

Cost-Utility of Routine Testing in Chronic Urticaria/Angioedema: A Cohort Study



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What is already known about this topic? Current urticaria guidelines recommend limiting testing. There is little evidence to support any biomarker as a diagnostic or prognostic tool in chronic urticaria/angioedema (CUA).

What does this article add to our knowledge? Biomarkers used to evaluate CUA rarely have an impact on management and outcome of disease. Although hardly having any impact on diagnosis, prognosis, and management of CUA, tests represent an important source of cost generation.

How does this study impact current management guidelines? These results show the low impact test results have on the management and outcome of CUA and how these tests substantially increase expenditures directly related to CUA, thereby strengthening current guideline recommendations to limit testing.

BACKGROUND: Chronic urticaria/angioedema (CUA) guidelines recommend limiting tests to diagnose and assess prognosis, activity, and severity. Routine testing in CUA might substantially increase cost of disease without benefiting outcome. **OBJECTIVE:** To evaluate the utility of tests in CUA and how they influence the cost of disease.

METHODS: We reviewed 725 electronic medical records of patients who were evaluated for CUA between 2010 and 2018 at a tertiary care center. The sample was gathered through the search of *International Classification of Diseases Ninth and Tenth Revision* codes pertaining to CUA. Analyses were made to evaluate changes in outcome for patients on whom at least 1 test was performed to evaluate CUA, the costs generated by these tests, and the tendencies to order specific tests from 2010 through 2018.

RESULTS: Of 725 patients (age median, 47 years; women, 73.1%), 543 (74.8%) had at least 1 test performed. Tests had an elevated percentage of normal results (>90%). Five patients (0.9%) had a change in outcome and 8 patients were given a different diagnosis (0.1% each). Evaluation, management, and tests accounted for most of the costs. Costs remain similar between 2010-2014 (mean, \$569) and 2015-2018 (mean, \$569).

CONCLUSIONS: In CUA, tests rarely uncover underlying conditions or lead to changes in management and outcome, but they substantially increase the costs generated by the disease. Adherence to current recommendations to limit testing might help in reducing the financial burden of CUA and improve delivery of care. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:2823-32)

Key words: Chronic urticaria; Tests; Costs; Utility; Changes in outcome

INTRODUCTION

Chronic urticaria/angioedema (CUA) is characterized by the presence of wheals, angioedema, or both for more than 6 weeks.¹ Its prevalence is estimated to be in the range of 0.3% to 1% of the general population.²⁻⁵ However, the burden of disease is substantial and diagnosis and treatment consume a large amount of resources. This translates into significant costs for patients and health care systems.⁶⁻⁹ Current guidelines—first published in 2011 and updated in 2014 and 2018—recommend limited testing unless patient history or physical examination warrants

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Abbreviations used

Anti-TPO- Anti-thyroid peroxidase

BETOS- Berenson-Eggers Type of Service

CBCw/diff- Complete blood cell count with differential

CIndU- Inducible urticaria

CUA- Chronic urticaria/angioedema

E&M- Evaluation & management

HCP- Health care professional

ICD-9- International Classification of Diseases, Ninth Revision

ICD-10- International Classification of Diseases, Tenth Revision

PCP- Primary care provider

TD- Thyroid disease

any diagnostic procedures.^{1,10,11} It is unclear how well these guidelines are accepted or how effective they have been in reducing testing and associated costs. Our hypothesis was that testing in CUA does not influence the diagnosis, management, or outcome but does influence cost of care. We also assessed if there have been any changes in the tendency to order tests since the 2014 guideline update.

METHODS

We received approval by the institutional review board at our institution for a retrospective record review through electronic medical record Epic (Epic Systems Corp, Verona, Wis), waiving the need for informed consent for the use of unidentified data. As previously done, we used *International Classification of Diseases, Ninth Revision (ICD-9), Clinical Modification* (708.1, 708.2, 708.3, 708.4, 708.5, 708.8, 708.9, and 995.1) and *International Classification of Diseases, Tenth Revision* (L50.0, L50.1, L50.2, L50.3, L50.4, L50.5, L50.6, L50.8, L50.9, and T78.3) codes for urticaria, to search for patients evaluated for urticaria at our institution between 2010 and 2018.² Patients seen for a different diagnosis, had urticaria for 6 weeks or less, or were enrolled in other research protocols were excluded.

Evaluations occurring between 2010 and 2014 were considered “preguidelines,” and evaluations occurring between 2015 and 2018 (ie, after publication of the 2014 update and allowing a whole year to become familiarized with it) were considered “postguidelines.” Information was collected regarding demographic (age at evaluation, sex, race) and disease characteristics (*ICD-9* and *ICD-10* codes, age at symptom onset, previous diagnosis of chronic urticaria, disease character, history of hypothyroidism, history of atopic disease, exacerbating medications at visit), treatment information (management at visit, laboratory tests ordered), and outcomes (management after visit, whether or not management/outcomes were altered by results of laboratory tests, and alternative diagnoses found as a result of laboratory tests).

Standardized costs were obtained from our institution’s cost data warehouse based on patient encounters and treatments. Costs not associated with outpatient visits nor directly relating to care for urticaria were excluded. Medicare reimbursement was assigned to all professional billed services, the appropriate Medicare Cost Report cost-to-charge ratios were multiplied by the charges for all hospital billed services, and all resulting costs were adjusted to 2017 dollars with the Gross Domestic Product Implicit Price Deflator.¹² As done previously, expenditures generated from CUA evaluations were assessed by defining both total costs and by categorizing costs into

TABLE I. Characteristics at moment of evaluation

Variable	Summary (N = 725), n (%)
Year of evaluation	
2010-2014 (preguidelines)	467 (64.4)
2015-2018 (postguidelines)	258 (35.6)
Demographic characteristics	
Age at evaluation (y)	47 (17-90)
Sex (female)	530 (73.1)
Race	
White	556 (77.4)
Black	68 (9.5)
Asian or Pacific Islander	33 (4.6)
Hispanic or Latin American	50 (7.0)
Other	11 (1.5)
HCP providing the initial evaluation concerning urticaria	
Allergy	293 (40.4)
Dermatology	219 (30.2)
PCP	172 (23.7)
ED	5 (0.7)
Rheumatology	26 (3.6)
Hematology	1 (0.1)
Other	9 (1.2)
Previous diagnosis of chronic urticaria	285 (39.3)
Disease character	
Urticaria and angioedema	216 (29.8)
Urticaria only	520 (71.7)
Inducible urticaria	66 (9.1)
History of hypothyroidism	96 (13.2)
History of atopic disease (more than 1 is possible)	
Asthma	62 (8.6)
Allergic rhinitis	99 (13.7)
Eczema	14 (1.9)
None	592 (81.7)
Management at visit (more than 1 is possible)	
First-generation antihistamine at licensed dose	317 (43.7)
First-generation antihistamine at high dose	21 (2.9)
Second-generation antihistamine	345 (47.6)
Second-generation antihistamine at high dose	28 (3.9)
H ₂ blocker	97 (13.4)
Montelukast sodium	58 (8.0)
Topical steroids	50 (6.9)
Systemic steroids	138 (19.0)
Omalizumab	27 (3.7)
Dapsone	6 (0.8)
Cyclosporine	11 (1.5)
Epinephrine autoinject	23 (3.2)
Sulfasalazine	1 (0.1)
Doxepin hydrochloride	41 (5.7)
None	127 (17.5)
The sample median (minimum, maximum) is given for continuous variables.	
Information was unavailable regarding race (N = 7)	

ED, Emergency department.

