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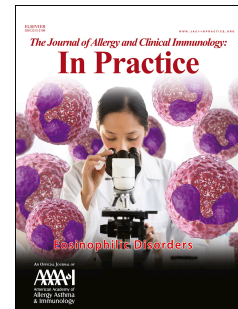
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46 **Abbreviations and Acronyms**

CIndU	Chronic inducible urticaria
CU	Chronic urticaria
CI	Confidence interval
CSU	Chronic spontaneous urticaria
EAI	Epinephrine autoinjector
UCT	Urticaria control test
UCARE	Urticaria Centers of Reference and Excellence
CSTT	Cold-stimulation time test
CTT	Critical temperature threshold

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Highlights Box

What is already known about this topic?

Cold urticaria is a type of chronic inducible urticaria that causes significant morbidity and bears a risk of life-threatening allergic reactions.

What does this article add to our knowledge?

This study aims to determine the prevalence of cold urticaria among cases of chronic urticaria and chronic inducible urticaria, to assess the management of cold urticaria and to determine the prevalence of associated anaphylaxis.

How does this study impact current management guidelines?

Allergists and dermatologists should be vigilant for cold urticaria in patients presenting with chronic urticaria, especially because of the risk of anaphylaxis.

Keywords: Chronic inducible urticaria, chronic urticaria, physical urticaria, cold urticaria, anaphylaxis, cold-induced urticaria, cold contact urticaria, urticaria

Abstract

Background

Cold urticaria is a subtype of chronic inducible urticaria (CIndU) associated with significant morbidity and a risk of anaphylaxis. Few studies have assessed the prevalence, management, and prevalence of associated anaphylaxis of cold urticaria.

Objectives

To evaluate the prevalence of cold urticaria among CIndU and chronic urticaria (CU) cases, to assess the management of cold urticaria and to determine the prevalence of associated anaphylaxis.

Methods

PubMed and EMBASE were searched for studies pertaining to cold urticaria and/or CIndU published in the last 10 years. Meta-analyses were conducted to evaluate: the prevalence of cold urticaria among CIndU and chronic urticaria (CU) cases, the management of cold urticaria with H1-antihistamines and omalizumab and the prevalence of associated anaphylaxis.

Results

Twenty-two studies were included in the systematic review and 14 in the meta-analysis. The pooled prevalence of cold urticaria among CU and CIndU cases were 7.62% (95%CI: 3.45%, 15.99%; $I^2=98\%$) and 26.10% (95%CI: 14.17%, 43.05%; $I^2=97\%$), respectively. Cold urticaria was managed by H1-antihistamines in 95.67% (95%CI: 92.47%, 97.54%; $I^2=38\%$) of patients and omalizumab in 5.95% (95%CI: 2.55%, 13.27%; $I^2=83\%$) of patients. The pooled prevalence of anaphylaxis among cold urticaria cases was 21.49% (95%CI: 15.79%, 28.54%; $I^2=69\%$).

Conclusion

Cold urticaria constitutes an appreciable proportion of CIndU and CU cases and is predominantly managed with H1-antihistamines, with a minority of patients receiving omalizumab. Anaphylaxis is not rare, and epinephrine auto-injector (EAI) prescription may be considered.

Introduction

Chronic urticaria (CU) is characterized by the presence of pruritic wheals (commonly referred to as hives) and/or angioedema that persist for at least six weeks(1). CU occurring in the absence of a specific trigger (such as cold/exercise/heat) is defined as chronic spontaneous urticaria (CSU)(2, 3). Chronic inducible urticaria (CIndU) can co-exist with CSU and is defined as a specific trigger eliciting the hives(4). CIndU is further subclassified into physical and non-physical urticaria based on the type of trigger(5).

Cold urticaria is a type of physical urticaria triggered by skin exposure to cold air, liquids, or objects(4). The pathogenesis of cold urticaria is not well established. It is postulated that cold induces autoallergen formation, leading to IgE-mediated mast cell degranulation and subsequent hives(6, 7). It is reported that cold urticaria has an annual incidence of 0.05%(8), and it may be more prevalent in colder climates(9). The diagnosis of cold urticaria is often confirmed with an ice cube test. This test consists of placing an ice cube in a plastic bag on a patient's skin for 5 minutes and observing whether wheal forms within 20 minutes(4). Recently, the TempTest has been developed as a standardized diagnostic tool for cold urticaria, which also determines the threshold temperature at which symptoms develop(4, 10). If both the ice cube test and TempTest are negative, then further testing may be required to diagnose atypical cold urticaria. This testing involves immersing the patient's arm in a cold-water bath, but this should be done with caution as it can elicit anaphylaxis(4, 7). Cold urticaria is treated by avoiding cold triggers, non-sedating second-generation H1-antihistamines at regular and up to four-fold doses and, in recalcitrant cases, omalizumab may be considered(1, 11-13). Notably, cold urticaria causes significant morbidity due to the continuous vigilance required to avoid cold triggers and is the only CIndU reported to cause

life-threatening reactions (*i.e.*, anaphylaxis)(14). No studies have analyzed the impact of cold urticaria on patients' quality of life(7).

To our knowledge, no systematic reviews or meta-analyses have been conducted in the last 10 years assessing the prevalence, management, or resolution rate of cold urticaria or the prevalence of associated anaphylaxis. To address these knowledge gaps, we conducted a systematic review and meta-analysis.

