Curr Treat Options Allergy (2018) 5:302–309
DOI 10.1007/s40521-018-0174-4

Contact Dermatitis (A Gimenez-Arnau, Section Editor)

# Contact Urticaria and Protein Contact Dermatitis—a Frequently Hidden Diagnosis

*Austin Jiang, MS*[1,*]
*Howard Maibach, MD*[2]

**Address**
[*,1]University of Cincinnati College of Medicine, Cincinnati, OH, 45208, USA
Email: austinjiang13@gmail.com
[2]University of California, San Francisco, CA, 94143, USA

Published online: 17 May 2018


This article is part of the Topical Collection on *Contact Dermatitis*

**Keywords** Contact uricaria · Protein contact dermatitis · Immunologic contact urticaria · Nonimmunologic contact urticaria

## Abstract

*Purpose of review* We hope that this review can assist in the classification, diagnosis, prevention, and treatment of a contact urticaria syndrome (CUS), a syndrome in which the understanding of such is still evolving.
*Recent findings* CUS and protein contact dermatitis (PCD) can be defined as an immediate inflammatory reaction of the skin following contact with an external substance. Erythema, wheals, and eczema, as well as other manifestations can occur as a result of this inflammatory reaction. Many low molecular weight substances and proteins are known to produce these immediate skin contact reactions. These reactions affect many occupations such as health care workers, bakers and cooks, and farmers. Nonetheless, as a subset of contact dermatitis, CUS is often misdiagnosed in part due to a lack of understanding and mild severity of its clinical manifestations.
*Summary* A detailed history that elicits environmental and occupational contacts, duration of contacts as well as a detailed understanding of CUS is fundamental to its proper diagnosis.

## Introduction

Contact urticaria syndrome (CUS) was first defined in the literature in 1975 by Maibach and Johnson as a wheal and flare response on the skin after exposure to an external substance [1]. They characterized CUS into three subdivisions: nonimmunologic contact urticaria (NICU), immunologic contact urticaria (ICU), and uncertain

cause; these subdivisions remain to this day. After contact with the triggering substance, CUS will typically manifest immediately—between minutes to an hour or so.

Protein contact dermatitis (PCD) was first defined in 1976 by Hjorth and Roed-Petersen as immediate dermatitis after exposure to proteins [2]; PCD can be considered a subset of CUS. This review covers the symptoms and clinical manifestation, mechanisms, testing, and treatment of CUS and PCD.

## Symptoms and physical exam

The primary lesion of CUS is flare and wheal, containing three major features: transient edema of dermal tissue, surrounding reflex erythema, and intense pruritus or itch at the same time [3••]. Upon contact with the urticarial agent, there is redness at the site and then whealing within 10–30 min after contact. Whealing reaches maximal size at 45 min or so after contact and within approximately 2 h swelling disappears. Redness can persist for as long as 6 h. Other symptoms such as generalized cutaneous reactions, allergic rhinitis, allergic asthma, or anaphylactic reactions may also occur. Symptoms are determined by the anatomic site of exposure, exposure timing, and exposure extent.

Immunologic contact urticaria can be categorized into four clinical stages of severity. Stage 1 is characterized by localized urticaria and itching, tingling, or burning sensations. Stage 2 is characterized by onset of urticaria from point of contact to generalized urticaria. Stage 3 and 4 include extracutaneous symptom. Stage 3 is characterized by any of the following: allergic asthma, allergic rhinitis, allergic conjunctivitis, orolaryngeal symptoms, or gastrointestinal symptoms. Finally, Stage 4 is anaphylactic or anaphylactoid reactions. Being the most severe stage of CUS reactions, it can be life threatening.

Symptoms of protein contact dermatitis are consistent with those of contact dermatitis. Pruritus is the hallmark symptom, and may be accompanied by erythema [3••]. Vesicles develop rapidly due to spongiosis of the epidermis and continue developing for the following days [4•]. As PCD often affects the hands, paronychia, periungual edema, erythema, and lichenification are seen as well [5, 6]. If there is long-term exposure to the allergen/irritant, lichenification of the affected skin can occur, leading to eczema, the most common adverse reaction to contact substances [3••]. How immunologic contact urticaria leads to dermatitis remains unknown.

## Pathophysiology

The mechanisms behind CUS are incompletely understood.

NICU is the most common cause of CUS. NICU can occur without prior exposure to the causative substance. Symptoms occur due to vasogenic mediators without involvement of the immune system [7]. The clinical manifestations of NICU do not usually go further than Stage 1, remaining localized to the site of contact. NICU reactions to agents including benzoic acid, cinnamic acid, and dimethylsulfoxide were not inhibited by antihistamines [8].

On the other hand, non-steroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid (ASA) have shown to inhibit NICU reactions. This

knowledge, combined with demonstrated release of prostaglandin D2 without histamine release, suggests that prostaglandin and not histamine release is partially responsible for NICU.

