Contact Urticaria

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Until now we assumed new cases of Contact Urticaria (CoU) were exceptional findings; each year adding new substances to long lists of triggers. But is this condition really exceptional? CoU is an important clinical manifestation part of the Contact Urticaria Syndrome (CUS). CoU still is often under- or misdiagnosed. We should disseminate knowledge of this entity among our medical colleagues, among patients, and among health authorities involved in occupational health. CoU impairs daily activities, quality of life and can be life threating, but if it's correctly diagnosed it can be prevented and successfully treated.

The concept of contact dermatitis includes any inflammatory skin reaction to direct or indirect contact with noxious agents in the environment. Although the main clinical expression of contact dermatitis is eczema, contact urticaria (CoU) and lichenoid eruptions are also described. The earliest recorded reports include Pliny the Younger who, in the first century A.D., noticed individuals with severe itching when cutting pine trees. Patch and prick testing are considered the main tools for discovering the responsible agent.

In the last decades, we've learned that proteins and also low molecular weight molecules that can induce Immediate Cutaneous Reactions (ICSR)

Contact Urticaria (CoU) and Contact Urticaria Syndrome (CUS)

CUS comprises a heterogeneous group of ICSR reactions that usually appear within minutes after contact with eliciting substances. Occasionally systemic involvement can be present. Maibach and Johnson [1] defined it as an entity in 1975. Since then and nowadays its scientific interest increased, and new cases are continuously reported, providing information concerning new trigger factors and clinical features.

Contact Urticaria (CoU) refers to a wheal and flare reaction following external contact with a substance, usually appearing within 30 minutes and clearing completely within hours, without residual signs [2]. Fisher introduced the term in 1973, but this phenomenon has long been recognized [3]. Urticarial lesions to nettles and hairy caterpillars were

reported in the 19th century and continue being reported today [4]. In a survey carried out in 1224 adults in Spain, contact wheals and pruritus were noticed by 52.1% and 100% respectively of people who suffered cutaneous symptoms induced by the pine processionary moth [5]. Naturally occurring urticariogens were used therapeutically as rubefacients, counter-irritants and also vesicants [6].

In 1976, Hjorth and Roed-Petersen defined Protein Contact Dermatitis (PCD as an immediate dermatitis induced after contact with proteins [7-9]. Thirty-three food caterers suffering exacerbation of itch immediately after contact with meat, fish and vegetables followed by erythema and vesicles were described. Application of the relevant foods to the affected skin resulted in either urticaria or eczema [10]. Atopy and PCD are associated in approximately 50% of affected patients [11].

Patients suffering CUS can develop CoU and/or dermatitis/eczema immediately after the contact with the trigger substance. These ICSR can appear on normal or eczematous skin, can be induced by the same trigger factor and can be suffered by the same patient.

Epidemiology and Occupational relevance of Contact Urticaria

It is unlikely that CoU is rare, especially among atopic individuals, but no figures on its prevalence in the general population are available. The global incidence of CUS is not known. ICSR are common in dermatological practice [12-17]. With the exception of natural rubber latex (NRL allergy, trigger factors for only isolated cases or short series of patients are described [18]. The symptoms of CoU are usually mild, of short duration, and limited to small skin areas. The diagnostic tests are rarely performed, because neither patients nor physicians are interested in the mechanisms of these minor symptoms. Thus the probable diagnosis of CoU is seldom recorded in patient files. The general knowledge on the epidemiology of CoU is largely based on the statistics of certain countries that register occupational cases of contact urticaria.

NRL caused an epidemic of occupational CoU in health care workers in the 1990s due to escalating glove use in this sector.[19] In an international meta-analysis from studies

performed in 1990–2003, IgE-mediated allergy to NRL ranged from 1.4–1.65% in the general population, and from 4.1–5% in the health care worker population.[20] New cases of NRL allergy have decreased significantly, especially after health authorities have required the use of low-allergen/low-protein non-powdered protective gloves. The prevalence of immediate NRL allergy in Western Europe is approximately 1% or less. [20]

There is limited data on the prevalence of ICSR other than NRL allergy. Skin contact reactions are a part of the clinical spectrum of many common immediate-type hypersensitivity reactions, providing that the skin is exposed to a significant extent to the allergen in question. This is probably not the case with airborne allergens such as pollen, but other allergens, such as animal dander and excretions cause skin contact reactions.

