Courage + Khazaka electronic GmbH
Mathias-Brüggen-Str. 91 * 50829 Köln, Germany
Phone: +49-221-956499-0 * Fax: +49-221-956499-1

Literature List
TempTest® and Cold Urticaria

Y. Inuzuka, K. Yamamoto-Hanada, M. Saito-Abe, Y. Ohya, **Pediatric cold-induced anaphylaxis and evaluation using TempTest®**, Allergology International, April 2022

Cold urticaria is a type of physical urticaria among inducible urticarias. It is characterized by pruritic edemas and angioedema, which occur when the patient is exposed to cold. Several aspects of cold urticaria, such as epidemiology, pathogenesis, and natural history, have not yet been elucidated. Furthermore, some cases of urticaria-causing anaphylaxis have been overlooked as idiopathic anaphylaxis. We performed a standardized TempTest® technology (Courage + Khazaka, Germany) to make a precise diagnosis and determine critical temperature thresholds (CTTs) for inducing anaphylaxis. In this study, we report a pediatric case of cold-induced anaphylaxis, which could be diagnosed with the CTT using the TempTest®.

M. Herrero-Fernandez, T. Montero-Vilchez, P. Diaz-Calvillo, M. Romera-Vilchez, A. Buendia-Eisman, S. Arias-Santiago, **Impact of Water Exposure and Temperature Changes on Skin Barrier Function**, J. Clin. Med. 2022, 11, 298

The frequency of hand hygiene has increased due to the COVID-19 pandemic, but there is little evidence regarding the impact of water exposure and temperature on skin. The aim of this study is to evaluate the effect of water exposure and temperature on skin barrier function in healthy individuals. A prospective observational study was conducted. Temperature, pH, transepidermal water loss (TEWL), erythema and stratum corneum hydration (SCH) were measured objectively before and after hot- and cold-water exposure and TempTest® (Microcaya TempTest, Bilbao, Spain) contact. Fifty healthy volunteers were enrolled. Hot-water exposure increased TEWL (25.75 vs. 58.58 g·h-1·m-2), pH (6.33 vs. 6.65) and erythema (249.45 vs. 286.34 AU). Cold-water immersion increased TEWL (25.75 vs. 34.96 g·h-1·m-2) and pH (6.33 vs. 6.62). TEWL (7.99 vs. 9.98 g·h-1·m-2) and erythema (209.07 vs. 227.79 AU) increased after being in contact with the hot region (44 °C) of the TempTest. No significant differences were found after contact with the cold region (4 °C) of the TempTest. In conclusion, long and continuous water exposure damages skin barrier function, with hot water being even more harmful. It would be advisable to use cold or lukewarm water for handwashing and avoid hot water. Knowing the proper temperature for hand washing might be an important measure to prevent flares in patients with previous inflammatory skin diseases on their hands.

M. Maurer, A. Schutz, K. Weller, M. Gorczyza, A. Peveling-Oberhag, P. Staubach, H. F. Merk, M. Metz, **Omalizumab in cold urticaria: Results of a randomized placebo-controlled trial,** 3rd GA2LEN GLOBAL URTICARIA FORUM BERLIN, 29-30 NOVEMBER 2016 and J. Allergy Clin. Immunol., 2017

Cold urticaria (ColdU) is a severe form of physical urticarial characterized by wheals and angioedema following cold exposure. ColdU is often of long duration, debilitating, sometimes associated with severe systemic reactions including anaphylactic shock, and often resistant to antihistamines, the first line treatment. Several case reports suggest that ColdU patients can benefit from treatment with omalizumab which is licensed for the treatment of asthma and chronic spontaneous urticaria.

M. Gorczyza, N. Schoepke, K. Krause, T. Hawro, M. Maurer, **Patients with chronic cold urticaria may benefit from doxycycline therapy,** Br J Dermatol. 2017 Jan; 176(1): p. 259-261

No abstract available

H. Shizukawa, K. Iwamoto, T. Hiragun, M. Hide, **Temperature Threshold of a Case of Cold Contact Urticaria Evaluated with TempTest®**, J Environ. Dermatol. Cutan. Allergol. 11 (2), p. 138-143, 2017

