Contact Urticaria Syndrome

Edited by

Ana M. Giménez-Arnau ▪ Howard I. Maibach

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Edited by

Ana M. Giménez-Arnau, MD, PhD
Department of Dermatology
Universitat Pompeu Fabra
Universitat Autònoma de Barcelona
Barcelona

Howard I. Maibach, MD
Department of Dermatology
University of California at San Francisco
San Francisco, California

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We hope that this textbook can be useful for you in your routine professional tasks. We encourage you to work in this field, promoting an increase of knowledge especially about the unmet needs. Just a common approach through the clinical expression of the syndrome, the diagnostic tools, and the contact triggers involved will help to answer the questions that we have regarding epidemiological, mechanistic, or prognosis aspects. We, as editors, welcome comments or suggestions for the next edition.

Contents

Preface

It has been nearly four decades since contact urticaria syndrome was described for the first time (Maibach and Johnson, *Archives of Dermatology* 1975; 111:726–730). At that time diethytoluamide was responsible for an immediate type of hypersensitivity reaction characterized by contact-induced wheals. Since then, immediate skin contact reactions, pruritus, dermatitis, or urticaria were described as induced by multiple contact triggers. The increasing interest in this field was the reason for the book *Contact Urticaria Syndrome*, edited by Amim and Maibach in 1997. This text showed what was known at that time and summarized the experience of clinical investigators worldwide.

Since then, our knowledge about the contact urticaria syndrome has increased, especially during the epidemic of contact urticaria induced by latex. Through isolated or short series of reported cases, we've learned that proteins, but also low-molecular-weight substances, are capable of inducing the signs and symptoms. And, obviously slowly, the approach to the pathogenesis and the individual behavior of each trigger helps to better understand why these immediate contact reactions can be expressed through different clinical patterns. This updated book about contact urticaria syndrome extends previous experience.

But even now, in the twenty-first century, immediate cutaneous skin reactions such as pruritus, eczema, or wheals are underdiagnosed. Still dermatologists, allergologists, and occupational physicians rarely make the immediate diagnosis of contact skin reactions. Habitually, the simple question, "When did your symptoms start?" or "What was the interval between the contact and the symptom appearance?" is missing. Hopefully, the clinical experience summarized here will lead to a more accurate diagnostic approach. The appropriate diagnostic tool can be selected just by using a detailed history. And the appropriate diagnosis will lead to a better preventive and therapeutic approach. This is obviously important whenever a disease has a demonstrated impact in the quality of life and occupational relevance.

Contributors

Kristiina Aalto-Korte
Finnish Institute of Occupational Health
Control of Hypersensitivity Diseases
Helsinki, Finland

Flemming Andersen
Department of Dermatology and Allergy Centre
Odense University Hospital
Odense, Denmark

Klaus E. Andersen
Department of Dermatology and Allergy Centre
Odense University Hospital
Odense, Denmark

F. Augey
Lyon Hospitals
University of Lyon1
Pierre-Benité, France

F. Bérard
Lyon Hospitals
University of Lyon1
Pierre-Benité, France

Jonathan A. Bernstein
Department of Internal Medicine
University of Cincinnati College of Medicine
Cincinnati, Ohio

M. Braire-Bourrel
Lyon Hospitals
University of Lyon1
Pierre-Benité, France

Magnus Bruze
Department of Occupational and Environmental Dermatology
University Hospital
Malmö, Sweden

Vincent Cunanan
Department of Dermatology
University of California, San Francisco
San Francisco, California

Christopher J. Dannaker
Department of Dermatology
University of California, San Francisco
San Francisco, California

Parastoo Davari
Department of Dermatology
University of California, Davis
Davis, California

Ana M. Giménez-Arnau
Hospital del Mar
Barcelona, Spain

Elena Giménez-Arnau
Dermatology Laboratory
Strasbourg Institute of Chemistry
Strasbourg, France

Margarida Gonçalo
Department of Dermatology
University Hospital and Faculty of Medicine
University of Coimbra
Coimbra, Portugal

An Goossens
Department of Dermatology
University Hospital Leuven
Campus Sint-Raphaël
Leuven, Belgium

Eva Helaskoski
Finnish Institute of Occupational Health
Control of Hypersensitivity Diseases
Helsinki, Finland

Monica Hindsén
Department of Occupational and Environmental Dermatology
University Hospital
Malmö, Sweden

Majken G. Hougaard
Dermato-Allergology
University Hospital Copenhagen
National Allergy Research Centre
Gentofte Hospital
Copenhagen, Denmark

Marléne Isaksson
Department of Occupational and Environmental Dermatology
Skane University Hospital
Lund University
Malmö, Sweden

Riitta Jolanki
Finnish Institute of Occupational Health
Control of Hypersensitivity Diseases
Helsinki, Finland

Outi Kuuliala
Finnish Institute of Occupational Health
Control of Hypersensitivity Diseases
Helsinki, Finland

Arto Lahti
Department of Dermatology
University of Oulu
Oulu, Finland

Antti Lauerma
Skin and Allergy Hospital
Helsinki University Central Hospital
Helsinki, Finland

Howard I. Maibach
Department of Dermatology
University of California, San Francisco
San Francisco, California

Maria Estela Martinez-Escala
Dermatology Department
Hospital del Mar Medical Research Institute
Autonomous University of Barcelona
Barcelona, Spain

Pascale Mathelier-Fusade
Dermatology and Allergology Department
Tenon Hospital
Paris, France

Marcus Maurer
Department of Dermatology and Allergy
Charité—University of Medicine Berlin
Berlin, Germany

Martin Metz
Department of Dermatology and Allergy
Charité—University of Medicine Berlin
Berlin, Germany

Charlotte G. Mortz
Allergy Department
Jiménez Díaz Foundation
Centers of Biomedical Research Network (CIBER)
Carlos III Institute
Ministry of Economy and Competetiveness
Madrid, Spain

J.F. Nicolas
University of Lyon1
Lyon Hospitals
Pierre-Benité, France

Rosemary Nixon
Occupational Dermatology Research and Education Centre
Carlton, Victoria, Australia