Some hints of the prevalence of CoU can be found in the literature, although skin symptoms are seldom reported in larger series of immediate allergy. About one third of birch pollen sensitive patients also react to cross-reactive fruit and vegetables. In 1977, Hannuksela and Lahti reported skin contact symptoms in a series of 152 birch pollen-allergic patients who also reacted to at least two different allergens in a scratch-chamber test of 25 different fruits and vegetables. Of the 52 patients who reacted to raw potato, 17 had itching and/or urticaria-like oedema of the hands after peeling potatoes; of the 59 apple-positive patients 4 had itchy dermatitis of the hands after handling apples, and of the 46 carrot-positive patients 6 had similar symptoms after peeling carrots [21] .In a Spanish series of 197 children with IgE-mediated fish allergy, 29 children had cutaneous symptoms after skin contact with fish [22] . Peach allergy is another example of an immunological hypersensitivity reaction whose clinical spectrum includes skin reactions. Among 30 peach-allergic patients in Northern Spain, there were six cases of contact urticaria [23]. Authors of the study did not comment on whether or not the contact urticaria cases were occupational. In Australia, peanut butter under an occlusive dressing was applied to the healthy skin of 281 children who were prick-test-positive to peanut. A total of 114 of the children had an urticaria reaction [24].

In the occupational setting CUS seems to be common although a precise statistical analyses is difficult to obtain in most of the countries because of underreporting. In a few countries, CoU has been classified as a separate occupational skin disease. This is the case in Finland since 1989. The "Finnish Register of Occupational Diseases" (1990-1994) showed that CoU was the second most frequent cause of occupational dermatosis (29.5%), after contact allergic dermatitis (70.5%) [25-26] . The trigger agents were cow dander (44.4%), natural rubber latex (23.7%) and flour, grains or feed (11.3%) [27]. A smaller proportion of occupational CoU was found in a retrospective study done in a tertiary level clinic specializing in occupational dermatology in Melbourne, Australia, showing an 8.3% CoU prevalence [28]. Hands, arms and face were the most frequent body area involved. Atopy was a significant risk factor for natural rubber latex, foodstuffs or ammonium persulfate CoU. Health workers, food handlers and hairdressers were the most common occupations affected. More recently, a survey conducted in 335 restaurant, catering and fast-food employees in Singapore showed occupational irritant contact dermatitis was more common (10%) with CoU reported in only two patients, caused by lobster and prawn [29]. The nature of the exposure will probably determine the percentage of CoU risk.

Consultant dermatologists in the UK report occupational skin diseases to EPIDERM, a voluntary surveillance system. Occupational physicians have a similar scheme called OPRA. In 1996–2001, most cases of CoU were attributed to rubber materials or foods and flour. CoU was diagnosed particularly in the health and social services and in food and organic material manufacturing [30]. In EPIDERM, CoU was relevant in 4% of the cases of occupational skin disease. In accordance with the Australian data, the rates for CoU among women were twice those among men. In 2002–2005, 336 contact urticaria cases were reported to EPIDERM; 41% of these were co-diagnosed with contact dermatitis, and 75.5% were associated with exposure to NRL [31]. When data from EPIDERM and OPRA were combined, cases of CoU peaked in 1996, but have since declined [32]. According to the Finnish Register of Occupational Diseases, in 2005–2010 there were 329 (10.4%) notified as occupational cases of CoU or PCD among a total of 3170 notified cases of occupational skin disease. These figures are comparable with the Australian data. The earlier Finnish statistics only comprised suspected cases, and the