Molecular structure of the agent is an important factor in the development of NICU. Slight alterations in the molecular structure of the NICU causing agent can impact its irritant properties, possibly due to differing propensities to release prostaglandin [9].

ICU has a mechanism similar to other Type I hypersensitivity reactions as it is mediated by allergen specific IgE. Thus, unlike NICU, it requires presensitization and appears after repeated exposure. Upon IgE binding to mast cells, basophils, Langerhans cells, and eosinophils degranulation leads to histamine release along with other vasoactive substances [10]. This can lead to mucus secretion, airway muscle contraction and the other extracutaneous symptoms seen in Stage 3 and Stage 4 CUS. It can be more dangerous than NICU due to reactions that occur away from the area of contact, possibly ending with anaphylactic shock and death.

PCD mechanism is not understood. A combination of type I and type IV reactions has been suggested as an explanation; PCD could be an eczematous IgE-mediated reaction through proteins [11]. Protein contact with the skin may cause ICU with PCD. Future insights into these mechanisms may aid our general knowledge of all forms of dermatitis.

## Agents of CUS

Both low molecular weight chemicals (molecular weight < 1000) and proteins (molecular weight 10,000-several hundred thousand) can lead to CUS [12].

NICU is often caused by stinging nettles from *Urtica dioica*. Other agents include preservatives, fragrances, flavorings in cosmetics, toiletries, topical medications, industrial chemicals, or foodstuffs such as benzoic and sorbic acid (Table 1) [9, 10].

ICU also has a wide range of causes. A previously common cause of ICU was natural rubber latex allergy, found in rubber materials. The prevalence of a latex reaction was estimated to be 0.7% in the general population and up to 17% in health care workers, but the incidence decreased since, due to the increased use of low-protein, low-allergenic, powder-free gloves [13, 14]. Risk factors for sensitization to latex protein include atopy and prolonged exposure through a damaged epidermis [10]. Plant or animal proteins, drugs and preservatives, and metals and other chemicals also have the capability to induce ICU (Table 1) [15]. Contact with chlorhexidine gluconate, a decontaminant commonly used in hospitals, has been identified to cause IgE-mediated anaphylaxis, particularly in patients during general anesthesia [16]. Polyethylene glycols have also been observed to cause ICU [17]. Skin contact with corticosteroids, beer, sodium hypochlorite, soy products, and cotton have been identified in case reports as rare causes of ICU [18–22].

The proteins that cause PCD can be divided into these four groups: group 1: fruits, vegetables, spices plants and woods; group 2: animal proteins; group 3: grains; group 4: enzymes [4•, 23]. PCD reactions to proteins in rubber latex have also been reported, although they are not as common as ICU reactions to rubber latex [23].

**Table 1. Agents of contact urticaria**

| Type of contact urticaria | Agents | |
|---|---|---|
| NICU | Cinnamaldehyde | Benzoic acid |
| | Cinnamic acid | Methyl nicotinate |
| | 3-pyridinecarboxaldehyde (strong) | 2-pyridinecarboxaldehyde (weak) |
| | Diethyl fumarate | Dimethyl sulfoxide (DMSO) |
| | Glycolic acid | Sorbic acid |
| | Benzaldehyde | Menthol |
| | Vanillin | Anisyl alcohol |
| | Eugenol | Chloroform |
| ICU | Penicillin | Ceriman |
| | Anhydrides for epoxy | Paul flower |
| | Persulphates in hair bleaching | Tulips |
| | *Ficus benjamina* | Crysanthemums |
| | Yucca plant | *Limonium tatarium* |
| | Fish | Mugwort |
| | Latex | Seminal Fluid |
| PCD | Rubber latex | Amniotic fluid |
| | Seafood | Dairy products |
| | Fruits | Vegetables |
| | α-amylase | γ-amylase |
| | barley | Wheat |

# Epidemiology

Prevalence of CUS within the general population is unknown. It is speculated that the condition often goes underdiagnosed as the symptoms are often minor, of short duration, and diagnostic testing is not routinely performed.

Of the cases reported, CUS is common in the occupational setting. A 12-year retrospective study in Australia demonstrated that of the 151 people diagnosed with CUS, 94.7% were work related. Health workers, food handlers, and hairdressers were most commonly affected. In this study, 65% of these patients were atopic and women were more likely to be affected than men (63 vs. 37%) [24]. Other occupations with an increased risk of developing CUS include agricultural and dairy workers, electronic workers, veterinarians, gardeners, and those using lip plumpers [7]. In patients susceptible to a CUS causing agent, any occupation that exposes them to an agent from Table 1 places them at risk for developing CUS.

A study done on occupational contact urticaria done between 2001 and 2010 reported 251 cases of CUS. Half of these cases were due to rubber latex

and a majority of these were in health care workers. It was noted however that CUS significantly declined throughout this time period—this decline was attributed to the banning of rubber latex gloves from French hospitals. Other substances that caused CUS in this study were vegetal proteins, animal proteins, and hair bleaching products [25].