Evy Paulsen
Department of Dermatology and Allergy Centre
Odense University Hospital
Odense, Denmark

Paolo Daniele Pigatto
Department of Biomedical Science for Health
University of Milan
and
Galeazzi Hospital
Milan, Italy

Eduardo Rozas-Muñoz
Dermatology Department
Hospital del Mar Medical Research Institute
Autonomous University of Barcelona
Barcelona, Spain

T. Rustemeyer
Department of Dermatology-Allergology
VU University Medical Center Amsterdam
Amsterdam, the Netherlands

Denis Sasseville
Department of Medicine (Dermatology)
McGill University Health Centre
Montréal, Quebec, Canada

Joaquín Sastre
Allergy Department
Jiménez Díaz Foundation
Centers of Biomedical Research Network (CIBER)
Carlos III Institute
Ministry of Economy and Competetiveness
Madrid, Spain

Oliver Schmetzer
Department of Dermatology and Allergy
Charité—University of Medicine Berlin
Berlin, Germany

Frank Siebenhaar
Department of Dermatology and Allergy
Charité—University of Medicine Berlin
Berlin, Germany

Angèle Soria
Dermatology and Allergology Department
Tenon Hospital
Paris, France

Monica Stanciu
Department of Medicine (Dermatology)
McGill University Health Centre
Montréal, Quebec, Canada

Päivikki Susitaival
North Carelia Central Hospital
Joensuu, Finland

Sari Suomela
Finnish Institute of Occupational Health
Control of Hypersensitivity Diseases
Helsinki, Finland

Jacob P. Thyssen
Department of Dermato-Allergology
University Hospital Copenhagen
Hellerup, Denmark

Ryan Toholka
Occupational Dermatology Research and Education Centre
Carlton, Victoria, Australia

Rossano Hermes Valsecchi
Department of Dermatology
Bergamo General Hospital
Bergamo, Italy

Lien Verhulst
Department of Dermatology
University Hospital Leuven
Campus Sint-Raphaël
Leuven, Belgium

1

Contact Urticaria Syndrome: Definition, History, Etiology, and Relevance

Ana M. Giménez-Arnau and Howard I. Maibach

Skin is the target organ of environmental agents. Through epidermal and dermal homeostasis, the cutaneous tegument has the main task of preserving our life. At least five fundamental skin roles can be defined: mechanical barrier function, melanogenesis, immunological barrier function, thermoregulation, and environmental perception. The epidermal and dermal binomiun is by itself a complex and complete immunological organ. The epidermal presence of specific specialized antigen-presenting cells, the Langerhans cells as well as local lymphocytes, join with the dermal presence of pluripotential cells, as mast cells, making the skin an immunologically very active organ. Skin is vital.

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, others as urticaria, contact urticaria, or lichenoid eruptions, are described. Contact dermatitis was recognized as a disease in ancient times. The earliest recorded reports include Pliny the Younger who, in the first century A.D., noticed individuals with severe itching when cutting pine trees. The history of contact dermatitis in the twentieth century is indistinguishable from the history of patch testing, which is considered the main tool for discovering the etiology is a chemical or a protein as the responsible agent.

The main objective of this book is to explain, from different perspectives, a special type of contact dermatitis that often is misdiagnosed: contact urticaria syndrome (CUS). It is misdiagnosed because traditionally type I (immunoglobulin E [IgE] immediate) and type IV (lymphocyte delayed) cutaneous reactions were identified with specific clinical expressions: immediate wheals for type I and delayed eczema for type IV. Even the available diagnostic tools used for etiological study of these patients are traditionally different for the suspected type I or type IV reactions. During the past decades, we've learned that proteins and low-molecular-weight molecules can induce immediate cutaneous reactions clinically expressed with pruritus, wheals, and eczema through an immunological pathway that still necessitates being completely understood.

Definition and History of the Birth of CUS

CUS comprises a heterogeneous group of immediate contact inflammatory reactions that usually appear within minutes after contact with eliciting substances. Occasionally, systemic involvement can be present. It was defined as an entity in 1975 by Maibach and Johnson.[1] Since then, its scientific interest has 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; it usually appears within 30 minutes and clears completely within hours without residual signs.[2] The term was introduced by Fisher (1973), but this phenomenon has long been recognized.[3] Urticarial lesions to nettles and hairy caterpillars were reported in the nineteenth century and continue being reported today.[4] In a randomly designed survey carried out in 1224 adults in Spain, contact wheals and pruritus were noticed by the 52.1% and 100%, respectively, of people who suffered cutaneous symptoms induced by pine processionary.[5] Furthermore, some naturally existing urticariogens were used therapeutically as rubefacients, counterirritants, and vesicants.[6]

Hjorth and Roed-Petersen defined (1976) protein contact dermatitis (PCD) as characterizing an immediate dermatitis induced after contact with proteins.[7–9] Thirty-three food caterers suffered exacerbation of an itch immediately after contact with meat, fish, and vegetables, which was followed by erythema and vesicles. 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 contact with the trigger substance. These immediate contact reactions can appear on normal or eczematous skin. Wheals are the characteristic symptoms in CoU. Eczema appears rapidly on the hands in PCD. Both cutaneous symptoms and entities can be induced by the same trigger factor and can be suffered by the same patient.

CUS, CoU, and PCD are conditions characterized by the immediate development of contact skin reactions (immediate contact skin reactions) mainly consisting of pruritus, wheals, and/or eczema.

CUS as Occupational Dermatosis: History and Unmet Needs

The global incidence of CUS is not known, but immediate contact reactions are common in dermatological practice.[12–17] With the exception of latex allergy showing prevalence of 5%–10%, the rest of the trigger factors are just isolated cases or describe a small series of patients.[18] In the occupational setting, CUS seems to be common, although a precise statistical analysis is difficult to obtain in most of the countries because of underreport.[19] In a few countries, CoU has been classified as a separate occupational skin disease. This has been 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%).[20,21] The trigger agents were cow dander (44.4%), natural rubber latex (23.7%), and flour, grains, or feed (11.3%).[21] A lower proportion of occupational CoU was found in a retrospective study done in a tertiary-level clinic specializing in occupational dermatology in Melbourne, Australia, which showed an 8.3% CoU prevalence.[22] Hands, arms, and face were the most frequent body areas 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, in a survey conducted in 335 restaurants, catering and fast-food employees in Singapore showed as more commonly having occupational dermatosis irritant contact dermatitis (10%), with occupational CoU urticaria sporadically reported just in two patients caused by lobster and prawn.[23] The nature of the exposure will probably determine the percentage of CoU risk.