number of notified cases was not available. The number of CoU and/or PCD cases seems to have decreased. In 1990–1994 the number of suspected new cases was 815 (an average of 163 suspected cases/year) [33], while in 2005–2010 there was only an average of 74 new suspected cases/year. In line with the Australian and the UK data, as regards the notified cases, CoU and/or PCD was more common among women (62%) than among men (38%). In 2005–2010, the most common causes of the notified cases were cow dander (48%), flour, grain or animal feed (17%), natural rubber latex (10%) and other food (9%). As only the primary diagnosis is recorded in the Finnish register, some cases are not registered. This is particularly the case when allergic contact dermatitis is considered more important. Industrial enzymes have lost some their relative significance when compared to 1990–1994 data (1.7% vs. 0.7%), but decorative plants have not (1990–1994, 1.6% vs. 2005–2010, 2.2%). The main risk of industrial enzymes is sensitization of the respiratory tract, and only a small minority of sensitized patients have skin contact reactions.

The majority of CoU cases are caused by protein-containing organic material, and the mechanism is usually IgE-mediated. Occupational contact urticaria caused by low molecular weight (LMW) chemicals is rare. In Finland they comprised only about 3% of the notified occupational CoU and PCD cases in 2005–2010. The mechanism of chemical-induced contact urticaria is sometimes IgE-mediated, but in most cases the mechanism remains unknown. Ammonium persulfate was the most common LMW chemical, followed by organic acid anhydrides.

Occupational CoU in European health care workers shows a prevalence from 5 to 10%, whereas in the general population it lies between 1 and 3%. Other occupations with a high risk to develop CoU include food handlers or people involved in agriculture, farming, floriculture, plastics, pharmaceutical and other laboratories, as well as hunters, veterinarians, biologists or hairdressers. Atopy favors further sensitization where protein allergens are concerned. [34]

The classification of occupational dermatosis of the “International Code of Diseases (ICD)-11 includes contact dermatitis joint with CoU. Occupational screening

questionnaires including specific questions searching for urticaria symptoms are very few. The long version of the Nordic Occupational Skin Questionnaire (NOSQ-2002) is one of them including nine questions about urticaria symptoms [35]. A standardized method to evaluate the occupational relevance of CoU, such as the Mathias´ criteria, [36] already developed for occupational contact dermatitis would be desirable.

Regarding prognosis of occupational CoU, in a six-month follow-up study of 1048 patients diagnosed with an occupational skin disease at the Finnish Institute of Occupational Health (FIOH), patients with CoU or PCD had the most favourable prognosis compared to those with occupational allergic contact dermatitis and occupational irritant contact dermatitis [37]. This material also comprised patients with CoU as a sole diagnosis. In a recent Danish report on work-related hand dermatoses in food-related occupations, patients with PCD had experienced more severe and frequent consequences than patients with other diagnoses [38]. In Finland, the long-term outcome of NRL allergy was studied in 160 adult patients a median of three years after diagnosis. In their working environment, all gloves had been changed to either low-allergen NRL or non-NRL gloves. Not one of 71 health care workers had changed jobs because of NRL allergy, and the prevalence of hand eczema had decreased significantly (54% vs. 38%) [39] .

Evolving knowledge about the mechanisms involved in Contact Urticaria

The mechanisms underlying ICSR are partially understood. Each trigger substance has its own mechanism of action.

Non-immunologic CoU (NICoU) is due to vasogenic mediators without involvement of immunological processes. Urticariogens may act following different patterns. The most classic example concerns dimethyl sulphoxide (DMSO), which damages the blood vessels, making them leaky and inducing mast cell degranulation [40]. Antihistamines do not inhibit reactions to DMSO and other NICoU responsible agents, but acetylsalicylic acid and nonsteroidal anti-inflammatory drugs do (both orally and topically); therefore, a role for prostaglandins has been suggested [41-43]. Release of prostaglandin D2 without

concomitant histamine release has been demonstrated following topical application of sorbic acid and benzoic acid [44,45]. Capsaicin pre-treatment (which depletes substance P) does not impair NICoU, but does inhibit the allergen prick test flare of immunologic CoU (ICoU) [46]. Non-specific tachyphylaxis of variable duration has been associated with various urticariogens [47]. Sharp hairs from animals or spines from plants penetrating the skin can deliver a cocktail of irritant chemicals or pro-inflammatory mediators causing NICoU [48].

