

Health care burden and treatment patterns in commercially insured children with chronic idiopathic/spontaneous urticaria: A real-world study in the United States

Paul Williams, M.D.,¹ Abhishek Kavati, Ph.D.,² Dominic Pilon, M.A.,³ Yongling Xiao, Ph.D.,³ Maryia Zhdanova, M.A.,³ Maria-Magdalena Balp, M.D., M.Sc.,⁴ Patrick Lefebvre, M.A.,³ Benjamin Ortiz, M.D.,² and Vivian Hernandez-Trujillo, M.D.⁵

ABSTRACT

Background: Chronic idiopathic urticaria (CIU)/spontaneous urticaria (CSU) is defined by the presence of wheals, angioedema, or both for ≥ 6 weeks, with or without an identifiable trigger. Real-world health care data among children with CIU/CSU remain scarce.

Objectives: To describe treatment patterns, health care resource utilization (HRU), and costs in pediatric patients with CIU/CSU (< 12 years old) and to compare these with pediatric patients without CIU/CSU.

Methods: A commercial administrative claims data base (September 2013 to June 2016) was used. The CIU/CSU cohort included pediatric patients with either two or more claims for a diagnosis of urticaria ≥ 6 weeks apart or one or more claims for a diagnosis of urticaria and one or more claims for a diagnosis of angioedema ≥ 6 weeks apart (index was defined as the first claim). The control cohort comprised pediatric patients without urticaria or angioedema (index randomly assigned). Patients with < 6 months of eligibility before and after the index date were excluded. HRU and costs were compared between the cohorts during the observation period after propensity score matching.

Results: A total of 6109 pediatric patients with CIU/CSU were selected, and 6107 were 1:1 matched with controls. The patients with CIU/CSU who had a mean $\pm$ standard deviation age of 4.58 ± 3.36 years, and 47.9% were girls. CIU/CSU-related medication use increased after diagnosis (e.g., baseline versus 6-month follow-up, 2.2 versus 8.0% for non-sedating prescription H₁ antihistamines; 7.4 versus 17.4% for oral corticosteroids). Relative to the controls, the patients with CIU/CSU had higher rates of HRU (incidence rate ratios of 1.71, 2.39, and 2.07 for inpatient, emergency department, and outpatient visits, respectively; all $p < 0.01$), and higher all-cause per patient per year costs (mean cost differences of \$2090, \$1606, and \$483 for total, medical, and pharmacy costs, respectively; all $p < 0.01$).

Conclusion: This study highlighted unmet needs in pediatric patients with CIU/CSU who had increased medication (e.g., oral corticosteroids) and HRU burden after a diagnosis for CIU/CSU, and higher rates of HRU and costs relative to those without CIU/CSU.

(Allergy Asthma Proc 39:201–211, 2018; doi: 10.2500/aap.2018.39.4129)

Chronic idiopathic urticaria (CIU) and chronic spontaneous urticaria (CSU) are defined by the presence of wheals, angioedema, or both for at least 6 weeks with

or without an identifiable trigger.^{1–3} Non-sedating H₁ antihistamines (hereinafter referred to as H₁ antihistamines) constitute the standard of care for urticaria, and dosage can be gradually increased up to fourfold of the approved dose as a second-line treatment.^{1–3} Third-line treatments, such as leukotriene receptor antagonists, H₂ histamine blockers, oral corticosteroids (OCS), and omalizumab can be used in combination with H₁ antihistamines for patients who do not respond well to H₁ antihistamine monotherapy.^{1–3} Although these treatment guidelines are for adults, the same is recommended in children based on clinical consensus. For pediatric chronic urticaria cases, treatments approved by the U.S. Food and Drug Administration include the H₁ antihistamines cetirizine,⁴ fexofenadine,⁵ desloratadine,⁶ and levocetirizine⁷ for patients > 6 months old; and loratadine⁸ for patients > 2 years old.

Unlike adult CIU/CSU, pediatric CIU/CSU is often associated with infections,^{9,10} which indicates that disease etiology and treatment efficacies may be

From the ¹Northwest Asthma and Allergy Center, Everett, Washington, ²Novartis Pharmaceuticals Corporation, East Hanover, New York, ³Analysis Group, Inc., Montréal, Québec, Canada, ⁴Novartis Pharma AG, Basel, Switzerland, ⁵Herbert Wertheim School of Medicine, Florida International University, Miami, Florida

This research was funded by Novartis Pharmaceuticals Corporation. Medical writing assistance was provided by Samuel Rochette, an employee of Analysis Group, Inc.

P. Lefebvre, D. Pilon, Y. Xiao, and M. Zhdanova are employees of Analysis Group, Inc., a consulting company that has received research grants from Novartis Pharmaceuticals Corporation to conduct this study. A. Kavati and B. Ortiz are employees of Novartis Pharmaceuticals Corporation. M.-M. Balp is an employee of Novartis Pharma AG. P. Williams and V. Hernandez-Trujillo received consulting fees from Novartis Pharmaceuticals Corporation

Presented in part at the 2017 European Academy of Dermatology and Venereology Conference, September 13–17, 2017, Geneva, Switzerland

Address correspondence to Dominic Pilon, M.A., Analysis Group, Inc., 1000 De la Gauchetière West, Suite 1200, Montréal, Québec, Canada H3B 4W5

E-mail address: dominic.pilon@analysisgroup.com

Published online February 19, 2018

Copyright © 2018, OceanSide Publications, Inc., U.S.A.

different among adults and children.^{11,12} The literature on pediatric CIU/CSU remains scarce,¹³ with only a few studies that analyzed clinical outcomes.^{14,15} The prevalence of pediatric CIU/CSU was estimated at 0.1–0.3% in the United Kingdom.¹⁶ Another study, conducted in Spain, reported the prevalence of urticaria among patients <14 years old referred to an allergy department as 7%, among whom 18% of the patients had chronic cases.¹⁷ Few studies characterized the CIU/CSU economic and health care burden^{18–22} and even fewer investigated this matter for different age groups of CIU/CSU,²¹ such as for children. Accordingly, this study aimed to address two objectives (1): to describe baseline characteristics, treatment patterns, health care resource utilization (HRU), and costs in pediatric (<12 years old) patients with CIU/CSU, and (2) to assess the incremental HRU and costs associated with pediatric CIU/CSU by comparing these outcomes with those observed in pediatric patients without CIU/CSU diagnoses.

METHODS

Data Source

Insurance claims from the Truven Health Analytics MarketScan Commercial Claims and Encounters data base (September 1, 2013, to June 30, 2016) included information on outpatient (OP) and inpatient medical claims, OP prescription drug dispensing claims, and eligibility. The data bases were fully compliant with the Health Insurance Portability and Accountability Act, and, thus, no ethics board review was required.