Methods

Search Strategy

PubMed and EMBASE databases were searched for original, peer-reviewed articles in English or French published between January 2011 and May 2021, inclusively (search last updated May 21, 2021). Search terms included: “cold urticaria”, “cold contact urticaria”, “inducible urticaria” or “cold induced urticaria” in the title/abstract. On EMBASE, conference abstracts were excluded from the search. Relevant articles were selected by two independent reviewers (C.P. and S.G.). In the case of disagreements on the inclusion of an article, a third independent reviewer (M.B.S.) adjudicated. The inclusion criteria were observational studies of at least 10 patients diagnosed with cold urticaria reporting on the clinical characteristics, prevalence, management, or resolution of cold urticaria. Exclusion criteria consisted of studies with less than 10 patients diagnosed with cold urticaria, literature/systematic reviews, and studies focused on familial cold urticaria/autoinflammatory syndromes. In cases where multiple studies reported similar data on overlapping patient populations, only the most recent study was included to avoid double counting patients. All studies, with the exception of reviews, were read completely and articles in which cold urticaria prevalence data could not be extracted were excluded. When data required for the review were missing from the manuscript at least two attempts were made to contact the authors in order to include the appropriate data in the results.

Definitions

Anaphylaxis for the purpose of this article was defined as a systemic reaction involving two organ systems and/or hypotension associated with a cold trigger(15). Management with H1-antihistamines or management with omalizumab were defined as the patient receiving and/or being prescribed at any time point the treatment regardless of the frequency of dosing or indication.

Quality Assessments

The quality of the included articles was assessed by two independent reviewers (C.P and S.G.) via the Checklist for Prevalence Studies from the Joanna Briggs Institute(16). The criteria evaluated included sample frame and size, recruitment method, sufficient description of study setting and participants, adequate data coverage, validity of diagnostic method (defined as a positive result to the ice cube test, TempTest or cold-water bath test), appropriate statistical analysis, response rate and justification/absence of missing data (Table E1).

Data Extraction

The following data (if reported) were extracted from the included articles by two independent reviewers (C.P. and S.G.): author(s') name(s), year of publication, country, study design, population studied, age at symptom onset, sex, diagnostic method, prevalence of cold urticaria among CIndU and CU, triggers, management (*i.e.*, use of H1-antihistamines, use of omalizumab), response to treatment, resolution rate and definition of resolution, prevalence of anaphylaxis among cold urticaria cases and triggers of anaphylaxis (Table 1 and Table E2). To avoid double counting patients, in cases where two articles reported statistics on overlapping patient populations, only unique statistics and/or statistics on the larger patient population were reported/included in the meta-analysis.

Meta-Analyses

Among the studies described in the systematic review, studies were included in the meta-analyses if they met the following criteria: sample size ≥ 30 , appropriate sample frame, and 6/9 criteria fulfilled in the quality assessment (Table E1). A sample size of at least 30 for inclusion in

the meta-analysis was used because according to the central limit theorem it allows for the assumption of normal distribution(17).

Statistical Analyses

Five meta-analyses with logit transformation were conducted using the random-effects model (due to high heterogeneity) via the DerSimonian and Laird method to calculate the pooled estimate of 1) the prevalence of cold urticaria among cases of CU; 2) the prevalence of cold urticaria among cases of CIndU; 3) the use of H1-antihistamines in the treatment of cold urticaria; 4) the use of omalizumab in the treatment of cold urticaria; and 5) the prevalence of anaphylaxis among cases of CU. Meta-analyses were performed with R software (2020, version 4.0.0), using the meta(18) and metafor(19) packages. Pooled prevalences are presented with a 95% confidence interval (CI), an I^2 statistic to quantify heterogeneity, τ^2 to quantify inter-study variance and a chi squared test (X^2) to assess whether heterogeneity is due to chance alone ($p < 0.10$ representing significant heterogeneity beyond chance).

Results

Search Results

The search returned a total of 481 articles, consisting of 241 and 240 articles from EMBASE and PubMed, respectively (Figure 1). After duplicates were removed, 272 articles were screened by title and abstract for relevance. Of these articles, 76 were excluded because they were reviews, and the remaining 196 articles were read in full. Subsequently, 174 articles were excluded, and the remaining 22 articles were included in the systematic review and underwent data extraction (Table 1 and Table E2) and quality assessment (Table E1). A total of 14 studies met the criteria for inclusion in the meta-analyses.

Quality Assessment

Quality assessment was performed by the Checklist for Prevalence Studies from the Joanna Briggs Institute (Table E1)(16). The main quality concerns were inadequate sample size and inadequately described study setting and subjects. One study (4.55%) was deemed low quality because of inappropriate sample frame and less than 6/9 criteria filled on quality assessment (20).

Population Characteristics

The 22 articles (one cross-sectional, 11 retrospective and 10 prospective studies) included in the systematic review comprised 19 articles reporting on unique patient populations, which included a total of 1135 patients, and three articles reporting different statistics on overlapping populations. Of these 19 articles, five (26.3%) articles studied only adults, whereas five (26.3%) studied only children and the remaining nine (47.4%) studied both populations. Mean and median age of symptom onset of cold urticaria were reported in six and two studies, respectively. Median age of symptom onset was 8-8.5 years in pediatric studies(21, 22), 22-27 years in the studies

including adults and children(23-25) and 33 years in an adult study(26). Mean age of symptom onset was 32 years in a study of children and adults(14) and 34.8 years in an adult study(27). The majority of studies reporting patients' sex revealed a higher proportion of females than males with cold urticaria (10 studies, 52.6-80% female)(14, 23-31). However, three out of four (75.0%) pediatric studies reporting patients' sex found approximately even proportions of females and males (49.4-50% female)(21, 22, 32). Among the studies reporting their diagnostic methods (n=16), the majority (93.8%) used the ice cube test, 50.0% used the TempTest and 18.8% used the cold-water bath, while only one study, by Komarow et al., reported using additional diagnostic methods(14, 21-30, 32-36). These methods included total body cold exposure at 4°C and evaporative cooling(34). The remaining three studies reporting on unique patient populations did not report on the diagnostic methods used(20, 31, 37).

