European Dermatology Forum

European Dermatology Forum Guideline for the definition, diagnostic testing and management of chronic inducible urticarias

Update and revision of the EAACI/GA²LEN/EDF/UNEV 2009 consensus panel recommendations

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The definition, diagnostic testing and management of chronic inducible urticarias – update and revision of the EAACI/GA^{2}LEN/EDF/UNEV 2009 consensus panel recommendations

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Introduction

These recommendations for the definition, diagnosis and management of chronic inducible urticaria (CIndU) extend, revise and update our previous consensus report on physical urticarias and cholinergic urticaria (1), a joint initiative of the EAACI (European Academy of Allergology and Clinical Immunology) Dermatology Section, the GA^{2}LEN (Global Allergy and Asthma European Network) task force on urticaria, the EDF (European Dermatology Forum) and UNEV (urticaria network e.V.). Changes to the 2009 consensus report reflect the results of studies published since then.

Chronic inducible urticarias

Chronic inducible urticarias (CIndUs) are a subgroup of chronic urticaria, a group of diseases characterized by the recurrence of itchy wheals and/or angio-edema for longer than 6 weeks (Table 1, (2)). Most CIndUs present with wheals, angio-edema, or both. Within the group of CIndU, symptomatic dermographism / urticaria factitia, cold and heat urticarias, delayed pressure urticaria, solar urticaria, and vibratory angioedema are defined as physical urticarias. Non-physical CIndUs include cholinergic urticaria, contact urticaria and aquagenic urticaria. CIndUs, in contrast to chronic spontaneous urticaria (CSU), are characterized by the need for specific triggers for wheals, angioedema or both of these symptoms to develop. Wheals and angio-edema in CIndU patients develop only and reproducibly in response to the trigger stimulus that is specific for their condition (e.g. cold exposure in cold urticaria). CIndU signs and symptoms are usually confined to skin areas that are exposed to the specific trigger. Individual patients may exhibit two or more CIndUs, and in rare cases, two or more concurrent triggers are needed to produce urticarial signs and symptoms. It is important to accurately

identify and characterize the eliciting trigger and individual trigger thresholds and to distinguish CIndUs from CSU (Table 1). Cholinergic urticaria, contact urticaria and aquagenic urticaria, in contrast to physical urticarias, are not triggered by a physical factor, but by active and passive warming, in the case of cholinergic urticaria and by skin contact with wheal/angioedema-inducing substances and water in contact urticarial and aquagenic urticaria, respectively. Rare variants and atypical forms of CIndU exist but are not included in this set of recommendations. CIndUs are diagnosed based on the patient history and the results of provocation testing. In all patients with a history suggestive of CIndU, provocation testing should be performed if possible to confirm the diagnosis. Patients with severe CIndU may develop systemic signs and symptoms during provocation testing. These can range from dizziness, vertigo, vomiting/diarrhea, and wheezing up to anaphylactic shock. As a consequence, provocation testing in CIndU patients should be done only by physicians trained and experienced in the emergency treatment of allergic responses and where facilities for emergency treatment are available.

Since CIndU patients may exhibit more than one subtype of urticaria, all CIndU triggers suspected to be relevant (e.g. heat, cold, UV, pressure, vibration, stroking, exercise) should be tested. In patients with CIndU who also exhibit CSU, the latter should be diagnosed and managed as recommended by the current version of the international guideline (2). Similar to CSU (3, 4), CIndUs can cause severe quality of life impairment, and CIndUs may have important occupational and employment implications.

General recommendations for the diagnostic workup in CIndU patients

The diagnosis of CIndU relies on a thorough history and provocation testing. Although the eliciting triggers of inducible urticarias can usually be identified, their underlying causes are unknown (except contact urticaria). Differential diagnoses such as autoinflammatory disorders and bradykinin-mediated angioedema can usually be ruled out from the history (5). The

diagnostic workup in CIndU is, therefore, aimed at confirming the diagnosis and assessing disease activity. The results of provocation testing are influenced by a number of factors including patients' treatment. As a consequence, symptomatic treatment should be discontinued prior to testing if possible. Antihistamines should be stopped at least 3 days before testing (allowing 5 plasma half-lives of drug elimination) and glucocorticosteroids 7 days before testing. Some patients may not tolerate stopping treatment before provocation testing and, in these, provocation responses must be interpreted with caution.

The aims of provocation testing are to 1. determine the relevant trigger(s) in individual patients and 2. assess trigger thresholds. Trigger threshold measurements are useful for counseling patients on the avoidance of relevant triggers as well as for measuring and monitoring treatment responses. Testing of provocation triggers and thresholds should, therefore, be done before and during therapy. Repeated provocation tests can help to optimize treatment. Testing should be done at skin sites that were not affected by urticaria in the last 24 hours. This is because such skin sites may exhibit unresponsiveness during a refractory period after urticarial reactions. In patients with cholinergic urticaria, provocation testing should be done after at least 24 hours of absence of symptoms. Provocation tests in physical urticaria should be performed at the recommended skin sites (see below and Figure 1). This allows for comparing test results with those in other patients and published results. In patients with negative provocation responses but a strong suspicion of CIndU from the history, the test should be repeated. In such cases, skin sites which, according to the patient, have previously but not recently (within the last three days) been affected, should be used, and patients should be reassessed for the use of any medication that may suppress test reactions. In some patients with CIndU, the diagnosis cannot be confirmed by standard provocation testing although the clinical history is highly suggestive. Usually, provocation testing, in positive patients, results in the rapid development of urticarial reactions. In cold urticaria and symptomatic dermographism, for example, wheals usually develop within minutes after provocation. An exception to this rule is the onset of positive test

responses in delayed pressure urticaria. Here, it is necessary to wait for several hours, and it may, therefore, be advisable to rely on patients to report positive provocation test response.