Study Design

The first and second objectives were addressed by using a retrospective cohort and retrospective matched-cohort designs, respectively. For patients in the CIU/CSU cohort, the index date was defined as the date of the first CIU/CSU-related diagnosis (*i.e.*, idiopathic urticaria [*the International Classification of Diseases, Ninth Revision, Clinical Modification* {ICD-9-CM} code 708.1x; *the International Classification of Diseases, Tenth Revision, Clinical Modification* {ICD-10-CM} code L50.1xx], other urticaria [ICD-9-CM code 708.8x; ICD-10-CM code L50.8xx], unspecified urticaria [ICD-9-CM code 708.9x; ICD-10-CM code L50.9xx], or angioedema [ICD-9-CM code 995.1x; ICD-10-CM code T78.3]). For the control cohort, the index date was randomly assigned such that the distribution of the time from the start of the continuous eligibility period to the index date in the control cohort was similar to that observed in the CIU/CSU cohort. The baseline period was defined as the 6-month period before the index date. The observation period spanned the period between the index date and the earliest date of health plan disenrollment or the end of data availability.

Inclusion and Exclusion Criteria

Because no specific diagnosis code exists for CIU/CSU, identification of patients with CIU/CSU relied on an established claims-based algorithm.^{22,23} Briefly, patients were included in the CIU/CSU cohort if they had (1) at least two independent claims with a diagnosis of idiopathic, other, or unspecified urticaria at least 6 weeks apart; or (2) at least one claim with a diagnosis of idiopathic, other, or unspecified urticaria, and at least one other claim with a diagnosis of angioedema at least 6 weeks apart. Patients in the control cohort had no diagnoses for idiopathic, other, or unspecified urticaria, or for angioedema during the study period. For both cohorts, only the patients <12 years old at the index date and with a minimum of 6 months of continuous eligibility before and after the index date were included.

Study Measures

Study measures included patients' baseline characteristics, treatment patterns, and all-cause versus CIU/CSU-related HRU and costs (*i.e.*, pharmacy and medical costs). HRU and medical costs were reported by the type of service: inpatient, emergency department (ED), and OP (broken down into urgent care facility, home care, office, ambulatory surgery center, and other OP visits). Treatment patterns were evaluated during the first 6, 12, and 24 months of follow-up among the patients with sufficient follow-up, and included (1) the proportions of patients prescribed specific CIU/CSU-related treatments, (2) pill burden of any drug (the ratio of the total number of drug pills prescribed to the number of days during a given period), and (3) types of medical specialists visited. All-cause HRU and costs per patient per year (PPPY) were calculated for both cohorts, whereas CIU/CSU-related HRU and costs, identified by using the aforementioned CIU/CSU-related diagnosis codes, were calculated only for the CIU/CSU cohort.

Statistical Analysis

Descriptive statistics were used to summarize patient baseline characteristics, baseline all-cause HRU and costs, and treatment patterns. Means $\pm$ standard deviations (SD) and medians were used to describe continuous variables; frequencies and percentages were used to describe categorical variables. Patients were matched 1:1 based on the propensity score (PS) to adjust for differences in baseline characteristics between the CIU/CSU and control cohorts.²⁴ Briefly, PS, defined as the probability of a given patient to be in the CIU/CSU cohort, was estimated by using a multivariate logistic regression model conditional on age, gender, region, insurance

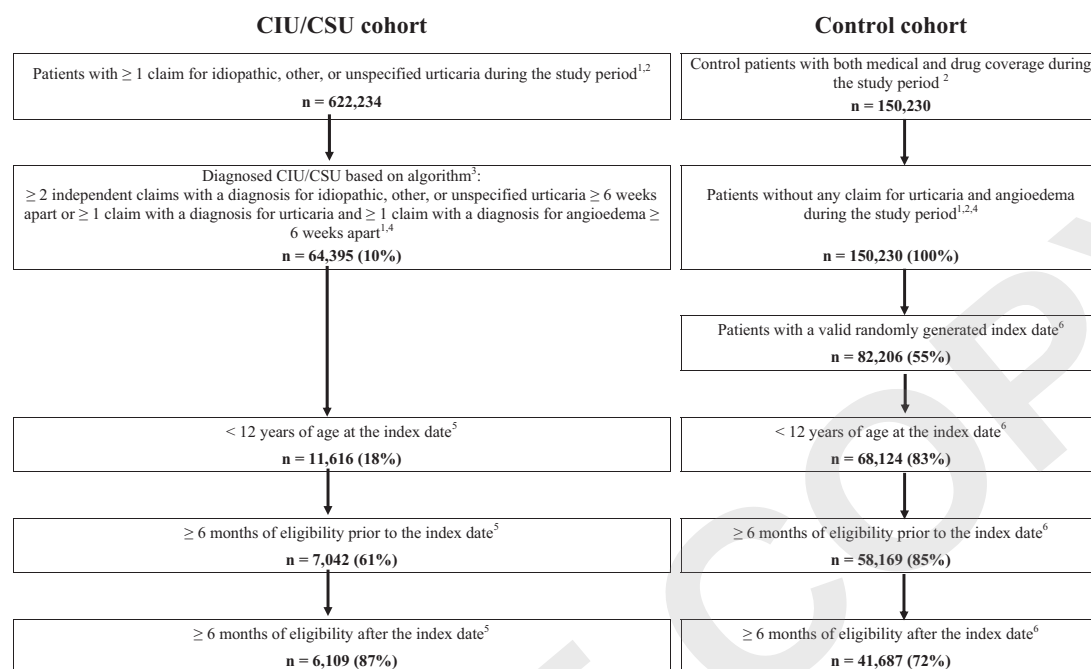


Figure 1. Cohort selection flow charts. Notes: (1) Idiopathic urticaria: ICD-9-CM code 708.1x, and ICD-10-CM code L50.1xx; other urticaria: ICD-9-CM code 708.8x and ICD-10-CM code L50.8xx; unspecified urticaria: ICD-9-CM code 708.9x and ICD-10-CM code L50.9xx; (2) the study period was from September 1, 2013, to June 30, 2016; (3) claims algorithm was validated by Ref. 23; (4) angioedema: ICD-9-CM code 995.1x and ICD-10-CM code T78.3; (5) the index date for the CIU/CSU cohort was the date of the first claim for idiopathic, other unspecified urticaria, or angioedema during the study period; and (6) the index date for the control cohort was randomly selected to mimic the index date of the patients with CIU/CSU. Note that a patient with a randomly generated index date that was beyond the end of his or her enrollment period was excluded.

