initial control, higher initial UAS7 and UCT scores, and food sensitization were risk factors for inadequate disease control. Although the evaluation of allergic sensitization is not essential based on the current CSU guidelines,^{14,21,22} our results suggest that it may help predict the urticaria control status in the clinical setting.

TABLE 2 Odds ratios and confidence intervals of the associated factors for the non-well-controlled (partly and poorly) group

	Univariate		Multivariate	
	aOR (95% CI) ^a	P-value	aOR (95% CI) ^a	P-value
Sex (M:F)	1.13 (0.67–1.91)	.641	1.38 (0.79–2.41)	.265
Age (yr)	1.02 (0.95–1.08)	.633	1.00 (0.93–1.07)	.971
CSU only vs CSU + CIU	1.19 (0.68–2.07)	.544	1.15 (0.64–2.05)	.651
Duration of symptoms at diagnosis (mo)	1.00 (0.98–1.02)	.938	1.00 (0.98–1.02)	.866
UCT ₁₂ duration (wks) ^b	1.09 (1.05–1.13)	.000	1.09 (1.05–1.13)	<.001
Initial UAS7	1.06 (1.03–1.09)	.000	1.06 (1.03–1.09)	<.001
Initial UCT	0.89 (0.80–0.98)	.015	0.87 (0.79–0.97)	.008
Treatment response for the first-step medication	0.45 (0.25–0.81)	.007	0.42 (0.23–0.79)	.007
UCT 12 medication (2 nd AH usual dose vs others)	4.74 (2.55–8.82)	.000	5.61 (2.82–11.14)	<.001
Oral corticosteroid	1.99 (0.70–5.70)	.198	2.32 (0.78–6.97)	.132
Allergic history	1.52 (0.90–2.58)	.118	1.34 (0.75–2.40)	.316
Asthma	1.41 (0.65–3.10)	.386	1.26 (0.55–2.88)	.582
Allergic rhinitis	1.04 (0.60–1.83)	.886	0.79 (0.40–1.55)	.490
Atopic dermatitis	1.58 (0.87–2.87)	.133	1.78 (0.96–3.32)	.069
Food allergy	1.82 (0.88–3.78)	.107	1.73 (0.79–3.78)	.167
Family history of allergic disease	0.97 (0.58–1.64)	.920	1.00 (0.58–1.73)	.996
Sensitization to any allergen	1.32 (0.71–2.43)	.379	0.97 (0.49–1.94)	.935
Inhalant sensitization	0.87 (0.51–1.46)	.594	0.63 (0.35–1.15)	.134
Food sensitization	1.95 (1.14–3.32)	.014	1.88 (1.03–3.46)	.041
Food	Ref	.005	Ref	.012
Monosensitization	1.25 (0.63–2.48)	.519	1.24 (0.60–2.56)	.571
Multiple sensitization	2.75 (1.48–5.13)	.001	2.91 (1.41–6.01)	.004
Positive ASST	0.69 (0.26–1.84)	.451	0.67 (0.23–1.97)	.465
Positive ANA	0.73 (0.33–1.61)	.433	0.68 (0.30–1.53)	.347
TEC	1.00 (1.00–1.00)	.226	1.00 (1.00–1.00)	.471
ESR	1.01 (0.98–1.05)	.532	1.01 (0.97–1.04)	.679
Log_IgE	1.57 (0.93–2.65)	.093	1.34 (0.75–2.40)	.316
Thyroid function abnormality	1.35 (0.56–3.24)	.501	1.31 (0.52–3.31)	.568

Abbreviations: AH, antihistamine; ANA, antinuclear antibody; aOR, adjusted odds ratio; ASST, autologous serum skin test; CI, confidence interval; CIU, chronic inducible urticaria; CSU, chronic spontaneous urticaria; ESR, erythrocyte sedimentation rate; TEC, total eosinophilic count; UAS, urticaria activity score; UCT, urticaria control test.

^aAdjusted for age, sex, allergic history (asthma, allergic rhinitis, or atopic dermatitis), family history of allergic diseases (father, mother, or sibling), and Log_IgE.

^bDuration to reach the first 12 or more points of UCT.

