

## LETTER TO THE EDITOR

# Mucosal angioedema involving the oropharynx signals severe cold urticaria: COLD-CE study insights

Dear Editor,

Cold urticaria manifests with a wide range of reaction severity, from localized wheals and cutaneous angioedema to cardiovascular, respiratory and gastrointestinal symptoms.<sup>1,2</sup> Interestingly, not all individuals react to the ingestion of cold food or drinks.<sup>3,4</sup> This clinical variability remains poorly understood, highlighting the need for better phenotyping in ColdU.

Typical ColdU (ColdU<sup>T</sup>) is diagnosed by whealing within 10 min on skin exposed to a melting ice cube or the TempTest® device (either version 4.0 [TT4] with a 4–44°C gradient, or the older version 3.0 [TT3] with 12 fixed 4–26°C probes). The critical stimulation time threshold (CSTT) and critical temperature threshold (CTT) indicate the shortest exposure time and highest temperature needed to elicit a wheal.<sup>5</sup> These parameters vary substantially among patients,<sup>5,6</sup> and their associations are not yet fully understood. Magerl et al. reported a correlation between CTTs obtained via TT4 and TT3.<sup>7</sup>

This analysis expands on our previous COLD-CE study report,<sup>5</sup> which identified oropharyngeal and laryngeal symptoms as risk factors for systemic reactions. In the present analysis, we define these symptoms as mucosal angioedema involving the oropharynx (MAO), characterized by a sensation of swelling of the tongue, pharynx or larynx and examine this phenotype in depth. A total of 535 patients with ColdU<sup>T</sup> were recruited from 2019 to 2025, including 123 additional patients enrolled after the first phase of the study. All underwent cold stimulation testing (CST) with an ice cube and/or TempTest®. Patients receiving omalizumab ( $n=55$ ) at enrolment were included based on CST results obtained prior to treatment, and only their clinical histories were analyzed.

Statistical analyses were performed using IBM SPSS V25.0, with a significance level set at  $p < 0.05$ . Numerical variables were non-normally distributed and expressed as medians and interquartile ranges (IQR), while categorical variables were presented as counts and percentages. The Mann–Whitney and Fisher's exact tests were used for continuous and categorical variables, respectively. Correlations were assessed with Spearman's rho ( $r$ ), interpreted as weak (0.10–0.29), moderate (0.30–0.50) or strong ( $>0.50$ ).<sup>8</sup>

MAO triggered by ingestion of cold food or drinks was reported by 32.1% of patients and was significantly associated

with generalized wheals ( $p < 0.001$ ), cutaneous angioedema ( $p < 0.001$ ) and systemic symptoms (cardiovascular:  $p < 0.001$ ; respiratory:  $p < 0.001$ ; gastrointestinal:  $p = 0.001$ ). MAO was also linked to a higher number of relevant cold triggers ( $p < 0.001$ ), including weaker stimuli like localized contact with cold liquids or surfaces (both  $p < 0.001$ ). Moreover, MAO patients had shorter CSTTs and higher CTTs measured with TT4 (both  $p < 0.001$ ), and reported greater quality-of-life impairment per the Dermatology Life Quality Index (DLQI)<sup>9</sup> (Table 1).

To our knowledge, this is the first demonstration that shorter CSTTs correlate with higher CTTs and larger wheal diameters, suggesting that patients who react quickly may also do so at higher temperatures and with more pronounced skin responses (Table 2). Among patients with results from both the ice cube and TempTest® ( $n = 318$ ), 80.8% tested positive on both, 2.5% only on the TempTest® and 16.7% only on the ice cube test. This suggests that the ice cube test may detect lower-temperature reactivity or responses not strictly temperature-dependent. Unlike the variable-sized ice cube, the TT4 has a standardized 2 mm probe width, which allows for consistent wheal size assessment and additional insight into cold sensitivity.

These findings highlight MAO as a clinically relevant, high-risk feature within ColdU<sup>T</sup>. We recommend routine assessment of MAO in ColdU<sup>T</sup> patients to guide management, including patient education on preventive measures and the prescription of adrenaline autoinjectors.<sup>10</sup> Additionally, we suggest its inclusion in future disease severity scoring systems.

## KEYWORDS

anaphylaxis, angioedema, cold urticaria, skin tests, urticaria

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## FUNDING INFORMATION

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**TABLE 1** Clinical features of patients with and without mucosal angioedema involving the oropharynx (MAO).