plan, year of index date, and the Quan-Charlson comorbidity index (Quan-CCI).^{25,26} Differences before and after PS matching were assessed by using standardized differences, and a value of $<10\%$ indicated well-balanced characteristics.²⁷ Univariate Poisson and linear regression models were used to compare all-cause HRU and costs between the PS-matched cohorts. Results were reported as incidence rate ratios, and mean cost differences (MCD) for HRU and costs, respectively. The robust variance estimation was used to estimate the 95% confidence intervals (CI) for incidence rate ratios and to account for the correlation in the PS-matched data. A bootstrap approach (500 resamples) with a robust variance estimator was used to estimate the 95% CIs for MCDs to account for the non-normal distribution of the cost data. All cost data were adjusted to 2016 dollars based on the U.S. Consumer Price Index. All analyses were performed by using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

A total of 64,395 patients with CIU/CSU were identified, among whom 6109 were pediatric patients who met all inclusion criteria for the CIU/CSU cohort, whereas a total of 41,687 pediatric patients were included in the control cohort (Fig. 1). In the CIU/CSU

cohort, the mean $\pm$ SD age was 4.58 ± 3.36 years, and approximately half of the patients (47.9%) were girls (Table 1). Moreover, 34.9% of the patients had atopic conditions, among which eczema and/or atopic dermatitis (15.9%), allergic rhinitis (12.2%), and asthma (10.2%) were the most prevalent. Most common diagnoses in the CIU/CSU cohort during the baseline period were related to routine checks (51.2%) and respiratory infections (16.5–25.2%).

After 6 months of follow-up, compared with baseline, patients with CIU/CSU had more claims for the following CIU/CSU-related drug categories (Table 2): prescription H₁ antihistamines (8.0 versus 2.2%), OCS (17.4 versus 7.4%), leukotriene receptor antagonists (11.5 versus 6.5%), prescription H₂ histamine blockers (7.2 versus 2.6%), and anxiolytics (10.3 versus 2.8%). Pediatricians were consulted by a majority of the children (74.2% at baseline versus 81.4% at 6 months of follow-up), and more patients with CIU/CSU visited allergists/immunologists (6.7% at baseline versus 43.9% at 6 months of follow-up) as well as other specialists (albeit to a lesser extent). After 6 months of follow-up, the proportion of patients who received combination therapies was small ($\leq 1.3\%$) and the mean $\pm$ SD pill burden was 1.89 ± 3.60 dispensing units/day.

Table 1 Baseline characteristics, health care resource utilization, and costs in the unmatched and PS-matched CIU/CSU and control cohorts*

	Unmatched Sample			PS-Matched Sample		
	CIU/CSU Cohort (<i>n</i> = 6109)	Control Cohort (<i>n</i> = 41,687)	Standardized Difference#	CIU/CSU Cohort (<i>n</i> = 6107)	Control Cohort (<i>n</i> = 6107)	Standardized Difference#
Matching factors:						
Age, mean ± SD (median)§	4.58 ± 3.36 (4.00)	6.10 ± 3.33 (6.00)	32.1%	4.58 ± 3.36 (4.00)	4.57 ± 3.36 (4.00)	0.1%
Girls, no. (%)	2928 (47.9)	20,310 (48.7)	1.6%	2927 (47.9)	2925 (47.9)	0.1%
Region of residence, no. (%)§						
South	2416 (39.5)	17,286 (41.5)	3.9%	2415 (39.5)	2424 (39.7)	0.3%
Northeast	1386 (22.7)	6926 (16.6)	15.3%	1385 (22.7)	1396 (22.9)	0.4%
North-central	1164 (19.1)	8985 (21.6)	6.2%	1164 (19.1)	1157 (18.9)	0.3%
West	1077 (17.6)	7984 (19.2)	3.9%	1077 (17.6)	1069 (17.5)	0.3%
Unknown	66 (1.1)	506 (1.2)	1.3%	66 (1.1)	61 (1.0)	0.8%
Type of insurance plan, no. (%)§						
PPO	3646 (59.7)	24,898 (59.7)	0.1%	3644 (59.7)	3659 (59.9)	0.5%
CDHP and HDHP	1210 (19.8)	8883 (21.3)	3.7%	1210 (19.8)	1218 (19.9)	0.3%
HMO and POS with capitation	703 (11.5)	4317 (10.4)	3.7%	703 (11.5)	696 (11.4)	0.4%
POS and EPO	386 (6.3)	2477 (5.9)	1.6%	386 (6.3)	383 (6.3)	0.2%
Comprehensive	76 (1.2)	560 (1.3)	0.9%	76 (1.2)	73 (1.2)	0.4%
Unknown	88 (1.4)	552 (1.3)	1.0%	88 (1.4)	78 (1.3)	1.4%
Year of index date, no. (%)						
2014	3441 (56.3)	24,122 (57.9)	3.1%	3441 (56.3)	3445 (56.4)	0.1%
2015	2663 (43.6)	17,538 (42.1)	3.1%	2661 (43.6)	2660 (43.6)	0.0%
2016	5 (0.1)	27 (0.1)	0.6%	5 (0.1)	2 (0.0)	2.1%
Quan-Charlson comorbidity index, mean ± SD (median)¶	0.13 ± 0.37 (0.00)	0.06 ± 0.26 (0.00)	15.9%	0.13 ± 0.36 (0.00)	0.13 ± 0.36 (0.00)	0.3%
Nonmatching factors:						
CIU/CSU-related comorbidities, no. (%)¶						
Atopic conditions	2129 (34.9)	5138 (12.3)	55.0%	2128 (34.8)	1136 (18.6)	37.3%
Eczema/dermatitis	974 (15.9)	2005 (4.8)	37.1%	974 (15.9)	418 (6.8)	28.9%
Allergic rhinitis	747 (12.2)	2259 (5.4)	24.2%	747 (12.2)	398 (6.5)	19.7%
Asthma	622 (10.2)	1675 (4.0)	24.2%	621 (10.2)	548 (9.0)	4.1%
Food and other allergies	520 (8.5)	97 (0.2)	41.3%	520 (8.5)	19 (0.3)	40.8%
Atopic dermatitis	497 (8.1)	873 (2.1)	27.7%	497 (8.1)	202 (3.3)	20.9%
Other conditions						
Conjunctivitis	289 (4.7)	928 (2.2)	13.7%	289 (4.7)	177 (2.9)	9.6%
Urticaria (ICD-9-CM code 708.x, ICD-10-CM code L50.x)	262 (4.3)	0 (0.0)	29.9%	262 (4.3)	0 (0.0)	—