General recommendations for the management of CIndUs

Activation of skin mast cells with release of histamine and other proinflammatory mediators leads to the signs and symptoms of CIndUs. In CSU, underlying causes of mast cell activation include autoreactivity (including functional autoantibodies), infectious diseases, and food or drug intolerance (2). In contrast, the underlying causes of CIndUs remain to be identified. As diagnostic measures do not reveal underlying causes or lead to specific therapeutic options, the diagnostic workup in CIndU should be limited to confirmation of the diagnosis and the assessment of disease activity by assessing trigger thresholds, where possible. The therapy should focus on the avoidance of the trigger factor and symptomatic treatment with the goal of reaching complete symptom control and the prevention of CIndU signs and sysmptoms

Symptomatic treatment of CIndU targets mast cells, either by inhibition of mast cell activation (e.g. omalizumab, ciclosporin) or by blocking mast cell mediators (e.g. H1 antihistamines, leukotriene receptor antagonists). As only very few studies on the treatment of most subtypes of CIndU have been performed in the last decades, symptomatic therapy schemes are often adopted from the study results and guideline recommendations for CSU (2). Interestingly, some CIndUs can be treated by desensitization to triggers. This phenomenon has been described for cold urticaria (6, 7), heat urticaria (8), and solar urticaria (9). Although CIndU can present with a very chronic course (Table 2), with rare exceptions, CIndU patients experience spontaneous remission.

To identify effective treatment options for CIndUs, we performed a MEDLINE search and complemented the results by documenting additional published evidence known to us (Table 3). For our MEDLINE search (pubmed.com), the first search strategy was to search for the

established terms for the CIndU subtypes combined with the limitation "Controlled Clinical Trial". The second search strategy was to search for the established terms for the CIndU subtypes combined with the term "treatment". The third search strategy was to search for the established terms combined with the individual terms for certain medical interventions, e.g. "PUVA", "antihistamines", or "cetirizine". Only studies/reports on treatment approaches that are applicable and appropriate nowadays and which showed predominantly a benefit for the patients were included. Evidence levels (EL) assigned to treatment options on the basis of the evidence identified are A for double blind controlled trials, B for case series with more than five patients per treatment option, and C for case reports and case series of five or less than five patients, and 0 for no published evidence (adopted from the GRADE, Grading of Recommendations, Assessment, Development and Evaluation, categorization of ELs). In addition, we designated selected treatment options as "recommended best practice" , based on our clinical experience.

Symptomatic dermographism

Symptomatic dermographism (SD, Syn. urticaria factitia, dermographic urticaria), the most common physical urticaria (Table 2), is characterized by itching and/or burning skin and the development of itchy wheals (and in rare cases angio-edema) due to shearing forces on the skin, which may be brought about during rubbing, scratching or scrubbing (Table 2). SD should be differentiated from simple dermographism, where whealing, but not pruritus, occurs after firm stroking of the skin (10-12). Other types of dermographism such as white dermographism (in atopic patients) are unrelated to SD.

For the diagnosis of SD, a smooth blunt object (closed ball pen or a wooden spatula) should be held perpendicular to the skin and used to apply a light stroking pressure on the volar forearm or upper back. The skin at the test site should be unbroken and free of obvious signs of infection or inflammation. A response is considered positive if a pruritic palpable wheal is present within

10 minutes of provocation. A wheal response without itch indicates simple dermographism (a common physiological variant).

A calibrated dermographometer is commercially available (HTZ Limited, New Addington, UK). It has a spring-loaded smooth steel tip of 2.3 mm in diameter. The pressure on the tip can be varied by turning a furled head at the top of the instrument. The scale settings from 0 to 15 are equivalent to a range of tip pressures from approximately 20 to 160 g/mm^2 (196-1569 kPa). The tool needs to be calibrated before its use in the clinical setting to adjust the applied pressure to the desired values. The development of a pruritic palpable wheal to applied pressure of less than 36g/mm^2 is considered diagnostic of symptomatic dermographism. The tool´s adjustability allows for determining the patient's trigger threshold (10, 13). Recently, a simplified dermographographic tester was developed (14). This instrument (FricTest®; Moxie, Berlin, Germany) consists of a disinfectable plastic comb with four tips (which are 3.0, 3.5, 4.0 and 4.5 mm in length, respectively), which apply graded shearing forces to the skin, thus allowing for the determination of the trigger threshold. Each tip is 3 mm in diameter and has a slightly rounded end to minimize traumatization of the skin. To obtain a response, the instrument is placed vertically so that the tips are touching the skin, and then stroked once from across the width of the volar surface of the forearm for a distance of approximately 60 mm. A response to dermographic testing is considered positive if a pruritic palpable wheal of ≥ 3 mm width is present within 10 min of provocation.

In addition to trigger avoidance, the first line therapy for SD is a non-sedating second-generation H1-antihistamine at the licensed dose (evidence level A, recommended best practice). In patients who do not obtain complete control with this treatment, increasing the dose up to four times is recommended (evidence level 0, recommended best practice) (2, 15, 16). Third line treatment options include omalizumab (evidence level B, recommended best practice) (2, 17, 18) and ciclosporin (evidence level B) (19). Photo- and photochemotherapy (evidence level B) has also been reported to be effective (20-24).

Cold urticaria

Cold urticaria (ColdU, Syn. acquired cold urticaria or cold contact urticaria) is defined by the appearance of wheals after contact cooling and rewarming of the skin (Table 1) (12, 25, 26). ColdU is the second most common form of physical urticaria. Its estimated annual incidence is 0.05% (27). ColdU often develops in young adults. Women show a slightly higher prevalence (28). Symptoms typically occur within minutes after skin contact with cold air, liquids or solid objects and persist for an hour (25, 29, 30). Severe cases may show systemic involvement including anaphylaxis (31). ColdU is often of long disease duration, reportedly 4.8 to 7.9 years (27, 28, 32).

