

## Clinical Communications

### Variability in diagnosis and management of acquired cold-induced urticaria

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#### Clinical Implications

- Acquired cold-induced urticaria (ACU) is a rare condition for which diagnosis and management are not standardized. Improved understanding of the frequency of systemic reactions in subjects with ACU and indications for epinephrine autoinjector prescription would be beneficial.

#### TO THE EDITOR:

Acquired cold-induced urticaria (ACU) is a rare condition (0.05%) and is typically characterized as mild skin symptoms upon exposure to a cold stimulus (eg, hives).<sup>1</sup> However, patients with ACU may also be at risk of experiencing systemic reactions (eg, respiratory distress such as wheezing or shortness of breath or hypotension with dizziness, sensation of fainting, disorientation, or shock), especially when large areas of the body are exposed to cold water during aquatic activities.<sup>2,3</sup> Several studies suggest that the rate of systemic reactions due to ACU is significant. In a retrospective case series, Alangari et al<sup>2</sup> reported that 11 of 30 (36.7%) children with ACU had a history of systemic symptoms. A prospective study of patients demonstrated that 16 of 62 (25.8%) individuals with ACU who were older than 30 years experienced severe systemic reactions,<sup>4</sup> and additional studies reported a 40% to 41% risk of systemic reactions for patients with ACU.<sup>1,5</sup> Overall, the rate of reported systemic reactions is high for this population.

Targeting prescriptions of epinephrine autoinjectors to groups who are at a higher risk of systemic reactions would be ideal if such a group could be identified. In a recent urticaria Practice Parameter, it is suggested for those treating ACU “prescribe injectable epinephrine for patients judged to be at increased risk of systemic reactions.”<sup>6</sup> Individuals at increased risk are described as (1) those with positive cold stimulation time test (CSTT) results of less than 3 minutes and (2) those with laryngeal symptoms induced by exposure to cold food or drink.<sup>7</sup> However, a review of the available studies suggests that these criteria would miss many of those at a higher risk for systemic reactions. For example, laryngeal symptoms are rare (4% [9 of 220 patients])<sup>1</sup> and significantly lower than the frequency of systemic reactions. The CSTT is not standardized, and many patients with ACU have systemic reactions despite a positive CSTT of more than 3 minutes or with a negative CSTT. For example, Wanderer et al<sup>8</sup> reported that 32% (6 of 19) of patients with cold-induced systemic reactions had a negative CSTT or a positive one at more than 3 minutes. Alangari et al<sup>2</sup> reported that none of the systemic reactions in their pediatric cohort could have been predicted on the basis of results of their CSTT. Therefore, the Practice Parameter guidance for detecting high-risk patients may not be

sensitive or practical. As an important note, The EAACI/GA<sup>2</sup>LEN/EDF/UNEV guidelines do not mention epinephrine in the treatment of cold urticaria.<sup>9</sup>

To better understand the potential scope of the problem and understand clinical practice, we studied the current practice of allergy and immunology specialists in regard to how frequently, when, and for which symptoms they prescribe an epinephrine autoinjector for their patients with ACU. An anonymous 9-question electronic survey (Table 1) was distributed via email to a random sample (20%) of US and international members of the American Academy of Allergy, Asthma & Immunology (AAAAI). Potential participants were sent 2 email reminders during the study period, May to June 2017. This study was deemed exempt human research by the Icahn School of Medicine at Mount Sinai institutional review board. Descriptive analysis was performed with GraphPad Prism 7 software (GraphPad Software, Inc, La Jolla, Calif).