## Diagnosis

The first step of diagnosing CUS is a full medical history. The patient should be asked about duration of symptoms, wheal distribution, exposure to suspected allergens/substances, symptoms, medications, and other diseases including atopic diseases. It should be stressed whether the patient has burn, sting, and/or itch minutes after the exposure.

There is a proposed protocol for testing immediate contact dermatitis reactions (Fig. 1). It begins with an "open test" on non-affected skin. With each negative reaction, "open testing" progresses from open application on normal skin to occlusive application on slightly affected skin.

Invasive testing is used if "open testing" is inconclusive. For this, "Prick testing" or a "Prick by Prick" test is used, the former with commercial reagents and the latter with fresh material (e.g., food allergens, pollens, sauces). A small volume of allergen (5–10 nL) is applied to a lancet which is used to puncture the skin. A positive prick test relies on the allergen coming in contact with mast cells, and is assessed after 15–20 min. The diameter of the wheal and flare reaction is measured.

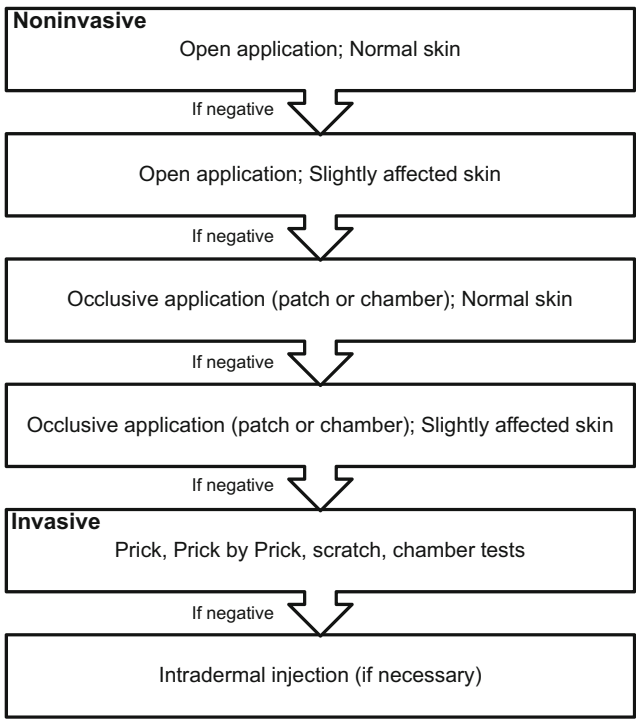


**Fig. 1.** Protocol for testing for contact urticaria (modified from (3)).

A "rubbing test" may be used if open testing is negative. It is conducted by gently rubbing the allergen against the skin. A "scratch test" can be used when a nonstandard allergen is studied. However, it must be considered that a scratch test is less standardized and less sensitive than a prick test. For both the rubbing test and scratch test, a Prick test with histamine hydrochloride is used as a positive control and aqueous sodium hydroxide is the negative reference.

Skin tests have been documented to produce life-threatening reactions; thus, trained personnel must conduct these tests in the presence of resuscitation equipment [26]. This is standard when extracutaneous symptoms have been noted.

Contact urticaria can also be diagnosed through molecular diagnosis [27]. This method measures the allergen sensitization of a patient by measuring the specific IgE level to possible allergens proteins. This method can improve specificity, distinguish cross-reactivity from true concomitant sensitization and improve indication and selection of suitable allergens for immunotherapy. Methods for measuring specific IgE levels have been used for animal and plant proteins including those contained in meat, fish, dogs, cats, horses, peanut, soybean, and wheat. These tests should always be correlated with clinical history as IgE levels do not always translate into clinical symptoms.

## Treatment

Proper treatment of CUS requires identifying the causative agent and avoidance of that agent. Thorough history taking and appropriate use of clinical testing are key to identification of the agent. After initial exposure, further avoidance of the agent will improve symptoms of contact urticaria and PCD. Patients must be educated on what to avoid once a diagnosis of CUS has been made. The importance of avoidance in treatment of CUS cannot be understated. In the case of rubber latex allergy, a common cause of CUS, guidelines have been put in place to prevent exposure in those at occupational risk.

Given that exposure may still occur after identification of CUS-causing agents, symptomatic treatment exists. Second-generation H1 antihistamines are the first-line treatment of CUS. They are known to decrease both the number and duration of wheals. H2 antagonists are sometimes used in conjunction with H1 antagonists, as 15% of skin receptors are H2 receptors. In refractory cases, a higher dose of antihistamine—up to fourfold the licensed dose of second-generation H1 antihistamines—is recommended before moving on to second line [7, 28].

Systemic corticosteroids should be reserved for acute, systemic symptoms of CUS and is not recommended for long term management [7].

## Compliance with Ethical Standards

**Conflict of Interest**

Austin Jiang declares that he has no conflict of interest. Howard Maibach declares that he has no conflict of interest.

**Human and Animal Rights**
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance


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