Provocation tests should be performed by applying a cold stimulus to forearm skin. Cold provocation methods include the traditional ice cube test, testing with cool packs or cold water baths, and TempTest® measurements (Fig. 1). If an ice cube is used for testing, it should be melting within a thin plastic bag to avoid cold damage of the skin and to prevent direct water contact to avoid confusion with aquagenic urticaria if the test is positive (33). The use of cold water baths requires special care, because this method carries a risk of inducing systemic reactions. TempTest® is a Peltier element-based provocation device. The TempTest® 4.0 model (Courage & Khazaka, Köln, Germany) has a single Peltier element (length: 350 mm, width: 2 mm) that provides a continuous temperature gradient along its length (from 4°C to 44°C) (34). The use of TempTest® allows for reproducible and standardized cold (and heat) provocation tests and the identification of temperature and stimulation time thresholds (34, 35). Cold provocation testing should be performed for 5 minutes. In some patients shorter or longer provocation times may be appropriate, e.g. 30 seconds (in patients who are very sensitive and/or afraid of massive reactions) or up to 20 minutes in patients with a positive history but no wheal after standard testing (32, 36, 37). Alternative test methods may be required in patients with a

negative ice cube test, e.g. an arm can be immersed in cold water at 5–10°C for 10 minutes. Test sites should be inspected and test responses should be assessed 10 minutes after the end of provocation testing. The test should be considered positive if the test site shows a palpable and clearly visible wheal and flare type skin reaction. This reaction is, in most cases, associated with itch and/or a burning sensation.

In patients who show a positive test reaction, threshold testing should be performed if possible. Threshold testing is done to determine the stimulation time threshold or the temperature threshold. The stimulation time threshold (32) is the shortest duration of cold exposure sufficient to induce a positive test reaction. Stimulation time thresholds are determined by varying the time of cold application needed to induce a wheal and flare type skin response. Stimulation time threshold tests can be done with an ice cube or TempTest® (Fig. 1). Ice cube stimulation time thresholds of ≤ 3 minutes are associated with higher disease activity (32). The temperature threshold of ColdU patients, i.e. the highest temperature sufficient to induce a positive test reaction, can be assessed with TempTest®, but not by ice cube testing. Temperature thresholds should be determined whenever TempTest® is available, as this information can help patients to avoid risky situations in their daily lives. Temperature threshold measurements are useful for assessing disease severity and activity as well as the efficacy of therapy (38).

The underlying causes of ColdU are currently unknown. Targeted causal treatment is, therefore, not possible. Antibiotic treatment with doxycycline or penicillin for several weeks can induce remission in some patients (27, 39). All patients need to be counselled to avoid prolonged skin contact with objects that are below their threshold temperatures.

The first line symptomatic treatment is a non-sedating H1 antihistamine (evidence level A, best practice recommendation). This recommendation is supported by several controlled studies (40-42). In many patients, however, a standard dosed antihistamine does not provide complete protection, even when used every day. High doses of H1-antihistamines are more effective in ColdU than standard-doses (43-47) and should be tried in patients who do not respond to a

standard dosed antihistamine (evidence level A, best practice recommendation). Treatment options for antihistamine-resistant ColdU patients include omalizumab treatment (evidence level B, best practice recommendation) (18, 48-50) and cold desensitization (evidence level B) (6, 7, 51). Desensitization, i.e. the reduction of skin sensitivity to cold by repeated cold exposure, has been reported to protect from symptom development. However, this treatment can induce anaphylactic shock during induction and should, therefore, only be performed under expert physician supervision (51), and maintenance of tolerance requires daily cold showers. The compliance to proceed with the therapy in a home setting is poor (52). Anakinra (anti-IL-1) and etanercept (TNF inhibitor) reportedly showed beneficial responses in selected cases (evidence level C) (53, 54).

Heat urticaria

Heat urticaria (Syn. heat contact urticaria) is an exceptionally rare physical urticaria defined by the appearance of wheals after contact heating of the skin within minutes of exposure (Table 1) (55, 56). Heat urticaria must be differentiated from cholinergic urticaria and from solar urticaria. Provocation testing should be performed by applying a hot stimulus to the skin of the volar forearm. Heat provocation methods that can be used for skin testing include testing with metal/glass cylinders filled with hot water, hot water baths, or TempTest® measurements (Fig. 1). Heat should be applied for 5 min at temperatures of up to 44°C. In some patients shorter or longer provocation times and higher temperatures may be appropriate. Test sites should be inspected and test responses should be assessed 10 min after provocation testing. The test is considered positive if the test site shows a palpable and clearly visible wheal and flare type skin reaction. This reaction is, in most cases, accompanied by itch and/or associated with a burning sensation. In patients who show a positive test reaction, stimulation time and/or temperature thresholds should be determined. This helps to determine the disease activity and to assessing

the response to therapy. Treatment options for heat urticaria are limited. Non-sedating antihistamines, alone or in combination with an H2 blocker, have been reported to be effective (evidence level C, best practice recommendation) (57, 58). Some case reports suggest that omalizumab may be beneficial in difficult to treat patients (evidence level C, best practice recommendation) (59, 60).

Delayed pressure urticaria

Delayed pressure urticaria (DPU) is defined by the appearance of a skin swelling response after the application of a sustained pressure stimulus to the skin (Table 1) (61-63). Like other CIndUs, DPU may occur with other forms of chronic urticaria, including spontaneous disease (64). Responses occur between 30 minutes and 12 hours (usually 6-8 hours) after exposure to pressure and may last up to 72 h. The principle of testing is the application of sustained pressure to the skin. Test methods include the suspension of weights over the shoulder (7 kg on a 3 cm shoulder strap), the application of rods, lowered vertically onto the skin and supported in a frame, on the back, the thigh, or the forearm, and the use of a dermographometer. The latter two methods allow for reproducible measurements and the assessment of thresholds.

In the literature, the use of many different rod diameters and weights (with a wide range of pressures applied to the patient) is reported. Lawlor and coworkers, for example, used a rod of 1.5 cm diameter with weights of 2.29 kg (127 kPa) to 4.79 kg (266 kPa) for up to 15 min on the back (62). Barlow used rods that were 1.5 cm in diameter and weights of 2.5 kg (139 kPa) and 3.5 kg (194 kPa) resting on the anterior thighs for 20 minutes (64). The 5 kg rod used at the Charité Hospital on the patient's forearms for 15 minutes measures 5.5 cm in diameter (20.7 kPa). When testing with the dermographometer, the device should be applied perpendicularly at 100 g/mm^2 (981 kPa) for 70 seconds on the upper back.