Prevalence

The prevalence of cold urticaria among CU cases was reported by 12 studies. Among these, ten (83.3%) articles noted the prevalence to be less than 10% (1.7-8.8%)(14, 27-29, 31, 35-39). Two studies, one Canadian and one Spanish, documented a greater prevalence of 18.4% and 18.8%, respectively, among CU cases(32, 33). Thomsen et al. reported the prevalence of cold urticaria among CU cases refractory to four-fold doses of antihistamines and persisting for at least two months as 18.4%(20).

Cold urticaria prevalence among CIndU cases was recorded by 13 studies. Among these, nine (69.2%) reported a prevalence of less than 25%, ranging from 7.8-23.3%(28, 29, 31, 35-40). Notably, four (30.8%) articles noted a higher prevalence ranging from 35.1-62.5%(27, 32-34). Moreover, among cases of CIndU refractory to four-fold doses of antihistamines and persisting for at least two months, the prevalence of cold urticaria was 47.5%(20).

Triggers

Six studies reported the specific triggers eliciting cold urticaria symptoms. Among these, four studies reported that cold water was the most common trigger in 62.9-92.0% of patients(14, 21, 23, 24, 26). Two studies reported cold air/weather as the most common trigger (58.1-82.2% of patients)(14, 21, 23, 24, 26, 28). Cold objects/surfaces and ingestion of cold food/beverages triggered hives in 37.8-73.3% and 6.8-20.0% of patients, respectively(14, 21, 23, 24, 26, 28). Moreover, Bizjak et al. reported that 44.4% of patients were triggered by localized contact with cold liquids (*i.e.*, washing hands)(26). No studies specified the temperatures of cold triggers.

Management

A total of 12 studies reported the management strategies of cold urticaria. H1-antihistamines were the most common medications used for management of cold urticaria, used in 89.7-100% of patients at up to four-fold doses (10 studies)(14, 21, 23-25, 27, 30-32, 35). Nine studies reported cold urticaria management with omalizumab in 0-22.0% of patients(14, 21, 23, 25, 27, 30-33, 41). Cyclosporine use was recorded by four studies in 2.0-4.1% of patients(14, 23, 27, 31). H2-antihistamine use was reported in three studies in 1.7-15.2% of patients(21, 24, 30, 31). Oral corticosteroid use was documented in two pediatric studies in 0.24%(21) and 2.5%(32) of patients, one adult study in 14.8%(27) and one pediatric and adult study in 36.4%(31) of patients. Less commonly reported medications used to manage cold urticaria were doxepin (one study, 0.24%), antileukotrienes (two studies, 3.6-12.1%) and sodium cromoglycate (one study, 2.0%)(21, 30, 32).

Response to Treatment

Cold urticaria response to treatment was documented by three studies. Miles et al. reported symptom control (urticaria control test (UCT) ≥ 12) by H1-antihistamines alone in 66.7% of patients (n=24)(32). However, no patients managed with omalizumab or corticosteroids exhibited symptom control(32). Using the same definition of symptom control, another study recorded 100.0% and 76.0% of patients were controlled with omalizumab (n=7) and H1-antihistamines (n=38), respectively(23). Deza et al. documented symptom control (improvement of symptoms until the patient reports that they do not interfere with daily life) in 100% of patients managed with omalizumab (n=3) and 84.9% of patients taking H1-antihistamines (n=62)(14). Of the patients controlled by H1-antihistamines, 33.9% (n=21) were taking the recommended dose, 50% (n=31) required up dosing to two-fold the recommended dose and 16.1% (n=10) required a greater than two-fold dose(14).

Resolution Rate

The resolution rate of cold urticaria was reported in five of the studies. Five- and 10-year resolution rates in an adult study were 13.8% and 42.6%, respectively(27). Two studies on pediatric and adult patients documented five- and 10-year resolution rates ranging from 17.9-26.6% and 24.5-44.5%, respectively(14, 24). One study in adults reported a four-year resolution rate of 50%(36) and a pediatric study reported a six-year resolution rate of 58.1%(32).

Anaphylaxis

Data on anaphylaxis was reported in 11 studies. The prevalence of anaphylaxis among cold urticaria cases varied considerably, ranging from 0-34.3%(14, 21, 23-28, 30, 31, 36). Notably, no fatalities were recorded in any of the studies. No studies elaborated on the treatment or the recovery time of the anaphylactic episodes. Three studies documented swimming as the most common

trigger of anaphylaxis (77.6-100%)(21, 24, 28). In addition to swimming, Yee et al. reported that 8% of anaphylaxis cases were triggered by cold air, 6.3% by contact with cold water (*i.e.*, splashed with cold water), 6.3% by ingestion of cold food/beverage and 1.8% by receipt of intravenous fluids(21). Another study reported exposure to cold water as a trigger in 92.9% of anaphylaxis cases(14). Kulthanan et al. documented only one case of anaphylaxis, which was triggered by washing clothes in cold water(27). No studies specified the temperatures of cold triggers of anaphylaxis.