TABLE II. ICD-9 and ICD-10 codes

Code	Summary (N = 725), n (%)
ICD-9 code	
708.1 Idiopathic urticaria	18 (2.5)
708.2 Urticaria due to cold and heat	1 (0.1)
708.3 Dermatographic urticaria	31 (4.3)
708.4 Vibratory urticaria	0 (0.0)
708.5 Cholinergic urticaria	3 (0.4)
708.8 Urticaria, unspecified	197 (27.2)
708.9 Other specified urticaria	296 (40.8)
995.1 Angioneurotic edema, not elsewhere classified	6 (0.8)
ICD-10 code	
L50.0 Allergic urticaria	4 (0.6)
L50.1 Idiopathic urticaria	7 (1.0)
L50.2 Urticaria due to cold and heat	2 (0.3)
L50.3 Dermatographic urticaria	7 (1.0)
L50.4 Vibratory urticaria	0 (0.0)
L50.5 Cholinergic urticaria	2 (0.3)
L50.6 Contact urticaria	0 (0.0)
L50.8 Other urticaria	85 (11.7)
L50.9 Urticaria, unspecified	66 (9.1)
T78.3 Giant urticaria	0 (0.0)

the relevant Berenson-Eggers Type of Service (BETOS) classification, which assigns Healthcare Common Procedure Coding System and Current Procedural Terminology codes to 1 of 7 possible clinical categories (Evaluation & Management [E&M], Procedures, Imaging, Tests, Durable Medical Equipment, Other [includes drugs, immunizations, and injections], and Unclassified).^{13,14} BETOS categories 1, 2, 4, and 6 (E&M, Procedures, Tests, and Other, respectively) were found to include Healthcare Common Procedure Coding System and Current Procedural Terminology codes related to CUA care, whereas categories 3, 5, and 7 were excluded for not being in direct relation to CUA. Costs were compared for all patients from 2010 to 2017 because internal costing for 2018 was not yet available. Comparison time frames were defined as pre-2015 and post-2015, which correspond to preguidelines and postguidelines periods.

Statistical analysis

Continuous variables were summarized with the sample median and range. Categorical variables were summarized with number and percentage of patients. The proportions of patients who had specific tests performed were compared between the preguidelines and postguidelines periods using Fisher exact test. Comparisons of management at visit and management after visit were made using a paired McNemar test. No adjustment was made for multiple testing in these exploratory analyses, and *P* values less than .05 were considered to be statistically significant. All statistical tests were 2-sided. Statistical analyses were performed using SAS (version 9.4; SAS Institute, Inc, Cary, NC).

RESULTS

We included 725 consecutive patients; 530 (73.1%) were women and 556 (77.4%) were white. The median age at the moment of evaluation was 47 years (range, 17-90 years) and the

median age at symptom onset or first event of urticaria was 45 years (range, 5-90 years). A total of 467 (64.4%) evaluations happened in the preguidelines period and 258 (35.6%) in the postguidelines period. Disease character was most commonly urticaria only (71.7%), and 285 patients (39.3%) had a previous diagnosis of chronic urticaria. The most common managements at time of evaluation (more than 1 was possible) were second-generation antihistamines (second-generation H₁-antihistamines) at licensed dose (47.6%), first-generation antihistamines (43.7%), systemic steroids (19.0%), and none (17.5%). Allergy, dermatology, and primary care providers (PCPs; included General Internal Medicine and Family Medicine) were the top 3 health care professionals (HCPs) providing the initial evaluation concerning urticaria, accounting for 40.4%, 30.2%, and 23.7% of the visits, respectively. A full description regarding year of evaluation, demographic characteristics, HCP providing the evaluation, disease character, patient history (eg, hypothyroidism and history of atopic disease), and management at moment of evaluation is given in Table I.

Table II presents the complete list of ICD-9 and ICD-10 codes, the number of patients with each code, and the percentage each code represents for the whole sample. The most common ICD-9 codes were "708.9: other specified urticaria" (40.8%) and "708.8: urticaria, unspecified" (27.2%), and the most common ICD-10 code was "L50.8: Other Urticaria" (11.7%).

A total of 543 patients (74.8%) had at least 1 test performed. The most commonly ordered tests were complete blood cell count with differential (CBCw/diff; *n* = 327 [41.5%]), anti-nuclear antibodies (*n* = 301 [41.5%]), thyroid-stimulating hormone (*n* = 300 [41.4%]), serum protein electrophoresis (*n* = 265 [36.6%]), and thyroid antibodies (anti-thyroid peroxidase [anti-TPO]; *n* = 246 [33.9%]). Most test results were normal in greater than or equal to 90% of patients. The tests with the lowest proportion of normal results were skin biopsy (26.5%), CBCw/diff (62.7%), total IgE (64.7%), skin prick testing (66.7%), and Hepatitis B surface antibody (74.1%). Table III presents the complete list of tests performed in at least 1 patient, and the number and percentage of normal results for each test.

A comparison of the proportion of patients who had specific tests performed between the preguidelines and postguidelines time periods is presented in Table IV. Compared with preguidelines, the postguidelines period had a significantly lower proportion of patients with an anti-Fc-epsilon-R1-alpha test (*P* < .0001), *Helicobacter pylori* antibody test (*P* < .0001), liver function test (*P* = .014), renal profile (*P* = .0001), serum specific IgE test (*P* = .009), thyroxine (*P* = .013), and total complement (*P* = .014). Conversely, a significantly higher proportion of patients seen in the postguidelines period had an antinuclear antibody (*P* = .049), chronic urticaria basophil activation (*P* < .0001), chronic urticaria index panel (*P* < .0001), erythrocyte sedimentation rate (*P* = .023), IgA total (*P* < .0001), total IgE (*P* = .002), thyroid antibodies (*P* = .022), tryptase (*P* = .033), or vitamin D (*P* < .0001) compared with the preguidelines period. The workup was most commonly ordered by Allergy (*N* = 275 [37.9%]), Dermatology (*N* = 234 [32.2%]), or PCP (*N* = 64 [8.8%]).