Table 1 Continued

	Unmatched Sample			PS-Matched Sample		
	CIU/CSU Cohort (<i>n</i> = 6109)	Control Cohort (<i>n</i> = 41,687)	Standardized Difference#	CIU/CSU Cohort (<i>n</i> = 6107)	Control Cohort (<i>n</i> = 6107)	Standardized Difference#
The top five most common diagnoses, no. (%)¶						
Routine health check, (ICD-9- CM code V20.2)	3182 (52.1)	16,068 (38.5)	27.5%	3182 (52.1)	3002 (49.2)	5.9%
Acute upper respiratory infections (ICD-9-CM code 465.9)	1539 (25.2)	4959 (11.9)	34.7%	1539 (25.2)	1011 (16.6)	21.4%
Need for prophylactic vaccination against influenza (ICD-9-CM code V04.81)	1352 (22.1)	6800 (16.3)	14.8%	1352 (22.1)	1115 (18.3)	9.7%
Acute pharyngitis (ICD-9-CM code 462)	1070 (17.5)	4331 (10.4)	20.7%	1070 (17.5)	646 (10.6)	20.1%
Unspecified otitis media (ICD- 9-CM code 382.9)	1006 (16.5)	3296 (7.9)	26.4%	1006 (16.5)	691 (11.3)	15.0%
Fever (ICD-9-CM code 780.60)	1006 (16.5)	3104 (7.4)	28.1%	1005 (16.5)	627 (10.3)	18.3%
Baseline HRU (all-cause, PPPY), mean ± SD (median)¶						
Inpatient visits	0.04 ± 0.44 (0.00)	0.01 ± 0.18 (0.00)	5.7%	0.04 ± 0.43 (0.00)	0.02 ± 0.22 (0.00)	3.6%
Inpatient days	0.19 ± 3.40 (0.00)	0.06 ± 1.98 (0.00)	3.4%	0.18 ± 3.28 (0.00)	0.08 ± 1.43 (0.00)	2.8%
Length of inpatient stay among patients with ≥1 inpatient visit	4.83 ± 8.78 (3.00)	4.84 ± 8.71 (3.00)	0.1%	4.79 ± 8.82 (3.00)	4.00 ± 3.98 (3.00)	8.2%
ED visits	0.54 ± 1.26 (0.00)	0.21 ± 0.77 (0.00)	22.3%	0.54 ± 1.26 (0.00)	0.26 ± 0.85 (0.00)	18.2%
Outpatient/other visits	10.04 ± 13.91 (6.00)	5.17 ± 9.41 (2.00)	29.0%	10.03 ± 13.86 (6.00)	6.41 ± 10.46 (4.00)	20.8%
Urgent care facility visits	0.28 ± 0.92 (0.00)	0.13 ± 0.64 (0.00)	12.5%	0.28 ± 0.92 (0.00)	0.15 ± 0.66 (0.00)	10.7%
Home care visits	0.59 ± 7.36 (0.00)	0.22 ± 4.51 (0.00)	4.3%	0.59 ± 7.36 (0.00)	0.38 ± 6.18 (0.00)	2.2%
Office visits	8.99 ± 10.45 (6.00)	4.74 ± 7.70 (2.00)	32.8%	8.97 ± 10.37 (6.00)	5.79 ± 7.74 (4.00)	24.6%
Ambulatory surgery center visits	0.01 ± 0.19 (0.00)	0.01 ± 0.44 (0.00)	0.3%	0.01 ± 0.19 (0.00)	0.02 ± 0.41 (0.00)	0.9%
Other outpatient visits	0.17 ± 2.25 (0.00)	0.06 ± 0.77 (0.00)	4.6%	0.17 ± 2.25 (0.00)	0.07 ± 0.66 (0.00)	4.2%
Baseline health care costs (all-cause, US \$2016, PPPY), mean ± SD (median)¶						
Total health care costs	4086 ± 32,436 (1187)	1733 ± 18,571 (364)	6.3%	3966 ± 31,057 (1185)	2297 ± 12,910 (589)	5.0%
Pharmacy costs	519 ± 3255 (17)	235 ± 3532 (0)	5.9%	513 ± 3220 (17)	235 ± 1373 (0)	7.9%
Medical costs	3567 ± 31,438 (907)	1498 ± 18,103 (297)	5.7%	3453 ± 30,158 (907)	2062 ± 12,391 (469)	4.3%

Table 1 Continued

	Unmatched Sample			PS-Matched Sample		
	CIU/CSU Cohort (<i>n</i> = 6109)	Control Cohort (<i>n</i> = 41,687)	Standardized Difference#	CIU/CSU Cohort (<i>n</i> = 6107)	Control Cohort (<i>n</i> = 6107)	Standardized Difference#
Inpatient costs	1087 ± 24,821 (0)	341 ± 16,443 (0)	2.5%	1026 ± 24,357 (0)	371 ± 6174 (0)	2.6%
ED costs	434 ± 1920 (0)	160 ± 1252 (0)	12.0%	434 ± 1920 (0)	231 ± 1777 (0)	7.8%
Outpatient/other costs	2045 ± 8604 (747)	997 ± 5132 (271)	10.5%	1993 ± 7563 (747)	1460 ± 8665 (425)	4.6%
Urgent care facility visits	33 ± 233 (0)	19 ± 284 (0)	3.8%	33 ± 233 (0)	29 ± 526 (0)	0.6%
Home care visits	113 ± 1490 (0)	76 ± 3455 (0)	1.0%	113 ± 1490 (0)	161 ± 7088 (0)	0.7%
Office visits	1861 ± 8098 (696)	883 ± 3512 (257)	11.1%	1809 ± 6980 (696)	1242 ± 4677 (408)	6.8%
Ambulatory surgery center visits	24 ± 356 (0)	14 ± 295 (0)	2.3%	24 ± 356 (0)	23 ± 392 (0)	0.2%
Other outpatient visits	14 ± 265 (0)	6 ± 223 (0)	2.5%	14 ± 265 (0)	6 ± 109 (0)	3.0%
Observation period, mean ± SD (median), days	516 ± 195 (519)	501 ± 183 (511)	5.7%	516 ± 195 (519)	501 ± 183 (509)	5.6%

PS = propensity score; CIU = chronic idiopathic urticaria; CSU = chronic spontaneous urticaria; SD = standard deviation; PPO = preferred provider organization; CDHP = consumer-directed health plan; HDHP = high-deductible health plan; HMO = home maintenance organization; POS = point of service; EPO = exclusive provider organization; ICD-9-CM = the International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM = the International Classification of Diseases, Tenth Revision; HRU = health care resource utilization; PPPY = per patient per year; ED = emergency department.