The pathogenesis of immunological CoU (ICoU) including the oral allergy syndrome (OAS) reflects a type I hypersensitivity reaction, mediated by allergen-specific immunoglobin E (IgE) in a previously sensitized individual [49-52]. Skin challenge involves allergen penetration through the epidermis, IgE binding on mast cells, its degranulation, and subsequent release of histamine and other vasoactive substances as prostaglandins, leukotrienes and kinins.

A combination of type I and type IV allergic skin reactions, the latter supported by positive delayed patch tests, has been suggested as PCD pathogenesis [53,54]. It has been speculated that PCD is an eczematous IgE-mediated reaction through proteins. PCD shows a similar reaction pattern to aeroallergen-induced atopic eczema or dermatitis [55].

Clinical manifestations of Contact Urticaria and Contact Urticaria Syndrome

CUS clinical symptoms are determined by the route, duration and extent of exposure, the inherent sensitizing properties of the allergen, and an individual's genetic and/or acquired susceptibility.

CoU is defined by its primary lesion, which is named wheal or hive. There is transient edema of the dermal tissue and a surrounding reflex erythema with itch or sometimes burning sensation at the same time. [56] [59] The wheal has a fleeting nature and the skin return to its normal appearance usually within 1-24 hours [57].

CoU belongs to the group of inducible urticarias [58]. CoU is characterized by a local immediate and/or delayed urticarial reaction at sites of epidermal or transdermal contact with certain agents. CoU is the oldest form of urticaria recorded. The association of nettles and urticaria was discussed in the Greek literature more than 2000 years ago [59].

The clinical appearance of the primary lesion of CoU does not differ from that of other types of urticaria. Depending of the type of contacting the wheal can show different aspects. Nettles of plants habitually cause linearly arranged wheals. Punctate wheals arise exactly the site where the stinging hairs penetrate the skin. The shape of the wheals can change with time. Intense reactions induce confluent lesions. Wheals can start in a follicular pattern if the contactant penetrates through the hair follicles. The associated local symptoms are tingling, itching and sometimes burning at the sites of the wheal.

The wheals start with redness at the site of contact, followed by whealing at the same site within 10-30 minutes after contact. The maximal size is reached 45 minutes afterward, and within 2 h, the swelling disappears. Redness can persist even 6 hours, exceptionally more than 24 hours. Contact urticaria can reappear after 4-5 hours. This dual response has been demonstrated experimentally in the ears of BALB/mice and in humans [60]. Delayed onset of contact urticaria was also described, after repeated applications of the trigger substance [61]. The time course and intensity of contact urticaria lesions differ depending of the nature of the eliciting agent. This variability may also be due to differences in the reactivity of the cells that secrete the vasoactive amines or the sensitivity of the target tissue to the mediators or chemical released.

Contact induced angioedema shows a sudden, erythematous or skin colored swelling of the lower dermis and subcutis with frequent involvement below mucous membranes up to 72 hours.

CUS has been classified in four stages. Stages 1 and 2 show cutaneous symptoms. Stage 1 includes flare reactions, wheals and eczema as well as symptoms such as itching, tingling or burning sensation. When CoU is present it shows itchy wheals which are usually strictly limited to contact areas and which disappear within a few hours without

residual lesions. Chronic paronychia with redness and swelling of the proximal nail fold after handling food [62] and natural rubber latex [63] can also be observed in PCD. Stage 2 refers to the development of generalized urticaria after a local contact. Stages 3 and 4 include extracutaneous reactions or symptoms that may also occur as part of a more severe reaction. Stage 3 may include bronchial asthma, rhino-conjuntivitis, orolaryngeal symptoms or gastrointestinal dysfunctions. [64,65] .By contact or in the case of a volatile allergen, rhino-conjuntivitis and asthma may accompany the skin manifestations, as occurs with bakers who are in continuous contact with flour. Abdominal pain, diarrhea and oral allergy syndrome may develop when the allergen comes in contact with the oropharyngeal mucosa [66,67]. [67] Finally, in stage 4, anaphylactic or anaphylactoid reactions may occur as the most severe type of CUS manifestation. Contact urticaria can be life threatening: certain substances, such as latex protein, can induce anaphylaxia and even death.