Health care workers in Europe show a known prevalence of occupational CoU from 5% to 10%, whereas in the general population, it lies between 1% and 3%. Other occupations shows also a high risk for developing CoU because there are food handlers or people involved in agriculture, farming, floriculture, plastics, pharmaceutical and other laboratories, and hunters, veterinarians, biologists, or hairdressers. Atopy favors further sensitization where protein allergens are concerned.[24]

The classification of occupational dermatosis of the International Code of Diseases-11 includes contact dermatitis jointly with contact urticaria. Occupational screening questionnaires including specific questions searching for urticaria symptoms are very few. The long version of the Nordic Occupational Skin Questionnaire is one of them, including nine questions about urticaria symptoms.[25] A standardized method to evaluate the occupational relevance of CoU, such as that already developed for occupational contact dermatitis with Mathias' criteria [26], would be desirable.

Evolving Knowledge about the Mechanisms Involved in CUS

The mechanisms underlying immediate contact skin reactions are partially understood. Each trigger substance has its own mechanism or mechanisms of action.

Nonimmunologic contact urticaria (NICoU) is due to vasogenic mediators without involvement of immunological processes. Urticariogens may act following different patterns. The most classic example concerns dimethylsulfoxide, which damages the blood vessels, making them leaky and inducing mast cell degranulation.[27] 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.[28–30] Release of prostaglandin D2 without concomitant histamine release has been demonstrated following topical application of sorbic acid and benzoic acid.[31,32] Capsaicin pretreatment (which depletes substance P) does not impair NICoU, but does inhibit the allergen prick test flare of immunologic CoU (ICoU).[33] Nonspecific tachyphylaxis of variable duration has been associated with various urticariogens.[34] Sharp hairs from animals or spines from plants penetrating the skin can deliver a cocktail of irritant chemicals or pro-inflammatory mediators causing NICoU.[35]

The pathogenesis of ICoU reflects a type I hypersensitivity reaction, mediated by allergen-specific IgE in a previously sensitized individual.[36] 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.

Oral Allergy Syndrome (OAS) is generally the result of an IgE-mediated type I allergic response. People with birch pollinosis show cross-reactivity because its structural homology with Rosaceae fruits such as apples or peaches.[37–39] Nevertheless, some other foods such as peanuts (Ara h1 and 2) or fruits can induce OAS independently of pollinosis.

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.[40,41] 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.[42]

Demonstrated Responsible Agents of CUS

Proteins (molecular weight 10,000 to several hundred thousand) and chemicals (molecular weights below 1,000) can trigger CUS.[43]

Plant or animal proteins, chemicals such as drugs and preservatives, or more diverse substances such as metals and industrial chemicals can induce ICoU. Raw fruits and vegetables are a common cause of ICoU in daily life. Natural rubber latex allergy focused global interest in ICoU at the end of the twentieth century. Latex sensitization risk factors include atopy and prolonged exposure via damaged epidermis (e.g., glove wearers with hand eczema). Low-molecular-weight molecules normally act as haptens; nevertheless, for some of them IgE antibodies have been also demonstrated as, for example, sensitized workers reactive to platinum and nickel–serum albumin complexes.[44,45]

NICoU is defined by stinging nettle wheals induced from *Urtica dioica*. Other responsible agents are preservatives, fragrances, and flavorings in cosmetics, toiletries, topical medications, or foodstuffs such as benzoic and sorbic acid.[46] Household, industrial, insecticide, and laboratory chemicals can also induce NICoU.

Few substances elicit mixed features of NICoU and ICoU through an unestablished mechanism other than IgE, which is involved in ammonium persulfate-induced CoU, where specific IgG and IgM activate the complement cascade through the classical pathway.[47–49] Immediate reactions to formaldehyde do seem to be mediated by IgE, with a prostaglandin role suspected because of thromboxane B_2 and prostaglandin PGF_2 increased levels.[50,51]

A huge number of compounds can be responsible of occupational and nonoccupational CUS, including animal products, plants and plant derivatives, foods, fragrances, cosmetics, flavorings, medications, preservatives, disinfectants, enzymes, metals, and miscellanea of different substances. Tables 1.1 through 1.6 include most of the compounds that have been registered in the literature.[52–129]

TABLE 1.1

Animals, Plants, and Derivatives (Natural Products) Responsible for Immediate Contact Reaction

Animals and their derivatives

- Ammiotic fluid[a,b]
- Anisakis simplex
- Blood[a,b]
- *Brucella abortus*[b]
- Calf[a]
- Cow[a]
- Caterpillars[c]
- Cephalopodos (*Loligo vulgaris*)[a]
- Chironomus[b]
- Cockroaches[a,b]
- Corals[c]
- Dander[a,b]
- Dogs; milk, seminal fluid[a]
- Gut (pig)[a,b]
- Guinea pig[a,b]
- Hair (rat, mice)[a,b]
- Horse
- Human hair
- Jellyfish[b,c]
- Liver (mouse)[a]
- Locust Tee[a,b]
- *Lumbrineris impatiens*
- Mites[a,b]
- Moths[c]
- *Nereis diversicolor*
- Pig[a]
- Pearl oysters[a]
- Placenta (cow)[a,b]
- Saliva[b]
- Sarcophaga carnaria
- Rat[a]
- Roe deer
- Seminal fluidb
- Serum (amphibian)[a,b]
- Silk[b]
- Spider mite[a,b]
- Urine (mice, rat)[a,b]
- Worms[a]