*Patients in the CIU/CSU cohort were matched with patients in the control cohort by using a 1:1 ratio based on the PS.

#The standardized difference was calculated by dividing the absolute difference in means (for continuous variables) or proportions (for binary variables) of the two cohorts by using the pooled SDs of both cohorts; a standardized difference of <10% was considered as the distribution of the given variable is well balanced between the cohorts.

\$Measured at the index date.

¶Measured during the baseline period defined as the 6-month period before the index date.

||Most common diagnoses were assessed based on the prevalence in the CIU/CSU cohort, and the prevalence of the same diagnoses was reported for the control cohort.

Table 2 Treatment patterns during the baseline period and the observation period in the CIU/CSU cohort

	Baseline Period	Observation Period		
	Patients with CIU/CSU (n = 6109)	At the 6-mo Follow-up (n = 6109)	At the 12-mo Follow-up (n = 4444)	At the 24-mo Follow-up (n = 1191)
CIU/CSU claims, mean $\pm$ SD (median), no. claims	0.43 $\pm$ 1.23 (0.00)	1.06 $\pm$ 2.14 (0.00)	1.71 $\pm$ 3.48 (0.00)	2.61 $\pm$ 6.26 (0.00)
Individual CIU/CSU treatment use, no. (%)				
Nonsedating prescription H ₁ antihistamines	132 (2.2)	489 (8.0)	442 (9.9)	138 (11.6)
Cetirizine	86 (1.4)	291 (4.8)	257 (5.8)	80 (6.7)
Desloratadine	3 (0.0)	10 (0.2)	12 (0.3)	6 (0.5)
Fexofenadine	2 (0.0)	7 (0.1)	8 (0.2)	2 (0.2)
Levocetirizine	36 (0.6)	186 (3.0)	167 (3.8)	53 (4.5)
Loratadine	7 (0.1)	14 (0.2)	22 (0.5)	9 (0.8)
Other antihistamines	33 (0.5)	68 (1.1)	73 (1.6)	28 (2.4)
Oral corticosteroids	454 (7.4)	1061 (17.4)	956 (21.5)	308 (25.9)
Cortisone acetate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dexamethasone	41 (0.7)	45 (0.7)	52 (1.2)	18 (1.5)
Hydrocortisone	4 (0.1)	3 (0.0)	3 (0.1)	1 (0.1)
Methylprednisolone	6 (0.1)	47 (0.8)	36 (0.8)	12 (1.0)
Prednisolone	281 (4.6)	661 (10.8)	609 (13.7)	193 (16.2)
Prednisone	137 (2.2)	365 (6.0)	321 (7.2)	112 (9.4)
Immunosuppressant agents	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leukotriene receptor antagonists	400 (6.5)	705 (11.5)	653 (14.7)	178 (14.9)
Montelukast	400 (6.5)	705 (11.5)	653 (14.7)	178 (14.9)
H ₂ histamine blockers	161 (2.6)	442 (7.2)	397 (8.9)	117 (9.8)
Cimetidine	0 (0.0)	6 (0.1)	3 (0.1)	1 (0.1)
Ranitidine	144 (2.4)	379 (6.2)	340 (7.7)	101 (8.5)
Famotidine	11 (0.2)	61 (1.0)	57 (1.3)	14 (1.2)
Nizatidine	9 (0.1)	5 (0.1)	6 (0.1)	2 (0.2)
Anti-inflammatory agents	1 (0.0)	2 (0.0)	2 (0.0)	2 (0.2)
Anxiolytics	173 (2.8)	627 (10.3)	510 (11.5)	161 (13.5)
Antidepressants	36 (0.6)	48 (0.8)	45 (1.0)	20 (1.7)
Pill burden, dispensing units, mean $\pm$ SD (median)*	—	1.89 $\pm$ 3.60 (0.89)	1.65 $\pm$ 3.02 (0.86)	1.41 $\pm$ 2.58 (0.76)
Physician specialty, no. (%)#				
Dermatology	265 (4.3)	501 (8.2)	511 (11.5)	193 (16.2)
Allergy and immunology	410 (6.7)	2684 (43.9)	2117 (47.6)	618 (51.9)
Pediatric	4533 (74.2)	4972 (81.4)	3818 (85.9)	1068 (89.7)
Acute care hospital	1769 (29.0)	2433 (39.8)	2215 (49.8)	695 (58.4)
Family practice	926 (15.2)	1120 (18.3)	1045 (23.5)	358 (30.1)
Laboratory	918 (15.0)	1706 (27.9)	1574 (35.4)	556 (46.7)
Emergency medicine	736 (12.0)	1035 (16.9)	1023 (23.0)	361 (30.3)
Radiology	649 (10.6)	724 (11.9)	848 (19.1)	331 (27.8)
Urgent care facility	408 (6.7)	486 (8.0)	513 (11.5)	205 (17.2)
Other§	2591 (42.4)	3222 (52.7)	2900 (65.3)	903 (75.8)

CIU = chronic idiopathic urticaria; CSU = chronic spontaneous urticaria; SD = standard deviation.

*Calculated by dividing the total number of dispensing units over a given assessment period by the duration of the assessment period.

#Physician specialty was defined as having a claim with a physician specialty during the observation period; a physician specialty was identified by using the variable "Provider type," provided by Truven based Truven Health standard values; a patient may have multiple physician specialties during the baseline period.

§The remaining other physician specialties were merged together with the most commonly reported being otolaryngology, medical physician, internal medicine, nurse practitioner, multispecialty physician group, pathology, anesthesiology, and supply center.

All the 6109 patients with CIU/CSU were matched 1:1 with control patients. Matching resulted in cohorts balanced in terms of demographics and Quan-CCI (Ta-

ble 1). CIU/CSU-related comorbidities were more prevalent in the CIU/CSU cohort relative to the control cohort. The mean $\pm$ SD duration of the observation

