

Acquired Cold-Induced Urticaria in Pediatric Patients: A 22-Year Experience in a Tertiary Care Center (1996-2017)



Christina S.K. Yee, MD, PhD^{a,b,*}, Kristel El Khoury, PharmD, MPH^{a,b,*}, Sultan Albuhairei, MD^{a,b,*}, Ana Broyles, MD^{a,b}, Lynda Schneider, MD^{a,b}, and Rima Rachid, MD^{a,b} Boston, Mass

What is already known about this topic? Patients with acquired cold urticaria (ACU) may experience life-threatening systemic reactions upon exposure to cold. ACU in pediatric patients has not been well evaluated.

What does this article add to our knowledge? Anaphylaxis occurred in 19% of pediatric patients with ACU, mostly triggered by swimming. Positive cold-stimulation test result was significantly associated with grade 3 reactions. However, 12% of patients with negative test results had anaphylaxis.

How does this study impact current management guidelines? Cold stimulation testing may help identify pediatric patients with ACU at increased risk of anaphylaxis. However, anaphylaxis can still occur despite a negative test result. Management should include epinephrine prescription and discussion about anaphylaxis risk factors including swimming.

BACKGROUND: Acquired cold-induced urticaria (ACU) has not been well evaluated in pediatrics.

OBJECTIVE: To further evaluate the presentation of ACU in children and associated risk of anaphylaxis.

METHODS: A retrospective chart review was performed in children 18 years or younger diagnosed with ACU at Boston Children's Hospital (US, Northeast) from 1996 to 2017.

RESULTS: A total of 415 patients with ACU were identified, aged 4 months to 18.3 years at the time of diagnosis, with similar male:female distribution. Most patients had a history of atopic disease (78.3%), and 25.8% had other urticaria. Around two-third of patients experienced only localized cold-induced symptoms (grade 1), whereas 14.0% had diffuse cutaneous symptoms (grade 2) as the most severe reaction, and 18.6% experienced anaphylaxis (grade 3). Swimming triggered 77.6% of grade 3 reactions, whereas the rest were secondary to ingestion of cold food or beverages, or cold air or cold water exposure. Seven percent of subjects had more than 1 episode of anaphylaxis. Cold stimulation test (CST) was performed in 61.7% of patients, and the result was positive in 69.9% of those tested. Positive CST result was significantly associated with increased

risk of anaphylaxis. There was a 11.7% rate of anaphylaxis among patients with negative CST result. Disease resolution at any point in the study period was documented in 8.9% of patients and was associated with a negative history of anaphylaxis.

CONCLUSIONS: In the largest study to date on ACU, grade 3 reactions occurred in about a fifth of patients. Positive CST result was associated with a higher risk for anaphylaxis from ACU. Epinephrine prescription and patient/family counseling about risk factors for grade 3 reactions are recommended. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:1024-31)

Key words: Acquired cold urticaria; Cold-induced urticaria; Anaphylaxis; Cold stimulation test; Ice-cube test; Chronic urticaria; Atopy; Physical urticaria; Pediatric; Children

INTRODUCTION

Acquired cold-induced urticaria (ACU) is a form of physical urticaria characterized by the development of hives, angioedema, or both upon cold exposure.¹⁻⁵ The estimated incidence is 0.05%.^{4,6} Although most patients develop only localized symptoms from cold exposure, subjects are at risk of developing life-threatening reactions.^{1,2,4,7,8} Wanderer et al initially reported that 38% of 50 patients had severe reactions.² A previous retrospective study from our institution found a similar rate (37%) of anaphylaxis (systemic reactions with respiratory and/or hypotensive symptoms) in 30 pediatric patients.⁷ In other studies of adults or mixed age groups, the rate of anaphylaxis ranged from 28.3% to 40%.^{1,4,9} However, the true likelihood of anaphylactic reactions associated with cold exposure is difficult to ascertain and may vary by age and geographic location.

Cold stimulation test (CST), which most commonly consists of applying an ice cube to the skin to produce a wheal and flare response, may help diagnose patients with ACU. CST does not

^aDivision of Immunology, Boston Children's Hospital, Boston, Mass

^bDepartment of Pediatrics, Harvard Medical School, Boston, Mass

* These authors contributed equally to this work.

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Corresponding author: Rima Rachid, MD, Division of Immunology, Boston Children's Hospital, 300 Longwood Ave, Boston, MA 02115. E-mail: rima.rachid@childrens.harvard.edu.

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Abbreviations used

ACU- acquired cold-induced urticaria

BCH- Boston Children's Hospital

CIU- chronic idiopathic urticaria

CST- cold stimulation testing

IQR- interquartile range

identify all patients with ACU; up to 41.7% of patients have a negative CST result.^{7,10} Some patients may exhibit response at a range of temperatures using specialized apparatus¹¹ not widely used in the clinical setting. Patients with cold-induced urticaria/angioedema but negative or atypical response to CST may have 1 of several types of atypical ACU, such as systemic ACU, cold-dependent dermatographism, and cold-induced cholinergic urticaria.^{3,12}

First-line treatment consists of avoidance of immersion in cold water and/or situations of rapid systemic cold exposure.^{13,14} Medical therapy consists primarily of H1-antihistamines,¹⁵⁻²⁰ though immunomodulatory therapies such as omalizumab,²¹⁻²⁶ anakinra,²⁷ and reslizumab²⁸ have been tried off-label for treatment-refractory ACU.