Diagnostic tools useful to make an etiological diagnosis in Contact Urticaria

Diagnosis of CUS is based on full medical history and skin testing with suspected substances. *In vitro* techniques are available for only a few allergens, including latex. The simplest cutaneous provocation test for ICoU, NICoU and immediate contact dermatitis as PCD is the "open test." The suspected substance is applied and gently rubbed on slightly affected skin or on a normal-looking 3x3 cm area of the skin, either on the upper back or the extensor side of the upper arm. Often it is desirable to apply contact urticants to skin sites suggested by the patient´s history. A positive result is edema and/or erythema typical of CoU. Immunological and non-immunological contact reactions usually appears within 15-20 minutes. Non-immunological contact reactions tend to resolve within 45-60 minutes[NS1]. ICoU can also show a delayed onset, although this is rare.

When the open test results are negative, "prick testing" of suspected allergens is often the method of choice for immediate contact reactions. "Scratch test" and "chamber scratch test" (contact with a small aluminium chamber for 15 minutes are less standardized than the prick test, but are useful when a non-standard allergen must be

studied. Histamine hydrochloride serves as the positive control and aqueous sodium hydroxide as negative reference (Fig.1) When[NS2] other than cutaneous organs are involved, it is important to begin ICoU testing with much diluted allergen concentrations and to use serial dilutions to minimize allergen exposure. When testing with poorly or non-standardized substances, control tests should be assessed on at least 20 people to avoid false positive interpretation. Non-steroidal anti-inflammatory drugs and antihistamines should be avoided because of the risk of false negative results. Following the recommended protocol is important for minimizing the occurrence of hazardous extracutaneous reactions. Life-threatening reactions have been documented during skin tests; therefore, caution is advised, especially when testing certain occupational substances. Skin tests should be performed only if resuscitation equipment and trained personnel are readily available [68-70] .

Skin tests and specific IgE determinations in the diagnosis of CoU and respiratory disease caused by low-molecular-weight chemicals are even less standarized. Some chemicals induce IgE-mediated allergy. Open application tests (skin provocations) are planned individually. Commercial prick test substances are not available for chemicals, neither are diagnostic guidelines. Examples of testing procedures can be found in the literature, but they usually describe only single cases or small series of cases. Some prick tests were performed with protein conjugates of various LMW chemicals for over 20 years by the FIOH. Some chemicals can be prick-tested in water solutions, but Human Serum Albumin (HAS)-hapten conjugates are preferred at FIOH. Prick tests with HSA conjugates are valuable in the diagnosis of immediate acid anhydride allergy (a group of reactive chemicals used in epoxy resin).

Diagnosis of occupational respiratory disease is based on inhalation challenge tests at FIOH.[71]

Agents responsible for Contact Urticaria and the Contact Urticaria Syndrome

Proteins (molecular weight 10,000 to several hundred thousands) and also chemicals (molecular weights below 1,000) can trigger CoU included as an entity in the CUS. Plant or animal proteins, chemicals such as drugs and preservatives, or more diverse

substances such as metals and industrial chemicals can induce ICoU. Low molecular weight molecules normally act as haptens; nevertheless, for some of them IgE antibodies have been also demonstrated as e.g. sensitized workers reactive to platinum and nickel–serum albumin complexes [72-73].
NICoU was defined by stinging nettles wheals induced from Urtica dioica. Other responsible agents are preservatives, fragrances and flavorings in cosmetics, toiletries, topical medications or foodstuffs as benzoic and sorbic acid [74]. Household, industrial, insecticide and laboratory chemicals can also induce NICoU.
A few substances elicit mixed features of NICoU and ICoU through an unestablished mechanism. In ammonium persulfate induced CoU, antigen specific IgG and IgM activate the complement cascade through the classical pathway [75-77]. Immediate reactions to formaldehyde seem not to be mediated by IgE, with a prostaglandin role suspected because of increased levels of thromboxane B_2 and prostaglandin PGF_2 [78-79].