Meta-Analyses

Among the 22 articles on cold urticaria included in the systematic review, eight were excluded as their sample size was less than 30 or the sample frame of participants described was not appropriate.

Prevalence

Meta-analyses for the prevalence of cold urticaria among CU and CIndU cases were conducted. Five articles provided data on prevalence of cold urticaria among CU cases. The pooled estimate was found to be 7.62% (95%CI: 3.45%, 15.99%; $I^2=98\%$; Figure 2A). Data on the prevalence of cold urticaria among CIndU cases was provided in six articles. The pooled estimate was 26.10% (95%CI: 14.17%, 43.05%; $I^2=97\%$; Figure 2B).

Management

Meta-analyses for the percent of patients with cold urticaria managed with H1-antihistamines and omalizumab were conducted. Nine articles provided data on percentage of H1-antihistamine use among cold urticaria cases. The pooled estimate was found to be 95.67% (95%CI: 92.47%, 97.54%; $I^2=38\%$; Figure 3A). Data on omalizumab use in the management of cold urticaria cases was provided in nine articles. The pooled estimate was 5.95% (95%CI: 2.55%, 13.72%; $I^2=83\%$; Figure 3B).

Anaphylaxis

Eight articles reported data on anaphylaxis in cold urticaria cases. The pooled estimate was 21.49% (95%CI: 15.79%, 28.54%; $I^2=69\%$; Figure 4).

Discussion

Our study is the first to assess through a systematic review and/or meta-analysis the prevalence, triggers, management, resolution rate and risk of anaphylaxis of cold urticaria. We assessed the pooled prevalence of cold urticaria among CU and CIndU cases, determined to be approximately 8% and 26%, respectively. Fricke et al. assessed the worldwide point prevalence of CU by meta-analysis to be 0.7% (95%CI: 0.2, 1.4; $I^2=100\%$)(42), using this estimate and the prevalence of cold urticaria among CU we determined, we expect the point prevalence of cold urticaria to be 0.056% (95%CI: 0.016, 0.112). Therefore, cold urticaria is present in approximately six per 10 000 people worldwide at any given time point. Cold urticaria also makes up a significant portion of CU and CIndU cases and physicians should be vigilant to diagnose cold urticaria in patients presenting with urticaria, especially because of the risk of anaphylaxis. These results should be interpreted with caution, however, because of the heterogeneity between studies (reflected by the I^2 values of 97-98%). Cold urticaria prevalence is reported to be inversely associated with average temperatures in January(9), which may explain some of the heterogeneity between studies. Indeed, cold urticaria was most prevalent among CIndU cases and second most prevalent among CU cases in the Miles et al. studies located in Montreal, Canada, which has the coldest climate among all the study locations included in the meta-analyses(32). However, the Polish study by Jankowska-Konsur et al. reported a lower prevalence of cold urticaria among CU and CIndU cases than studies conducted in Spain and Italy, despite having a colder climate(14, 31, 35). Large scale multi-centre studies are required to assess whether a definitive association exists between average temperature and prevalence of cold urticaria.

We determined that the vast majority of cold urticaria cases were managed by H1-antihistamines. It is not elaborated in the articles why certain patients were not managed with H1-

antihistamines or how they were managed; however, it is possible that their cold urticaria was managed by cold avoidance alone. We found that 66.7-84.9% of patients managed with H1-antihistamines exhibited a well controlled UCT score or improved symptoms. Several H1-antihistamines have undergone clinical trials for the treatment of cold urticaria. Desloratadine significantly increased mean cold-stimulation time test (CSTT) and significantly decreased critical temperature thresholds (CTT) compared to placebo at 5mg and 20mg doses(43). Additionally, less patients developed wheals in response to cold stimulation while on 5mg and 20mg of desloratadine compared to controls(43). CTTs are significantly decreased in patients receiving 20mg of desloratadine compared to 5mg(44). Similarly, bilastine and rupatadine have shown a protective effect on CTT. Bilastine at 20mg and 80mg significantly reduced CTTs, with higher doses being more effective(45). At an 80mg dose of bilastine response rate was 95% and 60% of participants were symptom free(45). Rupatadine at 20mg and 40mg doses significantly reduced CTTs and increase CSTT compared to placebo (46, 47) and 52% of patients demonstrated a complete lack of symptoms in response to cold provocation(47). The lack of UCT use in the conducted clinical trials on the treatment of cold urticaria hinders comparison with our real-world data.

Current EAACI/GA²LEN/EDF/WAO recommendations suggest that treatment options for patients with cold urticaria recalcitrant to four-fold doses of second-generation antihistamines include omalizumab, antibiotics or cold desensitization, although the latter two are based only on observational data from case reports or small case series(4). Presented data shows that approximately 6% of patients with cold urticaria were treated with omalizumab. However, it is unclear whether the patients included in the meta-analysis were receiving omalizumab for cold urticaria or for another indication (*i.e.*, co-existing CSU). Although cold urticaria is an off-label use of omalizumab, several case reports and prospective studies have documented its efficacy in

managing cold urticaria(48-51). Additionally, one clinical trial has demonstrated that omalizumab significantly decreases critical temperature thresholds compared to placebo in patients with cold urticaria refractory to antihistamines(52). In contrast, our real-world data reveals that omalizumab management resulted in well controlled UCT scores/improved symptoms in 100% of patients in two studies(14, 23), whereas 0% of patients in another study exhibited well controlled UCT scores on omalizumab(32).