A 19-year-old woman was referred to our hospital because of the development of itchy wheals and flare upon exposure to coldness for 10 years. She had been treated with several antihistamines, but none were effective. We diagnosed her symptoms as cold contact urticaria with a positive ice cube test and her disease history. We treated her with medications classified as supplementary medications, including an antileukotrien and cyclosporine, which is classified as an experimental medication, in

addition to various antihistamines. However, none of them brought her substantial improvement of the symptoms beyond seasonal fluctuations. In order to make objective evaluations of her disease severity and the effects of treatments, we measured her critical temperature threshold under treatments with different medications using TempTest® 4.0, an electronic device designed for monitoring thresholds to induce symptoms of cold contact urticaria. Both wheals and flare with itching were induced when she stopped all medications, whereas only flare with clear margins and no wheals were seen when she took any antihistamine. Thus, the effectiveness of the treatment was successively visualized by this device, resulting in better satisfaction with and adherence to medication by the patient.

M. Sánchez-Borges, L. González-Aveledo, F. Caballero-Fonseca, A. Capriles-Hulett, **Review of Physical Urticarias and Testing Methods**, Curr Allergy Asthma Rep. 2017 Aug;17(8): p. 51

Purpose of review: This review aims to update the information available on the prevalence, clinical picture, diagnostic methods, and treatment of urticarias induced by external physical stimuli. Recent findings: Physical urticarias are present in up to 5% of the general population, and in 10 to 50% of patients with chronic urticaria. Recent investigations have provided evidence that the presence of physical urticaria alone or when comorbid with chronic spontaneous urticaria is associated with a worse prognosis and duration. Most frequent subtypes of physical urticaria are dermographism and delayed pressure urticaria. The diagnosis is established through specific provocation tests and the management encompasses avoidance measures, pharmacologic therapy with nonsedating antihistamines, and alternative medications in refractory cases.

J.G. Holm, T. Agner, S.F. Thomsen, **Diagnostic properties of provocation tests for cold, heat, and delayed-pressure urticarial**, Eur J Dermatol. 2017 Aug 1;27(4): p. 406-408

No abstract available

M. Metz. A. Schutz, K. Weller, N. Schoepke, A. Peveling-Oberhag, P. Staubach, S. Müller, T. Jakob, M. Maurer, **Omalizumab in symptomatic dermographism: Results of a randomized, placebo-controlled trial,** 3rd GA2LEN GLOBAL URTICARIA FORUM BERLIN, 29-30 NOVEMBER 2016

Symptomatic dermographism (SDerm), also known as urticaria factitia, is a very frequent form of physical urticaria. SDerm is chronic, debilitating, and often resistant to antihistamines, the first line treatment. Case reports suggest that omalizumab may be effective.

M. Abajian, L. Curto-Barredo, K. Krause, E. Santamaria, I. Izquierdo, M.K. Church, M. Maurer, A. Giménez-Arnau, **Rupatadine 20 mg and 40 mg are Effective in Reducing the Symptoms of Chronic Cold Urticaria**, Acta Derm Venereol. 2016 Jan;96(1): p. 56-9

Chronic cold urticaria (ColdU) is a rare disease characterized by mast cell-mediated wheals and angioedema following cold exposure. Second-generation H1-antihistamines, such as rupatadine, are the recommended first-line therapy. As of yet, the effects of rupatadine up-dosing on development of ColdU symptom have only been partially characterized. Two-centre, randomized, double-blind, 3-way crossover, placebo-controlled study in patients with a confirmed ColdU was designed to assess the effects of up-dosing of rupatadine. A total of 23 patients were randomized to receive placebo, rupatadine 20 mg/day, and rupatadine 40 mg/day for 1 week. The primary outcome was change in critical temperature thresholds and critical stimulation time thresholds after treatment. Secondary endpoints included assessment of safety and tolerability of rupatadine. Both 20 and 40 mg rupatadine were highly effective in reducing critical temperature thresholds ($p < 0.001$) and critical stimulation time thresholds ($p < 0.001$). In conclusion, rupatadine 20 and 40 mg significantly reduced the development of chronic cold urticaria symptom without an increase in adverse effects.