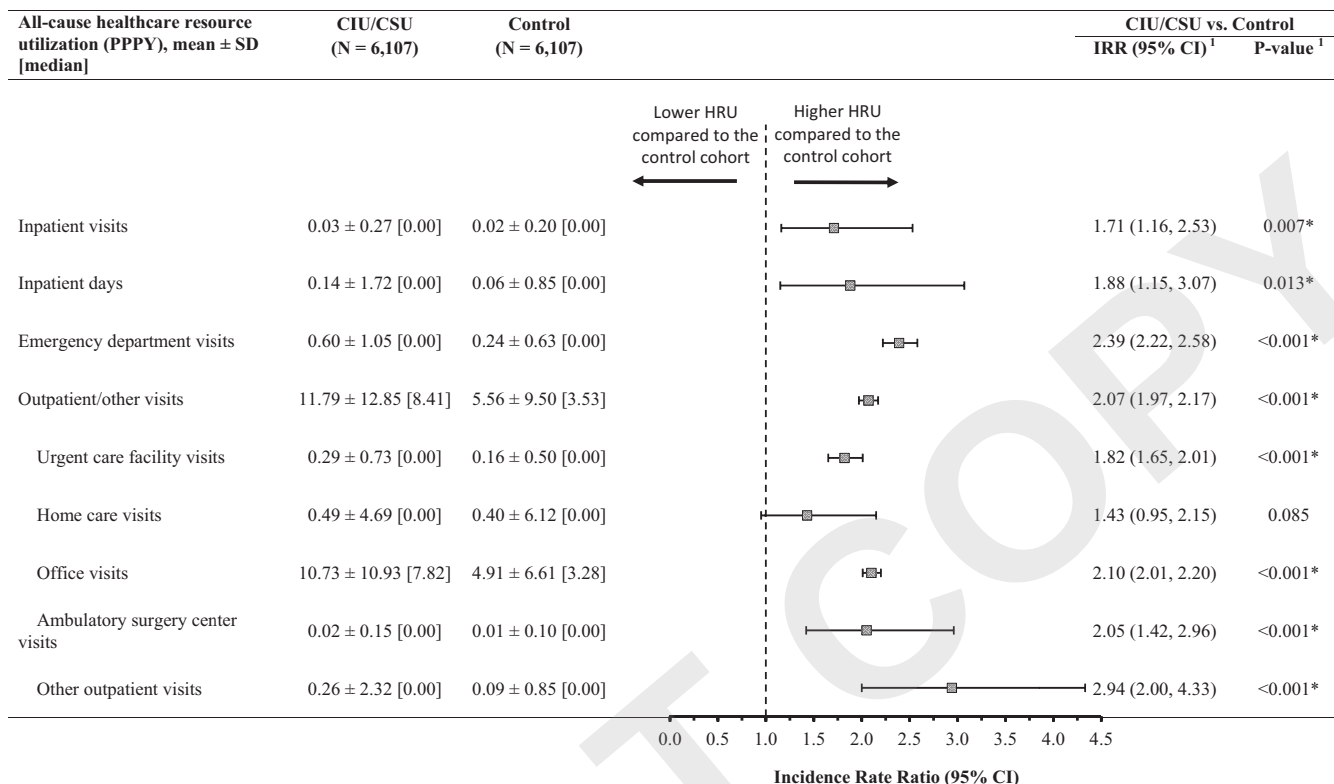


Figure 2. Comparison of health care resource utilization between the PS-matched CIU/CSU and control cohorts during the observation period. Note: (1) The incidence rate ratios were estimated by using univariate Poisson models for the PS-matched cohorts. The 95% CIs and *p* values for incidence rate ratios were calculated by using the robust variance estimator to account for the correlation in the matched data. PS = propensity score; CIU = chronic idiopathic urticaria; CSU = chronic spontaneous urticaria; CI = confidence interval; IRR = incidence rate ratio; PPPY = per patient per year; SD = standard deviation.

period was similar between the cohorts (CIU/CSU cohort of 516 ± 195 days versus control cohort of 501 ± 183 days; standardized difference, 5.6%).

Comparing the all-cause HRU between the matched cohorts revealed that the patients with CIU/CSU stayed in the hospital 1.9 times longer, had 1.7 times more hospitalizations, 2.4 times more ED visits, and 2.1 times more OP visits than the control patients (all $p < 0.05$) (Fig. 2) during the observation period. All the categories of OP visits except for home care visits were also significantly more frequent among the patients with CIU/CSU compared with the control patients.

During the observation period, pharmacy costs (MCD \$483 PPPY [95% CI, \$378–\$626 PPPY]) and medical costs (MCD \$1606 PPPY [95% CI, \$1043–\$2287 PPPY]) were significantly ($p < 0.001$) higher among the patients with CIU/CSU compared with the control patients, which resulted in a higher total health care cost (MCD \$2090 PPPY [95% CI, \$1483–\$2808 PPPY]; $p < 0.001$) (Table 3). Incremental OP costs (MCD \$913 PPPY [95% CI, \$641–\$1163 PPPY]; $p < 0.001$) represented the majority (56.8%) of incremental medical costs. All the categories of OP costs, except home care costs, were higher among the patients with CIU/CSU compared with the control patients (all $p < 0.05$).

Compared with all-cause costs in the CIU/CSU cohort, CIU/CSU-related costs were lower (e.g., the mean $\pm$ SD for all-cause total health care cost was $\$4079 \pm \$20,781$ PPPY versus $\$455 \pm \$1152$ PPPY for CIU/CSU-related) and represented $\sim 25\%$ ($\$455/\$2090$) of the incremental total health care costs (Table 3). Similarly, CIU/CSU-related HRU represented only a minority of all-cause HRU (data not shown).

DISCUSSION

To the best of our knowledge, this was one of the first studies that described pediatric CIU/CSU treatment patterns and compared HRU and costs between a pediatric CIU/CSU and control populations, which thereby highlighted the incremental disease burden of pediatric CIU/CSU. Of note, matching resulted in cohorts with similar demographics and baseline comorbidities, as illustrated by the balanced mean Quan-CCI. Thus, the comparisons presented in this study allowed us to estimate the incremental CIU/CSU burden relative to patients without CIU/CSU, who are otherwise similar, by using an established approach in the cost of illness studies.²⁸

In this study, an analysis of treatment patterns indicated that the medication burden and visits to aller-

Table 3 Comparison of health care costs between the PS-matched CIU/CSU and control cohort during the observation period