Onset is reported to be most common in early adulthood,^{1,2,9,29} though presentation as early as age 3 months has been reported.³⁰ Rare forms of cold-induced urticaria include familial cold autoinflammatory syndromes and PLCG2-associated antibody deficiency and immune dysregulation.³¹⁻³⁴ ACU is a more common cause of pediatric cold-induced urticaria. Studies focusing exclusively on ACU in children have been limited. To further evaluate the presentation of this condition in pediatric patients, we conducted a retrospective 22-year chart review of patients diagnosed with ACU at Boston Children's Hospital (BCH), a tertiary care center in the Northeastern United States.

METHODS

Data collection

We performed an electronic medical chart review for patients seen at the BCH in the outpatient Allergy Program, with visits coded for urticaria (*International Classification of Diseases, Ninth Revision* 708.1) or temperature-induced urticaria (*International Classification of Diseases, Tenth Revision* L50.2) generated by an I2B2 database search. We included patients younger than 19 years who were given an ACU physician-diagnosis based on a history of cutaneous urticaria, angioedema, and/or anaphylaxis associated with cold exposure. Data collected included age, sex, associated atopic and/or immune conditions, presence of other urticaria, family history of atopy and ACU, severity of ACU reaction, medical treatment, duration of symptoms, CST results, and laboratory testing (including eosinophil count, IgE level, cryoglobulin testing, thyroid function and antibody testing, and IgE-receptor antibody and/or tryptase level). Chart screening and data collection were split between 3 authors (C.Y., K.E., S.A.), and data for each patient were reviewed by at least 1 other reviewer. We also performed an I2B2 search to generate the total number of new patient-visits for any diagnosis, seen in the Allergy Program per year from 1996 to 2017. This research was approved by the BCH Institutional Review Board.

TABLE I. Characteristics of ACU in pediatric patients

Characteristic	Value
Patients' demographic characteristic	
Patients, n	415
Age at diagnosis (y), range	0.33-18.3
0-5	124 (30%)
6-11	155 (37.3%)
12-18	136 (32.7%)
Age at diagnosis (y), median (IQR)	8.4 (5.0-13.0)
Age at onset (y), range	0.1-18.25
0-5	120 (28.9%)
6-11	142 (34.2%)
12-18	96 (23.1%)
Unknown	57
Age at onset (y), median (IQR)	8.0 (4.6-12)
Sex	
Male	210 (50.6%)
Female	205 (49.4%)
Triggers, n (% of all patients)	
Direct contact with cold water/objects	372 (89.6%)*
Cold air	341 (82.2%)*
Swallowing cold liquids or foods	41 (9.9%)*
Family history, n (% of all patients)	
Family history of cold urticaria	24 (5.8%)
Family history of atopy	304 (73.3%)
Symptom severity (n, % of all patients)	
Reaction severity*	
Grade 1	412 (99.3%)
Grade 2	70 (17.1%)
Grade 3	77 (18.6%)
Most severe reaction (highest grade per patient)	
Grade 1	280 (67.4%)
Grade 2	58 (14.0%)
Grade 3	77 (18.6%)
Multiple reactions	
Grade 2	14 (3.4%)
Grade 3	29 (7.0%)

Percentages indicate the numbers as a percent of all patients.

*May total greater than 100% because patients may be present in multiple categories.

Cold stimulation test

CST was performed by ice-cube challenge testing. An ice cube in a plastic bag or nonlatex glove was applied on the volar surface of the forearm for 5 minutes followed by 5 to 10 minutes of rewarming. The test result was interpreted as positive when a wheal appeared over the application site. If the test result was negative at 5 minutes, the test was repeated for 10 minutes followed by 5 to 10 minutes of rewarming. Wheal size was measured as diameter in millimeter along the longest axis of the wheal.

Reaction triggers and severity

We grouped ACU reaction triggers into 3 categories: direct contact with cold water or cold objects, exposure to cold air, and swallowing cold drinks and foods. Reaction severity was graded by the authors using a modified classification from that described by Wanderer et al.² Reactions were assigned to 1 of 3 grades: grade 1 (localized urticaria and/or angioedema), grade 2 (generalized urticaria and/or angioedema without other symptoms), and grade 3 (severe systemic reactions consisting of urticaria and/or angioedema