Regarding management and outcomes after evaluation, of the 543 patients who had any test performed, only 5 (0.9%) had a change in management on the basis of test results. Additional diagnoses were identified in only 8 patients (0.8% combined) as

TABLE III. Laboratory values

Laboratory test	No. of patients who had the test performed	n (%) of patients with a normal test result
ANA	301	289 (96.0)
Anti-Fc-epsilon-R1-alpha	224	177 (79.0)
C1 inhibitor	124	116 (93.5)
C1 function	114	114 (100.0)
C1q	113	97 (85.8)
C2	3	3 (100.0)
C3	123	122 (99.2)
C4	209	198 (94.7)
CBCw/diff	327	205 (62.7)
CBC without differential	32	29 (90.6)
Anti-CCP antibody	43	43 (100.0)
Chest X-ray	16	16 (100.0)
CIU basophil activation	41	32 (78.0)
CRP	91	79 (86.8)
CU index panel	161	123 (76.4)
Direct bilirubin	56	55 (98.2)
Anti-dsDNA antibody	64	63 (98.4)
ESR	198	189 (95.5)
Hepatitis B core antigen	19	19 (100.0)
Hepatitis B surface antibody	27	20 (74.1)
Hepatitis B surface antigen	28	28 (100.0)
Hepatitis C antibody	40	40 (100.0)
Histamine level	4	4 (100.0)
HIV	7	7 (100.0)
<i>Helicobacter pylori</i> antibody	45	39 (86.7)
IgA total	54	48 (88.9)
IgE total	221	143 (64.7)
Jo 1 antigen	143	143 (100.0)
La antigen	147	146 (99.3)
Latex allergen	1	1 (100.0)
LFT	215	200 (93.0)
Microsomal antibody	1	1 (100.0)
Myeloperoxidase	28	27 (96.4)
Peripheral smear	1	1 (100.0)
Proteinase	26	25 (96.2)
Renal profile	215	198 (92.1)
Rheumatoid factor	66	65 (98.5)
Anti-RNP antibody	143	137 (95.8)
Ro antigen	148	146 (98.6)
Scl 70 antibody	145	145 (100.0)
Serum specific IgE	38	36 (94.7)
Skin biopsy	102	27 (26.5)
Skin prick testing	45	30 (66.7)
Smith antigen antibodies	141	140 (99.3)
SPEP	265	234 (88.3)
Strep antibodies profile	3	3 (100.0)
T3	15	15 (100.0)
T4	112	111 (99.1)
Thyroid antibodies (anti-TPO IgE antibody)	246	204 (82.9)
Total bilirubin	67	66 (98.5)
Total complement	33	33 (100.0)
Tryptase	114	112 (98.2)

(continued)

TABLE III. (Continued)

Laboratory test	No. of patients who had the test performed	n (%) of patients with a normal test result
TSH	300	278 (92.7)
UA	58	51 (87.9)
Vitamin D	77	70 (90.9)

ANA, Antinuclear antibody; CBC, complete blood cell count; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; CU, chronic urticaria; dsDNA, double-stranded deoxyribonucleic acid; ESR, erythrocyte sedimentation rate; LFT, liver function test; RNP, ribonucleic protein; SPEP, serum protein electrophoresis; T3, triiodothyronine; T4, thyroxine; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone; UA, urinalysis.

a result of a test. Use of high-dose second-generation H₁-antihistamines was significantly higher after evaluation, with only 3.9% of the patients before evaluation and 48.7% after evaluation ($P < .0001$). Also, omalizumab was prescribed in 27 patients (3.7%) before evaluation and in 53 patients (7.3%) after evaluation ($P < .0001$). Table V presents information on management after visit as well as changes in outcome or lack thereof and alternative diagnoses.

Analysis of costs generated by CUA

As presented in Table VI, analysis of the cost generated by CUA evaluations showed no significant differences between the preguidelines and postguidelines periods regarding total cost. Total costs ranged from \$4 to \$2573 (mean, $\$569 \pm \$416$; median, \$470) in the preguidelines period and from \$14 to \$2431 (mean, $\$569 \pm \$414$; median, \$464) in the postguidelines period ($P = .9744$). Most costs were incurred in BETOS categories 1 and 4. E&M (BETOS 1) accounted for as much as \$1827 of the total, followed by Tests (BETOS 4), which cost as much as \$1365. Median costs were consistent across preguideline and postguideline time frames in BETOS categories 1, 2, and 6, and there was only a slight nonsignificant difference in mean costs within BETOS 4 (\$149-\$154).

DISCUSSION

We have analyzed the diagnostic evaluations of 725 patients with CUA over a 9-year period at a tertiary care center where 543 had at least 1 test performed. More than 5000 tests were performed in the evaluation of these patients, most of which were within normal range; and except for 5 cases (0.9%), tests with abnormal results did not lead to changes in management or outcome. Our data reinforce current recommendations to minimize testing.

Performing tests for evaluation of CUA is still a common practice. Most tests are performed to assess for pathogenesis, prognosis (eg, time to remission and disease activity/severity), and response to treatment.¹⁵⁻²⁶ However, the evidence is still limited and we need well-designed, randomized controlled trials if we intend to prove biomarkers' utility as routine tests. Most of the time, tests are unnecessary because rarely do their results influence the diagnosis, prognosis, and course of treatment, identify exogenous causes, or uncover underlying conditions.^{2,27}

CUA is a clinical diagnosis and the course of treatment should target total symptom control.¹¹ PCPs (mid-level providers, internists, and family physicians) frequently evaluate patients with CUA.^{6-8,28} In fact, PCPs were the third most likely to evaluate

TABLE IV. Comparison of the proportion of patients who had specific laboratory tests performed between the preguidelines (2010-2014) and the postguidelines (2015- 2018) time periods