Fifty-one respondents participated in the survey (response rate, 10.4%); 64.7% of the respondents worked in private practice and 29.4% have been practicing for more than 20 years, 76% reported managing 3 or more patients with ACU, and 82% perform cold stimulation testing in evaluating ACU. Most respondents (86.3%) reported that less than 10% of their patients with ACU have experienced a systemic reaction, and 45.1% reported that this rate of systemic reactions was in concordance with that reported in the literature (Figure 1). A total of 48% of responders “infrequently prescribe an epinephrine autoinjector (<10% of the time)” for patients with ACU, whereas 13.7% of respondents always prescribe it. A total of 76.9% of responders prescribe an epinephrine autoinjector on the basis of reported symptoms or history. The most common reason for prescribing epinephrine was a history of laryngeal symptoms with cold beverages (54.3%) followed by patient participation in water-related activities (14.3%) and cold-related activities such as skiing (8.6%).

Most responders perform cold stimulation testing to confirm the diagnosis in patients suspected to have ACU. Survey participants reported lower rates of systemic reactions in their patients with ACU than what has been reported in the literature, and they underestimate the incidence of systemic reaction in subjects with ACU that is reported in the literature (10% compared with 40%). In this context, most of the respondents did not routinely prescribe an epinephrine autoinjector for their patients with ACU. For those who do prescribe epinephrine autoinjectors, most appear to be following practice parameter guidance by prescribing to patients at a higher risk of systemic reaction (patients with laryngeal symptoms on ingestion of cold beverages or participation in water-related activities).

There were several limitations to this study. This was not a standardized, validated questionnaire, and it was distributed only to members of the AAAAI. The response rate was low (10.4%); however, this response rate is typical for this type of AAAAI survey, which is usually 10% to 15%. These results are also subject to recall bias, and selection bias was a factor because only interested people chose to participate. Thus, these results may not be generalizable and instead may reflect the experiences of a subset of the AAAAI membership.

**TABLE I.** Anonymous 9-question electronic survey distributed to members of the AAAAI

1. How many years have you been practicing Allergy and Immunology?
  - A. <5
  - B. 5-<10
  - C. 10-<20
  - D. 20-30
  - E. >30
2. What is your primary practice setting?
  - A. Private practice
  - B. Academic center
  - C. Other
3. How many patients with ACU did/do you clinically manage?
  - A. 0-2
  - B. 3-5
  - C. 6-10
  - D. >10
4. What testing are you performing in your office for ACU?
  - A. I do not perform any testing; it is a clinical diagnosis
  - B. I perform a cold stimulation test
  - C. I perform a CSTT
  - D. I use an automated temperature probe
5. What percentage of your patients with ACU has experienced a systemic reaction when exposed to the cold?
  - A. <10%
  - B. 10%-<30%
  - C. 30%-50%
  - D. >50%
6. To your knowledge, what is the percentage of systemic reaction for patients with ACU reported in the literature?
  - A. <10%
  - B. 10%-<30%
  - C. 30%-<50%
  - D. 50%-70%
  - E. >70%
7. How often do you prescribe epinephrine autoinjectors for patients with ACU?
  - A. Never (0%)
  - B. Rarely (<10%)
  - C. Occasionally (10%-49%)
  - D. Usually (50%-99%)
  - E. Always (100%)
8. If you prescribe epinephrine autoinjectors for patients with ACU, what approach do you follow?
  - A. I always prescribe it for this diagnosis
  - B. I prescribe it on the basis of symptoms or history
  - C. I prescribe it on the basis of testing
  - D. I do not prescribe it for this diagnosis
9. If you prescribe epinephrine autoinjectors on the basis of specific patient characteristics, which ones listed below would warrant a prescription? (Check all that apply)
  - A. Lip edema
  - B. Laryngeal symptoms with cold beverages
  - C. Asthma
  - D. Generalized hives
  - E. Presence of atopy (except for food allergy for which you would have already prescribed an epinephrine autoinjector)
  - F. Presence of an underlying disease (such as cryoglobulinemia, lymphoma, hepatitis C)
  - G. Existence of severe cold urticaria in a family member
  - H. Time to hive on testing
  - I. Size of the hive/wheel upon cold test stimulation
  - J. Participates in water-related activities (swim, sailing, rowing, etc)
  - K. Participates in cold-related activities (skiing, snowboarding, snowshoeing, etc)
  - L. Other \_\_\_\_\_

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