M. Bertolln-Colilla, G. Deza, L. Curto-Barredo, R. M. Pujol, A. M. Gimenez-Arnau, **Threshold's value in acquired cold urticaria: Prognostic and therapeutic monitoring,** 3rd GA2LEN GLOBAL URTICARIA FORUM BERLIN, 29-30 NOVEMBER 2016

Background: Acquired cold urticaria (ACU) is an inducible urticaria characterized by local or systemic manifestations after cold exposure. Although diagnosis is primarily based on clinical history, assessment of thresholds would be helpful to establish ACU severity and monitor therapeutic efficacy. Data about efficacy of anti-IgE therapy for severe and refractory cases are currently scarce. Objectives: To assess and correlate the baseline temperature threshold (CTT) and critical stimulation time threshold (CsTT) with ACU severity score and prognosis. Furthermore, the usefulness of assessing the therapeutic response to antihistamines and omalizumab in refractory cases as a first line treatment was considered.

M.E. Martinez-Escala, L. Curto-Barredo, L. Carnero, R.M. Pujol, A.M. Giménez-Arnau, **Temperature thresholds in assessment of the clinical course of acquired cold contact urticaria: a prospective observational one-year study.** Acta Derm. Venereol. 2015 Mar; 95(3): p. 278-282

Cold contact urticaria is the second most common subtype of physical urticaria. Cold stimulation standardized tests are mandatory to confirm the diagnosis. The aim of this study is to define the utility of determining thresholds (critical time and temperature) in assessment of the clinical course of typical acquired cold contact urticaria. Nineteen adult patients (10 women and 9 men; mean age 45 years) were included in the study and the diagnosis was confirmed with the ice-cube test and TempTest® 3.0. Patients were treated continuously for one year with 20mg/day rupatadine (anti-H1). Thresholds measurements were made before and after treatment. Improvements in temperature and critical time thresholds were found in the study sample, demonstrating the efficacy of continuous treatment with rupatadine. In most cases association with a clinical improvement was found. We propose an algorithm for the management of acquired cold contact urticaria based on these results.

M. Magerl, M. Abajian, K. Krause, S. Altrichter, F. Siebenhaar, ,M. K. Church, **An improved Peltier effect-based instrument for critical temperature threshold measurement in cold- and 2 heat-induced urticaria,** J. Eur. Acad. Dermatol. Venereol. 2014: in press. IF (2013): 2.78

Background: Cold- and heat-induced urticaria are chronic physical urticaria conditions in which wheals, angioedema or both are evoked by skin exposure to cold and heat respectively. The diagnostic work up of both conditions should include skin provocation tests and accurate determination of critical temperature thresholds (CTT) for producing symptoms in order to be able to predict the potential risk that each individual patient faces and how this may be ameliorated by therapy. Objective: To develop and validate TempTest 4, a simple and relatively inexpensive instrument for the accurate determination of CTT which may be used in clinical practice. Methods: TempTest 4 has a single 2 mm wide 350 mm U-shaped Peltier element generating a temperature gradient from 4 °C to 44 °C along its length. Using a clear plastic guide placed over the skin after provocation, CTT values may be determined with an accuracy of 1 °C. Here, TempTest 4 was compared with its much more expensive predecessor, TempTest 3, in inducing wheals in 30 cold urticaria patients. Results: Both TempTest 4 and TempTest 3 induced wheals in all 30 patients between 8 ° and 28 °C. There was a highly significant ($P < 0.0001$) correlation between the instruments in the CTT values in individual patients. Conclusion: The TempTest 4 is a simple, easy to use, licensed, commercially available and affordable instrument for the determination of CTTs in both cold- and heat-induced urticaria.

T. Zuberbier, W. Aberer, R. Asero, C. Bindslev-Jensen, Z. Brzoza, G. W. Canonica, etc., **The EAACI/GA2LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update;** Allergy 69 (2014) 868–887 © 2014 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd

Abstract: This guideline is the result of a systematic literature review using the 'Grading of Recommendations Assessment, Development and Evaluation' (GRADE) methodology and a structured consensus conference held on 28 and 29 November 2012, in Berlin. It is a joint initiative of the Dermatology Section of the European Academy of Allergy and Clinical Immunology (EAACI), the EU-funded network of excellence, the Global Allergy and Asthma European Network (GA2LEN), the European Dermatology Forum (EDF), and the World Allergy Organization (WAO) with the participation of delegates of 21 national and international societies. Urticaria is a frequent, mast cell-driven disease, presenting with wheals, angioedema, or both. The life-time prevalence for acute urticaria is approximately 20%. Chronic spontaneous urticaria and other chronic forms of urticaria do not only cause a decrease in quality of life, but also affect performance at work and school and, as such, are members of the group of severe allergic diseases. This guideline covers the definition and classification of urticaria, taking into account the recent progress in identifying its causes, eliciting factors and pathomecha nisms. In addition, it outlines evidence-based diagnostic and therapeutic approaches for the different subtypes of urticaria. This guideline was acknowledged and accepted by the European Union of Medical Specialists (UEMS).

