

LETTER

Adrenaline autoinjector is underprescribed in typical cold urticaria patients

To the Editor,

Intramuscular adrenaline is the first-line treatment for anaphylaxis and an adrenaline autoinjector (AAI) should be carried as a first-aid

measure by patients at risk.¹ Cold-induced anaphylaxis (ColdA), which may result in fatality,² is common in typical cold urticaria (ColdU), and risk factors for ColdA have recently been identified for

TABLE 1 Frequency of previous adrenaline treatment, AAI prescription or both stratified by ColdA caused by any cold trigger, complete cold water immersion or cold ambient air exposure

		ColdA		
		Any cold trigger ^a	Complete cold water immersion	Cold ambient air exposure
A. Mixed adult/pediatric	n = 372	145 (39%)	107 (29%)	53 (14%)
Adrenaline received ^b	12 (3%)	12 (8%)	8 (8%)	4 (8%)
AAI prescribed ^b	93 (25%)	54 (37%)	44 (41%)	15 (28%)
Both ^c	8 (2%)	8 (6%)	5 (5%)	3 (6%)
A ₁ . Temperate climate	n = 264	115 (44%)	94 (36%)	32 (12%)
Adrenaline received ^b	10 (4%)	10 (9%)	8 (9%)	2 (6%)
AAI prescribed ^b	78 (30%)	46 (40%)	41 (44%)	10 (31%)
Both ^c	6 (2%)	6 (5%)	5 (5%)	1 (3%)
A ₂ . Cold climate	n = 75	16 (21%)	10 (13%)	9 (12%)
Adrenaline received ^b	0	0	0	0
AAI prescribed ^b	11 (15%)	4 (25%)	3 (30%)	1 (11%)
Both ^c	0	0	0	0
A ₃ . Tropical climate	n = 33	14 (42%)	3 (9%)	12 (36%)
Adrenaline received ^b	2 (6%)	2 (14%)	0	2 (17%)
AAI prescribed ^b	4 (12%)	4 (29%)	0	4 (33%)
Both ^c	2 (6%)	2 (14%)	0	2 (17%)
B. Adult	n = 338	135 (40%)	98 (29%)	51 (15%)
Adrenaline received ^b	10 (3%)	10 (7%)	7 (7%)	3 (6%)
AAI prescribed ^b	85 (25%)	51 (38%)	42 (43%)	14 (28%)
Both ^c	7 (2%)	7 (5%)	5 (5%)	2 (4%)
C. Pediatric	n = 34	10 (29%)	9 (27%)	2 (6%)
Adrenaline received ^b	2 (6%)	2 (20%)	1 (11%)	1 (50%)
AAI prescribed ^b	8 (24%)	3 (30%)	2 (22%)	1 (50%)
Both ^c	1 (3%)	1 (10%)	0	1 (50%)

Note: Data are given as no. (%). ColdA was defined as an acute cold-induced involvement of the skin and/or visible mucosal tissue and at least one of the following: cardiovascular manifestations, difficulty breathing, or gastrointestinal symptoms. Cardiovascular manifestations were defined as hypotension or loss of consciousness and/or other signs or symptoms suggestive of hypotension (i.e., dizziness, sensation of fainting, and weakness). Difficulty breathing was defined as dyspnea, wheeze, or stridor.

Abbreviations: AAI, adrenaline autoinjector; ColdA, cold-induced anaphylaxis; n, number of patients.

^aAny cold trigger (i.e., complete cold water immersion, cold ambient air exposure, transition from cold outdoors to warm indoors, localized contact with cold liquids without immersion or ice, and contact with cold surfaces).

^bUnknown indication(s).

^cAdrenaline received and AAI prescribed.

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the first time.³ As of now, it is largely unclear how often patients with ColdU (i) receive adrenaline treatment and (ii) are provided with an AAI.² A study by Gernez et al. in the USA showed that 48% of allergy and immunology specialists prescribe an AAI to ColdU patients less than 10% of the time.⁴

Here, we present further results of the COLD-CE (i.e., comprehensive evaluation of ColdU and other cold-induced reactions) study,³ performed by the UCARE network.⁵ The study included 412 ColdU patients with whealing in response to local cold stimulation testing (i.e., typical ColdU). Concomitant chronic spontaneous urticaria was found in 10% ($n = 40$) of them. Of 372 patients with stand-alone ColdU, 69% ($n = 258$) were females and 91% adults (i.e., ≥ 18 years; $n = 338$). Their median age was 36 years (IQR 26–48).