A huge number of compounds can be responsible for occupational and non-occupational CUS including animal products, plants and plant derivatives, foods, fragrances, cosmetics, flavorings, medications, preservatives, disinfectants, enzymes, metals and miscellanea of different substances.

Natural rubber latex allergy focused global interest at the end of the 20th century. Latex sensitization risk factors include atopy and prolonged exposure via damaged epidermis e.g., glove wearers with hand eczema. The thirteen allergens of latex better identified and characterized are labeled Hev b1-13. Latex contains approximately 250 polypeptides, 56 of which have been identified as allergens , with a molecular weight of these proteins that varies from 4 to 200 KDa . The antigenic profiles differ between finished products and still raw material. The machining process (for example, the addition of ammonia) can in fact lead to a selective enrichment of chemical and heat-resistant proteins, that may in fact be denatured or complexed in new antigenic specificity [71].

Enzymes are complex proteins or glycoproteins produced by living organisms for the purpose of accelerating biochemical reactions and metabolic processes. Commonly

enzymes behave as allergens and are mostly responsible for ICSR mediated by specific IgE antibodies causing CoU and PCD, and the respiratory tract is often involved. Its occupational relevance should always be assessed, and primary preventive measures developed [71].

Plants in the environment as weeds, woods or ornamentals, cause CUS. ICoU is predominantly found in cultivated plants, whereas toxic or NICoU is most commonly seen in wild plants. Several species of plants have been reported to cause urticaria by unknown/unclassified mechanisms.

Agriculture has high rates of occupational skin diseases reported. Delayed contact allergy commonly occurs from pesticides; however, a scarcity of reports describe pesticide-induced CoU. Our present knowledge of contact urticaria to agricultural chemicals, and pesticides in particular, remains deficient.

Direct or indirect skin contact with animals and animal derived products occurs in numerous occupations, everyday life and hobbies. Proteins in animal epithelia, excretions and organs can cause both ICoU and NICoU. Individually tailored skin tests for both immediate allergy and specific IgE in blood are needed for diagnosing immediate allergy to animals or animal products. Commercial test materials can give false negative results, thus the skin tests should be made, if possible, with the same materials and in the same format as they have been causing the skin problems [68].

Food responsible for CUS includes fruits, vegetables, spice, plants, animal proteins, grains and enzymes. Food additive responsible for CUS include flavouring, fragrances and taste enhancers, preservatives agents and colourings agents and dyes [68]. Diagnostic tests need to be defined and standardized.

Seminal fluid hypersensitivity is increasingly being recognized as a cause of anaphylaxis and/or intermittent episodic vulvovaginitis. Localized seminal plasma hypersensitivity presents with immediate post-coital vulvovaginal burning, pain and swelling, rarely associated with vesicles, and can occasionally be present with systemic

involvement. It is believed that this condition is more common than recognized. Seminal plasma hypersensitivity can be demonstrated with a positive Prick Test reaction, RAST and specific RAST inhibition in addition to neutralization of passive transfer antibodies. The most effective treatment approach for women with ICoU seminal plasma hypersensitivity has been immunotherapy [68].

Topical drugs or, occasionally, systemic drugs that come in contact with the skin or mucosae, may induce CoU, which is certainly very often overlooked. Complementary tests (skin tests with immediate readings and, eventually, *in vitro* tests) are mandatory in certain situations, as a precise diagnosis of the culprit drug and a suggestion of alternative safe drugs, can be lifesaving. Any drug can induce an ICSR, but most cases have been described with betalactam antibiotics, topical anesthetics, and, more recently with antiseptics, like chlorhexidine [68].

Cosmetic components can cause CoU with or without systemic symptoms, sometimes life-threatening. CUS induced by components included in cosmetics is grossly under-diagnosed and under-reported because patients lack awareness. Hair-dye chemicals and bleaches, hair glue, antimicrobial agents and preservatives, fragrance components, toothpaste flavors, botanically-derived cosmetic ingredients, permanent makeup and tattoos and even alcohol are involved as responsible of contact urticaria syndrome [68].