Plants and derivatives

- Algae[b]
- Aloe (Morrow)
- Arugula[b]
- Birch[b]
- Bougainvillea
- Camomile[a]
- Camomlilla
- *Cannabis sativa*[a]
- Chrysanthemum[a,b]
- Cinchona[a]
- Coral[c]
- Corn powder
- Cotoneaster
- Crateagus (hawthorn)[b]
- Elm tree
- *Eruca sativa*[b]
- Eucalyptus[b]
- *Ficus benjamina*[b]
- Gerbera[a]
- *Grevillea juniperina*[c]
- *Hakea suaveolens*
- Larch
- Lichens
- Lilies[a,b]
- Lime (Tilia)
- *Limonium tartaricum*[a,b]
- Mahogany[a]
- Mulberry
- Obeche[a,b]
- *Phaseolus multiflorus*
- Parsley[b]
- Poppy flowers[b]
- Sea anemone[c]
- *Semecarpus anacardium*
- Sesame seeds[b]
- Sunflower seeds[b]
- Teak[b]
- Tobacco[a,b]
- Tropical woods[a,b]?
- Tulips[a,b]
- Verbena[a,b]

Plants derivatives

- Abietic acid
- Colophony[a,b]
- Cornstarch[a,b]
- Latex rubber[a,b]
- Turpentine[c]

Source: Updated and adapted from Gimenez-Arnau et al., *Eur. J. Dermatol*., 20, 1–11, 2010.

[a] Occupational.

[b] Immunologic.

[c] Nonimmunologic.

TABLE 1.2

Foods and Food Additives Responsible for Immediate Contact Reaction

Meat[b]

- Beef[a]
- Calf[a,b]
- Chicken[a]
- Codfish
- Ham (*Tyrophagus putrescentiae*)
- Lamb
- Liver
- Pork[a]
- Sausage
- Turkey

Fish[a,b,c]

- Cod[a]
- Crab
- Frog[a,b]
- Herring[a]
- Lobster[a]
- Lupin
- Oysters[a]
- Plaice[a]
- Pork[a]
- Raw fish[a]
- Seafood[b]
- Shrimp[a]

Other animal products

- Cheese[a]
- Eggs[a]
- Honey
- Milk[a]

Fruits[b]

- Almond[a]
- Apple[a]
- Apricot
- Apricot stone[a]
- Banan[a]
- Kiwi
- Litchi
- Lemon[a]
- Lemon peel[a]
- Lime[a]
- Mango
- Nuts[b]
- Orange
- Peach
- Peanuts
- Peanut butter
- Plum
- Strawberry[a]
- Watermelon[a]

Seeds[b]

- Sesame seeds[b]
- Sunflower seeds[b]

Grains[b]

- Buckwheat[a]
- Flour[a]
- Maize[a]
- Malt
- Rice[a]
- Wheat[a]
- Wheat bran

Vegetables[b]

- Asparagus[a,b]
- Arugula[b]
- Beans[a]
- Cabbage[a,b]
- Carrots[a]
- Castor bean[a,b]
- Celery[a]
- Chamomilla
- Chicori
- Chives
- Coffee been (green)[a,b]
- Cucumber pickle[a,b]?
- Dill[b]
- Endive[a,b]
- Fungi
- Garlic[a,b]
- Lettuce[a,b]
- Lime[a]
- Mentha[a]
- Mushrooms[a,b]
- Mustard[a,b]
- Onion[a,b]
- Parsley[a]
- Parsnip[a]
- Potato[a]
- Rice[7]
- Rocket
- Runner bean[c]
- Rutabaga (Swede)
- Salami casing molds[a,b]

TABLE 1.2 (*Continued*)

Foods and Food Additives Responsible for Immediate Contact Reaction

- Soybean[a]
- Stock (Matthiola incana)
- Tomato[a,b,c]
- Winged bean[a,b]

Flavoring and fragrances

- Balsam of Peru[b,c]
- Benzaldehyde[a,c]
- Benzoic acid
- Cinnamon oil
- Cinnamic acid[c]
- Cinnamic aldehyde[a,c]
- Gum arabic[a,b]
- Menthol[c]
- Vanillin[c]

Condiments and spices

- Cayenne pepper[c]
- Caraway[a]
- Coriander
- Curry[a]
- Paprika (*Capsicum annuum*)[a,b]
- Thyme[c]

Coloring agents

- Amaranth
- Allura red
- Cochineal red
- Ponceau
- Sunset yellow
- Tartrazine

Source: Updated and adapted from Gimenez-Arnau et al., *Eur. J. Dermatol*., 20, 1–11, 2010.
[a] Occupational.
[b] Immunologic.
[c] Nonimmunologic.

TABLE 1.3

Fragrances and Cosmetics Responsible for Immediate Contact Reaction

Hair care products

- Ammonium persulfate[a]
- Basic blue 99 (amino ketone dye)[b]
- Henna[a,b]
- Panthenol
- Protein hydrolysate[a]
- Paraphenylenediamine[a,b]

Emulsifiers

- Cetyl alcohol
- Polysorbate
- Sorbitan monolaurate
- Sorbitan monostearate
- Sorbitan sesquiolate
- Stearyl alcohol

Fragrances

- α-Amyl cinnamic aldehyde[c]
- Anysil alcohol[c]
- Balsam of Peru[a,b,c]?
- Cassia oil[c]
- Carvone[b]
- Cinnamic aldehyde[c]
- Cinnamic alcohol[c]
- Cinnamic acid[c]
- Coumarin[c]
- Eugenol[c]
- Geraniol[c]
- Hydroxycitronellal[c]

Other substances

- Allantoin
- Aloe gel[b]?
- Benzophenone[b,c]
- Colophony[b]
- Chamomile extract[b]?
- Chestnut peel[b]
- Elastin, fish-derived[b]
- Glycolic acid peel[b]
- Lecithin[b]?
- Melissa extract[b]?
- Pyrrolidone carboxylate[c]
- Propylene glycol[c]
- Resorcinol[c]
- Wheata,[b]
- Wool alcohol[b]

Source: Updated and adapted from Gimenez-Arnau et al., *Eur. J. Dermatol*., 20, 1–11, 2010.
[a] Occupational.
[b] Immunologic.
[c] Nonimmunologic.