Our systematic review reveals that the resolution rate of cold urticaria is low. This is similar to the low resolution rate reported in CSU, which is reported to be 10.3% per year in children(53) and 30-70% in 5 years in adults(54).

Among studies eligible for meta-analysis, we established that anaphylaxis occurred in over one fifth of patients with cold urticaria. Although most cases of cold urticaria are correctly managed with antihistamines(4), patients should be educated on avoiding high risk activities, like diving in cold water. Physicians managing patients with cold urticaria should consider prescribing an epinephrine auto-injector (EAI) given the anaphylaxis risk. However, there is controversy whether an EAI should be prescribed for all cases with cold urticaria. Indeed, Yee et al. reported EAI prescription in 89.2% of patients with cold urticaria(21), in contrast to 32% as reported by Stepaniuk et al.(30). Large scale studies assessing factors associated with higher anaphylaxis risk among patients with cold urticaria would contribute to the development of guidelines on the prescription of EAI in these cases.

Our study has some potential limitations. Few studies pertaining to cold urticaria have been published in the last 10 years, resulting in only 14 articles being included in our meta-analysis and, subsequently, large confidence intervals. Study quality was generally adequate; however, some had inadequate sample size and insufficiently described study participants and setting. There is

inconsistency in the diagnosis and definition of cold urticaria amongst studies. As a result, diagnostic method validity in the quality assessment was defined as a positive ice cube test, TempTest or cold-water bath test. However, misclassification bias may persist as three studies were included in the systematic review that did not report on the diagnostic methods, one of which was included in the meta-analyses. Variability in the diagnostic methods may also contribute to the high levels of heterogeneity seen in the meta-analysis of cold urticaria prevalence among CU and CIndU. The definition of cold urticaria resolution was inconsistent between studies, ranging from at least one winter season to at least 12 months without symptoms. Similarly, definitions of anaphylaxis varied between studies. Consequently, the ranges of resolution rates and pooled prevalence of anaphylaxis reported must be interpreted with caution and we recommend the development of a unifying definition of cold urticaria resolution and anaphylaxis. The prevalence of anaphylaxis among cases of cold urticaria may be overestimated because studies included in the meta-analysis were largely conducted at tertiary care centers which likely see more severe cases of cold urticaria. Finally, because there were insufficient data to perform subgroup analyses, our meta-analysis combines both pediatric and adult cold urticaria data, although, it is reported that certain types of urticaria differ in their management and presentation in children versus adults(55, 56). Hence, composite measurements may misrepresent both populations if pediatric and adult cold urticaria are distinct manifestations of the same disease.

Conclusions

Taken together, cold urticaria is not rare among CU and CIndU cases and frequently triggers anaphylaxis. H1-antihistamines are the predominant management strategy, followed by omalizumab. Physicians should be attentive for a history and symptoms consistent with cold urticaria in patients presenting with urticaria to educate patients on anaphylaxis avoidance and management. Further, future comprehensive multi-center studies on cold urticaria are required, potentially through the GA²LEN Urticaria Centers of Reference and Excellence (UCARE) network.

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Figure Legends:

Figure 1. Flow diagram of search results based on PRISMA guidelines(57) for conducting a systematic search and evaluation for article inclusion.

Figure 2. Meta-analyses for pooled estimates for prevalence of cold urticaria among CU cases (n = 5, A) and prevalence of cold urticaria among CIndU cases (n = 6, B).

Figure 3. Meta-analyses for pooled estimates of use of H1-antihistamines in the treatment of cold urticaria (n = 9, A) and use of omalizumab in the treatment of cold urticaria (n = 9, B).

Figure 4. Meta-analysis for the pooled estimate of cases of anaphylaxis among cold urticaria cases (n = 8).

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660 **Table 1.** Data Extraction Cold Urticaria Management, Prevalence and Anaphylaxis

Author	Management No. (%)	Response to Management No. (%)	Resolution Rate (Study Definition of Resolution)	Cold Urticaria Cases among CU Cases No. (%)	Cold Urticaria Cases among CIndU Cases No. (%)	Anaphylaxis No. (%)	Anaphylaxis Triggers No. (%)
Azkur et al.(28)	NR	NR	NR	15/222 (6.8)	15/89 (16.9)	1/15 (6.7)	Swimming: 1/1 (100)
Bal al.(22)	NR	NR	NR	NR	20/117 (17.1)	NR	NR
Bizjak al.(26)	NR	NR	NR	NR	NR	12/36 (33.3)	NR
Bizjak al.(41)	Omalizumab: 6/35 (17.1)	OPP	OPP	OPP	OPP	OPP	OPP
Caldeira et al.(38)	OPP	OPP	OPP	19/429 (4.4)	19/82 (23.2)	OPP	OPP
Colgecen et al.(29)	NR	NR	NR	15/369 (4.1)	15/144 (10.4)	NR	NR
Curto-Barredo et al.(39)	OPP	OPP	OPP	OPP	70/359 (19.5)	OPP	OPP
Deza al.(14)	H1-antihistamines: 73/74 (98.6) Cyclosporine: 3/74 (4.1) Omalizumab: 3/74 (4.1)	Controlled on H1-antihistamines: 62/73 (84.9) (1x dose: 21/62 (33.9), 2x dose: 31/62 (50), >2x dose: 10/62 (16.1)) Clinical improvement on cyclosporine: 1/3 (33.3) Controlled on omalizumab: 3/3 (100) (Controlled defined as improvement of signs and symptoms until patient does not report any interference of cold urticaria symptoms with daily life)	26.6% in 5 years 44.5% in 10 years (≥1 winter season with no symptoms without medication)	74/1030 (7.2)	NR	14/74 (18.9)	Cold water: 13/14 (92.9)
Deza al.(33)	Omalizumab: 9/54 (16.7) Other treatments NR	NR	NR	54/287 (18.8)	54/152 (35.5)	NR	NR
Deza al.(23)	H1-antihistamines: 50/50 (100) Omalizumab: 11/50 (22) Cyclosporine: 1/50 (2)	Controlled on H1-antihistamines: 38/50 (76) Controlled on omalizumab: 7/7 (100) (Controlled defined as UCT≥12)	NR	NR	NR	12/50 (24)	NR