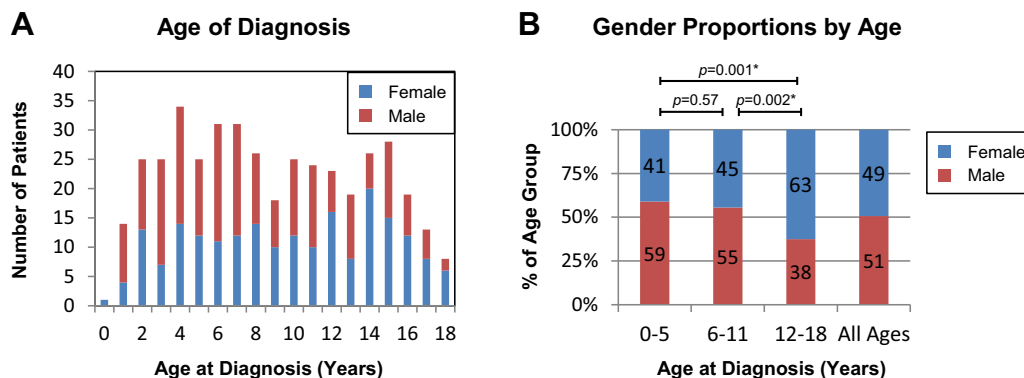


FIGURE 1. Age and sex at time of ACU diagnosis. **A**, Distribution of patients' age and sex. **B**, Sex distribution was equal overall (49.5% females, 50.6% males). The 12- to 18-year-old group had significantly more females (62.5%) than the 0- to 5-year-olds (41.1%; $P = .001$) and 6- to 11-year-olds (44.5%; $P = .002$). The 2 younger age groups were not significantly different ($P = .57$).

associated with airway, respiratory, and/or abdominal symptoms and/or cardiovascular or neurologic symptoms suggestive of hypotension including dizziness, lethargy, sensation fainting, disorientation, or shock/symptoms of shock).

Management

Treatment at the time of active ACU symptoms was recorded, including short-acting and long-acting H1-receptor blocker antihistamines, H2-receptor blocker antihistamines (ranitidine), and other medications (including montelukast, oral steroids, doxepin, and omalizumab). Documentation of epinephrine autoinjector prescription patterns included whether this was prescribed solely for ACU or, if noted, for any combination of ACU and other atopic disease, such as food allergy and/or *Hymenoptera* allergy.

Disease progression evaluation

ACU progression and response to treatment were documented on the basis of clinical notes in the electronic medical record. We considered ACU resolved if patients had no ongoing symptoms with cold water (including swimming) or air exposure for at least 1 winter period while not receiving antihistamines.

Statistical analysis

Descriptive statistics for medians, ranges, and quartiles (25th/75th percentiles) were calculated using Microsoft Excel. Statistical comparisons were performed in SPSS (IBM Corporation, Armonk, NY) and GraphPad Prism (La Jolla, Calif). Chi-square test was used to compare categorical variables. For continuous variables, we used Mann-Whitney U test to compare 2 groups, or Kruskal-Wallis test for more than 2 groups. All tests were 2-tailed. We considered P values of less than .05 as significant.

RESULTS

Demographic characteristics

Our I2B2 database search identified 963 patients with a billing code for urticaria (*International Classification of Diseases, Ninth Revision* 708.1), 259 patients coded for cold- or heat-induced urticaria (*International Classification of Diseases, Tenth Revision* L50.2), and 143,534 allergy new patient-visits, from 1996 to 2017.

As detailed in Table I, 415 patients met inclusion criteria. Age at diagnosis ranged from 4 months to 18.3 years (median, 8.4 years; first/third interquartile range [IQR], 5.0-13.0 years;

Figure 1, A). Males (50.6%) and females (49.4%) were equally represented overall (Figure 1, B). The proportion of females (62.5%) was significantly higher in the oldest patients (aged 12-18 years at diagnosis), compared with school-age (44.5%; $P = .002$) and younger children (41.1%; $P = .001$). Age of onset (age at first reported symptoms) ranged from 1 month to 18.25 years (median, 8.0 years; IQR, 4.6-12.0 years). Most patients (78.3%) had coexisting atopy (Table II). Allergic rhinitis was the most commonly associated atopic condition (59.6%), followed by asthma (46.9%), food allergy (33.4%), and atopic dermatitis (24.5%). In addition, a small subset of patients had medication allergies (12.5%), contact dermatitis (1.4%), and/or allergic colitis (0.5%).

Around one-fourth of patients (25.8%) also had another form of urticaria (Table II). Chronic idiopathic urticaria (CIU) (14.2% of patients) was the most common association. Other physical urticarias included exercise-induced urticaria (4.8%), dermatographism/pressure urticaria (4.6%), heat-induced urticaria (5.3%), and cholinergic urticaria (3.6%).

Autoimmune disease was recorded in 3.6% of patients, including juvenile idiopathic arthritis and autoimmune thyroid disease. Only 1.0% of patients had a diagnosis of antibody deficiency. One patient had a history of urticaria pigmentosa with normal tryptase level; 73.3% had a family history of atopy. Twenty-four study patients (5.8%) had a family history of cold-induced urticaria (Table II). No patient was identified with a genetic or clinical diagnosis of familial cold urticaria syndrome.

Reaction triggers and severity

The vast majority of patients experienced symptoms with cold contact (89.6% of patients) and cold air (82.2%), but far fewer reported pharyngeal symptoms with ingestion of cold substances (9.9%; Table I). Most patients experienced more than 1 type of trigger, with cold contact and cold air exposure (63.9% of patients) as the most common combination. Symptoms with all 3 triggers occurred in 8.4% of patients.