In a recent study, children with CU had a higher prevalence of sensitization to house dust mites and multiple sensitizations than those with acute urticaria, but there was no significant difference in the prevalence of sensitization to food.¹⁰ In another study, children sensitized to food or inhalant allergens spent more time on symptom improvement.¹⁶ In a study to identify factors associated with symptom free for 1 month without medication in 253 children with CU, sensitized children had a longer duration of CU.⁵ In our study, all children with CSU had a high prevalence of allergen (71.3%), food (48.2%), and inhalant (49.0%) sensitization. Sensitization to food, especially to multiple foods, was associated with an inadequate response to treatment. Although adult CSU patients with positive

ASST or positive SPT, mainly to house dust mite, had higher UAS scores,²³ no study has evaluated urticaria control status using the results of SPT and UAS, or UCT in children.

CD63 expression in CSU patients with allergic sensitization was significantly higher than that in those without sensitization.²⁴ A higher level of spontaneous basophil activation in CSU patients with allergic sensitization²³ suggested that allergic sensitization may be an underlying factor contributing to the pathogenesis of CSU. These results may support our findings, which indicated that there was more inadequate control of CSU among food-sensitized children. Further studies are required to identify the mechanism of the impact of allergen sensitization on CU control.

The prevalence of allergic diseases was higher in children and adults than in those without CSU.^{1,7,25} A strong link between CSU and allergic diseases was reported,⁹ and a history of atopic dermatitis was considered an important risk factor for the subsequent occurrence of CSU.¹¹ Several studies have shown an association between allergic diseases and CU compared with the normal population. In addition, our results showed that 51.0% of the patients had a history of allergic disease. However, we did not find an association between CU control status and a history of allergic diseases. We suspected that a history of atopic dermatitis might be a risk factor for inadequate response to medications ($P = .069$). Further studies are warranted to identify the association between atopic dermatitis and CU control using objective indicators.

When identifying the treatment steps for CU control and the response to management, most children had a favorable response to the usual dose of 2nd AH.^{25,26} Our results also showed that 58.8% of the total patients had used the usual dose of 2nd AH in order to achieve a UCT of 12 points. A total of 87.1% of the well-controlled group achieved 12 points of UCT within 3 months, but 82.8% of the partly controlled group required 6 months. The higher treatment steps and longer duration until the initial disease control and poor response to the first treatment were associated with inadequate control of CSU.

The higher UAS7 score at the first visit was associated with inadequate control of CSU in our study. Children with higher UAS7 at admission showed a longer persistence of symptoms and needed more medications to improve the symptoms.^{4,16} Therefore, UAS7 score and disease activity at the first visit seemed to be significant factors for controlling CSU. Furthermore, initial UCT scores were associated with CU control in the future. These findings suggest that active treatment for CU control may be required to maintain the subsequent control status.

Our study evaluated CU control using UCT and investigated the risk factors according to the CU control status. UCT was used to determine the level of disease control in CU patients as a validated tool in adults.^{17,18} Although UCT has not yet been validated in children, we found that UCT-based groups showed a reasonable correlation with the UAS7 score and the duration and medication until initial CU control. Hence, UCT may be a useful tool to evaluate CU control status in children. This is the first study to objectively evaluate CU control using UCT in children and to investigate the associated factors.

The present study had some limitations. This study was conducted in a single tertiary center. Therefore, selection bias might have occurred. Moreover, this study was a retrospective chart review that there might be data missing or inappropriate records about the use of rescue medication, personal and familial history of allergic diseases, and non-adherence. These might cause bias. Furthermore, because we defined allergic sensitization of patients who were unable to quit medication by MAST, a semi-quantitative method, careful interpretation is needed. However, in the regression analysis, multiple sensitizations to foods were more strongly associated with CU control than was monosensitization; thus, food sensitization may be an essential factor for CU control. We evaluated only

food sensitization and did not confirm the food allergy using the food provocation test. Because food sensitization is not equivalent to clinical food allergy, careful interpretation is needed. Despite this limitation, the present study may have strength because we used UAS and UCT as objective indicators to define the severity and control status and tried to categorize the patients according to the level of control in a relatively large number of patients. Our results may provide useful information regarding the control of CU in children.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTION

Yu-Mi Park: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Visualization (equal); Writing-original draft (equal). **Min-su Oh:** Conceptualization (supporting); Formal analysis (supporting); Investigation (supporting); Methodology (supporting); Writing-review & editing (supporting). **Ji-Won Kwon:** Conceptualization (lead); Investigation (lead); Methodology (lead); Supervision (lead); Writing-review & editing (lead).

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/pai.13319>.