Jain et al.(24)	H1-antihistamines: 35/39 (89.7) H2-antihistamines: 3/39 (7.7) Lifestyle modification: 16/39 (41)	NR	17.9% $\pm$ 6.2% in 5 years 24.5% $\pm$ 7.2% in 10 years (N=41, Definition of resolution NR)	NR	NR	28/99 (28.3)	Swimming: 28/28 (100)
Jankowska-Konsur et al.(31)	H1-antihistamines: 31/33 (93.9) Oral corticosteroids: 12/33 (36.4) H2-antihistamines: 5/33 (15.2) Antileukotriene: 4/33 (12.1) Cyclosporine: 1/33 (3.0) Omalizumab: 0/33 (0)	NR	NR	33/1091 (3.0)	33/424 (7.8)	2/33 (6.1)	NR
Komarow et al.(34)	NR	NR	NR	NR	33/76 (43.4)	NR	NR
Kulthanan et al.(27)	Second generation H1-antihistamines: 26/27 (96.3) First generation H1-antihistamines: 4/27 (14.8) Oral corticosteroids: 4/27 (14.8) Omalizumab: 2/27 (7.4) Cyclosporine: 1/27 (3.7)	NR	13.8% in 5 years 42.6% in 10 years (≥ 6 months not receiving any treatment without symptoms and with a negative provocation test)	27/1063 (2.5)	27/77 (35.1)	1/27 (3.7)	Washing clothes in cool water: 1/1 (100)
Miles et al.(32)	H1-antihistamines: 39/40 (98) Omalizumab: 3/40, (7.5) Oral corticosteroids: 1/40 (2.5)	Controlled on H1-antihistamines: 24/36 (66.7) Controlled on omalizumab and H1-antihistamines: 0/3 (0) Controlled on corticosteroids: 0/1 (0) (Controlled defined as UCT ≥ 12)	58.1% in 6 years (N=31; 1 year with no symptoms)	40/217 (18.4)	40/64 (62.5)	NR	NR
Napolitano et al.(35)	H1-antihistamines: 58/58 (100) Other treatments NR	NR	NR	58/1970 (2.9)	58/451 (12.9)	NR	NR
Park et al.(37)	NR	NR	NR	15/253 (5.9)	15/174 (8.6)	NR	NR
Paulino et al.(25)	H1-antihistamines: 52/52 (100) Omalizumab: 1/52 (1.9)	NR	NR	NR	NR	17/52 (32.7)	NR
Silpa-archa et al.(36)	NR	NR	50% in 40 months	20/1200 (1.7)	20/86 (23.3)	0/20 (0)	NR

