

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	<i>n</i> = 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	<i>n</i> = 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	<i>n</i> = 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	<i>n</i> = 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	<i>n</i> = 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	<i>n</i> = 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 AAI 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			
	Yes	No	p-value	Yes	No	p-value	Yes	No	p-value	Yes	No	p-value	
Mixed	Total, n = 372	117	255	.	184	188	.	146	226	.	63	309	.
	AAI ^a , n = 93	43 (37%)	50 (20%)	.001	54 (29%)	39 (21%)	.072	45 (31%)	48 (21%)	.049	17 (27%)	76 (25%)	.750
Adult	Total, n = 338	114	224	.	170	168	.	139	199	.	55	283	.
	AAI ^a , n = 85	42 (37%)	43 (19%)	.001	50 (29%)	35 (21%)	.079	42 (30%)	43 (22%)	.076	15 (27%)	70 (25%)	.735
Pediatric	Total, n = 34	3	31	.	14	20	.	7	27	.	8	26	.
	AAI ^a , n = 8	1 (33%)	7 (23%)	1.000	4 (29%)	4 (20%)	.689	3 (43%)	5 (19%)	.315	2 (25%)	6 (23%)	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

M. Bizjak has been a speaker and served on advisory boards for Novartis, outside the submitted work. S. F. Thomsen reports grants and non-financial support from Novartis, Sanofi, UCB, LEO Pharma, and Janssen, outside the submitted work. D. Fomina received honoraria from Novartis, Shire, Behring CSL and Sanofi, outside the submitted work. E. Borzova received honoraria for educational lectures from Novartis and Sanofi and research funding from GSK, outside the submitted work. K. Kulthanan reports grants from Novartis and received honoraria from Menarini and Takeda, outside the submitted work. R. Meshkova received honoraria from Novartis, outside the submitted work. S. Altrichter reports grants and personal fees from Astra-Zeneca, grants from Allakos, personal fees from Novartis, non-financial support from Moxie, grants from CSL Behring, grants from LEO Pharma, outside the submitted work. A. Bauer reports grants, personal fees and other from Novartis, personal fees and other from LEO Pharma, grants, personal fees and other from Sanofi/Regeneron, other from Amgen, other from Lilly, other from AbbVie, personal fees from Takeda, other from Pharvaris, outside the submitted work. C. Costa reports personal fees from Novartis, AstraZeneca, Menarini, Leti and Bial, outside the submitted work. R. Fachini Criado reports personal fees from Novartis, Takeda, Abbvie and Sanofi, outside the submitted work. L.F. Felipe Ensina reports personal fees from Novartis, Sanofi, Abbvie and Takeda, outside the submitted work. A.M. Giménez-Arnau reports grants and personal fees from Uriach, other from Genentech, grants, personal fees and other from Novartis, grants and personal fees from GSK, personal fees from Sanofi/Regeneron, personal fees from Amgen, personal fees from Thermo Fisher, grants from Instituto Carlos III, personal fees from LEO Pharma, personal fees from Almirall and personal fees from Avene, outside the submitted work. M. Gonçalves has been a speaker and/or advisor for Abbie, LEO Pharma, Lilly, Novartis, Pfizer, Sanofi and Takeda, outside the submitted work. J.G. Holm has been a speaker for Novartis, outside the submitted work. E. Kocatürk reports personal fees from Novartis, Sanofi and Menarini, outside the submitted work. M. Makris reports personal fees from Novartis, Chiesi Hellas, AstraZeneca, Pfizer, GSK and Menarini, outside the submitted work. S. Valle reports personal fees from Novartis, Takeda, CSL Behring and Astra-Zeneca outside the submitted work. N. Wagner is or recently was a speaker and/or advisor for and/or has received research funding or is/was involved in clinical trials of/from ALK-Abelló, Novartis Pharma GmbH, Allergopharma GmbH & Co KG, Sanofi-Aventis Deutschland GmbH, Shire/Takeda, Blueprint, Abbvie GmbH & Co KG. P. Xepapadaki reports personal fees from Uriach, Novartis, Nestle and Nutricia, outside the submitted work. M.