M. Abajian, N. Schoepke, S .Altricher, T. Zuberbier, M. Maurer, **Physical urticarias and cholinergic urticaria,** Immunol. Allergy Clin. North. Am. 2014: p. 34; 73-88. IF: TBD (IF 2013: 2.22)

Physical urticarias are a unique subgroup of chronic urticaria in which urticarial responses can be reproducibly induced by different specific physical stimuli acting on the skin. These conditions include urticaria factitia/symptomatic dermographism, delayed pressure urticaria, cold contact urticaria, heat contact urticaria, solar urticaria, and vibratory urticaria/angioedema. Physical urticarias and cholinergic urticarias are diagnosed based on the patients' history and provocation tests including trigger threshold testing where possible. Treatment is mainly symptomatic. Many patients benefit from avoiding eliciting

triggers, and desensitization to these triggers can be helpful in some physical urticarias and in cholinergic urticaria.

K. Krause, A. Spohr, T. Zuberbier, M. K. Church, M. Maurer, **Up-dosing with bilastine results in improved effectiveness in cold contact urticaria,** Allergy 2013: 68; p. 921-928. IF: 5.99

Background: Cold contact urticaria (CCU) is characterized by itchy wheal and flare responses due to the release of histamine and other pro-inflammatory mediators after exposure to cold. The treatment of choice is nonsedating antihistamines, dosages of which may be increased up to fourfold if standard doses are ineffective. Here, we assess the effects of a standard 20 mg dose and up-dosing to 40 and 80 mg of bilastine in reducing the symptoms of CCU and inflammatory mediator release following cold challenge. Methods: Twenty patients with CCU were included in this randomized, crossover, double-blind, placebo-controlled 12-week study. They received placebo, 20, 40 or 80 mg of bilastine daily each for 7 days with 14-day washout periods. The primary readout was change in critical temperature thresholds (CTT). Secondary readouts were changes in pruritus, levels of histamine IL-6, IL-8 and TNF-a collected by skin microdialysis and safety and tolerability of bilastine. Results: Bilastine 20 mg was highly effective ($P < 0.0001$) in reducing CTT. Up-dosing to 80 mg significantly ($P < 0.04$) increased its effectiveness. At this dose, 19 of 20 (95%) patients responded to treatment, with 12 of 20 (60%) becoming symptom free. Only one patient was refractory to treatment. Microdialysis levels of histamine, IL-6 and IL-8 assessed 1–3 h after cold challenge were significantly ($P < 0.05$) decreased following up-dosing with 80 mg bilastine. Bilastine treatment was well tolerated without evidence of increased sedation with dose escalation. Conclusions: Bilastine was effective in reducing the symptoms of patients with CCU. Increased efficacy of bilastine with fourfold up-dosing was without sedation and supports urticaria treatment guidelines.

N. Schoepke, G. Doumoulakis, M. Maurer, **Diagnosis of urticaria,** Indian J Dermatol. 2013 May-Jun; 58(3): 211–218

Acute urticaria do not need extensive diagnostic procedures. Urticaria activity score is a useful tool for evaluation of urticaria. Complete blood count, Erythrocyte sedimentation rate and C reactive protein are important investigations for diagnosis of infections in urticaria. Autologous serum skin test is a simple office procedure for diagnosis of auto reactive urticaria. Closed ball point pen tip is a simple test to diagnose dermographism.