ORCID

Yu-mi Park  <https://orcid.org/0000-0002-5807-9976>

Ji-won Kwon  <https://orcid.org/0000-0002-5129-928X>

REFERENCES

- Kim BR, Yang S, Choi JW, Choi CW, Youn SW. Epidemiology and comorbidities of patients with chronic urticaria in Korea: a nationwide population-based study. *J Dermatol*. 2018;45(1):10-16.
- Lee SJ, Ha EK, Jee HM, et al. Prevalence and risk factors of urticaria with a focus on chronic urticaria in children. *Allergy Asthma Immunol Res*. 2017;9(3):212-219.
- Cantarutti A, Dona D, Visentin F, et al. Epidemiology of frequently occurring skin diseases in Italian children from 2006 to 2012: a retrospective, population-based study. *Pediatr Dermatol*. 2015;32(5):668-678.
- Arik Yilmaz E, Karaatmaca B, Cetinkaya PG, Soyer O, Sekerel BE, Sahiner UM. The persistence of chronic spontaneous urticaria in childhood is associated with the urticaria activity score. *Allergy Asthma Proc*. 2017;38(2):136-142.
- Park H, Lee JY, Song A, et al. Natural course and prognostic factors of chronic urticaria in Korean children: a single center experience. *Asian Pac J Allergy Immunol*. 2019;37(1):19-24.
- Caffarelli C, Paravati F, El Hachem M, et al. Management of chronic urticaria in children: a clinical guideline. *Ital J Pediatr*. 2019;45(1):101.
- Lapi F, Cassano N, Pegoraro V, et al. Epidemiology of chronic spontaneous urticaria: results from a nationwide, population-based study in Italy. *Br J Dermatol*. 2016;174(5):996-1004.
- Goldstein S, Gabriel S, Kianifard F, Ortiz B, Skoner DP. Clinical features of adolescents with chronic idiopathic or spontaneous urticaria: review of omalizumab clinical trials. *Ann Allergy Asthma Immunol*. 2017;118(4):500-504.

9. Rosman Y, Hershko AY, Meir-Shafir K, et al. Characterization of chronic urticaria and associated conditions in a large population of adolescents. *J Am Acad Dermatol*. 2019;81(1):129-135.
10. Lee JB, Lee SH, Han MY, Yoon JW. Allergen sensitization and vitamin D status in young Korean children with urticaria. *Allergy Asthma Respir Dis*. 2017;5(3):153.
11. Kitsioulis NA, Papadopoulos NG, Kostoudi S, Manousakis E, Douladiris N, Xepapadaki P. Assessment of atopic dermatitis as a risk factor for chronic spontaneous urticaria in a pediatric population. *Allergy Asthma Proc*. 2018;39(6):445-448.
12. Beattie PE, Lewis-Jones MS. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. *Br J Dermatol*. 2006;155(1):145-151.
13. Olsen JR, Gallacher J, Finlay AY, Piguet V, Francis NA. Quality of life impact of childhood skin conditions measured using the children's dermatology life quality index (CDLQI): a meta-analysis. *Br J Dermatol*. 2016;174(4):853-861.
14. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2)LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy*. 2018;73(7):1393-1414.
15. Ye YM, Park JW, Kim SH, et al. Clinical evaluation of the computerized chronic urticaria-specific quality of life questionnaire in Korean patients with chronic urticaria. *Clin Exp Dermatol*. 2012;37(7):722-728.
16. Cho S-Y, Choi Y-C, Kim B-G, Jung J-A. Factors associated with the treatment of chronic spontaneous urticaria in children. *Allergy Asthma Respir Dis*. 2017;5(4):211.
17. Weller K, Groffik A, Church MK, et al. Development and validation of the urticaria control test: a patient-reported outcome instrument for assessing urticaria control. *J Allergy Clin Immunol*. 2014;133(5):1365-1372 e1-6.
18. Lee JH, Bae YJ, Lee SH, et al. Adaptation and validation of the Korean version of the urticaria control test and its correlation with salivary cortisone. *Allergy Asthma Immunol Res*. 2019;11(1):55-67.
19. Hawro T, Ohanyan T, Schoepke N, et al. The urticaria activity score-validity, reliability, and responsiveness. *J Allergy Clin Immunol Pract*. 2018;6(4):1185-1190.e1.
20. Konstantinou GN, Asero R, Maurer M, Sabroe RA, Schmid-Grendelmeier P, Grattan CE. EAACI/GA(2)LEN task force consensus report: the autologous serum skin test in urticaria. *Allergy*. 2009;64(9):1256-1268.
21. Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol*. 2014;133(5):1270-1277.
22. Ye YM, Jang GC, Choi SH, et al. Work group report on the management of chronic urticaria. *Allergy Asthma Respir Dis*. 2015;3(1):3.
23. Song Z, Zhai Z, Zhong H, Zhou Z, Chen W, Hao F. 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(5):e64142.
24. Chen Q, Zhai Z, Xu J, et al. Basophil CD63 expression in chronic spontaneous urticaria: correlation with allergic sensitization, serum autoreactivity and basophil reactivity. *J Eur Acad Dermatol Venereol*. 2017;31(3):463-468.
25. Lee XH, Ong LX, Cheong JY, et al. A stepwise approach in the management of chronic spontaneous urticaria in children. *Asia Pac Allergy*. 2016;6(1):16-28.
26. Kanchanapoomi K, Pacharn P, Visitsunthorn N, Jirapongsananuruk O. Medication used to control symptoms of chronic urticaria in children. *Asian Pac J Allergy Immunol*. 2018;38(2):114-119.