The test should be considered positive if the test site shows a delayed red palpable swelling. Test sites should be inspected and test responses should be assessed (by the patient or physician) approximately 6 hours after the end of provocation testing. The reaction is not usually associated with pruritus, but may be accompanied by a burning/painful sensation. DPU must be differentiated from symptomatic dermographism, which is immediate. Threshold testing should be performed in patients who show a positive test reaction. Threshold testing may allow the physician to assess disease activity and treatment responses.

DPU patients are advised to avoid static pressure, for instance by wearing soft shoes and tight clothing. Patients should understand that pressure is dependent on the weight encountered as well as the contact surface: When the weight force cannot be reduced, the contact area should be maximised. Recommended treatment regimens include non-sedating H1-antihistamines (evidence level B, best practice recommendation). The use of higher than standard doses is often needed and recommended in patients who do not show improvement with standard doses of antihistamines (evidence level 0, best practice recommendation). Other possible treatment options include dapsone (evidence level B) (65), sulfasalazine (evidence level B) (66, 67), omalizumab (evidence level B, best practice recommendation) (18, 68, 69), anti-TNF (evidence level C) (70), theophylline (evidence level C) (71) or the combination of antihistamines and montelukast (evidence level A) (72-74).

Solar urticaria

Solar urticaria (SolU) is defined by the appearance of a whealing response within minutes of exposure to sunlight (Table 1) (75, 76). A diagnosis of SolU is made based on history and provocation phototest results. Provocation testing should be performed by exposure to ultraviolet radiation and visible light. The use of sunscreens and photoactive medications should be avoided before phototesting. Solar simulators with filters (UV-A and UV-B) or monochromator (UV-A and UV-B, visible light) should be used for provocation. Provocation

should be done on the buttocks separately in the UV-A, broad band UV-B wavelength spectra and visible light range. UV-A should be tested on small tests areas at 6 J/cm^2 and UV-B at 60 mJ/cm^2. In patients with a negative reaction, photosensitivity to visible light can be tested by using a projector (e.g. slide projector) at a distance of 10 cm. In SolU patients, provocation leads to a rapid urticarial response at the site of exposure within 10 min (Fig. 1). The test should be considered positive if the test site shows a palpable and clearly visible wheal and flare reaction. Wheals elicited by provocation are itchy and/or associated with a burning sensation.

In patients with a positive test reaction, threshold testing should be performed by varying the dose of the radiation, e.g. by changing the time of exposure to the standard light source. This threshold testing (i.e. a minimal urticarial dose of an appropriate wavelength radiation) may allow for the determination of disease activity and response to therapy.

All SolU patients should avoid the sun, wear protective clothing or use high protection sunscreens, especially when the threshold is in the ultraviolet spectrum, and treat with non-sedating H1 antihistamines (evidence level A, best practice recommendation) (77). Tolerance to UV light can be achieved by desensitization (evidence level B) (78, 79). Omalizumab (evidence level C) (18, 76, 80, 81), intravenous immunoglobulin treatment (evidence level B) (82-85) and ciclosporin (evidence level C) (86) have been reported to be beneficial in some patients, but not in others (84, 85, 87-90). Afamelanotide, an alpha-MSH analogue and melanocortin receptor agonist, also reportedly protects SolU patients from the development of signs and symptoms (evidence level B) (91).

Vibratory angio-edema

Vibratory urticaria/angio-edema is defined by the presence of itching and swelling within minutes at the site of skin exposure to vibration (Table 2) (92, 93). For diagnostic purposes, vibratory angio-edema can be reproduced using a laboratory vortex mixer. The forearm is held on a flat plate laid on the vortex mixer which is run between 780 rpm (92) to 1380 rpm (94) for

5 minutes. The site of application should be assessed for swelling 10 minutes after testing (Fig. 1). Measurement of the circumference of the arm before and after the challenge at 3 points (wrist, mid-forearm, and elbow) can help to define a vibration-induced swelling.

Vibratory angio-edema is a very rare condition and no information on demographics is available. Only a few case reports on treatments are available. Beyond the avoidance of exposure to vibratory stimulation, some authors describe H1 antihistamines as effective treatment options (evidence level C, best practice recommendation). Omalizumab treatment failed to improve vibratory angio-edema in one case report (95).

Cholinergic urticaria

Cholinergic urticaria (CholU) is defined by itching, redness and papular whealing induced by exercise and passive warming (e.g. hot bath). In some patients, emotional stress and hot and spicy food or beverages can also elicit symptoms. A typical description is one of tiny short-lived wheals with a pronounced flare reaction that is frequently localised to the trunk and limbs (96-101). Usually, skin lesions last for 15 to 60 minutes. Other morphological patterns, including angio-edema, can occur. CholU must be differentiated from exercise-induced anaphylaxis, which is an anaphylactic reaction induced by physical activity only (102). Exercise induced anaphylaxis can be food or drug dependent. In exercise induced anaphylaxis, the skin symptoms usually start with distal pruritus (palmar, plantar, ears) followed by flushing and an erythematous or urticarial rash with large lesions. In contrast, CholU usually starts with small wheals, which may later converge.

Provocation testing should be performed to confirm CholU and to rule out exercise-induced anaphylaxis. Caution is advised in patients with pre-existing cardiac conditions. Pretesting examination should be done to record pre-existing skin lesions (e.g. acne papules), which may make assessment more difficult and can be marked with a pen before provocation to identify them. Moderate physical exercise appropriate to the patient's age and general condition should

be undertaken (e.g. on a treadmill or stationary bicycle). Exercise should be performed to the point of sweating and up to 15 minutes beyond or the onset of symptoms. Wearing warm clothing in a warm room facilitates the provocation tests. The test is positive if exercise challenge leads to the typical rash over 10 minutes. If the exercise provocation test is positive, a passive warming test should be done (at least 24h later, 42°C full bath for up to 15 minutes, body temperature should increase by ≥1.0°C) to exclude exercise induced anaphylaxis. Recently, a standardized protocol for diagnosing and measuring trigger thresholds using pulse-controlled ergometry has been published (103). For this pulse-controlled ergometry test, patients are seated on the bicycle ergometer and instructed to cycle in a pulse controlled manner, i.e. to speed up or slow down their pedalling speed to achieve an increase in pulse rate of 15 beats per minute every 5min to a final maximum increase of 90 beats per minute above the starting level at 30 min. Time to whealing correlates to disease severity, in other words: the sooner wheals appear, the more active the CholU.