Laboratory test	n (%) of patients who had the given test performed			Percentage difference: post minus pre	P value*
	Overall (N = 725)	Preguidelines (N = 467)	Postguidelines (N = 258)		
Anti-Fc-epsilon-R1-alpha	224 (30.9)	171 (36.6)	53 (20.5)	-16.1%	<0.0001
Renal profile	215 (29.7)	161 (34.5)	54 (20.9)	-13.5%	0.0001
LFT	215 (29.7)	153 (32.8)	62 (24.0)	-8.7%	0.014
<i>Helicobacter pylori</i> antibody	45 (6.2)	42 (9.0)	3 (1.2)	-7.8%	<0.0001
T4	112 (15.4)	84 (18.0)	28 (10.9)	-7.1%	0.013
C1 function	114 (15.7)	81 (17.3)	33 (12.8)	-4.6%	0.11
Serum specific IgE	38 (5.2)	32 (6.9)	6 (2.3)	-4.5%	0.009
Total complement	33 (4.6)	28 (6.0)	5 (1.9)	-4.1%	0.014
Rheumatoid factor	66 (9.1)	49 (10.5)	17 (6.6)	-3.9%	0.10
CCP	43 (5.9)	33 (7.1)	10 (3.9)	-3.2%	0.10
Skin prick testing	45 (6.2)	34 (7.3)	11 (4.3)	-3.0%	0.15
UA	58 (8.0)	42 (9.0)	16 (6.2)	-2.8%	0.20
CBC without differential	32 (4.4)	24 (5.1)	8 (3.1)	-2.0%	0.26
C3	123 (17.0)	82 (17.6)	41 (15.9)	-1.7%	0.61
Chest X-ray	16 (2.2)	13 (2.8)	3 (1.2)	-1.6%	0.19
T3	15 (2.1)	12 (2.6)	3 (1.2)	-1.4%	0.28
C1 inhibitor	124 (17.1)	82 (17.6)	42 (16.3)	-1.3%	0.68
Myeloperoxidase	28 (3.9)	19 (4.1)	9 (3.5)	-0.6%	0.84
C2	3 (0.6)	3 (0.6)	0 (0)	-0.6%	0.56
Proteinase	26 (3.6)	17 (3.6)	9 (3.5)	-0.2%	1.00
Latex allergen	1 (0.1)	1 (0.2)	0 (0.0)	-0.2%	1.00
Microsomal antibody	1 (0.1)	1 (0.2)	0 (0.0)	-0.2%	1.00
Smith antigen antibodies	141 (19.4)	91 (19.5)	50 (19.4)	-0.1%	1.00
Scl 70 antibody	145 (20.0)	93 (19.9)	52 (20.2)	0.2%	1.00
Ro antigen	148 (20.4)	95 (20.3)	53 (20.5)	0.2%	1.00
La	147 (20.3)	94 (20.1)	53 (20.5)	0.4%	0.92
Peripheral smear	1 (0.1)	0 (0.0)	1 (0.4)	0.4%	0.36
CRP	91 (12.6)	58 (12.4)	33 (12.8)	0.4%	0.91
Strep antibodies profile	3 (0.4)	1 (0.2)	2 (0.8)	0.6%	0.29
Hepatitis B core antigen	19 (2.6)	11 (2.4)	8 (3.1)	0.7%	0.63
Jo 1 antigen	143 (19.7)	91 (19.5)	52 (20.2)	0.7%	0.85
Anti-RNP antibodies	143 (19.7)	91 (19.5)	52 (20.2)	0.7%	0.85
Hepatitis B surface antibody	27 (3.7)	16 (3.4)	11 (4.3)	0.8%	0.55
HIV	7 (1.0)	3 (0.6)	4 (1.6)	0.9%	0.25
Skin biopsy	102 (14.1)	64 (13.7)	38 (14.7)	1.0%	0.74
dsDNA	64 (8.8)	39 (8.4)	25 (9.7)	1.3%	0.59
Histamine level	4 (0.6)	0 (0.0)	4 (1.6)	1.6%	0.016
SPEP	265 (36.6)	167 (35.8)	98 (38.0)	2.2%	0.57
Hepatitis C antibody	40 (5.5)	22 (4.7)	18 (7.0)	2.3%	0.23
Hepatitis B surface antigen	28 (3.9)	14 (3.0)	14 (5.4)	2.4%	0.11
Total bilirubin	67 (9.2)	39 (8.4)	28 (10.9)	2.5%	0.29
TSH	300 (41.4)	189 (40.5)	111 (43.0)	2.6%	0.53
C4	209 (28.8)	130 (27.8)	79 (30.6)	2.8%	0.44
C1q	113 (15.6)	68 (14.6)	45 (17.4)	2.9%	0.34
Direct bilirubin	56 (7.7)	30 (6.4)	26 (10.1)	3.7%	0.083
CBC with differential	327 (45.1)	204 (43.7)	123 (47.7)	4.0%	0.31
Tryptase	114 (15.7)	63 (13.5)	51 (19.8)	6.3%	0.033
ANA	301 (41.5)	181 (38.8)	120 (46.5)	7.8%	0.049
ESR	198 (27.3)	114 (24.4)	84 (32.6)	8.1%	0.023
Thyroid antibodies (anti-TPO IgE antibody)	246 (33.9)	144 (30.8)	102 (39.5)	8.7%	0.022
IgE total	221 (30.5)	124 (26.6)	97 (37.6)	11.0%	0.002

(continued)

TABLE IV. (Continued)

Laboratory test	n (%) of patients who had the given test performed			Percentage difference: post minus pre	P value*
	Overall (N = 725)	Preguidelines (N = 467)	Postguidelines (N = 258)		
Vitamin D	77 (10.6)	28 (6.0)	49 (19.0)	13.0%	<0.0001
CIU basophil activation	41 (5.7)	2 (0.4)	39 (15.1)	14.7%	<0.0001
IgA total	54 (7.4)	6 (1.3)	48 (18.6)	17.3%	<0.0001
CU index panel	161 (22.2)	39 (8.4)	122 (47.3)	38.9%	<0.0001

ANA, Antinuclear antibody; CBC, complete blood cell count; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; CU, chronic urticaria; ESR, erythrocyte sedimentation rate; dsDNA, double-stranded deoxyribonucleic acid; LFT, liver function test; RNP, ribonucleic protein; SPEP, serum protein electrophoresis; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone; T3, triiodothyronine; T4, thyroxine; UA, urinalysis.