We first considered the severity of all cold-induced symptoms experienced by each patient (Table I). Almost all patients (412 [99.3%]) had at least 1 documented grade 1 episode with mild, limited symptoms. Diffuse cutaneous symptoms (grade 2) were reported in 70 or 16.9% of patients (11 of these had CIU), and 18.6% had at least 1 documented episode of anaphylaxis (grade 3). Clinical documentation did not capture the number or specific

TABLE II. Associated diagnoses in pediatric patients with ACU

Associated conditions	n (%)
Other urticaria	107 (25.8)
Chronic idiopathic urticaria	59 (14.2)
Heat-induced urticaria	22 (5.3)
Exercise-induced urticaria	20 (4.8)
Dermatographism/pressure urticaria	18 (4.3)
Cholinergic urticaria	15 (3.6)
Acute idiopathic urticaria	8 (1.9)
Atopy	325 (78.3)
Allergic rhinitis	247 (59.5)
Asthma	194 (46.8)
Food allergy	139 (33.4)
Atopic dermatitis	102 (24.6)
Oral allergy syndrome	11 (2.65)
Other allergic conditions	59 (14.2)
Medication allergy	52 (12.5)
Contact dermatitis	6 (1.45)
Allergic colitis	2 (0.48)
Autoimmunity	15 (3.6)
Autoimmune hypothyroidism/hyperthyroidism	4 (1.0)
Periodic/recurrent fever	4 (1.0)
Inflammatory arthritis/juvenile idiopathic arthritis	3 (0.7)
Alopecia areata	3 (0.7)
Henoch-Schonlein Purpura	1 (0.24)
ITP	1 (0.24)
PANDAS	1 (0.24)
Raynaud syndrome	1 (0.24)
Vitiligo	1 (0.24)
Other immune disorders	5 (1.2)
Antibody deficiency	4 (1.0)
Cutaneous mastocytosis/urticaria pigmentosa	1 (0.24)

n is the number of patients with associated diagnosis. % is the percentage of all study patients (n = 415) with each associated diagnosis.

triggers for every grade 1 reaction. The most common trigger for grade 2 and grade 3 reactions (Figure 2, A) was swimming (77.4% of grade 2 and 77.6% of grade 3 reactions); 12.8% of grade 2 and 6.3% of grade 3 reactions were triggered by contact, primarily cold water exposure without immersion or swimming (such as being splashed with cold water, playing in a sprinkler, or playing in snow), and 12.8% of grade 2 and 8.0% of grade 3 reactions were precipitated by exposure to cold air or temperatures alone (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). Ingestion of cold food or beverages was associated with 6.3% of anaphylactic reactions and no grade 2 reactions (Table E2). Two patients (1.8% of grade 3 reactions) experienced in-hospital anaphylaxis with systemic cooling, one after the infusion of room temperature intravenous fluids and another while the surgical site was being irrigated with cool fluids.³⁵ No other cases of iatrogenic ACU reactions, or systemic reactions requiring hospitalization, were reported.

We next considered the most severe reaction documented for each patient and categorized patients by the highest grade of documented reactions (Table I and Figure 2, B). The percentage of patients who experienced only grade 1 symptoms was 67.4%, whereas 14.0% of patients had grade 2 symptoms without any documented anaphylaxis and 18.6% had at least 1 documented

episode of anaphylaxis. Of patients who experienced anaphylaxis, 37.7% had more than 1 grade 3 reaction (Table I).

Of patients who experienced anaphylaxis, 58.4% were female. However, sex was not a significant risk factor for grade 3 reactions ($P = .08$), nor was age ($P = .37$) or asthma ($P = .21$). Patients with anaphylaxis comprised a significantly larger proportion of nonatopic patients (26.7%) than atopic patients (15.3%; $P = .03$).

Symptoms associated with anaphylaxis were reported for 112 grade 3 reactions in 75 patients (Table III). Two patients did not have specific symptoms recorded, but were reported by clinicians as having had anaphylaxis. The most common symptoms were loss of consciousness, syncope or fainting (28.6%), dizziness or lightheadedness (25.9%), and difficulty breathing (25.0%). Throat tightness or discomfort was noted in 10.8% of reactions. No patients had fatal reactions.

Cold-stimulation test

Of 256 patients with CST documented, 69.9% had positive test results and 30.1% had negative test results (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). The proportion of patients with positive test results was 76.5% in the youngest subjects (0-5-year-olds), 63.6% in the 6- to 11-year-olds, and 69.7% in the oldest (12-18-year-olds), but this difference was not statistically significant ($P = .50$).

Time of application was not recorded for 52 patients. Ninety-two patients underwent CST for only 5 minutes due to patient inability to tolerate testing. Of these, 36.2% had a positive CST result. One hundred twelve subjects had CST for 10 minutes. Of these, 34% had positive results. Of patients with documented positive CST result at 5 minutes, 25% had anaphylaxis from ACU, compared with 21% of patients with positive results at 10 minutes. This difference was not significant ($P = .82$). CST did not lead to any adverse events or systemic reactions.

We evaluated correlation between CST result and history of anaphylaxis (Figure E1). For this analysis, we pooled patients whose highest reaction severity was grade 1 or grade 2, and compared their CST results with those of patients with grade 3 reactions. Among patients who developed anaphylaxis from ACU either before or after their CST evaluation, 84.7% had positive CST results, compared with 65.5% of patients tested who had no history of anaphylaxis. Positive CST result was significantly associated with likelihood of grade 3 reaction (χ^2 test, $P = .005$). Among our patient cohort, sensitivity of CST for history of anaphylaxis was 84.7%. Although the positive predictive value of CST for anaphylaxis was only 27.9%, the negative predictive value was 88.3%, with an 11.7% rate of anaphylaxis among patients with negative CST result.