In severely affected CholU patients, the avoidance of overheating is essential, but almost impossible. Thus, symptomatic treatment is the first choice therapy of CholU. Non-sedating H1 antihistamines (evidence level A, best practice recommendation) (104, 105) and updosing in non responders (evidence level 0, best practice recommendation) are effective in many patients, and there are reports on the efficacy of omalizumab (evidence level B, best practice recommendation) (106, 107), scopolamine butylbromide (evidence level C) (108), methantheliniumbromide (evidence level C) (109), combinations of propanolol, antihistamines and montelukast (evidence level C) (110) and treatments and injections with botulinum toxin (evidence level C) (111). Desensitization protocols involving regular physical exercise (evidence level B) or treatment with autologous sweat have been described in some patients (112, 113). High doses of danazol (600mg daily) were reported to be effective. However, the side effect profile of danazol restricts its use (evidence level A, no recommendation) (114-116) and dosing should be minimized.

Aquagenic urticaria

Aquagenic urticaria is a rare form of CIndU, in which contact with any source of water - regardless of its temperature- evokes wheals. Within 30 minutes after contact to water, patients develop urticarial lesions, mostly 1 to 2 mm in size. Most cases are sporadic, although familial incidence has also been reported (117, 118). Systemic symptoms are rare but have been described (119, 120). Aquagenic urticaria is sometimes associated with forms of physical urticaria. The pathomechanism remains unclear, however there is some evidence that water acts as a carrier for an epidermal antigen (121). The condition must be differentiated from aquagenic pruritus, cholinergic urticaria, cold urticaria and heat urticaria. These differential diagnoses should be ruled out before testing for aquagenic urticaria. For diagnosis of aquagenic urticaria, a compress or a towel soaked with 35-37 ^{o}C water or physiological saline is placed on the patient´s trunk. The compress or the towel can be taken off after 40 mins or earlier, if the patient reports pruritus and first wheals are seen at the skin test site. The test is positive if urticarial lesions develop inside the contact area within 10 mins after taking off the compress/towel. Antihistamines are described as being effective in some patients (evidence level C, best practice recommendation) (122, 123). In other patients a combination with UV therapy provided benefit (evidence level C) (124, 125). A special barrier cream was reported to be effective (evidence level C) (126).

Contact urticaria

Contact urticaria is defined by the development of urticarial lesions within minutes (usually within 30 minutes) after contact to an exogeneous agent. Contact Urticaria is one of the cutaneous manifestations of the Contact Urticaria Syndrome which can manifest as contact weals, systemic involvement and even anaphylaxis (127). Contact urticaria is divided into non-immunologic (NICU) and immunologic contact urticaria (ICU), indeterminate if the

mechanism is unclear. NICU can occur at the very first contact to the eliciting agent such as plants (e.g. stinging nettle), animals (e.g. jelly fish) or chemicals (e.g. cinnamon aldehyde) (128-132). NICU lesions are strictly limited to the areas where the eliciting agent came in contact to the skin. ICU, in contrast, is an IgE-mediated reaction to proteins or hapten forming molecules, and the reaction can spread beyond the area of contact into generalized urticaria, and even evolving into systemic symptoms (133-135). One of the most common eliciting agents in ICU used to be latex, but reactions to plants or plant products, animal products, drugs, cosmetics, and chemicals are also frequently described. ICU elicited by foods or plants may also lead to signs and symptoms in the oral cavity when ingested (136).

After a thorough history, provocation testing should be performed to confirm NICU and ICU, using open controlled application testing, skin prick test or closed patch tests for 20 min. No tests are necessary, when the eliciting agent is obvious, e.g. stinging nettles or jellyfish. ICU diagnostics should be completed by determination of specific IgE, if available. Avoidance of the eliciting agent is often possible and antihistamines can help to prevent and decrease contact urticaria symptoms. Occupational ICU should be managed as other occupational skin diseases, by eliminating the allergen from the direct work environment and other measures to reduce levels of allergen exposure (137, 138).

Areas in need of further research

The following issues require further studies and research. 1. The underlying causes of CIndU with the exception of contact urticaria remain unknown. Further studies are needed to better characterize the etiology and pathogenesis of CIndU. 2. The prevalence and incidence of CIndU need to be investigated and, since regional geographical differences are to be expected, this should be a global effort. 3. Despite the current improvement of diagnostic tools and test protocols for some CIndUs, e.g. cholinergic urticaria (103), further efforts are required to standardize and harmonize test protocols and to develop better tools for threshold testing in all

CIndUs. 4. Specific quality of life instruments for cold urticaria, symptomatic dermographism and cholinergic urticaria are under development, but tools for the other CIndUs are missing and should be developed.

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Statement of contribution

All authors have contributed to the development of this position paper and manuscript.

Table 1 Classification of urticarias

Chronic Urticaria Subtypes	
Chronic Spontaneous Urticaria	**Chronic Inducible Urticaria**
Spontaneous appearance of itchy wheals, angio-edema, or both ≥6 weeks due to known* or unknown causes	**Physical urticaria** Symptomatic dermographism[1] Cold urticaria[2] Delayed pressure urticarias[3] Heat urticaria[4] Vibratory angio-edema **Other inducible urticaria** Cholinergic urticaria Contact urticaria Aquagenic urticaria

*For example, autoreactivity, that is, the presence of histamine-releasing autoantibodies; [1]also called urticaria factitia, dermographic urticaria; [2]also called cold contact urticaria; [3]also called pressure urticaria; [4]also called heat contact urticaria.