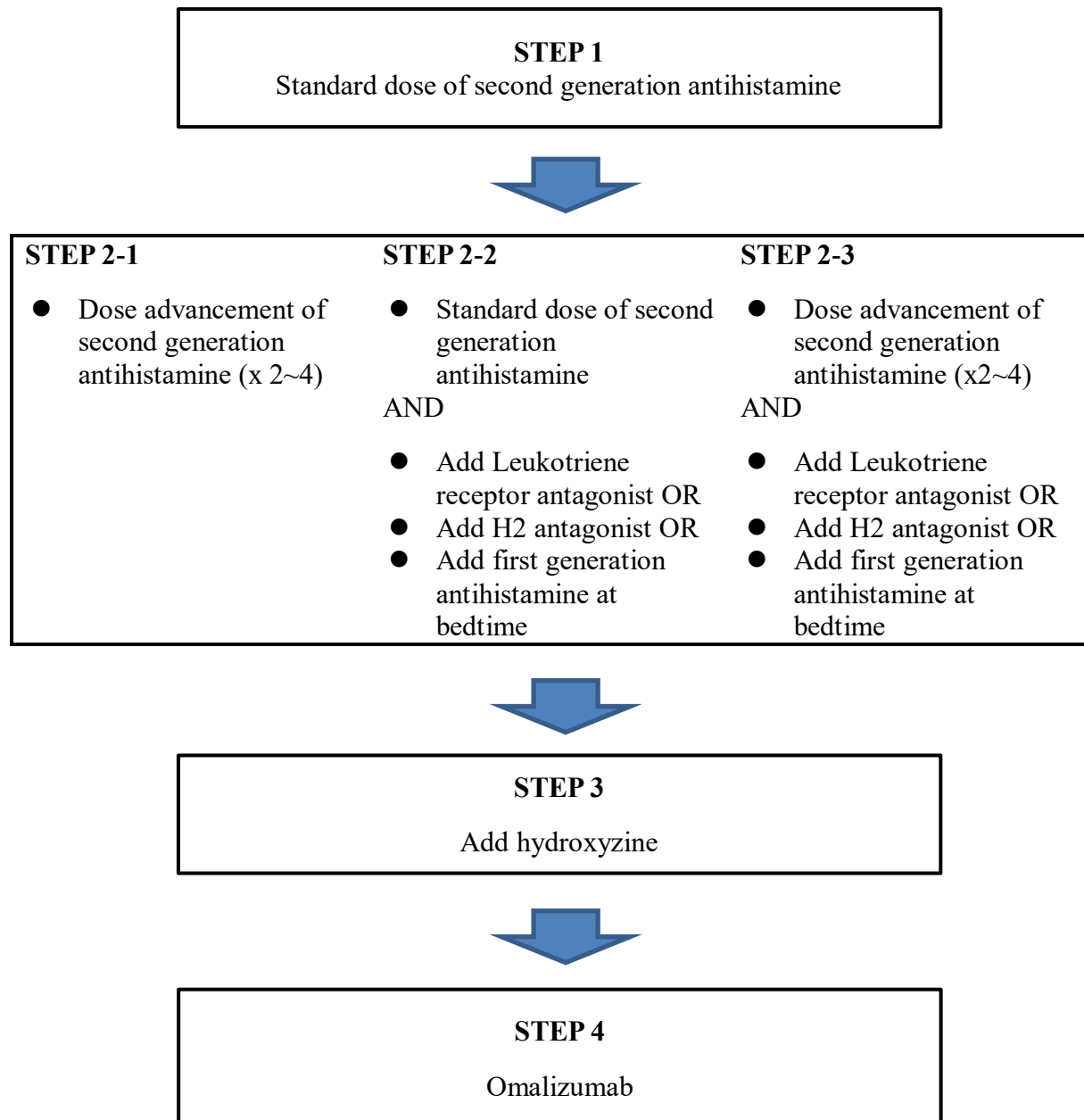
SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