In 96 patients with positive CST result for whom CST wheal size was recorded, wheal size increased with history of anaphylactic reaction. Median wheal size was 37.0 mm in 21 patients with a history of anaphylaxis (IQR, 5.5-47.5), or 13.0 mm in 75 patients without a history of anaphylaxis (IQR, 5.0-30.0). This comparison approached but did not reach statistical significance (Mann-Whitney U test, $P = .053$).

Management

For maintenance treatment, 93.0% of patients received long-acting H1-receptor antagonist antihistamines and 28.4% received short-acting H1-receptor antagonist antihistamines (Table IV). A small percentage of patients received other

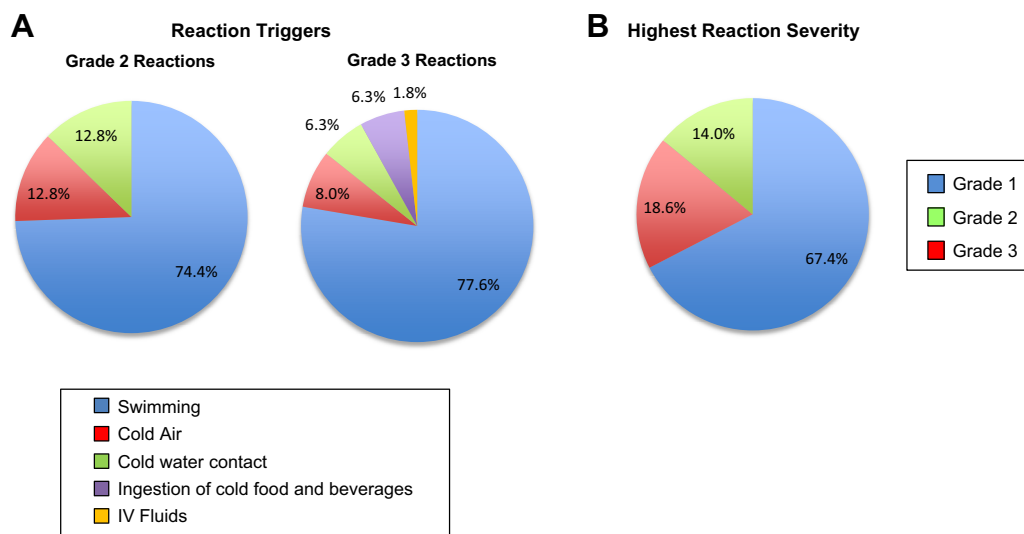


FIGURE 2. Reaction triggers and severity. **A**, Reaction triggers for grade 2 and grade 3 reactions. **B**, Percentage of highest reaction grade occurring in patients: grade 1 reactions (67.4%), grade 2 reactions (14.0%), and grade 3 reactions (18.6%). /V, Intravenous.

medications (montelukast, ranitidine, oral corticosteroid, and doxepin) concomitantly during periods of active ACU symptoms.

Five adolescent females received omalizumab, 3 for associated asthma and 2 for CIU. One patient had complete resolution of ACU symptoms with omalizumab (20.0%), while 4 reported improvement (80.0%). The vast majority of patients (89.2%) were prescribed an epinephrine autoinjector (Table IV).

Progression of symptoms and resolution

The progression of symptoms while on medications was documented in the medical record by the treating physician(s) for 182 patients. Of these, 154 (84.6%) were reported to have improved or resolved, while 28 (15.4%) were reported to be stable or worse.

Resolution of ACU symptoms at any point during the study period was documented in 36 of 415 patients (8.9%) at ages 1 to 20 years (median, 9.6; IQR, 4.1-16 years). Among these patients, only 2 (5.6%) had anaphylaxis, which was significantly lower than the number of patients who did not have resolution ($P = .04$). Atopy was not significantly associated with resolution of ACU ($P = .39$). Of patients with resolved ACU, 9 (25.0%) had a history of grade 2 reactions.

Laboratory studies

Laboratory results were recorded for 139 patients (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Apart from cryoglobulin levels, laboratory workup was generally obtained for coexisting food allergies or CIU. Positive cryoglobulins were noted in 1 of the 71 patients tested (1.4%), who had only grade 1 reactions. None of 40 patients tested had abnormal baseline tryptase level. Consistent with the high percentage of patients with atopy, 63 of the 139 patients tested (45.3%) had an elevated eosinophil count, and 68.9% of 135 patients tested had elevated total serum IgE. IgE-receptor antibody (chronic urticaria index) test was performed largely in patients with chronic urticaria and the result was positive in 14.3% of 47 patients tested. Up to 19.0% of patients

tested had abnormal thyroid autoantibodies and 4% had abnormal thyroid-stimulating hormone, though only 4 patients had documented diagnosis of associated thyroid disorder.

Changes in incidence of ACU diagnosis at the BCH over time

To evaluate whether the incidence of ACU diagnosis in our program has increased over time, we evaluated the number of new ACU diagnoses per 10,000 new allergy clinic visits for all diagnoses, over 5-year blocks (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org). The ACU incidence was lowest from 1998 to 2002 (18.9/10,000 new patient-visits) but similar from 2003 to 2017 (30.9-33.4/10,000 new patient-visits).