Table 2 Definition, frequency and duration of CIndUs

	Definition	Frequency*	Duration*
Symptomatic Dermographism	Itching and/or burning skin and the development of strip-shaped wheals due to shear force acting on the skin	1 to 5% in the general population (10, 139-141)	6.5 years with a great variance (142-144)
Cold Urticaria	Itchy wheals or angio-edema after cold exposure of the skin	Up to one third of all PhysU cases (145)	4.8 to 7.9 years (27, 28, 32)
Heat Urticaria	Itchy wheals after heat exposure of the skin	Very rare, no data available	Very rare, no data available
Delayed Pressure Urticaria	Erythematous skin swelling after the application of sustained pressure	37% of pts with CSU (64) but rare as a primary inducible urticaria	6 to 9 years (142, 146, 147)
Solar urticaria	Itchy wheals that occur after light (UV and/or visible light) exposure	Rare in general population, 0.08% of pts with CSU (75), 18% of patients who consult a hospital because of sun-light related skin problems(147)	3 to 6 years (148)(149)(150)
Vibratory angioedema	Cutaneous swellings immediately after exposure to vibration	Very rare, no data available	Very rare, no data available
Cholinergic Urticaria	Itchy wheals after active or passive warming	4-11.2% of population (151-153)	4 to 7.5 years (154, 155)
Aquagenic urticaria	Itchy wheals or angio-edema after skin contact with water	Very rare, no data available	Very rare, no data available
Contact Urticaria	Itchy wheals or angioedema after contact with eliciting agent	Variable, depending on elicitor	Variable, depending on elicitor

*For most CIndUs, no reliable data on prevalence, incidence and duration are available. The data presented is largely based on obeservational studies in small, preselected populations rather than from well designed epidemiological studies.

Table 3 Evidence table for treatment options for CIndUs

	Double-blind controlled trials	Case series or uncontrolled studies with >5 pts	Case reports or small case series
Symptomatic Dermographism	**Antihistamine:** -Acrivastine versus terfenadine in the treatment of symptomatic dermographism--a double-blind, placebo-controlled study. Boyle J, Marks P, Gibson JR. J Int Med Res. 1989;17 Suppl 2:9B-13B. -Prevention of signs and symptoms of dermographic urticaria by single-dose ebastine 20 mg. Magerl M, Schmolke J, Metz M, Zuberbier T, Siebenhaar F, Maurer M. Clin Exp Dermatol. 2009 Jul;34(5):e137-40 -The effect of cetirizine on symptoms and wealing in dermographic urticaria. Sharpe GR, Shuster S. Br J Dermatol. 1993 Nov;129(5):580-3 -[Effect of ketotifen in urticaria factitia and urticaria cholinergica in a crossover double-blind trial]. Cap JP, Schwanitz HJ, Czarnetzki BM. Hautarzt. 1985 Sep;36(9):509-11 -Symptomatic dermographism: natural history, clinical features laboratory investigations and response to therapy. Breathnach SM, Allen R, Ward AM, Greaves MW. Clin Exp Dermatol. 1983 Sep;8(5):463-76.	**Antihistamine:** -The effect of H1 and H2 histamine antagonists on symptomatic dermographism. Matthews CN, Boss JM, Warin RP, Storari F. Br J Dermatol. 1979 Jul;101(1):57-61. **Phototherapy:** -Narrowband ultraviolet B phototherapy is beneficial in antihistamine-resistant symptomatic dermographism: a pilot study. Borzova E, Rutherford A, Konstantinou GN, Leslie KS, Grattan CE. J Am Acad Dermatol. 2008 Nov;59(5):752-7. -UVB treatment of factitious urticaria. Johnsson M, Falk ES, Volden G. Photodermatol. 1987 Dec;4(6):302-4. -The effect of psoralen photochemotherapy (PUVA) on symptomatic dermographism. Logan RA, O'Brien TJ, Greaves MW. Clin Exp Dermatol. 1989 Jan;14(1):25-8. **Ciclosporin**: -Six cases of antihistamine-resistant dermographic urticaria treated with oral ciclosporin. Toda S, Takahagi S, Mihara S, Hide M. Allergol Int. 2011 Dec;60(4):547-50 **Omalizumab:** - Omalizumab is an effective and rapidly acting therapy in difficult-to-treat chronic urticaria: a retrospective clinical analysis. Metz, M., Ohanyan, T., Church, M. K., and Maurer, M.: J. Dermatol. Sci. 2014: 73; 57-62 **Others:** -Efficacy of H, antihistamine, corticosteroids and cyclophosphamide in the treatment of chronic dermographic urticaria. Kumar R, Verma KK, Pasricha JS. Indian J Dermatol Venereol Leprol. 2002 Mar-Apr;68(2):88-91	**Omalizumab**: -Anti-immunoglobulin E treatment of patients with recalcitrant physical urticaria. Metz M, Altrichter S, Ardelean E, Kessler B, Krause K, Magerl M, Siebenhaar F, Weller K, Zuberbier T, Maurer M. Int Arch Allergy Immunol. 2011;154(2):177-80 -Antihistamine-resistant urticaria factitia successfully treated with anti-immunoglobulin E therapy. Krause K, Ardelean E, Kessler B, Magerl M, Metz M, Siebenhaar F, Weller K, Worm M, Zuberbier T, Maurer M. Allergy. 2010 Nov;65(11):1494-5 - Retreatment with omalizumab results in rapid remission in chronic spontaneous and inducible urticaria. Metz, M., Ohanyan, T., Church, M. K., and Maurer, M.: JAMA Derm. 2014: 150; 288-290.
Cold Urticaria	**Antihistamine:** -Rupatadine 20 mg and 40 mg are Effective in Reducing the Symptoms of Chronic Cold Urticaria. Abajian M, Curto-Barredo L, Krause K, Santamaria E, Izquierdo I, Church MK,	**Omalizumab:** -Real-life experiences with omalizumab for the treatment of chronic urticaria. Sussman G, Hébert J, Barron C, Bian J, Caron-Guay RM, Laflamme S, Stern S.	**Omalizumab:** -Effective treatment of idiopathic chronic cold urticaria with omalizumab: report of 3 cases. Le Moing A, Bécourt C, Pape E, Dejobert Y, Delaporte E, Staumont-Sallé D.