TABLE 1.4

Drugs Responsible for Immediate Contact Reaction

- Acetylsalicylic acid
- Aescin[b]?
- Aminophenazone
- Ampicillin[b]
- Amoxicilin[a]
- Bacitracin[b]
- Benzocaine
- Benzoyl peroxide[b]
- Capsaicin[c]
- Carboxymethylcellulose sodium[b]
- Chloroform[c]
- Cephalosporins[a,b]
- Cisplatin[a,b]
- Chloramphenicol[b]
- Chlorpromazine
- Dinitrochlorobenzene
- Diphenylcyclopropenone[b]
- Dimethylsulfoxide[c]
- Donezepil
- Gentamycin[b]
- Guanidinium salts[a]
- Hexylene Glycol[b] (excipient)
- Iodochlorhydroxyquin[b]
- Ketoprofen
- Lidocaine
- Levofloxacine[b]
- Levopromazine[a]
- Lindane[b]
- Mechlorethamine[b]
- Methamizole[a]
- Mezlocillin[a,b]
- Neomycin[b]
- Nicotinic acid esters[c]
- *N,N*-diethyl-meta-toluamide (DEET)[b]
- Penicillin[a,b]
- Pentamidine isethionate[a,b]
- Phenothiazides[b]
- Pilocarpine
- Prophylphenazone
- Promethazine
- Pyrazolones[b]
- Rifamycin[b]
- Sodium fusidate[b]
- Steroids
- Streptomycin[a,b]
- Tar extracts[c]
- Tincture of benzoin[c]
- Uranium salts[a]
- Virginiamycin[b]

Source: Updated and adapted from Gimenez-Arnau et al., *Eur. J. Dermatol*., 20, 1–11, 2010.
[a] Occupational.
[b] Immunologic.
[c] Nonimmunologic.

TABLE 1.5

Preservatives Responsible for Immediate Contact Reaction

- Acetic acid
- Aescin polysulfate
- Alcohols[b,c]
  - Amyl
  - Ethyl
  - Butyl
  - Isopropyl
  - Benzyl[b,c]
- Ammonia[b]
- Benzoic acid[b,c]?
- Benzyl alcohol
- Bronoprol[c]
- Butilated hydroxytoluene[b]?
- Camphor[c]
- Chloramine[b]
- Chlorhexidine[b]
- Chlorine
- Chlorocresol[a,b,c]
- Formaldehyde[a,b,c]
- Gentian violet[b]
- Hexylene glycol[b]
- Imidazolidinyl urea[c]
- Kathon CG[c]
- Mercurochrome[b]
- α-phenylphenate[b]
- P-chlorocresol
- Parabens[b]?
- 2-phenoxyethanol
- Phenylmercuric acetate[a,b]
- Phenyl mercuric propionate[b]
- Polyethileneglycol
- Sodium benzoate[a,c]
- Sodium hypochlorite[b]
- Sorbic acid[c]
- Triclosan[b]

Source: Updated and adapted from Gimenez-Arnau et al., *Eur. J. Dermatol*., 20, 1–11, 2010.
[a] Occupational.
[b] Immunologic.
[c] Nonimmunologic.

TABLE 1.6

Miscellaneous Chemicals and Metals Responsible for Immediate Contact Reaction

- Acetyl acetone[b]
- Acid anhydrides[a,b]
- Acrylic acid[b]?
- Acrylic monomers[a,b]
- Aliphatic polyamide[a,b]
- P-aminodiphenylamine[a,b]
- Aminothiazole
- Aziridine[a,b]
- Benzonitrile[a]
- Butylhidroxytoluol
- Calcium hypochloride
- Carbamates[a,b]
- Carbonless copy paper[a,b]
- Chlorotalonil[a,b]
- Citraconin anhydride
- Denatonium benzoate[a,b]?
- Di(2-ethyhexyl)phthalate[a]
- Dicyanidiamide
- Didecyl dimethyl ammonium chloride[a,b]
- Diethylfumarate
- Diethyltoluamine[b]
- Dimethyl ammonium chloride[a]
- Didecyl dimethyl ammonium chloride
- Diclycidyl ether of bisphenol A[a,b]
- Formaldehyde resin[a,b]
- Fumaric acid
- Guanidinium salts[a]
- Methyl ethyl ketone[b]
- Monoamylamine[b]
- Naphta[a,c]
- Naphthylacetic acid
- Nitrile[a]
- Nylon[b]
- Oleylamide
- Phosphorus sesquisulfide
- Polypropylene[a]
- Potassium ferricyanide
- Sodium fluoride
- Sodium silicate
- Sodium sulfide
- Sulfur[c]
- Triphenyl phosphate[a]
- Trichloroethanol
- Uranium salts[a]
- Vinyl pyridine[a]
- Xylene[a]
- Zinc diethyldiothiocarbamate[a]
- Metals
  - Aluminum
  - Chromium[a,b]
  - Cobalt[a,b]
  - Copper
  - Gold
  - Iridium[a,b]
  - Mercury[b]?
  - Nickel[a,b]
  - Palladium
  - Platinum salts[a,b]
  - Rhodium[a]
  - Ruthenium
  - Tin
  - Zin[c]

Source: Updated and adapted from Gimenez-Arnau et al., *Eur. J. Dermatol*., 20, 1–11, 2010.
[a] Occupational.
[b] Immunologic.
[c] Nonimmunologic.

Looking for Answers to Challenges Afforded in This Second Edition of CUS

Until now, we assumed new cases of CoU, PCD, or CUS as exceptional findings, adding new triggers each year to long lists of substances. But is this condition really exceptional? General population-based epidemiological studies are still lacking. Proteins and low-molecular-weight chemicals can be responsible for clinical manifestations, urticaria, or eczema, which are a consequence of different pathogenic mechanisms. Are the intrinsic properties of the environmental trigger of CUS responsible for the specific immunological pathway involved? Sometimes the same substance can induce both clinical patterns. This fact opens the door for new insights into new immune

system pathways. Substances responsible for immediate contact skin reactions can be classified by molecular weight, mechanism of action, occupational relevance, or their common use in our daily life. Our diagnostic tools still are based in subjective assessment. How can we improve these tools? It will be useful to replace *in vivo* tests with effective *in vitro* testing for diagnostic purposes. How do we better understand the disease behavior to help us develop effective preventive measures? A correct etiological diagnosis is necessary. After the symptoms, controlling the development of concrete preventive measures is required. After reading this book, we will most likely conclude that CUS is a worldwide health problem that needs a global approach.