DISCUSSION

To our knowledge, this is the largest study in general and in pediatric patients in particular, reporting on 415 children with ACU evaluated over 22 years. Median age at diagnosis was 8.9 years. Patient ages were distributed similarly between 3 subgroups (0-5, 6-11, and 12-18 years), though 2 peaks were identified, around ages 4 and 15 years (Figure 1, A). Previous smaller studies have suggested that peak onset for ACU is in early adulthood, at age 18 to 25 years.^{1,2,9,29} Because we did not include adults, we could not deduce whether there is a peak of onset for this disease across all ages.

Some studies focusing on adult patients have reported differences in male or female predominance, with up to 66% incidence in female subjects,^{1,9,10,29} whereas others did not find any significant sex preponderance.^{2,4} We observed that overall, male and female children were diagnosed with ACU with equal frequency. However, there were more females (62.5%) in the older age group, whereas the younger patients were mostly males. Hence, it is possible that hormonal factors might influence the development of ACU in older children. In addition, a slightly higher percentage of females (58.4%) than males developed anaphylaxis.

TABLE III. Extracutaneous symptoms of anaphylactic reactions from ACU

Symptom	Reactions (n)	% total (n = 112)
Cardiovascular		
Chest pain	2	1.8
Cyanosis	2	1.8
Fatigue/lethargy	9	8.0
Hypotension	4	3.6
Pallor/mottling	7	6.3
Tachycardia	1	0.9
Respiratory		
Cough	4	3.6
Difficulty breathing	28	25.0
Hypoxia	1	0.9
Wheezing	6	5.4
Airway		
Difficulty swallowing	1	0.9
Throat tightness or discomfort	10	8.9
Tongue swelling	1	0.9
Gastrointestinal		
Diarrhea	1	0.9
Dry heaving	1	0.9
Nausea	1	0.9
Stomach pain	7	6.3
Vomiting	12	10.7
Neurologic		
Change in/loss of vision	10	8.9
Decreased alertness or slow speech	3	2.7
Dizziness/lightheadedness	29	25.9
Headache	5	4.5
Loss of consciousness, syncope, or fainting	32	28.6
Weakness/going limp	5	4.5
Other		
Neck, jaw, or leg pain	3	2.7
Not feeling well	7	6.3

Extracutaneous symptoms associated with anaphylaxis were reported for 112 grade 3 reactions in 75 patients. (Two patients did not have symptoms recorded.) Numbers indicate the number of reactions in which specific symptoms were reported, and the percentage of all reactions in which specific symptoms occurred.

Rates of systemic cold-induced reactions in other studies have varied from 29% to 40%.^{1,2,4,7,10,36} Although a third of our patients experienced generalized reactions (grade 2 or 3), only 18.6% experienced anaphylaxis. It is therefore possible that the risk of anaphylaxis may be smaller in the pediatric age group, though we could not conclude this firmly because we did not evaluate a large adult cohort from the same geographical location. Effects of behavioral risks such as regular swimming could not be evaluated in this study.

Unlike studies evaluating mostly or exclusively adult patients, where 22% to 42% of subjects with ACU were atopic,^{1,2,4,10,29} we found that more than three-quarters of our patients had concomitant atopy. History of anaphylaxis was significantly higher in patients with atopy than in those without. However,

TABLE IV. Treatment for pediatric ACU

Treatment	n	% all patients
Epinephrine		
Epinephrine autoinjector prescription	370	89.2
Specifically for cold urticaria	280	67.5
For cold urticaria and/or other indication	90	21.7
Not prescribed	45	10.8
Maintenance medications		
Any antihistamine	400	96.4
Short-acting H1-blocker antihistamine(s)	118	28.4
Long-acting H1-blocker antihistamine(s)	386	93.0
Other medications		
Montelukast	15	3.6
For ACU only	7	1.7
For ACU and another urticaria	5	1.2
For ACU and asthma	3	0.72
Ranitidine (H2-blocker antihistamine)	7	1.7
Oral corticosteroid	1	0.24
Doxepin	1	0.24
Omalizumab	5	1.2

Numbers and percentages represent patients documented to have been prescribed and/or received medications.

there was no significant association between asthma and the risk of anaphylaxis.

Similar to previous findings,^{1,4} more than one-fourth of our patients had a concomitant form of urticaria. Associated urticaria in general, and CIU specifically, was not associated with an increased rate of grade 3 reactions; rate of anaphylaxis among patients with CIU was 10.2%, compared with 18.6% in all patients.

CST results have differed between studies. The highest rate of positive results was observed in a Finnish study, where 90% of 220 subjects had a positive ice-cube test result, and 7.7% had negative ice-cube test result but positive cold immersion or cold-weather-cold-room test result.¹ Other studies evaluating mostly or only adults have reported a positive CST result rate of 71% to 83%.^{2,4,10} However, positive CST result was found in only 50% to 58% of children.^{7, 10} In our pediatric population, 70% of children tested had a positive CST result. Positive CST result was associated with a higher risk of developing grade 3 reactions. Furthermore, median CST wheal size was higher in patients who developed anaphylaxis, a finding that was very close to achieving significance ($P = .053$). Our findings are limited by the facts that only 256 (61.7%) patients in this study had CST performed and that only 96 patients (23%) had wheal size recorded. Nevertheless, because CST was performed in 256 subjects, this remains the largest study reporting on CST outcome in patients with ACU. Regarding the reasons for not performing testing, clinicians commonly cited the clarity of clinical reaction history, patient inability to tolerate testing (primarily due to young age), or current antihistamine treatment. Patients did not have CST repeated to test for resolution of ACU. Although conversion to negative CST result has been used to evaluate the clinical efficacy of antihistamines or other maintenance treatments in some studies,¹⁷ this was not routinely done at our institution.