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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

Additional supporting information may be found in the online version of the article at the publisher's website.

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SUPPORTING INFORMATION

We report on the same study cohort as in the manuscript Bizjak et al.¹

Introduction

Cold urticaria (ColdU) is a subtype of chronic inducible urticaria (CIndU). Wheals, angioedema or both, with or without systemic signs or symptoms (ie, respiratory, cardiovascular or gastrointestinal) occur rapidly in response to cooling of the skin and/or mucosal tissue and/or the whole body.¹⁻⁴ Patients with ColdU react to variable triggers including cold air, contact with solid surfaces, contact with cold liquids, and the ingestion of cold food or drinks.⁴ ColdU is classified into typical and atypical ColdU.^{1,2} The diagnosis of typical ColdU relies on the patient history and immediate whealing at the tested skin site on the volar forearm in response to local cold stimulation testing (CST) with an ice cube and/or the thermoelectric provocation device TempTest®.^{2,5} Both tests are endorsed by the 2016 EAACI/GA²LEN/EDF/UNEV consensus guidelines for CIndU.⁵ ColdU can also manifest with cold-induced anaphylaxis (ColdA), which may potentially result in fatality.^{2,6-14} Fatality rate remains unknown.^{1,2,15} ColdA is common in typical ColdU, and risk factors for ColdA have recently been identified for the first time.¹ 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.¹⁶

Study design

COLD-CE (ie, comprehensive evaluation of ColdU and other cold-induced reactions)^{1,2} is an international, cross sectional, observational study that was led by the University Clinic of Respiratory and Allergic Disease Golnik, Slovenia and Charité – Universitätsmedizin Berlin, Germany between May 2019 and May 2021. It was conducted in 30 additional GA²LEN (Global Allergy and Asthma European Network) UCAREs (Urticaria Centers of Reference and Excellence).¹⁷ The study was approved by the National Medical Ethics Committee of the Republic of Slovenia (KME0120-62/2019/4, 17.04.2019), Ethics Committee at Charité - Universitätsmedizin Berlin (EA1/069/19, 18.06.2019), and the local responsible Ethics Committees of other participating institutions as required. Dated and signed written informed

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consent was obtained for all patients. The checklist filled by physicians included 131 items about demographics and baseline patient characteristics, spectrum of clinical manifestations induced by cold and their triggering situations, CST results, treatment, and comorbidities. Physician also 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?”.

Study participants

This study included 551 ColdU patients who reported the presence of signs and/or symptoms of ColdU ≤ 12 months prior to evaluation (ie, inclusion criteria). They were recruited out of the normal, routine clinical care situation. H₁-antihistamines and systemic glucocorticoids were discontinued at least 3 and 7 days before CST, respectively.⁵

Detailed history regarding systemic reactions and their cold triggers was taken

Patients were asked whether they had ever experienced cold-induced itch, wheals, angioedema (on any location), hypotension (RR<90/60 mmHg) or loss of consciousness (ie, the most severe cardiovascular manifestation), or other signs or symptoms suggestive of hypotension (ie, dizziness, sensation of fainting, weakness), difficulty breathing (ie, dyspnoea, wheeze, stridor), or gastrointestinal symptoms. Secondly, patients were asked whether these reactions were triggered by complete cold water immersion (CWI), cold ambient air exposure, transition from cold outdoors to warm indoors, localized contact with cold liquids (without immersion) or ice, or contact with cold surfaces. The physician checklist also contained questions about previously diagnosed asthma.

Categorization of patients¹

We defined ColdA 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.^{1,2,4,18-20} Cardiovascular manifestations were defined as hypotension or loss of consciousness and/or other signs or symptoms suggestive of hypotension (ie, dizziness, sensation of fainting, weakness). Difficulty breathing was defined as dyspnoea, wheeze or stridor.