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2

Contact Urticaria Syndrome: Epidemiology and Occupational Relevance

Kristiina Aalto-Korte and Sari Suomela

Introduction

It is unlikely that contact urticaria (CoU) is rare, especially among atopic individuals, but no available figures on its prevalence in the general population are available. The literature mainly consists of case reports or small patient series, dominated by rare causes and severe generalized symptoms. According to our experience, the symptoms of CoU are usually mild, of short duration, and limited to small skin areas. The diagnostic test, an open application test, is 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. Patients with a suspected occupational skin disease, in turn, are investigated more thoroughly, at least in some centers. The general knowledge on the epidemiology of CoU is largely based on the statistics of certain countries that register occupational cases of CoU. The only exception are data on natural rubber latex (NRL) allergy, which is also reported in the general population. In occupational settings, CoU is quite common.

What Is Known about the Epidemiology of Nonoccupational Contact Urticaria?

Natural rubber latex caused an epidemic of occupational CoU in health care workers in the 1990s because of escalating glove use in this sector.[1] In an international meta-analysis from studies performed in 1990–2003, immunoglobulin E (IgE)-mediated allergy to NRL ranged from 1.4% to 1.65% in the general population, and from 4.1% to 5% in the health care worker population.[2] New cases of NRL allergy have decreased significantly, especially after health authorities have required the use of low-allergen/low-protein nonpowdered protective gloves.[1] The prevalence of immediate NRL allergy in Western Europe is approximately 1% or less.[1]

There are limited data on the prevalence of immediate contact reactions other than NRL allergy. Skin contact reactions are 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, in turn cause skin contact reactions. These contact reactions are common in certain occupations; among veterinarians for instance, but similar studies on nonoccupational exposure are lacking.

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 edema of the hands after peeling potatoes; of the 59 apple-positive patients, four had itchy dermatitis of the hands after handling apples; and of the 46 carrot-positive patients, six had similar symptoms after peeling carrots.[3] In a Spanish series of 197 children with IgE-mediated fish allergy, 29 had cutaneous symptoms after skin contact with fish.[4] 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 urticarial.[5] Authors of the study did not comment on whether the CoU 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 a urticaria reaction.[6]

Symptoms of Occupational Contact Urticaria and Associated Diseases

In regard to occupational CoU, the majority of patients have mild, local symptoms at the site of the external contact. These are of short duration, and the patients rarely report them to their physician. The area of skin contact is usually limited. If the exposure continues, it is possible that the initially local urticaria, for example, on the hands and forearms, may evolve to generalized urticaria. The patients may develop extracutaneous symptoms; rhinitis, asthma, or gastrointestinal symptoms, but these are rarely from skin contact. It is more common that these symptoms derive from the direct exposure of the respective organ (i.e., the respiratory or gastrointestinal tract). In fact, respiratory symptoms, allergic rhinitis, and asthma are common among patients with occupational contact urticarial,[7–9] but these symptoms usually arise from inhalation of the same allergen, for example, wheat flour. Skin symptoms may appear first before the patient develops rhinitis or asthma. "Oral allergy syndrome" and gastrointestinal symptoms may occasionally develop from eating the occupational allergen, but the majority of patients with occupational CoU can eat the food they are allergic to, such as wheat, without any problems. Nevertheless, the use of hydrolyzed wheat-containing soap caused an epidemic of immediate contact reactions in Japan, and a fairly large number of the Japanese patients also developed wheat-dependent, exercise-induced anaphylaxis, a syndrome resulting from indigestion of wheat and physical exercise.[10]

Intact skin is a relatively strong barrier to the systemic absorption of protein allergens. Allergens more easily penetrate mucosal membranes and wounds in the skin, and the resulting systemic absorption may lead to multiorgan symptoms (anaphylaxis). Massive exposure to the whole skin area may lead to severe symptoms; for example, anaphylaxis resulting from chlorhexidine bath.[11] Occupational CoU is often associated with hand dermatitis, which may represent protein contact dermatitis, irritant contact dermatitis, delayed allergic contact dermatitis from other allergens, atopic hand dermatitis, or chronic hand dermatitis. If the hand dermatitis heals, it is possible that the patient may no longer react to the allergen that earlier provoked clear, immediate urticaria symptoms when the hands were affected by dermatitis. This change is probably from an improvement of the skin barrier.

The allergens of immediate allergy are usually proteins of animal and plant origin, such as foods or natural rubber. CoU, asthma, rhinitis or anaphylactic symptoms can also be caused by low-molecular-weight (LMW) chemicals such as persulfates (hair bleaches), carboxyl acid anhydrides (electric industry), or chlorhexidine (a widely used antiseptic agent). Immediate chemical hypersensitivity is rare when compared with reactions to protein allergens. Protein contact dermatitis is naturally not caused by LMW chemicals.

Statistics on Occupational Contact Urticaria

Australian Data

Patients investigated in a tertiary-level specialist occupational dermatology clinic in Melbourne were reviewed from 1993 to 2004: CoU was diagnosed in 143 (9.9%) of 1443 patients with substantially or partially work-related dermatosis.[12] NRL was the cause in the majority of the cases (52%). Foods were the second most common cause, comprising 35% of the cases. The third most common cause was ammonium persulfate used in hair bleaches by hairdressers. CoU was more common among females than males (63% vs. 37%). Atopy was a significant risk factor for occupational CoU: 65% of the patients with this diagnosis were atopic. The most common sites of skin involvement were hands in 87% of the occupational CoU cases, followed by arms in 25% and the face in 21%. Occupational contact urticaria was most commonly seen among registered nurses (27 of 143; 19%) followed by chefs (26; 18%). CoU was diagnosed in 16% of the registered nurses with occupational skin

diseases, in 48% of the chefs with occupational skin diseases, and in 12% of the hairdressers with occupational skin diseases. CoU was the sole diagnosis in only 10% of the CoU cases.