*P values result from Fisher exact test. Statistically significant ($P < .05$) differences are highlighted in bold.

and order tests at our institution, preceded only by allergists and dermatologists, which makes it important for guidelines to reach other HCPs besides these 2 respective specialists. Current guidelines recommend assessing activity of disease through the Urticaria Activity Score 7, quality of life impairment with the Chronic Urticaria Quality of Life Questionnaire, and disease control through the Urticaria Control Test at every visit.¹¹ These are validated tools that help the HCP and the patient in the decision-making process.^{11,29-33}

CUA treatment includes avoidance of triggers and the following 4 lines of pharmaceutical treatment¹¹:

1. Second-generation H₁-antihistamines at licensed doses
2. Four-fold dose increase in second-generation H₁-antihistamines
3. Omalizumab in addition to second-generation H₁-antihistamines
4. Cyclosporine A + second-generation H₁-antihistamines

The fourth line of treatment is recommended for patients who have failed to respond to lines of treatment 1 to 3 (refractory CUA).¹¹ Regarding this line of treatment, mycophenolate mofetil, methotrexate, mizoribine, azathioprine, cyclophosphamide, hydroxychloroquine, dapsone, sulfasalazine, colchicine, and tacrolimus have been used in combination with antihistamines and—given the lack of high-quality evidence supporting the use of cyclosporine A as the sole alternative to omalizumab—their use as fourth line of treatment could become more frequent.³⁴⁻⁴⁶ Current guidelines recommend waiting periods (2 weeks or less to 6 months) to change lines of treatment on the basis of symptomatic control (ie, Urticaria Control Test and Urticaria Activity Score 7), and that lines of treatment 3 and 4 be prescribed by an experienced, specialized physician.¹¹

Based on the mechanism of action of omalizumab and its capability to reduce mast cell and basophil activity and FcεRI expression,^{47,48} biomarkers such as anti-TPO IgE antibody, total IgE, and FcεRI expression have been suggested as predictors of response to omalizumab, and severity and activity of disease.^{16,18,19,24-26} However, omalizumab has been shown to have high levels of effectiveness and safety in CUA and there is still no evidence strong enough to support the use of any test as predictor of these aspects.⁴⁸⁻⁵⁶ At our institution, there are 3 tests (anti—high-affinity IgE receptor alpha, CIU basophil activation, and chronic urticaria index) that measure quantity and/or activity of FcεRI. Combined, these tests were performed in 426 of the patients in our cohort and the results were normal in 332 (77.9%) of them without having influenced the outcome or management in any of the cases. Therefore, in adherence to

current guidelines, it is recommendable to prescribe omalizumab without further testing (unless warranted) to a patient with CUA if they have failed to respond to the first and second lines of treatment.

Thyroid disease (TD) has been related to CUA.⁵⁷ Biomarkers for TD have been studied as diagnostic and prognostic tools for CUA. A commonly reported association is the prevalence of elevated anti-TPO IgE antibody in patients with CUA compared with healthy subjects. Although patients with CUA have elevated anti-TPO IgE antibody, they are more frequently euthyroid than not, and it has been suggested that these antibodies may play a pathogenic role in CUA.^{16,18,26,58,59} Our data showed that 674 patients had at least 1 test evaluating TD or function (ie, thyroid-stimulating hormone, triiodothyronine, thyroxine, thyroid antibodies, or microsomal antibody). Of these, anti-TPO IgE antibody had the lowest percentage of normal results ($n = 246$ [82.9%]). Only 1 patient (0.18%) benefited from TD evaluation after being diagnosed with Hashimoto's thyroiditis (alternative/additional diagnosis, Table V), and none of these tests led to changes in management, which speaks against routinely screening for TD in CUA.

According to current guidelines, CBCw/differential, erythrocyte sedimentation rate, and C-reactive protein are the 3 recommended basic tests, and all other tests are considered extended workup.^{1,10,11} CBCw/differential was the most commonly ordered test, and it was also one of the tests with the lowest percentage of normal results ($n = 327$; normal result in 205 [62.7%]) preceded only by skin biopsy. Even with its frequently abnormal results, CBC w/differential played a role in an additional diagnosis of anemia of iron-deficiency in only 1 patient (0.1%) and did not change the outcome in any case. Erythrocyte sedimentation rate and C-reactive protein were ordered 198 and 91 times, respectively, and the results were normal in 189 (95.5%) and 79 (86.8%) cases. They led to no changes in outcome. Although these 3 tests are recommended, another study showed similar results in regard to their frequency of abnormality and low influence in management or outcomes.²

Skin biopsies performed under the presumptive diagnosis of CUA had the lowest percentage of normal results ($n = 102$; normal, 27 [26.5%]). These are also unwarranted unless the clinical presentation raises the need to rule out differential diagnoses.^{11,35,54} Features such as lesions that persist for more than 24 to 48 hours, are burning or painful rather than pruritic, leave discoloration after their resolution, and unresponsiveness to antihistamines may suggest conditions such as urticarial vasculitis or autoimmune disease.^{35,60} Also, systemic symptoms such

TABLE V. Information regarding management after visit, outcome changes, and alternative diagnoses

Variable	Summary (N = 725), n (%)
Management after visit (more than 1 is possible)	
First-generation antihistamine at licensed dose	184 (25.4)
First-generation antihistamine at high dose	16 (2.2)
Second-generation antihistamine	288 (39.7)
Second-generation antihistamine at high dose	353 (48.7)
H ₂ blocker	147 (20.3)
Montelukast sodium	59 (8.1)
Topical steroids	16 (2.2)
Systemic steroids	29 (4.0)
Omalizumab	53 (7.3)
Dapsone	4 (0.6)
Cyclosporine	8 (1.1)
Epinephrine autoinject	16 (2.2)
Sulfasalazine	0 (0.0)
Doxepin hydrochloride	118 (16.3)
None	32 (4.4)
Other	12 (1.7)
Patient outcome if testing was performed (N = 543)	
Tests led to no change in outcome	538 (99.1)
Tests led to change in outcome	5 (0.9)
Alternative diagnoses found if testing was performed (N = 543)	
Cushing's syndrome	1 (0.1)
Hashimoto's thyroiditis	1 (0.1)
Iron-deficiency anemia	1 (0.1)
Cold-induced urticaria	1 (0.1)
Scabies	1 (0.1)
Small-vessel vasculitis	1 (0.1)
Urticarial vasculitis	1 (0.1)
Vasculitis	1 (0.1)

as arthralgias, myalgias, abdominal pain, dyspnea, or ocular irritation might suggest urticarial vasculitis but may be present in up to 16% of patients with CUA.^{54,61} In our study, a skin biopsy confirmed the diagnosis of CUA in 72 of 75 patients with abnormal results. The remaining 3 abnormal results diagnosed urticarial vasculitis, small-vessel vasculitis, and vasculitis, respectively, as per pathology reports. Even though a skin biopsy benefited these 3 patients, they represent a very low percentage of alternative diagnoses due to testing (0.18% each) and changes in outcome (0.54% combined) and show that routine skin biopsies will rarely elucidate an underlying condition, result in better treatment, or change the outcome.