We explored ColdA induced by: (i) at least one of cold triggers trigger (ie, 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), (ii) complete cold water immersion, and (iii) cold air. Patients were also categorized into residents of countries with a temperate, cold or tropical climate as shown in Table S3.

Statistical analyses

The data were analyzed using IBM SPSS software V25 (IMB Inc., Armonk, New York). Descriptive measures included frequencies, proportions, ranges, and medians with the first and third quartile range. Categorical variables were assessed by the Fisher's Exact test and $p < .05$ was considered statistically significant.

Table S1. The frequency of previous adrenaline treatment, AAI prescription or both stratified by cardiovascular manifestations.

		Cardiovascular manifestations			Hypotension and/or loss of consciousness		
		Any ^a	CWI	Air	Any ^a	CWI	Air
A. Mixed adult/pediatric	<i>n</i> = 372	116 (31%)	88 (24%)	31 (8%)	48 (13%)	41 (11%)	10 (3%)
Adrenaline received ^b	12 (3%)	11 (10%)	7 (8%)	4 (13%)	8 (17%)	5 (12%)	3 (30%)
AAI prescribed ^b	93 (25%)	49 (42%)	41 (47%)	9 (29%)	24 (50%)	21 (51%)	4 (40%)
Both ^c	8 (2%)	7 (6%)	4 (5%)	3 (10%)	5 (10%)	3 (7%)	2 (20%)
A₁. Temperate climate	<i>n</i> = 264	95 (36%)	80 (30%)	18 (7%)	38 (14%)	35 (13%)	3 (1%)
Adrenaline received ^b	10 (4%)	9 (10%)	7 (9%)	2 (11%)	7 (18%)	5 (14%)	2 (67%)
AAI prescribed ^b	78 (30%)	42 (44%)	38 (48%)	5 (28%)	20 (53%)	19 (54%)	1 (33%)
Both ^c	6 (2%)	5 (5%)	4 (5%)	1 (6%)	4 (11%)	3 (9%)	1 (33%)
A₂. Cold climate	<i>n</i> = 75	9 (12%)	7 (9%)	2 (3%)	3 (4%)	3 (4%)	1 (1%)
Adrenaline received ^b	0	0	0	0	0	0	0
AAI prescribed ^b	11 (15%)	3 (33%)	3 (43%)	0	1 (33%)	1 (33%)	0
Both ^c	0	0	0	0	0	0	0
A₃. Tropical climate	<i>n</i> = 33	12 (36%)	1 (3%)	11 (33%)	7 (21%)	3 (9%)	6 (18%)
Adrenaline received ^b	2 (6%)	2 (17%)	0	2 (18%)	1 (14%)	0	1 (17%)
AAI prescribed ^b	4 (12%)	4 (33%)	0	4 (36%)	3 (43%)	1 (33%)	3 (50%)
Both ^c	2 (6%)	2 (17%)	0	2 (18%)	1 (14%)	0	1 (17%)
B. Adult	<i>n</i> = 338	106 (31%)	79 (23%)	29 (9%)	41 (12%)	35 (10%)	9 (3%)
Adrenaline received ^b	10 (3%)	9 (9%)	6 (8%)	3 (10%)	6 (15%)	4 (11%)	2 (22%)
AAI prescribed ^b	85 (25%)	46 (43%)	39 (49%)	8 (28%)	22 (54%)	20 (57%)	3 (33%)
Both ^c	7 (2%)	6 (6%)	4 (5%)	2 (7%)	4 (10%)	3 (9%)	1 (11%)
C. Pediatric	<i>n</i> = 34	10 (29%)	9 (27%)	2 (6%)	7 (21%)	6 (18%)	1 (3%)
Adrenaline received ^b	2 (6%)	2 (20%)	1 (11%)	1 (50%)	2 (29%)	1 (17%)	1 (100%)
AAI prescribed ^b	8 (24%)	3 (30%)	2 (22%)	1 (50%)	2 (29%)	1 (17%)	1 (100%)
Both ^c	1 (3%)	1 (10%)	0	1 (50%)	1 (14%)	0	1 (100%)

Note: Data are given as no. (%).