UK Data

Consultant dermatologists in the United Kingdom report occupational skin diseases to EPIDERM, a voluntary surveillance system. Occupational physicians have a similar scheme called OPRA. Between 1996 and 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.[13] In EPIDERM, CoU was relevant in 4% of the reported cases of occupational skin disease. In accordance with the Australian data, the rates for CoU among women were twice those among men. Between 2002 and 2005, 336 CoU cases were reported to EPIDERM; 41% of these were codiagnosed with contact dermatitis and 75.5% were associated with exposure to NRL.[14] When data from EPIDERM and OPRA were combined, cases of CoU peaked in 1996, but have since declined.[15]

Finnish Data

According to the Finnish Register of Occupational Diseases, between 2005 and 2010 there were 329 (10.4%) notified cases of CoU or protein contact dermatitis among a total of 3170 notified cases of occupational skin disease. These figures are comparable with the Australian data.[12] The earlier Finnish statistics only composed suspected cases, and the number of notified cases was not available. The number of CoU and/or protein contact dermatitis cases seems to have decreased: between 1990 and 1994, the number of suspected new cases was 815 (an average of 163 suspected cases/year),[16] whereas between 2005 and 2010, there was only an average of 74 new suspected cases/year. In line with the Australian and the UK data, in terms of the notified cases, CoU and/or protein contact dermatitis was more common among women (62%) than among men (38%).

Between 2005 and 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%) (Table 2.1). Because 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.

TABLE 2.1

Most Common Causes of Occupational Contact Urticaria and Protein Contact Dermatitis in 2005–2010 According to the Finnish Register of Occupational Diseases (329 Notified Cases; 125 Males)

Cause	Number of Cases	Males
Cow dander	158	66
Flour, grains, and animal feed	55	25
Natural rubber latex	32	4
Fish and shrimps	15	5
Other animals (pig, rat, mouse, dog)	12	4
Ornamental plants	9	0
Vegetables and fruits	6	3
Ammonium persulfate	5	0
Spices	4	3
Other food	4	1
Enzymes	3	1
Anhydrides	3	3
Chloramine T	1	0

A special feature of Finland is the large number of immediate cow dander allergies. Cows are kept inside all winter, and workers are exposed to cow dander to a greater extent than in other countries.

Flour, grain, and other foodstuff formed the second most significant group of materials that caused immediate skin contact allergy in Finland. In contrast to the Australian and UK data,[12,13] foods are now a much more significant cause than NRL. In addition to animal dander, farmers and other farm workers are exposed to animal feed, mostly oat and barley. Wheat flour is the most common foodstuff that causes immediate skin contact allergy in kitchen work.

Between 1990 and 1994, NRL allergy was the second most common allergen after cow dander and caused an average of 39 new suspected cases of CoU and protein contact dermatitis per year.[16] Currently, however, the significance of NRL allergy has decreased (from 2005 to 2010, an average of seven new suspected cases/year; Figure 2.1) in Finland. NRL gloves have been replaced with polyvinyl chloride gloves and also to some extent with nitrile gloves. In addition, the quality of NRL gloves in the Finnish market has improved according to repeated analyses of the allergen content of the NRL gloves.

Ammonium persulfate was the third most common cause of CoU in Australia, but in Finland it has never been so significant: between 2005 and 2010, only five reported cases (0.2%) were diagnosed.

Industrial enzymes have lost some their relative significance when compared with 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 has skin contact reactions.

The majority of CoU cases is caused by protein-containing organic material, and the mechanism is usually IgE-mediated. Occupational CoU caused by LMW chemicals is rare. In Finland they composed only about 3% of the notified occupational CoU and protein contact dermatitis cases in 2005–2010. The mechanism of chemical-induced CoU 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.

The occupations with the highest incidence of occupational CoU/protein contact dermatitis in Finland in 2005–2010 are presented in Table 2.2. Farm relief workers, farmers, and animal workers formed the largest group in absolute numbers of new cases (N = 181) because of the high number of cow dander allergy cases. In contrast to Australia and the United Kingdom, health care workers (N = 22) were only the third largest group in Finland, preceded by bakers, chefs, and other food-related occupations (N = 60). This is due to the relatively low number of NRL allergy in Finland. In line with the Australian data, hairdressers had a relatively high incidence of CoU in Finland.

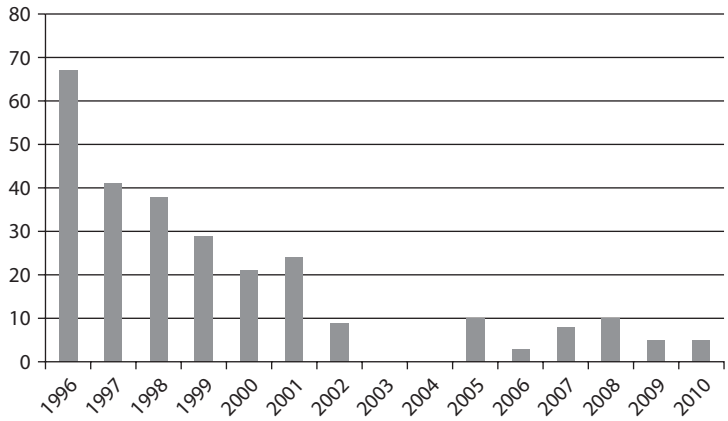

FIGURE 2.1 Incidence of suspected cases of occupational CoU and/or protein contact dermatitis resulting from natural rubber latex (number of new cases/year) according to the Finnish Register of Occupational Disease 1996–2010 (data for 2003 and 2004 are missing).