As we mentioned before, only 0.9% of our patients had a change in outcome based on test results. We discussed 3 in the paragraph above. Another patient had an elevated FcεRI and had already failed to respond to cyclosporine A + regular-dose second-generation H₁-antihistamines. Based on this and the patient's refusal to take omalizumab, a decision was made to start mycophenolate mofetil + 4-fold dose second-generation

H₁-antihistamines. However, to our knowledge, no level or activity of FcεRI (high or low) has been associated with better response to mycophenolate mofetil than to other immunosuppressive agents. The last of these patients had a positive ice cube test result and a history of generalized wheals when exposed to cold water or air as well as without exposure to these triggers. A positive ice cube test result, which consists in placing an ice cube in contact with skin and waiting for 5 minutes to observe a wheal and flare reaction, plus a suggestive history were key elements in diagnosing the patient with acquired cold urticaria.^{62,63} Acquired cold urticaria is a type of chronic inducible urticaria (CIndU), and CIndU is a subtype of chronic urticaria.^{11,54} CUA and acquired cold urticaria can coexist and are not mutually exclusive; in fact, up to 50% of patients with CUA present components of CIndU (wheals due to heat, cold, pressure, water, dermographism, etc).^{54,62-65} We saw a total of 66 patients (9.1%) who had components of CIndU.

Other studied biomarkers for CUA include complement factor C5a, IL-6 and IL-18, metalloproteinase-9, D-Dimer, and vitamin D.^{17,19,21,22,27,66} However, no molecule clearly influences the diagnosis, prognosis, or management and the differences found in trials lack statistical significance.

It is worth mentioning that some tests (total complement, serum specific IgE, thyroxine, *H pylori* antibody, liver function test, renal profile, and anti-high-affinity IgE receptor alpha) were ordered more frequently in the postguidelines period to a statistically significant degree. It is unclear whether clinicians ordered these tests because of particularities of the patients or other clinical background; however, the results of these tests had no influence on the treatment or outcome of the respective patients.

It has been shown that routine testing in CUA adds little value and does not influence the diagnosis and decision-making process.^{2,27} Our results support these data and imply that testing adds considerable cost. Expenses due to treatment, testing, and outpatient and inpatient evaluations of CUA can be significant to the point that, in some populations, the yearly direct costs are comparable to those generated by hypertension and diabetes mellitus.⁶⁻⁹ In our cohort, the total cost reached as much as \$2573, with E&M and Tests accounting for most of it. As suggested by the differences in the numbers and percentages of times a single test was ordered in the preguidelines and postguidelines periods, and the differences between costs in pre-2015 and post-2015 periods, the amount and type of tests ordered remain similar since 2010.

Study limitations

The following limitations of our study merit mention. This was a retrospective cohort study done at a tertiary care academic medical center; therefore, it may not be generalizable and could lead to a centripetal bias. However, the patients seen at such center are expected to be more complicated, yet our study shows a low rate of abnormal test results, which could be even lower at a primary care or community level. Most abnormal test results were abnormal to such a minimal degree that they could have been considered insignificant, leading to no further evaluations and potentially causing the oversight of underlying conditions. Evaluations and tests for CUA were not standardized between HCPs. We cannot discuss the utility of autologous serum testing in the evaluation of CUA because it was not performed in any of our patients. These limitations could be approached by future

TABLE VI. CUA-related costs pre(<2015) vs post (≥2015) 2010-2017 *

Eggers Type of Service (BETOS) Classification	1-Pre (N = 465)	2-Post (N = 260)	Total (N = 725)	P value
Total cost inflated to 2017 dollars				.9744†
N	465	260	723	
Mean ± SD	569 ± 416	569 ± 414	569 ± 415	
Median	470	464	468	
Q1, Q3	267, 753	267, 758	267, 755	
Range	4-2573	14-2431	4-2573	
BETOS 1 E&M				.5600†
N	465	260	723	
Mean ± SD	320 ± 257	331 ± 275	324 ± 263	
Median	216	216	216	
Q1, Q3	173, 387	151, 407	169, 394	
Range	0-1827	0-1588	0-1827	
BETOS 2 Procedures				.4462†
N	465	260	723	
Mean ± SD	24 ± 55	25 ± 50	24 ± 54	
Median	0	0	0	
Q1, Q3	0, 0	0, 0	0, 0	
Range	0-319	0-329	0-329	
BETOS 4 Tests				.8907†
N	465	260	723	
Mean ± SD	223 ± 228	211 ± 204	219 ± 220	
Median	149	154	151	
Q1, Q3	39, 355	54, 331	43, 349	
Range	0-1365	0-895	0-1365	
BETOS 6 Other				.5650†
N	465	260	723	
Mean ± SD	1 ± 9	1 ± 7	1 ± 8	
Median	0	0	0	
Q1, Q3	0, 0	0, 0	0, 0	
Range	0-67	0-53	0-67	

*Internal costing for 2018 unavailable at time of study.

†Wilcoxon.

prospective studies. To our knowledge, this is the largest cohort study evaluating the utility of tests in CUA and the first one to assess the costs directly generated by these tests.

CONCLUSIONS

CUA poses a high financial burden and very rarely do results derived from testing lead to changes in management or outcome. Therefore, CUA in the absence of concurrent, objective evidence of other related comorbidities should not be used as a platform to screen for other diagnoses or underlying conditions. Besides the guidelines, more accessible and user-friendly resources are currently available and aim to help clinicians and patients address this situation.^{67,68} Adherence to guideline recommendations to practice limited testing could substantially decrease evaluation costs and improve quality of care. HCPs should have an open discussion with their patients about evidence-based decisions regarding limited testing in CUA.