M. Magerl, M. Abajian, K. Krause, S. Altrichter, F. Siebenhaar, ,M. K. Church, **An improved Peltier effect-based instrument for critical temperature threshold measurement in cold- and 2 heat-induced urticaria,** J. Eur. Acad. Dermatol. Venereol. 2014: in press. IF (2013): 2.78

Background: Cold- and heat-induced urticaria are chronic physical urticaria conditions in which wheals, angioedema or both are evoked by skin exposure to cold and heat respectively. The diagnostic work up of both conditions should include skin provocation tests and accurate determination of critical temperature thresholds (CTT) for producing symptoms in order to be able to predict the potential risk that each individual patient faces and how this may be ameliorated by therapy. Objective: To develop and validate TempTest 4, a simple and relatively inexpensive instrument for the accurate determination of CTT which may be used in clinical practice. Methods: TempTest 4 has a single 2 mm wide 350 mm U-shaped Peltier element generating a temperature gradient from 4 °C to 44 °C along its length. Using a clear plastic guide placed over the skin after provocation, CTT values may be determined with an accuracy of 1 °C. Here, TempTest 4 was compared with its much more expensive predecessor, TempTest 3, in inducing wheals in 30 cold urticaria patients. Results: Both TempTest 4 and TempTest 3 induced wheals in all 30 patients between 8 ° and 28 °C. There was a highly significant ($P < 0.0001$) correlation between the instruments in the CTT values in individual patients. Conclusion: The TempTest 4 is a simple, easy to use, licensed, commercially available and affordable instrument for the determination of CTTs in both cold- and heat-induced urticaria.

M. Abajian, A. Mł ynek, M. Maurer, **Physical urticaria,** Curr. Allergy Asthma Rep. 2012: p. 12; 281-287. IF: 2.74

The physical urticarias are a heterogeneous subgroup of chronic urticarias in which wheals can be reproducibly induced by different specific physical stimuli such as cold, heat, pressure, vibration, or sunlight. Physical urticarias comprise up to 25 % of chronic urticarias and occur more frequently in young adults. Symptoms, i.e. wheal and flare responses or angioedema, are usually limited to the skin areas exposed to the eliciting stimulus. However, generalised urticaria with variable extracutaneous manifestations can also occur. Some patients may also present with more than one physical urticaria. Skin lesions in physical urticaria result from mast cell activation and mediator release. The mechanisms by which physical stimuli activate skin mast cells are not fully understood. Because of this, trigger

avoidance and symptomatic treatment are key therapeutic concepts for physical urticarias. Identification of the inducing physical trigger, including its individual thresholds, is necessary for an effective therapy. Here, we have summarized clinical features, diagnostic workup and therapy options for physical urticarias.

M. Magerl, D. Pisarevskaja, P. Staubach, P. Martus, M. K. Church, M. Maurer, **Critical temperature threshold measurement for cold urticaria: a randomised controlled trial of H1-antihistamine up-dosing,** Br. J. Dermatol. 2012: 166; p. 1095-1099. IF: 3.75

Background: Cold urticaria is a rare but severe and potentially lethal condition. It is primarily treated symptomatically with H(1) -antihistamines. However, patients have a variable response to these drugs and, to date, it has not been possible to predict readily the response to therapy of individual patients. Objectives: To assess the severity of the cold urticaria in naive patients and the response to therapy of patients treated with increasing doses of an H(1) -antihistamine by measurement of critical temperature thresholds (CTT) for producing weals on the forearm. Methods: This was a two-centre, hospital-based, double-blind, randomized, parallel-group study of patients with a confirmed diagnosis of cold urticaria of at least 6 months' duration. Patient groups received either a constant dose of desloratadine 5 mg daily for 6 weeks (n = 13), or escalating doses of desloratadine: 5 mg daily for the first 2 weeks, 10 mg daily for the second 2 weeks and 20 mg daily for the final 2 weeks (n = 15). Only one adverse event that appeared to be drug related was reported: mild fatigue after treatment with desloratadine 10 mg that lasted for about 3 weeks and resolved at the end of the study. Results: The desloratadine 5 mg daily dose produced a submaximal reduction of mean CTT which remained relatively constant over 6 weeks. Dose escalation increased efficacy, the reduction in mean CTT at four-times the standard daily dose being significantly greater (P = 0·03) than with the standard dose. Individually, no patient became symptom free (CTT < 4 °C) on 5 mg, while two became symptom free on 10 mg and a further three on 20 mg desloratadine daily. Conclusions: Measurement of CTT allows for individualized risk management and therapy in patients with cold urticaria.