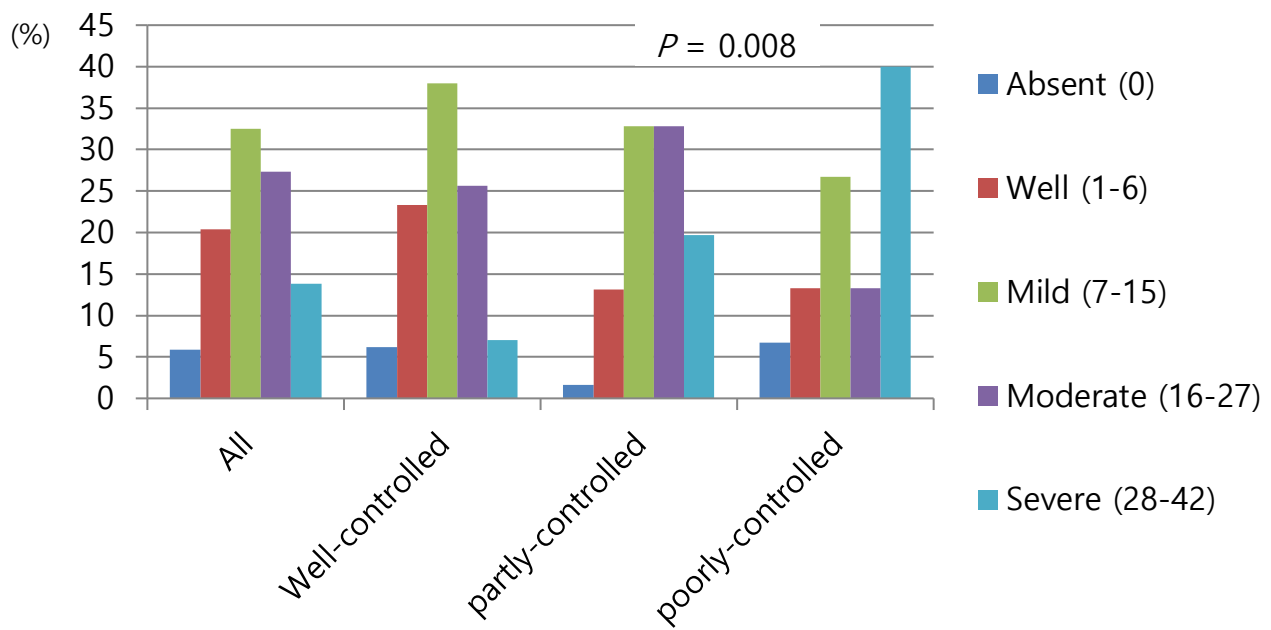
How to cite this article: Park Y-M, Oh M-S, Kwon J-W.

Predicting inadequate treatment response in children with chronic spontaneous urticaria. *Pediatr Allergy Immunol*. 2020;00:1-8. <https://doi.org/10.1111/pai.13319>