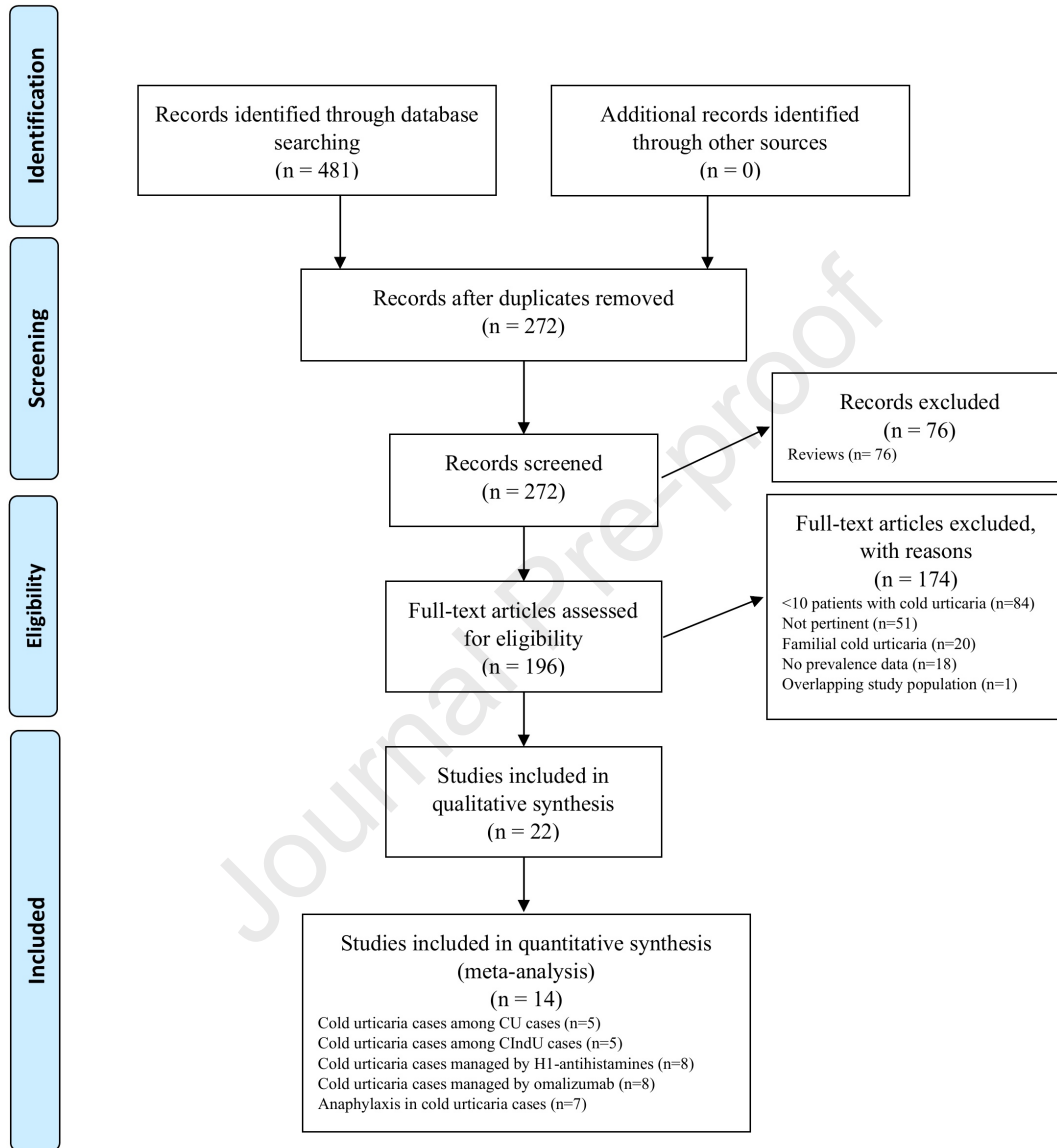
			(6 months without symptoms and negative to provocation tests after stopping medication)				
Stepaniuk et al.(30)	Second generation H1-antihistamines: 45/50 (90) H2 antihistamine: 3/50 (6) Omalizumab: 1/50 (2) Sodium cromoglycate:1/50 (2)	NR	NR	NR	NR	2/50 (4)	NR
Thomsen et al.(20)	NR	NR	NR	29/158 (18.4) ¹	29/61 (47.5) ¹	NR	NR
Yee et al.(21)	H1-antihistamines: 400/415 (96.4) Antileukotriene: 15/415 (3.6) H2-antihistamine: 7/415 (1.7) Omalizumab: 5/415 (1.2) Oral corticosteroids: 1/415 (0.24) Doxepin:1/415, (0.24)	NR	NR	NR	NR	77/415 (18.6)	Swimming: 87/112 (77.6) Cold air: 9/112 (8.0) Contact with cold water: 7/112 (6.3) Cold food/beverage: 7/112 (6.3) Receiving intravenous fluids: 2/112, (1.8) ²

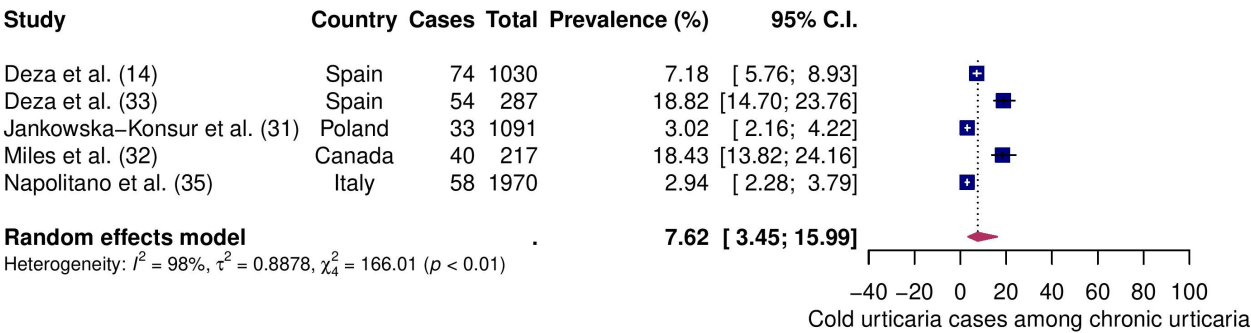
NR=Not reported

OPP= Overlapping patient population, statistics on this population are reported under another study (with an equivalent or larger population)

¹Only patients diagnosed with CU for a duration of greater than 2 months and is refractory to one to four-fold doses of H1-antihistamines

²Trigger was recorded for each individual episode of anaphylaxis





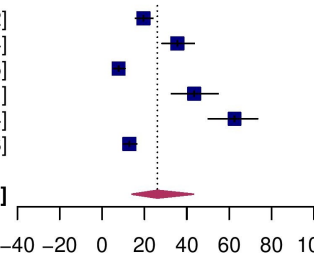
Study	Country	Cases	Total	Prevalence (%)	95% C.I.
Curto-Barredo et al. (39)	Spain	70	359	19.50	[15.72; 23.92]
Deza et al. (33)	Spain	54	152	35.53	[28.33; 43.44]
Jankowska-Konsur et al. (31)	Poland	33	424	7.78	[5.59; 10.75]
Komarow et al. (34)	United States	33	76	43.42	[32.78; 54.71]
Miles et al. (32)	Canada	40	64	62.50	[50.12; 73.44]
Napolitano et al. (35)	Italy	58	451	12.86	[10.07; 16.28]