Preservatives and disinfectants are well documented causes of allergic contact dermatitis, while CUS due to preservatives and disinfectants is less common. It is widely accepted that sodium benzoate, benzoic acid, benzyl alcohol and sorbic acid cause NICoU and formaldehyde, parabens, povidone-iodine, chloramine and chlorhexidine can cause ICoU. Preservatives and disinfectants may also cause generalized urticarial, bronchial asthma, rhinitis, conjunctivitis, otolaryngeal and gastrointestinal symptoms and even anaphylaxis. The mechanism of preservatives (e.g. isothiazolinones or formaldehyde releasers) responsible for ICSR is unknown [68].

Reactive dyes, usually an azo, anthraquinone or phthalocyanine derivative show different reactive functional groups to which carrier proteins bind to induce immune

responses. Reactive dyes can be responsible for CUS stages 1-4. Patch testing, prick testing, bronchial challenge tests, and detection of specific IgE to RD-human serum albumin conjugates in serum are used to assess responsible agents, but still need standardization [71]. To establish the relevance between the responsible reactive dyes and their presence in specific textiles is difficult.

Prevalence of CoU from hairdressing products is not fully documented, and only case reports and case series have been published. Hair shampoos, hair conditioners, hair dyes and bleaches, permanent wave preparations, fragrance and other styling products as sprays, gels, waxes, mousses, lotions and pomades has been described as responsible for CUS symptoms. Hairdressers require special education and specific preventive measures [71].

In spite of the frequent exposure to metals, few cases of CoU caused by metals have been reported. The metals involved in CoU are all members of the group called transitional metals (e.g nickel, cobalt or chromium). Metals are mainly allergenic as salts and not as the metallic form. The mechanism behind CoU caused by metals is unclear, but an IgE mediated mechanism in indicated since most cases are supported by a positive SPT to the metal [71].

Epoxy resin is commonly used in occupational and non-occupational setting**.** The Epoxy-resin system includes epoxy resins and other components as curing agents, reactive diluents, modifiers, and additives. Contact dermatitis caused by epoxy resin is often described in the literature although CoU from epoxy compounds has infrequently been reported and often represents occupational cases. Skin prick test with the patient's "own" epoxy resins aids the diagnosis. Further studies to standardize the diagnostic method are required [68,71].

Prevention and Treatment of Contact Urticaria and Contact Urticaria Syndrome

Discovering the responsible agent is required to identify the correct avoidance of the eliciting trigger. Avoidance of further exposure will improve occupational CoU.

Primary and secondary prevention are highly recommended [80,81]. Considering their good safety profile, second generation antihistamines must be considered the preferred first-line symptomatic treatment for most of CoU [82].Before considering alternative treatment, higher doses of antihistamines should be used. When dermatitis is present topical immunomodulation can be conducted using topical steroids. Severe cases of CUS require a short course of oral steroids or even treatment in an emergency unit.

Conclusions and Unmet needs in Contact Urticaria

CoU as part of the CUS is a worldwide health problem that needs a global approach. General population-based epidemiological studies are lacking and are desirable. Structural characteristics of certain proteins and chemicals can induce CoU clinical manifestations through different pathogenic mechanisms. The same substance can induce different clinical patterns. This fact opens the door for new insights into immune system pathways. Substances responsible for ICSR can be classified by molecular weight, mechanism of action, occupational relevance or their common use in our daily life. Our *in vivo* tests still based on subjective assessment ideally should be replaced by effective *in vitro* testing for diagnostic purposes. After symptom control, an appropriate etiological diagnosis and the development of concrete preventive measures is required.

Figure legend

Fig 1 . Positive Prick by Prick test in patients suffering CoU (in all the cases the upper positive control test is with histamine and the test included below is the negative control with sodium chloride) induced by 1a) positive aloe vera plant, 1b) positive green and white bean, 1c) positive nitril gloves (twice) and 1d) Lilly Astargazer positive leef stem and petal.

Recommended text books:

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2. Contact Urticaria Syndrome. Diagnosis and Management Editors: Giménez-Arnau AM and Maibach H. Springer 2018

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