Supplement figure 1. Treatment algorithm for chronic urticaria management

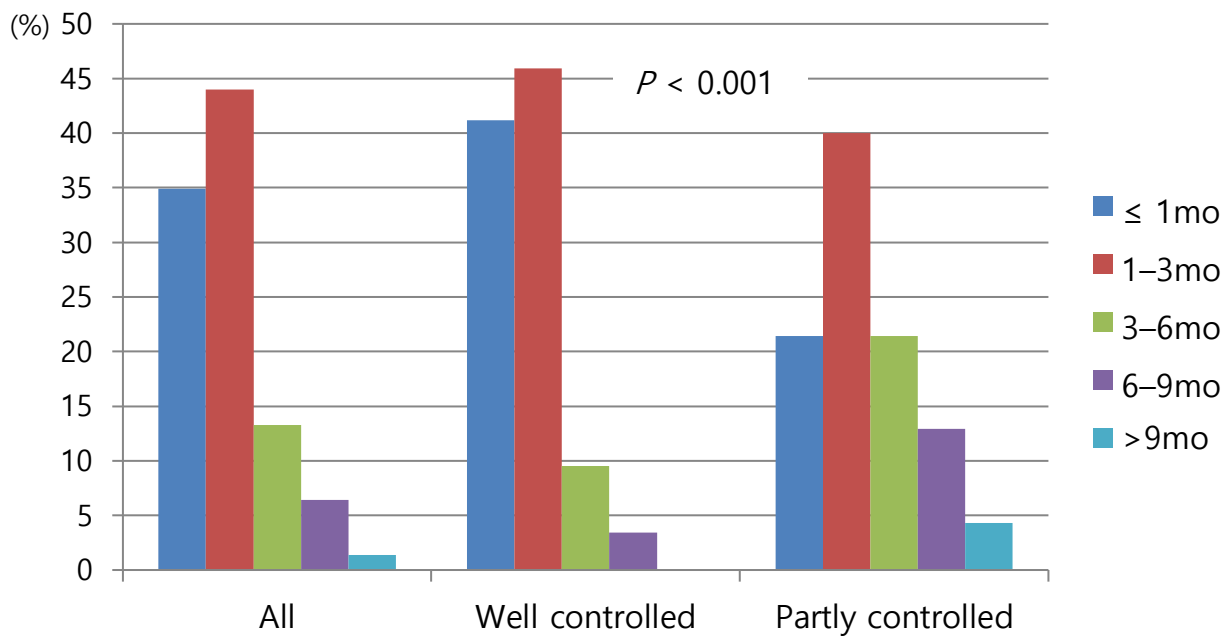


Supplement Figure 2.



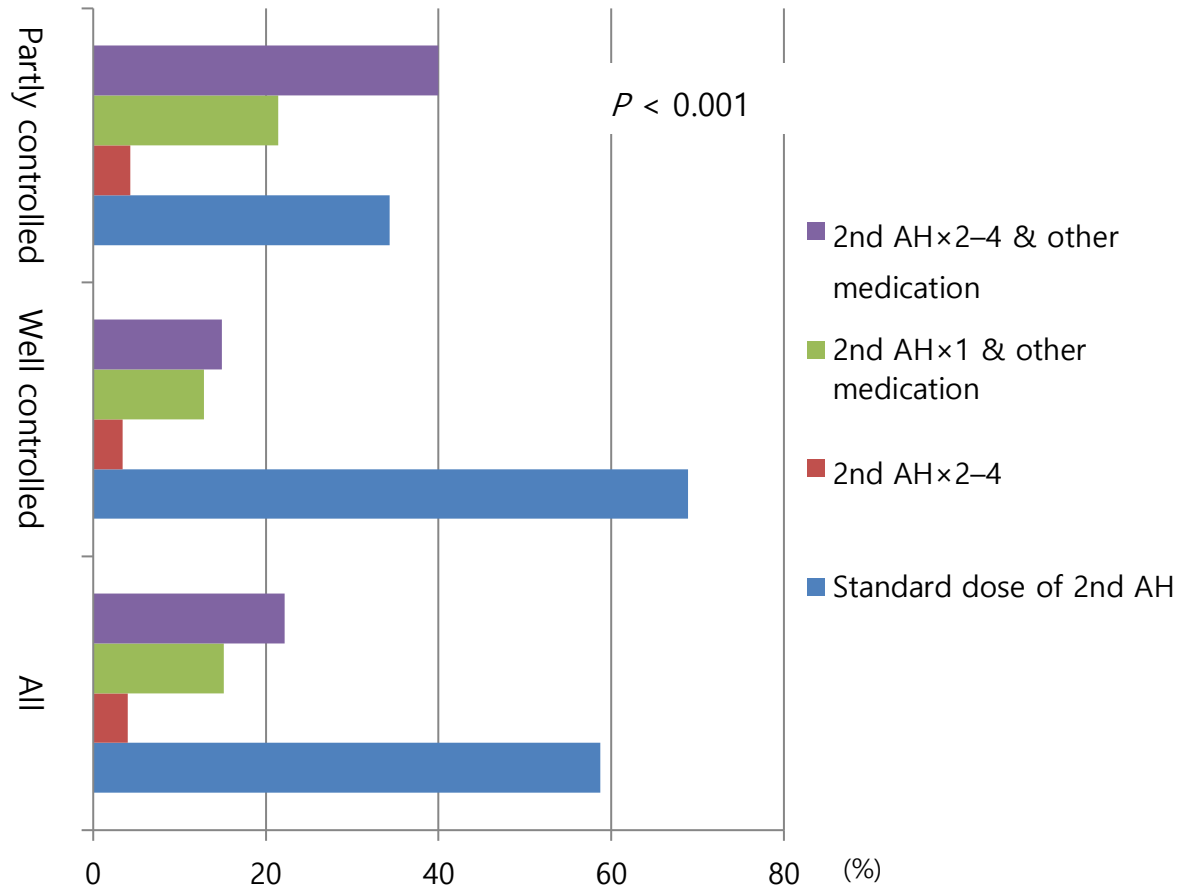
Supplement Figure 3.