M. Metz, E. Scholz, M. Ferrán, I. Izquierdo, A. Giménez-Arnau, M. Maurer, **Rupatadine and its effects on symptom control, stimulation time, and temperature thresholds in patients with acquired cold urticarial,** Ann. Allergy Asthma Immunol. 2010: p. 104; 86-92. IF: 2.80

Background: Patients with acquired cold urticaria (ACU) show itchy wheals during cold exposure. This disturbing condition involves histamine and platelet-activating factor in its pathogenesis. Rupatadine is a dual antagonist of both histamine and platelet-activating factor. Objective To assess rupatadine efficacy in preventing reactions to cold challenge in patients with ACU. Methods: A crossover, randomized, double-blind, placebo-controlled study in which 21 patients with ACU received rupatadine, 20 mg/d, or placebo for 1 week each is presented. The main outcome was the critical stimulation time threshold (CSTT) determined by ice cube challenge. Secondary outcomes included CSTT and the critical temperature threshold assessed by a cold provocation device (Temp*Test* 3.0), as well as scores for wheal reactions, pruritus, burning sensations, and subjective complaints after cold challenge. Results: After rupatadine treatment, 11 (52%) of 21 patients exhibited a complete response (ie, no urticaria lesions after ice cube provocation). A significant improvement in CSTT compared with placebo was observed after ice cube and Temp*Test* 3.0 challenge (*P* = .03 and *P* = .004, respectively). A significant reduction of critical temperature threshold (*P* < .001) and reduced scores for cold provocation-induced wheal reactions (*P* = .01), pruritus (*P* = .005), burning sensation (*P* = .03), and subjective complaints (*P* = .03) after rupatadine treatment were also found. Mild fatigue (n = 4), somnolence (n = 1), and moderate headache (n = 1) were reported during active treatment. Conclusion: Rupatadine, 20 mg/d, shows high efficacy and is well tolerated in the treatment of ACU symptoms.

A. Mł ynek, M. Magerl, F. Siebenhaar, K. Weller, R. Vieira dos Santos, T. Zuberbier, A. Zalewska-Janowska, M. Maurer, **Results and relevance of critical temperature threshold testing in patients with acquired cold urticaria.** Brit. J. Dermatol. 2010: 162; p. 198-200, IF: 4.35

Background: Acquired cold urticaria (ACU) is a physical urticaria characterized by local skin reactions after cold exposure. Objective markers of disease severity and activity would be helpful. Unfortunately, such markers are not yet available, even though stimulation time and temperature thresholds are promising candidates. Objectives: We assessed and correlated critical temperature thresholds (CTTs) with disease severity and activity in patients with ACU. Methods: CTTs were determined in 45 patients with ACU by Temp*Test* -based cold contact stimulation tests (Emo Systems GmbH, Berlin, Germany), and ACU severity and activity were assessed using Likert scales. Results: Patients with ACU exhibited mean ± SEM CTTs of 17 ± 6 °C (range 4–27 °C). These thresholds and their changes correlated with the severity (r = 0·53, P < 0·05) and activity of disease (r = 0·64, P < 0·05), respectively. Conclusions: These findings indicate that temperature threshold measurements may be

used for assessing disease severity and activity as well as the efficacy of therapeutic measures including novel treatment approaches for cold urticaria.

K. Krause, T. Zuberbier, M. Maurer, **Modern approaches to the diagnosis and treatment of cold contact urticaria,** Curr. Allergy Asthm. 2010: 10; 243-249. IF: 2.34

Cold contact urticaria (CCU) is a common subtype of physical urticaria characterized by itchy wheals and/or angioedema due to skin mast cell activation and the release of proinflammatory mediators after cold exposure. The underlying causes are largely unknown. When CCU is suspected, cold stimulation tests and threshold testing should be done to confirm the diagnosis and to determine the severity and course of CCU, respectively. Avoidance of critical cold exposure should be recommended but is often impossible, especially for severely affected patients with high temperature and low exposure time thresholds. Symptomatic treatment of choice is the use of modern, nonsedating antihistamines. Patients should be informed that complete protection from CCU symptom development may require increased doses of antihistamines. Standardizing cold provocation tests and further characterization of the natural course of CCU and its variants may lead to a better understanding of the disease-driving mechanisms.