	Total, <i>n</i> = 535	MAO		<i>p</i> -value
		Yes, <i>n</i> = 172 (32.1)	No, <i>n</i> = 363 (67.9)	
<b>Demographics and general characteristics</b>				
Age (years)	36.0 (26.0–49.0)	37.0 (26.3–48.0)	36.0 (26.0–49.0)	0.298
Age ≥18 years	496 (92.7)	168 (97.7)	328 (90.4)	<b>0.002<sup>a</sup></b>
Female gender	369 (69.0)	126 (73.3)	243 (66.9)	0.161
BMI	24.4 (21.8–27.8)	24.9 (22.1–28.7)	24.2 (21.6–27.4)	0.066
Age at ColdU onset (years)	29.0 (18.0–42.0)	30.0 (20.0–43.0)	29.0 (18.0–42.0)	0.426
Paediatric onset of ColdU	119 (22.2)	34 (19.8)	85 (23.4)	0.374
Disease duration (months)	48.0 (16.0–108.0)	48.0 (24.0–120.0)	42.0 (14.0–96.0)	0.229
Positive family history of ColdU	27 (5.0)	11 (6.4)	16 (4.4)	0.397
Country with air temp. recorded below 0°C	402 (75.1)	121 (70.3)	281 (77.4)	0.087
<b>Types of CRs</b>				
Wheals (localized or generalized)	518 (96.8)	167 (97.1)	351 (96.7)	1.000
Generalized wheals <sup>b</sup>	331 (61.9)	125 (72.7)	206 (56.7)	<b>&lt;0.001<sup>a</sup></b>
Maximal wheal duration (min)	30.0 (15.0–60.0), <i>n</i> = 506	30.0 (20.0–60.0), <i>n</i> = 157	30.0 (15.0–60.0), <i>n</i> = 349	0.256
Cutaneous angioedema <sup>c</sup>	312 (58.3)	120 (69.8)	192 (52.9)	<b>&lt;0.001<sup>a</sup></b>
Maximal cutaneous angioedema duration (min)	45.0 (20.0–90.0), <i>n</i> = 231	45.0 (20.0–120), <i>n</i> = 102	40.0 (20.0–60.0), <i>n</i> = 129	0.460
Any cardiovascular symptoms (with or without loss of consciousness)	149 (27.9)	74 (43.0)	75 (20.7)	<b>&lt;0.001<sup>a</sup></b>
Loss of consciousness or documented hypotension (<90/60 mmHg)	63 (11.8)	34 (19.8)	29 (8.0)	<b>&lt;0.001<sup>a</sup></b>
Difficulty breathing <sup>d</sup>	106 (19.8)	69 (40.1)	37 (10.2)	<b>&lt;0.001<sup>a</sup></b>
Gastrointestinal symptoms <sup>d</sup>	54 (10.1)	29 (16.9)	25 (6.9)	<b>0.001<sup>a</sup></b>
<b>Relevant triggers of CRs</b>				
Number of relevant triggers of CRs	3.0 (2.0–4.0)	4.0 (3.0–5.0)	3.0 (2.0–4.0)	<b>&lt;0.001<sup>a</sup></b>
Cold air	472 (88.2)	156 (90.7)	316 (87.1)	0.252
Full cold-water immersion	366 (68.4)	124 (72.1)	242 (66.7)	0.232
Localized skin contact with cold liquids	347 (64.9)	135 (78.5)	212 (58.4)	<b>&lt;0.001<sup>a</sup></b>
Localized skin contact with cold surfaces	316 (59.1)	136 (79.1)	180 (49.6)	<b>&lt;0.001<sup>a</sup></b>
Ingestion of cold food or drinks	183 (34.2)	172 (100)	11 (3.0)	<b>&lt;0.001<sup>a</sup></b>
<b>Aggravating factors of CRs</b>				
Wind	376 (70.3)	137 (79.7)	239 (65.8)	<b>0.001<sup>a</sup></b>
Increased summer humidity	170 (32.1)	67 (39.2)	103 (28.8)	<b>0.022<sup>a</sup></b>
<b>Associated symptoms and clinical signs</b>				
Itch	480 (92.3)	164 (97.0)	316 (90.0)	<b>0.004<sup>a</sup></b>
Earlobe itching	220 (41.1)	90 (52.3)	130 (35.8)	<b>&lt;0.001<sup>a</sup></b>
Fever	23 (4.3)	5 (2.9)	18 (5.0)	0.363
Malaise	106 (19.8)	40 (23.3)	66 (18.2)	0.201
<b>Comorbidities (medical diagnosis)</b>				
Chronic spontaneous urticaria	54 (10.1)	13 (7.6)	41 (11.3)	0.219
Atopic disease, any	204 (38.1)	68 (39.5)	136 (37.5)	0.703
Thyroid disease	79 (14.8)	25 (14.5)	54 (14.9)	1.000
Current or previous malignancy	12 (2.2)	4 (2.3)	8 (2.2)	1.000
Raynaud's phenomenon	35 (6.5)	15 (8.7)	20 (5.5)	0.190