Other studies have found that a wheal reaction at an application time of 0.5 to 3 minutes was associated with a higher risk of grade 3 reactions.^{1,2} We could not evaluate this specifically

because it was not standard protocol to apply the ice cube for less than 5 minutes. There was no difference in anaphylaxis risk in patients who had positive CST result at 5 minutes compared with 10 minutes.

Although most anaphylaxis occurred from swimming, cold air exposure and ingestion of cold food or beverage were also triggers of grade 3 reactions. Importantly, 12% of patients with negative CST result experienced anaphylaxis from ACU. Hence, our results strongly suggest that epinephrine autoinjector prescription be recommended for all patients with ACU.

Only 8.9% of our patient population had documented disease resolution. In previous studies, disease resolution in children was reported to be between 5% and 7.5%,^{7,10} compared with 22% to 33.3% of adults.^{9,10,29} Our and others' results suggest that disease resolution is lower in children. Interestingly, we found that grade 3 reactions were associated with a decreased rate of disease resolution, as observed by Katsarou-Katsari et al.⁴ However, our findings differed in relationship to atopy, which in our patients was not associated with a lesser rate of disease resolution.

The vast majority of our patients reported improvement on H1-antihistamine therapy. Corticosteroids, H2-blockers, and leukotriene inhibitors were prescribed in a few patients for refractory ACU. Given the retrospective nature of the study, we could not evaluate the duration of maintenance therapy and its effects on reducing anaphylaxis or improving quality of life. Future prospective studies are needed to better understand the effect of maintenance therapy on ACU outcome.

Anti-IgE therapy has been evaluated for treatment-refractory ACU with promising results.^{22,23} Five patients within our study group who received omalizumab all reported improvement or resolution of ACU symptoms, even though this was prescribed for other indications. This suggests that anti-IgE therapy could be further explored in patients with ACU, especially in those with refractory symptoms despite standard management, or who would like to continue to engage in aquatic activities despite a history of anaphylaxis.

Although 33% of patients had laboratory testing, we observed that these results overall were not significantly helpful in the clinical management of ACU. The patients with thyroid or antibody disease were not diagnosed at the time of ACU presentation, or at the time of laboratory workup. Consistent with the high rate of atopy, most patients had an increase in eosinophil count. One patient (1.4%) had a positive cryoglobulin level, with a negative rheumatology workup. Other studies found positive cryoglobulin in 1% to 9.8% of patients with ACU.^{1,9,29} Our results suggest that cryoglobulin testing may not be necessary in ACU.

This largest study on ACU suggests that this condition is more common in children than was previously thought. We found that a fifth of patients develop anaphylaxis, including 12% of patients with negative CST result. Although swimming was the major trigger for grade 3 reactions, these also occurred from cold air exposure, cold food/liquid ingestion, and/or cold water exposure without body immersion. In addition, more than one-third of patients had more than 1 episode of anaphylaxis. Allergists, patients, and families should be aware of the risk of severe reactions associated with ACU. A recent survey found that among the responders, most allergists do not prescribe epinephrine usually or always for ACU, and that more than 40% think that the risk of anaphylaxis is less than 10%.³⁷ Our study strongly suggests that patients/families should be counseled

about the risks of anaphylaxis, and that an epinephrine autoinjector should be prescribed for all pediatric patients with ACU. Furthermore, warming of intravenous or irrigation fluids should be considered before administration, in addition to potentially administering premedications before surgery.

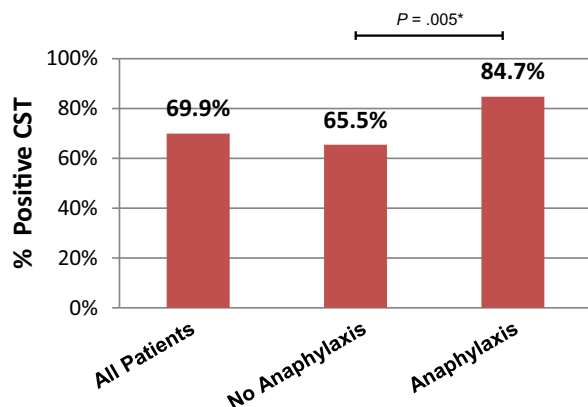
Our findings are limited by the retrospective nature of the study design, the lack of a survey to evaluate disease progression/resolution or query patient behaviors, and reliance on clinician report. Larger multicentered prospective studies are needed to further evaluate the natural history and progression of pediatric ACU, response to therapy, rate of anaphylaxis, and its association with CST outcome.