ColdA was defined as an acute cold-induced involvement of the skin and/or visible mucosal tissue and at least one of the following: cardiovascular manifestations, difficulty breathing, or gastrointestinal symptoms.³ It was diagnosed in 39% ($n = 145$) of patients. Physician collected data on baseline patient characteristics, clinical manifestations induced by different cold triggers, and answered the following: (i) “Did the patient ever receive adrenaline for the treatment of ColdU/ColdA by medical personnel or by AAI self-administration?” and (ii) “Was AAI prescribed before study enrollment?”. Only 8% ($n = 12$) of ColdA patients had received treatment with adrenaline, and 37% ($n = 54$) of patients had an AAI (Table 1). Hypotension was experienced by 13% ($n = 48$) of patients, but only 17% ($n = 8$) of them received adrenaline and only 10% ($n = 5$) both adrenaline treatment and AAI prescription (Table S1). Patients were also categorized based on the climate of their residency (Table S2). ColdA was more common in temperate than cold climate countries (44% vs. 21%, $p < 0.001$) and AAI was more often prescribed in the former (30% vs. 15%, $p = 0.011$). The frequency of ColdA did not significantly differ between temperate and tropical countries (44% vs. 42%, $p = 1.000$), but AAI was more often prescribed in the former (30% vs. 12%, $p = 0.038$). ColdA triggered by complete cold water immersion (e.g., at beaches) was diagnosed in 29% ($n = 107$) of patients, but only 8% ($n = 8$) of them received adrenaline (Table 1). AAI was more often prescribed in patients with oropharyngeal/laryngeal symptoms than those without (37% vs. 20%, $p = 0.001$; Table 2).

Our findings suggest that ColdA is undertreated and they call for changes in ColdU management. ColdA should be approached and treated like other types of anaphylaxis. Less than 10% of patients with ColdA received adrenaline and less than 40% of them have an AAI. ColdU patients need to be screened by specialists and non-specialists to identify those with ColdA risk factors (Table 2),³ which may also include underlying clonal mast cell disorder.⁶ Prescribing an AAI to patients at risk of ColdA needs to be combined with advice on avoidance of relevant cold triggers, a written treatment plan, and training and re-training in the use of the AAI. Efforts should also be made for AAIs to become accessible at public beaches and addition of ColdA in the list of indications for AAI¹ shall be considered.

TABLE 2 Frequency of AAI prescription in patients with characteristics that were identified as independent risk factors for ColdA by the COLD-CE study³

	Oropharyngeal/laryngeal symptoms		Angioedema, unknown/any location		Itchy earlobes		Asthma		p-value	p-value
	Yes	No	Yes	No	Yes	No	Yes	No		
Mixed	Total, $n = 372$	117	255	184	188	226	63	309		
	AAI ^a , $n = 93$	43 (37%)	50 (20%)	54 (29%)	39 (21%)	45 (31%)	17 (27%)	76 (25%)	.049	.750
Adult	Total, $n = 338$	114	224	170	168	199	55	283		
	AAI ^a , $n = 85$	42 (37%)	43 (19%)	50 (29%)	35 (21%)	42 (30%)	15 (27%)	70 (25%)	.076	.735
Pediatric	Total, $n = 34$	3	31	14	20	7	8	26		
	AAI ^a , $n = 8$	1 (33%)	7 (23%)	4 (29%)	4 (20%)	3 (43%)	2 (25%)	6 (23%)	.315	1.000

Note: Data are given as no. (%). Statistical significance of differences between patient groups was calculated by Fisher's exact test. Statistically significant p -values ($p < 0.05$) are in bold.

Abbreviations: AAI, adrenaline autoinjector; n , number of patients.

^aAAI prescribed, unknown indication(s).

KEYWORDS

adrenaline autoinjector, cold urticaria, COLD-CE, cold-induced anaphylaxis

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTION

M. Bizjak initiated, entitled, and designed the COLD-CE study, collected data, performed data quality controls, and developed the manuscript. D. Terhorst-Molawi and M. Maurer contributed to study design and provided critical input to the manuscript. M. Bizjak and D. Terhorst-Molawi were principal investigators. M. Bizjak and D. Dinevski performed statistical analyses. All authors contributed to the acquisition of data, interpretation of data, and manuscript development and approved it for publication.

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SUPPORTING INFORMATION

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