**TABLE 1** (Continued)

	Total, <i>n</i> = 535	MAO		<i>p</i> -Value
		Yes, <i>n</i> = 172 (32.1)	No, <i>n</i> = 363 (67.9)	
CST results				
Ice cube test				
Positive result	432 (95.6), <i>n</i> = 452	132 (95.7), <i>n</i> = 138	300 (95.5), <i>n</i> = 314	1.000
CSTT (s)	300 (120–300), <i>n</i> = 348	180 (60–300), <i>n</i> = 91	300 (180–300), <i>n</i> = 257	<0.001 <sup>c</sup>
Pseudopodial whealing	43 (9.5), <i>n</i> = 452	16 (11.6), <i>n</i> = 138	27 (8.6), <i>n</i> = 314	0.384
TT4				
Positive result	241 (77.5), <i>n</i> = 311	76 (81.7), <i>n</i> = 93	165 (75.7), <i>n</i> = 218	0.299
CTT (°C)	18.0 (14.0–23.0), <i>n</i> = 241	21.5 (16.0–25.0), <i>n</i> = 76	17.0 (12.0–22.0), <i>n</i> = 165	<0.001 <sup>c</sup>
Maximal wheal diameter (mm)	9.0 (5.0–13.0), <i>n</i> = 172	10.0 (7.0–12.0), <i>n</i> = 63	8.0 (5.0–13.0), <i>n</i> = 109	0.052
TT3				
Positive result	50 (98.0), <i>n</i> = 51	10 (100), <i>n</i> = 10	40 (97.6), <i>n</i> = 41	1.000
CTT (°C)	16.0 (14.0–20.5), <i>n</i> = 50	17.0 (14.0–21.0), <i>n</i> = 10	16.0 (14.0–21.5), <i>n</i> = 40	0.824
Maximal wheal diameter (mm)	14.0 (10.0–20.0), <i>n</i> = 41	20.0 (10.0–40.0), <i>n</i> = 7	13.0 (10.0–19.3), <i>n</i> = 34	0.244
PROMs				
DLQI score	5.0 (1.0–10.0), <i>n</i> = 535	6.0 (2.0–14.0), <i>n</i> = 172	4.0 (1.0–9.0), <i>n</i> = 363	0.002 <sup>c</sup>
UCT score	10.0 (6.0–13.0), <i>n</i> = 520	10.0 (5.0–13.0), <i>n</i> = 168	11.0 (7.0–13.0), <i>n</i> = 352	0.152
UCT ≥12	207 (39.8), <i>n</i> = 520	62 (36.9), <i>n</i> = 168	145 (41.2), <i>n</i> = 352	0.389

Note: Categorical variables are expressed as counts (percentages). Numerical variables are presented as medians (IQR). If data were not obtained for all patients, the patient numbers are displayed as “*n*” next to the results.

Abbreviations: BMI, body mass index; ColdU, cold urticaria; CRs, cold-induced reactions; CST, cold stimulation testing; CSTT, critical stimulation time threshold; CTT, critical temperature threshold; DLQI, Dermatology Life Quality Index; IQR, interquartile range; MAO, mucosal angioedema involving the oropharynx; *n*, number of patients; PROMs, patient-reported outcome measures; TT3, TempTest® version 3.0; TT4, TempTest® version 4.0; UCT, Urticaria Control Test.

<sup>a</sup>Fisher's exact test.

<sup>b</sup>Affecting more than two body regions.

<sup>c</sup>Deeper swellings with imprecise borders on any location on the skin, excluding MAO.

<sup>d</sup>Not specifically defined.

<sup>e</sup>Mann–Whitney test.

**TABLE 2** Spearman's correlation between local cold stimulation testing (CST) results.

	CSTT	CTT (TT4)	CTT (TT3)	Max wheal diameter (TT4)	Max wheal diameter (TT3)
CSTT	NA	−0.333***	−0.453**	−0.444***	.
CTT (TT4)	−0.330***	NA	NA	0.615***	NA
CTT (TT3)	−0.453**	NA	NA	NA	0.333*
Max wheal diameter (TT4)	−0.444***	0.615***	NA	NA	NA
Max wheal diameter (TT3)	.	NA	0.333*	NA	NA
Number or relevant cold triggers	−0.136*	0.220**	.	0.213**	.

Note: Statistical significance is indicated by asterisks: \* for  $p < 0.05$ , \*\* for  $p < 0.01$ , \*\*\* for  $p < 0.001$  and a dot (.) for  $p \geq 0.05$ .

Abbreviations: CSTT, critical stimulation time threshold; CTT, critical temperature threshold; NA, not applicable; TT3, TempTest® version 3.0; TT4, TempTest® version 4.0.

## CONFLICT OF INTEREST STATEMENT

Mojca Bizjak is or recently was a speaker and/or advisor for Novartis and Swixx BioPharma, outside the submitted work. Jonny Peter is or recently was a speaker and/or advisor for or received research funding from Takeda, Kalvista, Astria, CSL Behring, Sanofi, HAE international and Pharvaris, outside the submitted work. Ana Maria Giménez-Arnau

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#### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

#### ETHICAL APPROVAL

The study was approved by the National Medical Ethics Committee of the Republic of Slovenia (KME0120-62/2019/4), the Ethics Committee at Charit  Universit tsmedizin Berlin (EA1/069/19) and the Ethics Committees of the other participating institutions.

#### ETHICS STATEMENT

All patients provided written informed consent for participation and publication.

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