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Delayed Pressure Urticaria	**Antihistamine and/or Leukotriene antagonist:** - Desloratadine in combination with montelukast suppresses the dermographometer challenge test papule, and is effective in the treatment of delayed pressure urticaria: a randomized, double-blind, placebo-controlled study. Nettis E, Colanardi MC, Soccio AL, Ferrannini A, Vacca A. Br J Dermatol. 2006 Dec;155(6):1279-82. - Efficacy of montelukast, in combination with loratadine, in the treatment of delayed pressure urticaria. Nettis E, Pannofino A, Cavallo E, Ferrannini A, Tursi A. J Allergy Clin Immunol. 2003 Jul;112(1):212-3 -Comparison of oxatomide and clemastine in the treatment of chronic urticaria. A double blind study. Beck HI, Cramers M, Herlin T, Søndergaard I, Zachariae H. Dermatologica. 1985;171(1):49-51.	**Omalizumab** - Omalizumab is an effective and rapidly acting therapy in difficult-to-treat chronic urticaria: a retrospective clinical analysis. Metz, M., Ohanyan, T., Church, M. K., and Maurer, M.: J. Dermatol. Sci. 2014: 73; 57-62 **Others**: -Delayed pressure urticaria: response to treatment with sulfasalazine in a case series of seventeen patients. Swerlick RA, Puhar N. Dermatol Ther. 2015 -Theophylline as "add-on" therapy in patients with delayed pressure urticaria: a prospective self-controlled study. Kalogeromitros D, Kempuraj D, Katsarou-Katsari A, Gregoriou S, Makris M, Boucher W, Theoharides TC. Int J Immunopathol Pharmacol. 2005 Jul-Sep;18(3):595-602.	**Omalizumab**: - Successful treatment of severe delayed pressure angio-oedema with omalizumab. Rodríguez-Rodríguez M, Antolin-Amerigo D, Barbarroja-Escudero J, Sánchez-González MJ, Alvarez-Mon M. Allergol Immunopathol (Madr). 2014 Jan-Feb;42(1):78-80 - Anti-immunoglobulin E treatment of patients with recalcitrant physical urticaria. Metz M, Altrichter S, Ardelean E, Kessler B, Krause K, Magerl M, Siebenhaar F, Weller K, Zuberbier T, Maurer M. Int Arch Allergy Immunol. 2011;154(2):177-80 - Efficacy of omalizumab in delayed pressure urticaria: a case report. Bindslev-Jensen C, Skov PS. Allergy. 2010 Jan;65(1):138-9 **Others**:

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Contact urticaria	Not applicable	Not applicable	Not applicable

Patient information

Name:

Date of birth:

Abbreviations: W = Wheal
E = Erythema
A = Angio-edema
I = Itch

Document skin reaction with + or -

Provocation tests for inducible urticaria

Symptomatic dermographism (Urticaria factitia)

Testsite: Volar forearm or Upper back
Test: Moderate stroking of the skin with a blunt smooth object (e.g. closed ballpoint pen tip, wooden spatula), dermographic tester (36 g/mm^2), or Fric*Test* (longest pin)
Reading time: 10 minutes after testing

W	I

Date / Time _____ Test done by _____

Positive test = wheal & itch: Test trigger strength threshold →

Cold urticaria

Testsite: Volar forearm
Test: Melting ice cube in thin plastic bag, Temp*Test (*4-44ºC) for 5 minutes
Reading times: 10 minutes after testing

W

Date / Time _____ Test done by _____

Positive test = wheal: Test temperature threshold →

Heat urticaria

Testsite: Volar forearm
Test: Heat source, Temp*Test (*44-4 °C) for 5 minutes
Reading times: 10 minutes after testing

W

Date / Time _____ Test done by _____

Positive test = wheal: Test temperature threshold →

Delayed pressure urticaria

Testsite: Shoulder or Upper Back or Thighs or Volar forearm
Test: Suspension of weights over shoulder (7 kg, shoulder strap width: 3 cm) for 15 min or weighted rods (1.5 cm diameter: 2.5 kg; or 6.5 cm diameter: 5 kg) for 15 min. Dermographic tester at 100 g/mm^2 for 70 sec
Reading times: ≈6 hours after testing

A	E

Date / Time _____ Test done by _____

Positive test = angioedema & erythema: Test trigger strength threshold →

Solar urticaria

Testsite: Buttocks
Test: UVA 6 J/cm^2 & UVB 60 mJ/cm^2 (e. g. Saalmann Multitester SBC LT 400) & visible light (projector)
Reading times: 10 min after testing

	W
UVA	
UVB	
Visible light	

Date / Time _____ Test done by _____

Positive test = wheal: Test trigger strength threshold (UVA / UVB) →

Vibratory urticaria / angio-edema

Testsite: Volar forearm
Test: Vortex vibrator for 5 minutes, 1000 rpm
Reading times: 10 minutes after testing

A	W

Date / Time _____ Test done by _____

Positive test = angio-edema or wheal

Cholinergic Urticaria

Test 1: Exercise machine, e.g. bicycle trainer or treadmill. Exercise for 30 min, increase pulse rate by 3 beats/min every minute, **positive test = wheals. If positive, wait > 24 hours and perform**
Test 2: 42 ºC bath, monitor body temperature. Continue bath for 15 min after body temperature has increased by ≥ 1°C over baseline
Reading times: During test as well as immediately and 10 minutes after end of test

Test 1. Exercise	W	How long after begin of test?	→	**Test 2. Hot bath**	W
		____ minutes			

Patient information

Name:

Date of birth:

Abbreviations: W = Wheal
E = Erythema
A = Angio-edema
I = Itch

Document skin reaction with + or -

Threshold tests for inducible urticaria

Symptomatic dermographism (Urticaria factitia)

Testsite: Volar forearm / Upper back
Test: Use a dermographometer (e.g. dermographic tester or Fric*Test*)
Reading time: 10 minutes after testing
Threshold: Lowest trigger strength that results in wheal and itch

Fric*Test*	W	I
Pin 1 (shortest)		
Pin 2		
Pin 3		
Pin 4 (longest)		

Dermographic tester	W	I
Minimum trigger strength in g/mm²	_____ g/mm²	_____ g/mm²

Test done by _____
Date / Time _____

Cold urticaria

Testsite: Volar forearm
Test: Use Temp*Test* for 5 minutes
Reading time: 10 minutes after end of testing
Threshold: Highest temperature that results in wheal