(A)



Supplement Figure 3.

(B)



Appendix S1

Supplemental table: Participants' demographic characteristics (N=463)

	Total n=463	CSU vs CSU+CIU		<i>P</i> -value
		CSU only n=318	CSU+CIU n=145	
Sex (M:F) (%)	239:224 (51.6:48.4)	170:148 (53.5:46.5)	69:76 (47.6:52.4)	0.270
Age (years)	6.78 ±4.21	6.49±4.01	7.40±4.56	0.031
<1	14 (3.0%)	10 (3.1%)	4 (2.8%)	0.233
≥1, <3	69 (14.9%)	48 (15.1%)	21 (14.5%)	
≥3, <5	117 (25.3%)	84 (26.4%)	33 (22.8%)	
≥5, <10	154 (33.3%)	111 (34.9%)	43 (29.7%)	
≥10	109 (23.5%)	65 (20.4%)	44 (30.3%)	
Allergic history	236 (51.0%)	172 (54.1%)	64 (44.1%)	0.057
Asthma	53 (11.4%)	43 (13.5%)	10 (6.9%)	0.041
Allergic rhinitis	137 (29.6%)	95 (29.9%)	42 (29.0%)	0.913
Atopic dermatitis	120 (25.9%)	93 (29.2%)	27 (18.6%)	0.016
Food allergy	54 (11.7%)	40 (12.6%)	14 (9.7%)	0.436
Family history of allergic disease	224 (48.4%)	165 (51.9%)	59 (40.7%)	0.028
Duration of symptoms at diagnosis (mo)	7.29 ±12.0	7.22±12.6	7.43±10.7	0.854
Initial UAS7 (n=289)	14.5±10.2	14.2±10.1	15.0±10.3	0.563
Initial UCT (n=254)	7.55±3.17	7.81±3.15	6.96±3.14	0.048
ASST(n=157)	54/157 (34.4%)	38 (37.3%)	16 (29.1%)	0.379
ANA (n=230)	90/230 (39.1%)	62 (38.3%)	28 (41.2%)	0.767
ESR (mm/hr)	9.81±8.28	9.35±7.74	10.8±9.32	0.123
Sensitization, any	330 (71.3%)	229 (72.0%)	101 (69.7%)	0.658
Inhalation	223 (48.2%)	151 (47.5%)	72 (49.7%)	0.689
Food	227 (49.0%)	158 (49.7%)	69 (47.6%)	0.690

TEC(/mm ³)		247.1±196.4	257.4±207.2	224.8±169.4	0.088
Total geometric (IU/ml)	IgE, mean	97.8±3.4	95.5±3.6	103.1±3.2	0.538 [†]

Values are presented as number (percentage) or mean ± standard deviation.

[†] Mann-Whitney U test was used in the comparison of total IgE that showed non-parametric distribution.

CSU, chronic spontaneous urticaria; CIU, chronic inducible urticaria; UAS, urticaria activity score; UCT, urticaria control test; ASST, autologous serum skin test; ANA, anti-nuclear antibody; ESR, erythrocyte sedimentation rate; TEC, total eosinophilic count

Supplement Figure 2. Urticaria severity according to urticaria activity score (UAS)7 between groups

The mean UAS7 scores were higher in the non-well-controlled group than in the well-controlled group.

The percentages of severity of CSU in five steps: absent, well, mild, moderate, and severe. All subjects: 5.9%, 20.4%, 32.5%, 27.3%, and 13.8%; well-controlled group: 6.2%, 23.3%, 38.0%, 25.6%, and 7.0%; partly-controlled group: 1.6%, 13.1%, 32.8%, 32.8%, and 19.7%; poorly-controlled group: 6.7%, 13.3%, 26.7%, 13.3% and 40.0%, respectively.