	CIU/CSU, mean $\pm$ SD (median) (<i>n</i> = 6107)	Control, mean $\pm$ SD (median) (<i>n</i> = 6107)	CIU/CSU vs Control	
			Mean Cost Difference (95% CI)*	<i>p</i> Value
Observation period, days#	516 $\pm$ 195 (519)	501 $\pm$ 183 (509)		
All-cause pharmacy and medical costs (US \$2016, PPPY)	4079 $\pm$ 20,781 (1,649)	1990 $\pm$ 13,456 (530)	2090 (1483–2808)	<0.001*
All-cause pharmacy costs	721 $\pm$ 4,633 (148)	237 $\pm$ 1,732 (6)	483 (378–626)	<0.001*
All-cause medical costs	3359 $\pm$ 19,547 (1269)	1752 $\pm$ 12,996 (441)	1606 (1043–2287)	<0.001*
Inpatient visits	773 $\pm$ 17,035 (0)	378 $\pm$ 6149 (0)	396 (31–951)	0.024*
ED visits	489 $\pm$ 1,324 (0)	191 $\pm$ 863 (0)	298 (257–336)	<0.001*
Outpatient/other visits	2097 $\pm$ 5737 (992)	1184 $\pm$ 8834 (386)	913 (641–1163)	<0.001*
Urgent care facility visits	45 $\pm$ 350 (0)	20 $\pm$ 116 (0)	25 (16–37)	<0.001*
Home care visits	108 $\pm$ 1214 (0)	157 $\pm$ 6891 (0)	–49 (–235 to 69)	0.724
Office visits	1881 $\pm$ 5207 (920)	986 $\pm$ 5383 (367)	895 (673–1083)	<0.001*
Ambulatory surgery center visits	35 $\pm$ 345 (0)	16 $\pm$ 214 (0)	19 (8–30)	<0.001*
Other outpatient visits	27 $\pm$ 322 (0)	5 $\pm$ 70 (0)	22 (15–31)	<0.001*
CIU/CSU-related pharmacy and medical costs (US \$2016, PPPY)\$	455 $\pm$ 1152 (218)	NA	NA	NA
CIU/CSU-related pharmacy costs	28 $\pm$ 154 (0)	NA	NA	NA
CIU/CSU-related medical costs	427 $\pm$ 1129 (199)	NA	NA	NA
Inpatient visits	38 $\pm$ 630 (0)	NA	NA	NA
ED visits	87 $\pm$ 420 (0)	NA	NA	NA
Outpatient/other visits	302 $\pm$ 703 (161)	NA	NA	NA
Urgent care facility visits	11 $\pm$ 284 (0)	NA	NA	NA
Home care visits	2 $\pm$ 48 (0)	NA	NA	NA
Office visits	282 $\pm$ 633 (147)	NA	NA	NA
Ambulatory surgery center visits	0 $\pm$ 3 (0)	NA	NA	NA
Other outpatient visits	6 $\pm$ 41 (0)	NA	NA	NA

PS = propensity score; CIU = chronic idiopathic urticaria; CSU = chronic spontaneous urticaria; SD = standard deviation; CI = confidence interval; PPPY = per patient per year; ED = emergency department; NA = not applicable; ICD-9-CM = the International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM = the International Classification of Diseases, Tenth Revision, Clinical Modification.

*The mean cost differences were estimated by using univariate linear regression models for the PS-matched cohorts; the 95% CIs and *p* values for mean cost differences were based on bootstrap results (500 resamples) to account for the non-normal distribution of cost data and used the robust variance estimator to account for the correlation in the matched data.

#Observation period was defined as the period between the index date and the earlier date of the end of eligibility or the end of data availability.

\$CIU/CSU-related medical costs were identified by using diagnosis codes (i.e., CIU/CSU related: ICD-9-CM codes 708.1x, 708.8x, 708.9x, or 995.1x; ICD-10-CM codes L50.1, L50.8, L50.9, or T78.3); CIU/CSU-related pharmacy costs were defined as costs associated with the CIU/CSU treatments as listed in Table 2.

gists/immunologists increased after a CIU/CSU diagnosis. Moreover, a comparison of the pediatric CIU/CSU cohort with the control cohort revealed that the pediatric patients with CIU/CSU had HRU rates approximately twice as high as the control children, which translated to a disease burden of ~\$2100 PPPY in this subpopulation. Also, only a minority of HRU and all-cause costs were CIU/CSU related, which indicated that CIU/CSU was associated with comorbidities that significantly contributed to the disease health care burden. Further research is warranted to identify the cost drivers in CIU/CSU.

Although the relative proportion of prescribed H₁ antihistamines increased between baseline and the follow-up period, the proportion of patients who received antihistamine therapy was relatively low, despite H₁ antihistamines being a first-line treatment for chronic urticaria among the children.^{13,29} However, these numbers were likely underestimated due to availability of over-the-counter (OTC) antihistamines, which are not captured in insurance claims. In fact, 72% of the patients with CIU/CSU were reported to be under antihistamine treatment in a study when using medical records as a data source.²⁰

In addition, consistent with several other studies that mostly involved adult patients,^{20–22} our study indicated that OCS were one of the most frequently prescribed drug categories after a CIU/CSU diagnosis. However, this high proportion may represent brief courses of OCS therapy aimed to help patients gain better control over their symptoms before moving on to another therapy¹ instead of a long-term continuous treatment strategy. Moreover, the finding that allergists/immunologists were consulted by a larger proportion of the patients with CIU/CSU after the disease diagnosis supported the notion that primary care physicians often refer chronic urticaria cases to these specialists.^{30,31} This result was also consistent with findings from Zazzali *et al.*,²² who reported allergists/immunologists as the most frequent urticaria-care physicians in 42.7% of cases in a mostly adult patient population.²²

Among the HRU outcomes, the mean absolute number of office visits PPPY (10.73) was consistent with the number reported by Broder *et al.*²¹ for U.S. patients <5 years of age (12.2) and ages between 6 and 11 years old (10.5). Moreover, the fact that incremental medical costs were largely driven by incremental costs related to OP visits was consistent with the idea that CIU/CSU is essentially an OP disease.²⁰ In addition, the fact that urticaria-related HRU and costs represented ~25% of the health care burden indicated that a significant proportion of the CIU/CSU total burden could be explained by the presence of comorbidities associated with CIU/CSU and was consistent with similar results from Broder *et al.*²¹

Also, although quality of life related outcomes were not analyzed in the present study, previous studies in the literature indicate that CIU/CSU may have a considerable burden on the quality of life of pediatric patients, which leads to school absenteeism and decreased school performance among other factors.^{13,32} Although this study allowed us to estimate the incremental CIU/CSU burden relative to otherwise similar patients without CIU/CSU, comparing patients with CIU/CSU with those with another chronic condition, like asthma, could answer another interesting question, whether one condition has a higher burden than the other. Further research will be necessary to address this question.

Limitations

This study was subjected to a number of limitations. First, administrative claims data bases have inherent limitations, such as potential miscoding, billing inaccuracies, and missing data. Second, the reliability of the algorithm to identify CIU/CSU specifically among pediatric patients was not verified. Moreover, given that the currently available ICD-9-CM and ICD-10-CM codes did not allow differentiation of urticaria based on its duration, a few cases of atopic urticaria might have been included in the CIU/CSU cohort. Third, the randomly generated index date in the control cohort may not have been on a day when a patient had a medical visit, whereas the patients with CIU/CSU had a visit on the index date as well as associated costs. However, because costs of all CIU/CSU visits accounted for only ~10% of total health care costs in the CIU/CSU cohort, we did not expect costs of one visit to impact the conclusions. Fourth, antihistamines are now widely prescribed in the form of OTC drugs, which were not possible to capture by using insurance claims. However, Broder *et al.*²¹ estimated this missing cost at only \$25 PPPY, which indicated that OTC medications only mildly impacted the results. Fifth, pharmacy claims data did not necessarily imply that medications were actually taken. Patients might not have adhered to the treatment regimen as prescribed, and the actual consumption of medication may be overestimated. Sixth, this observational retrospective study may be biased by unmeasured confounders.