REFERENCES

- Zuberbier T, Asero R, Bindslev-Jensen C, Walter Canonica G, Church MK, Gimenez-Arnau A, et al. EAACI/GA(2)LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. *Allergy* 2009;64:1417-26.
- Tarbox JA, Gutta RC, Radojicic C, Lang DM. Utility of routine laboratory testing in management of chronic urticaria/angioedema. *Ann Allergy Asthma Immunol* 2011;107:239-43.
- Lapi F, Cassano N, Pegoraro V, Cataldo N, Heiman F, Cricelli I, et al. Epidemiology of chronic spontaneous urticaria: results from a nationwide, population-based study in Italy. *Br J Dermatol* 2016;174:996-1004.
- Gaig P, Olona M, Munoz Lejarazu D, Caballero MT, Dominguez FJ, Echechipia S, et al. Epidemiology of urticaria in Spain. *J Invest Allergol Clin Immunol* 2004;14:214-20.
- Zuberbier T, Balke M, Worm M, Edenharter G, Maurer M. Epidemiology of urticaria: a representative cross-sectional population survey. *Clin Exp Dermatol* 2010;35:869-73.
- Parisi CA, Ritchie C, Petriz N, Morello Torres C. Direct medical costs of chronic urticaria in a private health organization of Buenos Aires, Argentina. *Value Health Reg Issues* 2016;11:57-9.
- 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;16:313-21.
- Lacour JP, Khemis A, Giordano-Labadie F, Martin L, Staumont-Salle D, Hacard F, et al. The burden of chronic spontaneous urticaria: unsatisfactory treatment and healthcare resource utilization in France (the ASSURE-CSU study). *Eur J Dermatol* 2018;28:795-802.
- Maurer M, Abuzakouk M, Berard F, Canonica W, Oude Elberink H, Gimenez-Arnau A, et al. The burden of chronic spontaneous urticaria is substantial: real-world evidence from ASSURE-CSU. *Allergy* 2017;72:2005-16.
- Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, 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;69:868-87.
11. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, et al. The EAACI/GA(2)LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy* 2018;73:1393-414.
12. Visscher SL, Naessens JM, Yawn BP, Reinalda MS, Anderson SS, Borah BJ. Developing a standardized healthcare cost data warehouse. *BMC Health Serv Res* 2017;17:396.
13. Lee DW, Duszak R Jr, Hughes DR. Comparative analysis of Medicare spending for medical imaging: sustained dramatic slowdown compared with other services. *AJR Am J Roentgenol* 2013;201:1277-82.
14. Bazemore A, Petterson S, Peterson LE, Phillips RL Jr. More comprehensive care among family physicians is associated with lower costs and fewer hospitalizations. *Ann Fam Med* 2015;13:206-13.
15. Yan S, Chen W, Peng C, Zhu W, Chen M, Zhang J, et al. C reactive protein (CRP) rs3093059c predicts poor mizolastine response in chronic spontaneous urticaria patients with elevated serum CRP level. *Exp Dermatol* 2019;28:240-6.
16. Ulambayar B, Park HS. Anti-TPO IgE autoantibody in chronic urticaria: is it clinically relevant? *Allergy Asthma Immunol Res* 2019;11:1-3.
17. Tuchinda P, Kulthanan K, Chularojanamontri L, Arunkajohnsak S, Sriussadaporn S. Relationship between vitamin D and chronic spontaneous urticaria: a systematic review. *Clin Transl Allergy* 2018;8:51.
18. Sanchez J, Sanchez A, Cardona R. Causal relationship between anti-TPO IgE and chronic urticaria by in vitro and in vivo tests. *Allergy Asthma Immunol Res* 2019;11:29-42.
19. Marzano AV, Genovese G, Casazza G, Fierro MT, Dapavo P, Crimi N, et al. Predictors of response to omalizumab and relapse in chronic spontaneous urticaria: a study of 470 patients. *J Eur Acad Dermatol Venereol* 2019;33:918-24.
20. Liang SE, Hoffmann R, Peterson E, Soter NA. Use of dapsone in the treatment of chronic idiopathic and autoimmune urticaria. *JAMA Dermatol* 2019;155:90-5.
21. Ghazanfar MN, Thomsen SF. D-dimer as a potential blood biomarker for disease activity and treatment response in chronic urticaria: a focused review. *Eur J Dermatol* 2018;28:731-5.
22. Folci M, Heffler E, Canonica GW, Furlan R, Brunetta E. Cutting edge: biomarkers for chronic spontaneous urticaria. *J Immunol Res* 2018;2018:5615109.
23. Endo T, Toyoshima S, Kanegae K, Izaki S, Nishimori N, Ito M, et al. Identification of biomarkers for predicting the response to cyclosporine A therapy in patients with chronic spontaneous urticaria. *Allergol Int* 2019;68:270-3.
24. Deza G, March-Rodriguez A, Sanchez S, Ribas-Llaurado C, Soto D, Pujol RM, et al. Relevance of the basophil high-affinity IgE receptor in chronic urticaria: clinical experience from a tertiary care institution. *J Allergy Clin Immunol Pract* 2019;7:1619-1626.e1.
25. D'Auria E, De Amici M, Licari A, Caimmi S, Mantegazza C, Zuccotti G, et al. Basophil activation test in children with autoimmune chronic spontaneous urticaria: is it ready for clinical practice? *Immunobiology* 2019;224:30-3.
26. Chanprapaph K, Iamsung W, Wattanakrai P, Vachiramon V. Thyroid autoimmunity and autoimmunity in chronic spontaneous urticaria linked to disease severity, therapeutic response, and time to remission in patients with chronic spontaneous urticaria. *BioMed Res Int* 2018;2018:9856843.
27. Kozel MM, Bossuyt PM, Mekkes JR, Bos JD. Laboratory tests and identified diagnoses in patients with physical and chronic urticaria and angioedema: a systematic review. *J Am Acad Dermatol* 2003;48:409-16.
28. Carne E. Managing chronic spontaneous urticaria (hives) in primary care. *Nurs Stand* 2018;33:78-82.
29. Hawro T, Ohanyan T, Schoepke N, Metz M, Peveling-Oberhag A, Staubach P, et al. Comparison and interpretability of the available urticaria activity scores. *Allergy* 2018;73:251-5.
30. Baiardini I, Giardini A, Pasquali M, Dignetti P, Guerra L, Specchia C, et al. Quality of life and patients' satisfaction in chronic urticaria and respiratory allergy. *Allergy* 2003;58:621-3.
31. Mlynec A, Zalewska-Janowska A, Martus P, Staubach P, Zuberbier T, Maurer M. How to assess disease activity in patients with chronic urticaria? *Allergy* 2008;63:777-80.
32. Ohanyan T, Schoepke N, Bolukbasi B, Metz M, Hawro T, Zuberbier T, et al. Responsiveness and minimal important difference of the urticaria control test. *J Allergy Clin Immunol* 2017;140:1710-1713.e1711.
33. Weller K, Groffik A, Church MK, Hawro T, Krause K, Metz M, et al. Development and validation of the urticaria control test: a patient-reported outcome instrument for assessing urticaria control. *J Allergy Clin Immunol* 2014;133:1365-72.
34. Wood RA, Khan DA, Lang DM, Fasano MB, Peden DB, Busse PJ, et al. American Academy of Allergy, Asthma and Immunology response to the EAACI/GA(2) LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria 2017 revision. *Allergy* 2019;74:411-3.
35. Bernstein JA, Lang DM, Khan DA, Craig T, Dreyfus D, Hsieh F, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol* 2014;133:1270-7.
36. Antia C, Baquerizo K, Korman A, Alikhan A, Bernstein JA. Urticaria: a comprehensive review: treatment of chronic urticaria, special populations, and disease outcomes. *J Am Acad Dermatol* 2018;79:617-33.
37. 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. *J Am Acad Dermatol* 2012;66:767-70.
38. Kibsgaard L, Lefevre AC, Deleuran M, Vestergaard C. A case series study of eighty-five chronic spontaneous urticaria patients referred to a tertiary care center. *Ann Dermatol* 2014;26:73-8.
39. 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. *Ind J Dermatol Venereol Leprol* 2014;80:122-8.
40. Raghavendran RR, Humphreys F, Kaur MR. Successful use of mycophenolate mofetil to treat severe chronic urticaria in a patient intolerant to ciclosporin. *Clin Exp Dermatol* 2014;39:68-9.
41. 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. *Int J Dermatol* 2006;45:1224-7.
42. Bernstein JA, Garamone SM, Lower EG. Successful treatment of autoimmune chronic idiopathic urticaria with intravenous cyclophosphamide. *Ann Allergy Asthma Immunol* 2002;89:212-4.
43. Asero R. Oral cyclophosphamide in a case of cyclosporin and steroid-resistant chronic urticaria showing autoreactivity on autologous serum skin testing. *Clin Exp Dermatol* 2005;30:582-3.
44. Hashimoto T, Kawakami T, Ishii N, Ishii K, Karashima T, Nakama T, et al. Mizoribine treatment for antihistamine-resistant chronic autoimmune urticaria. *Dermatol Ther* 2012;25:379-81.
45. Tal Y, Toker O, Agmon-Levin N, Shalit M. Azathioprine as a therapeutic alternative for refractory chronic urticaria. *Int J Dermatol* 2015;54:367-9.
46. Khan DA. Alternative agents in refractory chronic urticaria: evidence and considerations on their selection and use. *J Allergy Clin Immunol Pract* 2013;1:433-440.e431.
47. Beck LA, Marcotte GV, MacGlashan D, Togias A, Saini S. Omalizumab-induced reductions in mast cell ϵ expression and function. *J Allergy Clin Immunol* 2004;114:527-30.
48. Saini S, Rosen KE, Hsieh HJ, Wong DA, Conner E, Kaplan A, et al. A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with h1-antihistamine-refractory chronic idiopathic urticaria. *J Allergy Clin Immunol* 2011;128:567-573.e561.
49. Maurer M, Rosen K, Hsieh HJ, Saini S, Grattan C, Gimenez-Arnau A, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med* 2013;368:924-35.
50. Maurer M, Altrichter S, Bieber T, Biedermann T, Brautigam M, Seyfried S, et al. Efficacy and safety of omalizumab in patients with chronic urticaria who exhibit IgE against thyroperoxidase. *J Allergy Clin Immunol* 2011;128:202-209.e205.
51. Kaplan A, Ledford D, Ashby M, Canvin J, Zazzali JL, Conner E, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. *J Allergy Clin Immunol* 2013;132:101-9.
52. Gastaminza G, Azofra J, Nunez-Cordoba JM, Baeza ML, Echechipia S, Gaig P, et al. Efficacy and safety of omalizumab (xolair(r)) for cholinergic urticaria in patients unresponsive to a double dose of antihistamines: a randomized mixed double-blind and open-label placebo-controlled clinical trial. *J Allergy Clin Immunol Pract* 2019;7:1599-1609.e1.
53. Hide M, Park H-S, Igarashi A, Ye Y-M, Kim T-B, Yagami A, et al. Efficacy and safety of omalizumab in Japanese and Korean patients with refractory chronic spontaneous urticaria. *J Dermatol Sci* 2017;87:70-8.
54. Antia C, Baquerizo K, Korman A, Bernstein JA, Alikhan A. Urticaria: a comprehensive review: epidemiology, diagnosis, and work-up. *J Am Acad Dermatol* 2018;79:599-614.
55. Zhao ZT, Ji CM, Yu WJ, Meng L, Hawro T, Wei JF, et al. Omalizumab for the treatment of chronic spontaneous urticaria: a meta-analysis of randomized clinical trials. *J Allergy Clin Immunol* 2016;137:1742-1750.e1744.
56. Saini SS, Bindslev-Jensen C, Maurer M, Grob JJ, Bulbul Baskan E, Bradley MS, et al. Efficacy and safety of omalizumab in patients with chronic