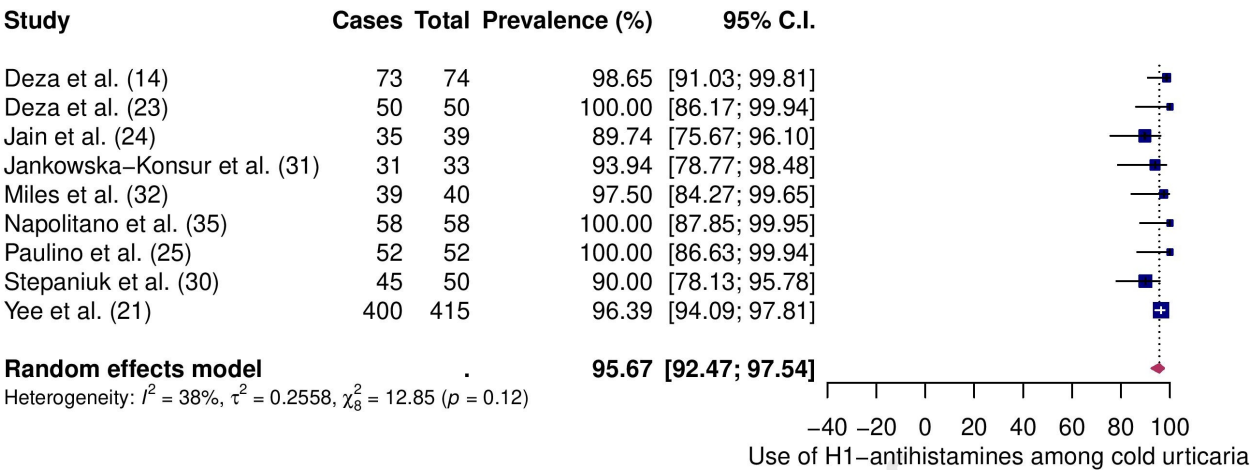
Random effects model

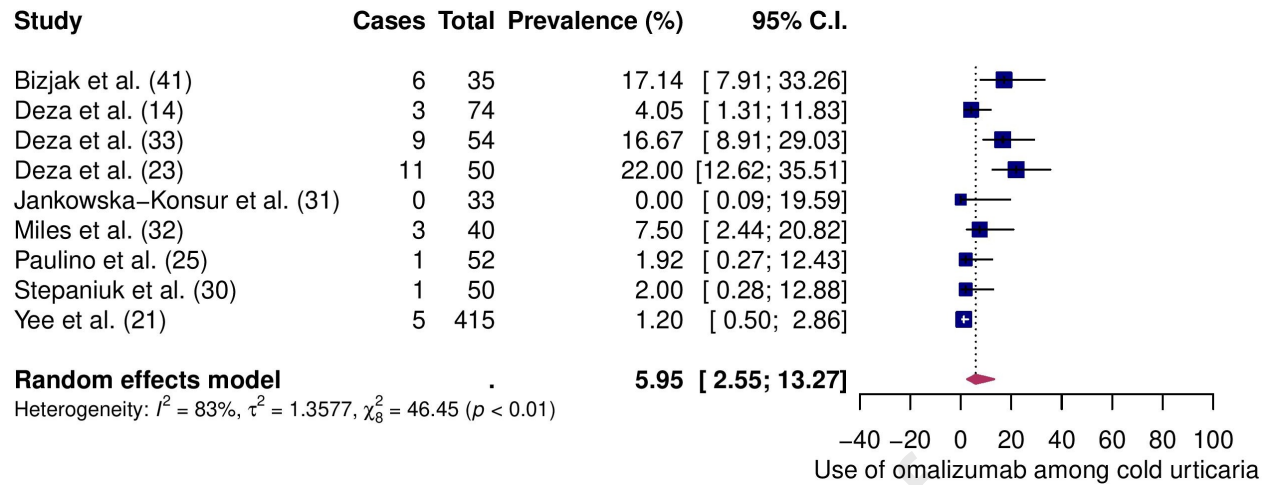
Heterogeneity: $I^2 = 97\%$, $\tau^2 = 0.8680$, $\chi^2_5 = 148.04$ ($p < 0.01$)

26.10 [14.17; 43.05]

-40 -20 0 20 40 60 80 100
Cold urticaria cases among chronic inducible urticaria







Study	Cases	Total	Prevalence (%)	95% C.I.
Bizjak et al. (26)	12	36	33.33	[20.00; 50.00]
Deza et al. (14)	14	74	18.92	[11.54; 29.45]
Deza et al. (23)	12	50	24.00	[14.16; 37.67]
Jain et al. (24)	28	99	28.28	[20.30; 37.92]
Jankowska-Konsur et al. (31)	2	33	6.06	[1.52; 21.23]
Paulino et al. (25)	17	52	32.69	[21.39; 46.44]
Stepaniuk et al. (30)	2	50	4.00	[1.00; 14.63]
Yee et al. (21)	77	415	18.55	[15.10; 22.59]

Random effects model

Heterogeneity: $I^2 = 69\%$, $\tau^2 = 0.1761$, $\chi^2_7 = 22.66$ ($p < 0.01$)

21.49 [15.79; 28.54]