CONCLUSION

Pediatric patients with CIU/CSU are treated similarly to adult patients due to the limited clinical and epidemiologic information on this subpopulation. This study showed that the patients with CIU/CSU who were <12 years of age had increased medication and health care burden after the CIU/CSU diagnosis, higher rates of HRU, and higher health care costs compared with pediatric patients without CIU/CSU. Moreover, this

study found that OCS were the most frequently prescribed drugs after the CIU/CSU diagnosis, whereas the proportion of patients with prescribed antihistamine therapy was relatively low. Overall, results of our study indicated that the pediatric patients with CIU/CSU had unmet needs and that a better understanding of the burden of illness in this population may help guide clinical practice.

REFERENCES

- Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol*. 2014; 133:1270–1277.
- 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: the 2013 revision and update. *Allergy*. 2014; 69:868–887.
- Beck LA, Bernstein JA, Maurer M. A Review of international recommendations for the diagnosis and management of chronic urticaria. *Acta Derm Venereol*. 2017; 97:149–158.
- U.S. Food and Drug Administration (FDA). Zyrtec (cetirizine hydrochloride) Tablets and Syrup, 2003. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/19835slr016,21150slr005,30346slr011_zyrtec_lbl.pdf.
- U.S. Food and Drug Administration (FDA). Allegra (fexofenadine hydrochloride) Full prescribing information, 2007. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020872s018,021963s002lbl.pdf.
- U.S. Food and Drug Administration (FDA). Clarinex (desloratadine) full prescribing information, 2014. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021165s017,021300s014,021312s015,021563s003lbl.pdf.
- U.S. Food and Drug Administration (FDA). Xyzal (levocetirizine dihydrochloride) full prescribing information, 2010. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022064s034lbl.pdf.
- U.S. Food and Drug Administration (FDA). Claritin (brand of loratadine) Product information, 2000. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/019658Orig1s048lbl.pdf.
- Legrain V, Taieb A, Sage T, Maleville J. Urticaria in infants: a study of forty patients. *Pediatr Dermatol*. 1990; 7:101–107.
- Mortureux P, Leaute-Labreze C, Legrain-Lifermann V, Lamireau T, Sarlangue J, Taieb A. Acute urticaria in infancy and early childhood: a prospective study. *Arch Dermatol*. 1998; 134:319–323.
- Sackesen C, Sekerel BE, Orhan F, Kocabas CN, Tuncer A, Adalioglu G. The etiology of different forms of urticaria in childhood. *Pediatr Dermatol*. 2004; 21:102–108.
- Poddighe D, De Amici M, Marseglia GL. Spontaneous (autoimmune) chronic urticaria in children: current evidences. *Diagnostic pitfalls and therapeutic management*. *Recent Pat Inflamm Allergy Drug Discov*. 2016; 10:34–39.
- Church MK, Weller K, Stock P, Maurer M. Chronic spontaneous urticaria in children: itching for insight. *Pediatr Allergy Immunol*. 2011; 22(pt. 1):1–8.
- 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; 38:136–142.
- Azkur D, Civelek E, Toyran M, et al. Clinical and etiologic evaluation of the children with chronic urticaria. *Allergy Asthma Proc*. 2016; 37:450–457.
- Khakoo G, Sofianou-Katsoulis A, Perkin MR, Lack G. Clinical features and natural history of physical urticaria in children. *Pediatr Allergy Immunol*. 2008; 19:363–366.
- Ibanez MD, Garde JM. Allergy in patients under fourteen years of age in *Alergologica* 2005. *J Investig Allergol Clin Immunol*. 2009; 19(suppl. 2):61–68.
- Parisi CA, Ritchie C, Petriz N, Morelo Torres C. Direct medical costs of chronic urticaria in a private health organization of Buenos Aires, Argentina. *Value Health Reg Issues*. 2016; 11:57–59.
- Tatar M, Antürk A, Oğuzhan GE, et al. Cost of treatment of chronic spontaneous urticaria in Turkey. *Health*. 2016; 8:1098–1103.
- Delong LK, Culler SD, Saini SS, Beck LA, Chen SC. Annual direct and indirect health care costs of chronic idiopathic urticaria: a cost analysis of 50 nonimmunosuppressed patients. *Arch Dermatol*. 2008; 144:35–39.
- Broder MS, Raimundo K, Antonova E, Chang E. Resource use and costs in an insured population of patients with chronic idiopathic/spontaneous urticaria. *Am J Clin Dermatol*. 2015; 16:313–321.
- Zazzali JL, Broder MS, Chang E, Chiu MW, Hogan DJ. Cost, utilization, and patterns of medication use associated with chronic idiopathic urticaria. *Ann Allergy Asthma Immunol*. 2012; 108:98–102.
- Cherepanov D, Raimundo K, Chang E, et al. Validation of an ICD-9-based claims algorithm for identifying patients with chronic idiopathic/spontaneous urticaria. *Ann Allergy Asthma Immunol*. 2015; 114:393–398.
- Bergstralh EJ, Kosanke JL. Computerized Matching of Cases to Controls. Technical report; 1995 April.
- Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992; 45:613–619.
- Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005; 43:1130–1139.
- Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Commun Stat Simul Comput*. 2009; 38:1228–1234.
- Jo C. Cost-of-illness studies: concepts, scopes, and methods. *Clin Mol Hepatol*. 2014; 20:327–337.
- Sanchez-Borges M, Asero R, Ansotegui IJ, et al. Diagnosis and treatment of urticaria and angioedema: a worldwide perspective. *World Allergy Organ J*. 2012; 5:125–147.
- Weldon D. Your patients are itching for answers. *Ann Allergy Asthma Immunol*. 2008; 100:191–192.
- Baptist AP, Baldwin JL. Physician attitudes, opinions, and referral patterns: comparisons of those who have and have not taken an allergy/immunology rotation. *Ann Allergy Asthma Immunol*. 2004; 93:227–231.
- Ferrer M. Epidemiology, healthcare, resources, use and clinical features of different types of urticaria. *Alergologica* 2005. *J Investig Allergol Clin Immunol*. 2009; 19(suppl. 2):21–26. □

Copyright of Allergy & Asthma Proceedings is the property of OceanSide Publications Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.