- idiopathic/spontaneous urticaria who remain symptomatic on h1 antihistamines: a randomized, placebo-controlled study. *J Invest Dermatol* 2015;135:67-75.
57. Rottem M. Chronic urticaria and autoimmune thyroid disease: is there a link? *Autoimm Rev* 2003;2:69-72.
 58. Najafipour M, Zareizadeh M, Najafipour F. Relationship between chronic urticaria and autoimmune thyroid disease. *J Adv Pharmaceut Technol Res* 2018;9: 158-61.
 59. Kolkhir P, Church MK, Weller K, Metz M, Schmetzer O, Maurer M. Auto-immune chronic spontaneous urticaria: what we know and what we do not know. *J Allergy Clin Immunol* 2017;139:1772-1781.e1771.
 60. Tosoni C, Lodi-Rizzini F, Cinquini M, Pasolini G, Venturini M, Sinico RA, et al. A reassessment of diagnostic criteria and treatment of idiopathic urticarial vasculitis: a retrospective study of 47 patients. *Clin Exp Dermatol* 2009;34: 166-70.
 61. Amsler E, Soria A, Vial-Dupuy A. What do we learn from a cohort of 219 French patients with chronic urticaria? *Eur J Dermatology* 2014;24:700-1.
 62. Sanchez-Borges M, Gonzalez-Aveledo L, Caballero-Fonseca F, Capriles-Hulett A. Review of physical urticarias and testing methods. *Curr Allergy Asthma Rep* 2017;17:51.
 63. Gernez Y, Sicherer SH, Wang J. Variability in diagnosis and management of acquired cold-induced urticaria. *J Allergy Clin Immunol Pract* 2018;6:1396-9.
 64. Weller K, Altrichter S, Ardelean E, Krause K, Magerl M, Metz M, et al. Chronic urticaria: prevalence, course, prognostic factors and impact [in German]. *Hautarzt* 2010;61:750-7.
 65. Stepaniuk P, Vostretsova K, Kanani A. Review of cold-induced urticaria characteristics, diagnosis and management in a western Canadian allergy practice. *Allergy Asthma Clin Immunol* 2018;14:85.
 66. Asero R, Marzano AV, Ferrucci S, Cugno M. D-dimer plasma levels parallel the clinical response to omalizumab in patients with severe chronic spontaneous urticaria. *Int Arch Allergy Immunol* 2017;172:40-4.
 67. Ten things physicians and patients should question. American Academy of Allergy Asthma & Immunology. Available from: <https://www.choosingwisely.org/clinician-lists/american-academy-allergy-asthma-immunology-chronic-urticaria/>. Accessed April 15, 2019.
 68. American Academy of Allergy Asthma & Immunology. Diagnostic testing and chronic urticaria—choosing wisely. 2014. Available from: <https://www.aaaai.org/conditions-and-treatments/videos/choosing-wisely/testing-urticaria>. Accessed April 15, 2019.