K. Krause, F. Degener, S. Altrichter, E. Ardelean, D. Kalogeromitros, M. Magerl, M. Metz, F. Siebenhaar, K. Weller, M. Maurer, **Kälteinduzierte Quaddeln und Angioödeme – Klassifikation, Diagnostik und Therapie,** Hautarzt 2010: 61; p. 743-749. IF: 0.45

Das Auftreten von Urtikaria und Angioödemen nach Kältekontakt ist charakteristisch für eine heterogene Gruppe von Erkrankungen, zu der die häufig vorkommende Kältekontakturtikaria, aber auch seltene erworbene atypische Kälteurtikariaformen und familiäre Erkrankungen zählen. Die erworbenen atypischen Kälteurtikariaformen können mitunter aus einer Kältekontakturtikaria hervorgehen. In der Regel bleibt das Auftreten bei lokalisierter Kälteexposition auf die Haut beschränkt. Dagegen gibt es unter den hereditären Formen eine Variante, das familiäre kälteinduzierte autoinflammatorische Syndrom (FCAS), das mit einer Reihe von zusätzlichen systemischen Beschwerden, wie z. B. Fieberschüben und Gelenkbeschwerden, einhergeht und als autoinflammatorische Erkrankung gilt. Im Folgenden wird ein Überblick über die klinischen Gemeinsamkeiten und Besonderheiten, Diagnostik und Therapie der einzelnen Entitäten gegeben.

K. Krause, E. Ardelean, B. Keßler, M. Magerl, M. Metz, F. Siebenhaar, K. Weller, T. Zuberbier, M. Maurer, **Causes, Triggers and Mechanisms of Physical Urticarias – Insights from Cold-Contact Urticaria**; www.advances-in-psoriasis.com; Vol. 1 Issue 3 2010

Diverse environmental stimuli, such as thermal and mechanical triggers or electromagnetic radiation, lead to clinical symptoms of physical urticarias, mostly localized whealing. These cutaneous wheal-and-flare reactions are caused by the activation of mast cells and their release of proinflammatory mediators. Usually, trigger factors can be easily identified by provocation tests, and subsequently avoided, at least partially. However, the underlying causes of physical urticarias are largely unknown. This article focuses on cold contact urticaria as a paradigm of physical urticarias in terms of clinical manifestation, diagnostic procedures, and known pathomechanisms.

F. Siebenhaar, F. Degener, T. Zuberbier, P. Martus, M. Maurer, **High-dose desloratadine decreases wheal volume and improves cold provocation thresholds as compared with standard dose treatment in patients with acquired cold urticaria: A randomized, placebo-controlled, crossover study,** J. Allergy Clin. Immunol. 2009: 123; p. 672-679. IF: 9.16

Background: Increased dosing of nonsedating antihistamines is recommended by the current European Academy of Allergology and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum guidelines on patients with acquired cold urticaria (ACU) who do not respond satisfactorily to the standard dose. Prospective data supporting this recommendation are scant. Objective: We sought to assess the effects of 5 and 20 mg of desloratadine and placebo on cold-induced urticarial reactions in patients with ACU. Methods: In this prospective, randomized, double-blind, 3-way crossover trial , patients with ACU (n = 30) received placebo, 5 mg of desloratadine, and 20 mg of desloratadine every day each for 7 days separated by 14-day washout periods. At the end of each treatment, patients underwent cold provocation with the TempTest 2.0/2.1 system, and urticarial reactions were assessed by using digital 3-dimensional time-lapse photography and thermography; the critical temperature threshold (CTT) and critical stimulation time threshold (CSTT) were measured. Adverse events (AEs) reported during the study were assessed. Results: Compared with placebo, 7 days of desloratadine at 5 and 20 mg/d significantly reduced the volume of cold-induced wheals and areas of hyperthermic skin and improved CTT and CSTT results. Desloratadine at 20 mg/d significantly reduced cold-induced wheal volume and CTT and CSTT values versus desloratadine at 5 mg/d.

Desloratadine was well tolerated, with no increased rate of somnolence or other AEs with 20 mg of desloratadine. Conclusions: Desloratadine at standard and high doses significantly improved objective signs of ACU provoked by cold exposure. Desloratadine at 4 times the standard dose significantly reduced ACU lesion severity versus 5 mg of desloratadine without an increase in AEs. This study supports current guidelines that increased desloratadine dosing might benefit patients with urticaria who do not respond to standard doses.