Abbreviations: AAI, adrenaline autoinjector; CWI, complete cold water immersion; *n*, number of patients.

^aAny cold trigger (ie, 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 & AAI prescribed.

Table S2. List of participating UCARE centers and their classification into climate groups.

Country (n=19)	Location (n=32)	Total, n=372*	Data from the Köppen-Geiger climate map ⁷					
			Classification	1st symbol (climate)	2nd symbol (precipitation)	3rd symbol (temperature)	Average annual temperature (°C) [†]	The coldest monthly average (°C) [†]
Argentina	Buenos Aires (n=2)	7	Cfa	Temperate	Without dry season	Hot summer	17.44	10.89
Brazil	São Paulo (n=2)	6	Cfa	Temperate	Without dry season	Hot summer	19.45	15.98
China	Guangzhou (n=2)	16	Cfa	Temperate	Without dry season	Hot summer	22.00	13.64
Georgia	Tbilisi	9	Cfa	Temperate	Without dry season	Hot summer	13.44	-0.51
Germany	Berlin	70	Cfa	Temperate	Without dry season	Hot summer	8.32	-1.57
Germany	Dresden	7	Cfa	Temperate	Without dry season	Hot summer	8.99	-0.03
Germany	Erlangen	5	Cfa	Temperate	Without dry season	Hot summer	7.61 [‡]	-1.68 [‡]
Greece	Athens (n=2)	33	Csa	Temperate	Dry summer	Hot summer	17.46	8.55
Iran	Mashhad	4	BSk	Temperate, arid	Steppe	Cold	13.89	1.26
Japan	Yokohama	2	Cfa	Temperate	Without dry season	Hot summer	15.28	4.98
Portugal	Coimbra	11	Csa	Temperate	Dry summer	Hot summer	15.06	9.45
Portugal	Lisbon	18	Csa	Temperate	Dry summer	Hot summer	16.49	10.82
Slovenia	Golnik	25	Cfb	Temperate	Without dry season	Warm summer	10.28 [‡]	-0.59 [‡]
South Africa	Cape Town	8	Csb	Temperate	Dry summer	Warm summer	21.52	17.87
Spain	Barcelona	19	Csa	Temperate	Dry summer	Hot summer	15.76	8.77
Turkey	Istanbul (n=2)	19	Csa	Temperate	Dry summer	Hot summer	14.43	5.72
United Kingdom	London	5	Cfb	Temperate	Without dry season	Warm summer	10.11	4.39
China	Beijing	1	Dwa	Cold	Dry winter	Hot summer	13.09	-3.91
Denmark	Copenhagen	18	Dfb	Cold	Without dry season	Warm summer	7.97	-0.35
Poland	Zabrze	13	Dfb	Cold	Without dry season	Warm summer	8.11 [‡]	-2.69 [‡]
Russian Federation	Kazan	5	Dfb	Cold	Without dry season	Warm summer	2.72	-13.91
Russian Federation	Moscow	21	Dfb	Cold	Without dry season	Warm summer	7.82	-3.00
Russian Federation	Smolensk	17	Dfb	Cold	Without dry season	Warm summer	3.99	-8.79
Brazil	Minas Gerais	11	Aw	Tropical	Savannah	/	21.33 [‡]	18.26 [‡]
Brazil	Rio de Janeiro	7	Af	Tropical	Rainforest	/	23.10	20.51
Kuwait	Safat	10	BWh	Tropical, arid	Desert	Hot	25.87 [‡]	12.79 [‡]
Thailand	Bangkok	5	Aw	Tropical	Savannah	/	28.11	25.49

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*Patients with typical cold urticaria.

†Values obtained from the Supplementary material of the Peel *et al* manuscript.¹⁸

‡Value obtained for the closest city.