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ONLINE REPOSITORY

A CST Positivity and Anaphylaxis**B Predictive Value of CST**

		Anaphylaxis		
		+	-	
CST	+	50	129	PPV 27.9%
	-	9	68	NPV 88.3%
		Sensitivity 84.7%	Specificity 34.5%	

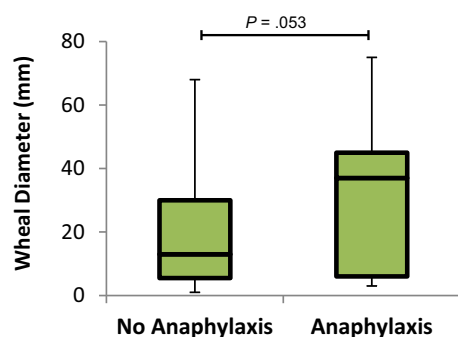
C CST Wheal Size and Anaphylaxis

FIGURE E1. A, CST in the whole cohort, and in patients with and without anaphylaxis. Patients with a history of anaphylaxis had a significantly higher rate of positive CST results (84.7%) than did those without (65.5%) ($P = .005$). **B**, Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of CST for anaphylaxis. **C**, Median wheal diameter of positive CST result was higher in patients with a history of anaphylaxis (37.0 mm; 95% IQR, 6.0-45.0) than in patients with no anaphylaxis (13.0 mm; IQR, 5.5-30.0); the difference approached but did not reach significance ($P = .053$, Mann-Whitney U test). Horizontal bar shows median. Boxes delineate first/third quartiles. Vertical bars show the range from minimum to maximum values.

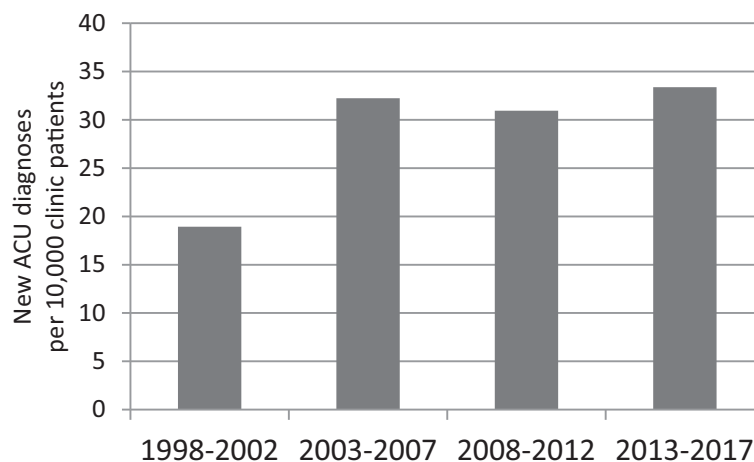


FIGURE E2. ACU new diagnosis over time. For each 5-year time period, shown are the number of patients newly diagnosed, per 10,000 new patients seen in allergy clinic.

TABLE E1. Laboratory studies

Laboratory test	Patients tested (n)	% of all patients tested	Patients with abnormal result (n)	% patients tested with abnormal result
Absolute eosinophil count	139	33	88	63
ALT	91	22	4	4
AST	91	22	7	8
CRP	89	21	9	10
Cryoglobulin	71	17	1	1.4
IgE	135	33	93	69
IgE Receptor (CU index)*	46	11	6	13
T4	62	15	0	0
Thyroglobulin antibody†	58	14	3	5
Thyroperoxidase antibody (TPO)‡	58	14	11	19
Tryptase (total)	40	10	0	0
Thyroid-stimulating hormone	70	17	3	4

ALT, Alanine transaminase; AST, aspartate transaminase; CRP, C-reactive protein; CU, chronic urticaria.

*Of 6 patients with ACU with positive anti-IgE-receptor antibody, 2 had concomitant CIU.

†Of 3 patients with ACU with positive thyroglobulin antibody, 1 had concomitant CIU.

‡Of 11 patients with ACU with positive anti-TPO, 6 had concomitant CIU.

TABLE E2. Characteristics of cold food/beverages and cold air–induced grade 3 reactions

Trigger: Cold food/beverage	Age at reaction (y)	Sex	Symptoms	Epinephrine use	CST result
Patient 1	12	F	Throat tightness, jaw pain, mandibular swelling, lip and tongue angioedema	No	Positive
Patient 2	18	M	Difficulty breathing, chest tightness, dizziness	No	Positive
Patient 3	17	F	Throat discomfort	Yes	Positive
Patient 4*	13	F	Throat itching and pain, dizziness, difficulty breathing	No	Positive
Patient 5	6	F	Difficulty breathing	No	Not done

Trigger: Cold air	Age at reaction (y)	Sex	Symptoms	Epinephrine use	CST result
Patient 1	4	F	Throat tightness, hives, angioedema	No	Positive
Patient 2	13	F	Tongue and lip angioedema, difficulty breathing, generalized hives	No	Positive
Patient 3	15	M	Difficulty breathing and throat tightness	No	Negative
Patient 4	16	F	Shortness of breath, hives	No	Negative
Patient 5	16	F	Wheezing, pruritic papular rash on exposed areas	No	Negative
Patient 6	1	F	Lethargy, sleepiness, hives and pruritis on exposed areas	No	Not done
Patient 7	2	F	Dizziness, generalized hives	No	Not done
Patient 8	5	M	Diffuse hives, nausea, vomiting, abdominal pain, throat itching, dizziness, headache	No	Not done
Patient 9	16	F	Symptoms unknown but described as anaphylaxis	Yes	Not done

F, Female; M, male.

*Patient had 3 separate grade 3 reactions with cold food/beverage.