Supplement Figure 3. Comparison of (A) symptom duration and (B) medication types at the time of initial disease control

(A) The duration of symptoms in the partly controlled group was longer than that in the well-controlled group at the time of initial disease. The percentage of duration in 5 steps: ≤ 1 month, >1 ; ≤ 3 months, >3 ; ≤ 6 months, >6 ; ≤ 9 months, >9 ; ≤ 12 months: all patients: 34.9%, 44.0%, 13.3%, 6.4%, and 1.4%; well-controlled: 41.2%, 45.9%, 9.5%, 3.4%, and 0%; partly controlled: 21.4%, 40.0%, 21.4%, 12.9%, and 4.3%, respectively.

(B) The treatment steps in the partly controlled group was higher than that in the well-controlled group at the time of initial disease. The percentage of medication in the usual dose of 2nd AH, 2nd AH ($\times 2-4$), usual dose of 2nd AH and other medications, and 2nd AH ($\times 2-4$) and other medications: 58.7%, 4.0%, 15.1%, and 22%; well-controlled: 68.9%, 3.4%, 12.8%, and 14.9%; partially controlled: 34.3%, 4.3%, 21.4%, and 40.0%, respectively.

Supplement. Antigen type and number by multiple allergen screening tests (MAST) and Skin prick test (SPT).

MAST

House dust, *D. pteronyssinus*, *D. farinae*, Cat epithelium & dander, Dog dander, Egg white, Milk, Cockroach, Peanut, Soy bean, Wheat, Alder, Birch, Oak, Common ragweed, Japanese hop, Mugwort, *Alternaria alternata*, *Cladosporium herbarum*, *Aspergillus fumigatus*, Crab, Shrimp, Mackerel, Cultivated rye, CCD, Peach, Apple, Sesame, Codfish, Tuna/Salmon, Plaice/Anchovy/Alaska Pollock, Lobster/Pacific squid, Eel, Blue mussel/Oyster/Clam/Scallop, Silkworm pupa, Pork, Beef, Chicken, Lamb meat, Cheese, cheddar type, Barley, Rice, Buckwheat, Yeast, Baker's, Corn, Carrot, Potato, Garlic/Onion, Celery, Cucumber, Tomato, Citrus mix, Strawberry, Kiwi/Mango/Banana, Sweet chestnut, Walnut, Hazel nut, Almond/Pine nut/Sunflower, Cacao

SPT

Aeroallergen 53

D. pteronyssinus, *D. farinae*, *Tyrophagus Putrescentiae*, Outer mold, *Alternaria*, Mold mix 2, *Fusarium*, *Candida*, *Mucor*, *Aspergillus fumigatus*, *A. niger*, *Penicilium mix*, Cat, Dog, Mouse, Chicken, Rabbit, Hamster, Goose, Horse, America CoB, Germany CoB, Tree1, Alder, Hazel, Poplar, Elm, Willow, Birch, Beech, Oak, Platanus, Japanese cedar, Ash, Box elder, False acacia, Pine, Grasses, Velvet, Orchard, Rye, Timothy, Kentucky blue grass, Mead, Nettle, Ragweed, Mugwort, chrysanthemum, Dandelion, Golden Rod, Plantain, Latex

Food/Aeroallergen mix

24: *D. pteronyssinus*, *D. farinae*, Cat, Dog, Horse, GCoB, Outer mold, *Mucor*, *Alternaria*, *Aspergillus fumigatus*, Mold mix 2, *Penicilium mix*, Grasses, Tree1, Weed mix, Ragweed, Mugwort, Wheat Flour, Cow's milk, Egg yolk, Egg white, Beef, Pork, Shrimp

53: *D. pteronyssinus*, *D. farinae*, Cat, Dog, Germany CoB, Outer mold, *Mucor*, *Alternaria*, *A. oryzae*, Mold mix2, *Penicillium mix*, Grasses, Tree 1, hoarse, weed mix, Ragweed, Mugwort, oak, Beech, Nettle, Poplar, Elm, Pine, Japanese cedar, Box elder, Hazel, Oat, Goosefoot, Ash, Alder, Birch, Timothy, Rye, Apple, Beef, chicken, Egg. White, Codfish, Almond, Lobster, Milk, Celery, Tomato, Peach, Peanut, Pork, Mussel, Shrimp, Strawberry, Bean flour, Tuna, Walnut, Wheat flour