Table S3. The frequency of previous adrenaline treatment, AAI prescription or both stratified by cold-induced difficulty breathing and gastrointestinal symptoms.

		Difficulty breathing			Gastrointestinal symptoms		
		Any ^a	CWI	Air	Any ^a	CWI	Air
A. Mixed adult/pediatric	<i>n</i> = 372	82 (22%)	53 (14%)	42 (11%)	39 (11%)	23 (6%)	20 (5%)
Adrenaline received ^b	12 (3%)	8 (10%)	5 (9%)	3 (7%)	6 (15%)	2 (9%)	4 (20%)
AAI prescribed ^b	93 (25%)	37 (45%)	27 (51%)	15 (36%)	12 (31%)	7 (30%)	5 (25%)
Both ^c	8 (2%)	7 (9%)	4 (8%)	3 (7%)	4 (10%)	1 (4%)	3 (15%)
A₁. Temperate climate	<i>n</i> = 264	60 (23%)	45 (17%)	22 (8%)	24 (9%)	19 (7%)	8 (3%)
Adrenaline received ^b	10 (4%)	6 (10%)	5 (11%)	1 (5%)	4 (17%)	2 (11%)	2 (25%)
AAI prescribed ^b	78 (30%)	31 (52%)	26 (58%)	10 (46%)	7 (29%)	6 (32%)	1 (13%)
Both ^c	6 (2%)	5 (8%)	4 (9%)	1 (5%)	2 (8%)	1 (5%)	1 (13%)
A₂. Cold climate	<i>n</i> = 75	9 (12%)	5 (7%)	7 (9%)	4 (5%)	3 (4%)	2 (3%)
Adrenaline received ^b	0	9 (100%)	5 (100%)	7 (100%)	4 (100%)	3 (100%)	2 (100%)
AAI prescribed ^b	11 (15%)	2 (22%)	1 (20%)	1 (14%)	1 (25%)	1 (33%)	0
Both ^c	0	9 (100%)	5 (100%)	0	4 (100%)	3 (100%)	2 (100%)
A₃. Tropical climate	<i>n</i> = 33	13 (39%)	3 (9%)	13 (39%)	11 (33%)	1 (3%)	10 (30%)
Adrenaline received ^b	2 (6%)	2 (15%)	0	2 (15%)	2 (18%)	0	2 (20%)
AAI prescribed ^b	4 (12%)	4 (31%)	0	4 (31%)	4 (36%)	0	4 (40%)
Both ^c	2 (6%)	2 (15%)	0	2 (15%)	2 (18%)	0	2 (20%)
B. Adult	<i>n</i> = 338	75 (22%)	48 (14%)	40 (12%)	34 (10%)	20 (6%)	18 (5%)
Adrenaline received ^b	10 (3%)	6 (8%)	4 (8%)	2 (5%)	4 (12%)	2 (10%)	2 (11%)
AAI prescribed ^b	85 (25%)	35 (47%)	26 (54%)	14 (35%)	11 (32%)	7 (35%)	4 (22%)
Both ^c	7 (2%)	6 (8%)	4 (8%)	2 (5%)	3 (9%)	1 (5%)	2 (11%)
C. Pediatric	<i>n</i> = 34	7 (21%)	5 (15%)	2 (6%)	5 (15%)	3 (9%)	2 (6%)
Adrenaline received ^b	2 (6%)	2 (29%)	1 (20%)	1 (50%)	2 (40%)	0	2 (100%)
AAI prescribed ^b	8 (24%)	2 (29%)	1 (20%)	1 (50%)	1 (20%)	0	1 (50%)
Both ^c	1 (3%)	1 (14%)	0	1 (50%)	1 (20%)	0	1 (50%)

Note: Data are given as no. (%).

Abbreviations: AAI, adrenaline autoinjector; CWI, complete cold water immersion; *n*, number of patients.

^aAny cold trigger (ie, 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 & AAI prescribed.

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