M. Magerl, E. Borzova, A. Giménez-Arnau, C. E. H. Grattan, F. Lawlor, P. Mathelier-Fusade, M. Metz, A. Mł ynek, M. Maurer, **The definition and diagnostic testing of physical and cholinergic urticarias – EAACI/GA²LEN/EDF/UNEV consensus panel recommendations,** Allergy 2009: 64; p. 1715-1721. IF: 6.38

The recommendations for the definition and diagnosis presented in this position paper are the result of a panel consensus meeting held in December 2008 in Berlin. This consensus meeting was a joint initiative of EAACI (European Academy of Allergology and Clinical Immunology) Dermatology Section, the EU-funded network of excellence, GA2LEN (Global Allergy and Asthma European Network), the EDF (European Dermatology Forum) and UNEV (urticaria network e.V.). The aim of these recommendations is to improve the diagnosis and management of patients with physical urticaria or cholinergic urticaria and to promote research and a better understanding of these diseases. Our recommendations used the paper produced by a 1996 expert meeting (1) and they acknowledge the latest changes in our understanding of physical urticarias and cholinergic urticaria as well as the recent development of novel diagnostic tools. In addition, this consensus paper highlights areas of need for further research.

M. Magerl, J. Schmolke, F. Siebenhaar, T. Zuberbier, M. Metz, M. Maurer, **Acquired cold urticaria symptoms can be safely prevented by Ebastine,** Allergy 2007: 62; p. 1465-1468. IF: 5.01

Background: Acquired cold urticaria (ACU) is a skin condition, in which exposure to cold results in wheals and itching and sometimes general systemic complications. It has a profound impact on patient quality of life. Second-generation antihistamines are recommended as the first-line treatment, but to date only a few have been scientifically tested for this condition. Aim: To assess the safety and efficacy of ebastine in preventing ACU symptoms. Methods: Twenty-two adult ACU patients participated in a double-blind crossover trial of 20 mg ebastine. The safety of ebastine was sensitively assessed with a psychometric battery testing cognitive performance and mood. After cold challenge, wheal and erythema were assessed by the investigator and the intensities of pruritus and burning were rated by the subject. Results: Ebastine had no negative impact on any of the parameters of cognitive performance or mood. It dramatically reduced the number of patients who experienced wheals, pruritus, and burning after challenge. Conclusion: Ebastine is safe and effective in preventing the symptoms of ACU.

F. Siebenhaar, K. Weller, A. Mł ynek, M. Magerl, S. Altrichter, R. Vieira dos Santos, M. Maurer, T. Zuberbier, **Acquired cold urticaria: clinical picture and update on diagnosis and treatment**, Clin. Exp. Dermatol. 2007: 32; p. 241-245. IF: 1.52

Acquired cold urticaria (ACU) is a frequent subtype of physical urticaria that is caused by the release of proinflammatory mast cell mediators after cold exposure. Although the underlying causes of ACU still remain to be clarified in detail, a wide range of diseases has been reported to be associated with ACU. This review gives an overview of the clinical picture, the differential diagnoses, diagnostic tests and the aetiology of ACU, and summarizes current and novel therapeutic options based on the currentliterature.

F. Siebenhaar, P. Staubach, M. Metz, M. Magerl, J. Jung, M. Maurer, **Peltier effect-based temperature challenge – an improved method for diagnosing cold urticaria,** J. Allergy Clin. Immunol. 2004: 114; p. 1224-1225. IF: 7.2

To the Editor: Acquired cold urticaria (ACU), a frequent form of physical urticaria, is characterized by weal and flare-type 1 2 skin reactions and/or angioedema after cold exposure.' ACU is diagnosed by a history of such symptoms and a positive immediate cold-contact stimulation test (CST), ie, the development of urticarial skin lesions at sites of cold challenge3. Various CSTs have been described, the most common of which involves the application of an ice cube to the skin.3'5 However, ice cube challenge tests (1) reportedly fail to confirm ACU in 1 of 5 affected patients,6 (2) are not suited or standardized to assess threshold temperatures of urticaria induction, and (3) occasionally result in cold damage at test sites. To develop a safer, more sensitive, and standardized CST procedure and to determine and monitor threshold temperatures of patients with ACU, we have generated and tested an

electronic device *(TempTest)* that allows testing of as many as 4 different temperatures using the Peltier effect.