Test done by _____
Wheal from 4°C to ____ °C
Date / Time _____

Heat urticaria

Testsite: Volar forearm
Test: Use Temp*Test* for 5 minutes
Reading time: 10 minutes after end of testing
Threshold: Lowest temperature that results in wheal

Test done by _____
Wheal from 44°C to ____ °C
Date / Time _____

Delayed pressure urticaria

Testsite: Volar forearm (rod), upper back (dermographic tester)
Test DPU test device, 15 minutes, diameter of applicator: 6.5 cm,
Reading times: ≈6 hours after testing
Threshold: Rod with lowest weight that results in angio-edema and erythema

kg	A	E
1		
2		
3		
4		
5		

Test done by _____
Date / Time _____

Solar urticaria

Testsite: Buttocks
Test: UVA / UVB irradiation (e.g. Saalmann Multitester SBC LT 400)
Reading times: 10 minutes after testing
Threshold: Lowest dose of irradiation that results in wheal

UVA (J/cm²)	W
2.4	
3.3	
4.2	
5.1	
6.0	

UVB (mJ/cm²)	W
24	
33	
42	
51	
60	

Test done by _____
Date / Time _____

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S1 Guideline – chronic inducible urticaria

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Conflicts of interests

The Work Under Consideration for Publication					
		Ana Gimenez-Arnau	**Martin Metz**	**Torsten Zuberbier**	**Marcus Maurer**
1	Grant	URIACH PHARMA	No	see list attached	No
2	Consulting fee or honorarium	URIACH PHARMA	No	see list attached	No
3	Support for travel to meetings for the study or other purposes	URIACH PHARMA	No	see list attached	No
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	URIACH PHARMA	No	see list attached	No
5	Payment for writing or reviewing the manuscript		No	no	No
6	Provision of writing assistance, medicines, equipment, or administrative support		No	No	No
7	Other		no	no	no

* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	Uriach Pharma, Genentech, Novartis		see list attached	Novartis, Genentech, Uriach, FAES, Moxie
2	Consultancy	Uriach Pharma, Genentech Novartis	Medixiline, Index Venture Management Jersey Ltd., Sanofi, Nerre, LORA Group, Jenapharm, Novartis	see list attached	Novartis, Genentech, Uriach, FAES, Moxie
3	Employment			No	no
4	Expert testimony			no	Novartis, Genentech, Uriach, FAES, Moxie
5	Grants/grants pending	Uriach Pharma, Novartis		see list attached	Novartis, Genentech,

					Uriach, FAES
6	Payment for lectures including service on speakers bureaus	Uriach Pharma MSD, Intendis-Bayer, ALMIRALL, Novartis, Menarini, GSK, Leo Pharma	Novartis, Charité, Bayer, MarDi, Dr. R. Pfleger, Urtimed, Klinikzentrum Bad Sulza, GlaxoKline, DDG, ADF, Jenapharm, Universität Münster, Roche, Ärztekammer Berlin, BVDD	see list attached	Novartis, Genentech, Uriach, FAES
7	Payment for manuscript preparation		Mediengruppe Oberfranken, Jenapharm, Moxie GmbH	No	No
8	Patents (planned, pending or issued)			No	No
9	Royalties			no	no
10	Payment for development of educational presentations	Uriach Pharma MSD, Intendis-Bayer, ALMIRALL, Novartis, Menarini, GSK, Leo Pharma		No	
11	Stock/stock options			No	no
no 12	Travel/accommodations/meeting expenses unrelated to activities listed**			no	
13	Other (err on the side of full disclosure)			no	no

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Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?			Secretary General GA²LEN First author of international Guidelines on urticaria	no

The Work Under Consideration for Publication					
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2	Consulting fee or honorarium		No	N/A	Novartis SunPharma
3	Support for travel to meetings for the study or other purposes	none	No	N/A	
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	none	No	N/A	CSL Behring
5	Payment for writing or reviewing the manuscript	none	No	N/A	
6	Provision of writing assistance, medicines, equipment, or administrative support	none	No	N/A	
7	Other	none	Sponsorship by Glaxo Smith Cline of the research in chronic spontaneous urticaria towards a PhD degree		

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Relevant financial activities outside the submitted work					
1	Board membership	n	No	N/a	
2	Consultancy	none	No	N/A	
3	Employment	Charité – Universitätsmedizin Berlin	No	N/a	
4	Expert testimony	none	No	N/A	
5	Grants/grants pending	Rahel-Hirsch-Stipend Charité	No	N/A	
6	Payment for lectures including service on speakers bureaus	GA2LEN-Workshop 2015	No	N/a	
7	Payment for manuscript preparation	none	No	N/a	
8	Patents (planned, pending or issued)	none	No	N/A	
9	Royalties	none	No	N/A	
10	Payment for development of educational	none	No	N/A	

	presentations				
11	Stock/stock options	none	No	N/A	
12	Travel/accommodations/meeting expenses unrelated to activities listed**	none	No	N/A	
13	Other (err on the side of full disclosure)	none	NA	N/A	

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Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	none	no	no	

The Work Under Consideration for Publication					
		P. Mathelier-Fusade	**Raisa Meshkova**	**Markus Magerl**	
1	Grant	None	not		
2	Consulting fee or honorarium	None	not		
3	Support for travel to meetings for the study or other purposes	None	Novartis Russia		
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	None	not		
5	Payment for writing or reviewing the manuscript	None	not		
6	Provision of writing assistance, medicines, equipment, or administrative support	None	not		
7	Other	None			

* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	None	not		
2	Consultancy	None	not	Biocryst, Shire (Viropharma),	
3	Employment	None	not		
4	Expert testimony	None	not		
5	Grants/grants pending	None	not		
6	Payment for lectures including service on speakers bureaus	None	not	Biocryst, CSL Behring, Novartis Shire (Viropharma), Pharming	
7	Payment for manuscript preparation	None	not		
8	Patents (planned, pending or issued)	None	not		
9	Royalties	None	not		
10	Payment for development of educational presentations	None	not		
11	Stock/stock options	None	not		
12	Travel/accommodations/meeting expenses unrelated to activities listed**	None	not		
13	Other (err on the	None	not		

	side of full disclosure)				

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Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	None			