TABLE 2.2

Occupations with the Highest Incidence of Occupational Contact Urticaria and Protein Contact Dermatitis in Finland in 2005–2010 (Notified Cases)

Occupation	Number of Cases in Total	Number of Cases per 10,000 Workers per Year	Main Causes
Farm relief worker	38	10.0	Cow (N = 30)
Bakers and confectioners	15	8.7	Flour (N = 14)
Farmers, animal workers	143	6.2	Cow (N = 123)
Chefs, cooks, cold buffet managers	30	2.3	Flour (N = 10), fish (N = 7)
Workers in bakery and chocolate industry	3	1.2	Flour (N = 2)
Hairdressers and barbers	7	0.9	Persulfates (N = 5)
Restaurant and kitchen managers	6	0.8	Flour (N = 2)
Dental nurses	3	0.7	Natural rubber latex (N = 3)
Laboratory workers	4	0.6	Rat, pepsin, natural rubber latex
Plastic product workers	2	0.6	Natural rubber latex
Garden and greenhouse workers	5	0.5	Plants (N = 5)
Dentists	1	0.3	Natural rubber latex
Meat and fish product workers	1	0.3	Pork
Painters	2	0.3	Natural rubber latex, epoxy resin
Nurses, midwives, assistant nurses	18	0.2	Natural rubber latex (N = 16)
Waiters and kitchen assistants	5	0.2	Flour (N = 4)

Risk Occupations

The occupations most at risk and the main causes of CoU/protein contact dermatitis are presented in Table 2.3.

Health Care Workers

Health care workers are the highest risk group in many countries because of NRL allergy. Other allergens in this sector include chlorhexidine, chloramine T, antibiotics, and other drugs.

NRL allergy can be prevented by using low-allergen/low-protein, nonpowdered gloves: new cases of NRL allergy have decreased significantly and even virtually disappeared in countries and hospital regions in which health authorities have required the use of such gloves.[1] Germany banned the use of powdered NRL gloves in 1998, and the incidence of NRL-induced CoU among health care workers decreased from 0.3 cases/1000 workers/year in 1996 to 0.07 cases/1000 workers/year in 2002.[17] In Finland between 2005 and 2010, the incidence of NRL allergy among dental nurses was also 0.07 cases/1000 workers/year, and among nurses, midwives, and assistant nurses 0.02 cases/1000 workers/year.

Food-Related Occupations

A recent Danish report describes 372 cases of occupational hand dermatosis in food-related occupations over a 10-year period: 22% had protein contact dermatitis and 2.4% CoU. Substantially more patients reacted in skin prick tests to fresh foods than to food extracts.[18] The low number of flour allergy compared with the Finnish figures is striking: in the Danish study, flours were tested as commercial extracts, whereas in Finland these test substances were abandoned in the early 1990s because of their low allergen content. Suspensions of flour are used instead of commercial extracts, and many patients reacting to these test substances also have urticaria reactions in an open application test with flours.

TABLE 2.3

Risk Occupations and Main Causes of Contact Urticaria

Risk Occupation	Main Causes
Health care workers	Natural rubber latex, chlorhexidine, chloramine T, antibiotics
Bakers	Flour and enzymes
Cooks and other food handlers	Vegetables, grain, fruits, fish, seafood, other food
Veterinarians, slaughterhouse workers, butchers	Animal proteins
Farmers, domestic animal attendants	Animal dander, grain
Hairdressers	Persulfates, protein hydrolysates
Gardeners, florists	Plants
Workers in manufacture of electrical machines	Acid anhydrides
Fishermen	Fish, seafood

Plant-Related Occupations

In a Danish study on occupational skin symptoms among 253 gardeners and greenhouse workers, 67 (27%) workers had had plant-related, short-lived skin symptoms, implying CoU. Prick tests with plants were performed on 105 workers, and 35 (33%) had positive reactions to at least one plant. The majority of these people had had CoU (24; 69%). Mucosal eye and nasal symptoms were also common (22; 63%), and two had asthma (6%).[7]

Animal-Related Occupations

Veterinarians and animal attendants belong to occupations at risk of immediate skin allergy to animal dander and excretions. In a sample of 1416 Californian veterinarians, almost one in five reported animal-related skin symptoms. Of these, 65% reported symptoms related to only one animal and 66% of the reported symptoms appeared in minutes after contact.[19] In the same material, respiratory symptoms were also common and often appeared in people who had skin symptoms.[9] In a Finnish study of 245 laboratory animal workers, 156 completed a questionnaire on work-related symptoms. Forty-seven of these were examined for laboratory animal allergy. In 26 challenge tests with live animals, 12 workers showed immediate skin symptoms, three had rhinitis, and seven had both skin symptoms and rhinitis.[20] In a population of 2005 Finnish farmers, 172 reported hand or forearm dermatoses in a questionnaire, and 138 attended a clinical examination. Immediate cow dander allergy was diagnosed in 28 patients.[21]

Prognosis of Occupational Contact Urticaria and Protein Contact Dermatitis

In a six-month follow-up study of 1048 patients diagnosed with an occupational skin disease at the Finnish Institute of Occupational Health, patients with CoU or protein contact dermatitis had the most favorable prognosis compared with those with occupational allergic contact dermatitis and occupational irritant contact dermatitis.[22] This material also comprised patients with CoU as a sole diagnosis (without hand eczema). In a recent Danish report on work-related hand dermatoses in food-related occupations, patients with protein contact dermatitis had experienced more severe and frequent consequences than patients with other diagnoses.[23] 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%).[24]

Conclusions

Data on the epidemiology of CoU are limited, because the disease often remains undiagnosed from the mildness of symptoms. The only exception is NRL allergy, which caused an epidemic in the 1990s among health care personnel and sensitized 1%–2% of the general population. NRL allergy can be prevented by using low-allergen/nonpowdered NRL gloves, and this has resulted in a decrease in the number of new cases in several European countries. CoU is relatively common among patients with occupational dermatosis: 5%–10% of cases have CoU. Various foods form an important group of allergens that sensitize bakers and other food handlers. Animal dander, ornamental plants, and enzymes are other sensitizing proteins that cause CoU. Hairdressers may develop CoU from persulfates in hair bleaches.

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3

Contact Urticaria Syndrome: How It Is Clinically Manifested and How to Diagnose It

Ana M. Giménez-Arnau

Contact urticaria syndrome (CUS), contact urticaria (CoU), and protein contact dermatitis (PCD) are conditions characterized by the immediate development of a contact skin reaction showing clinically different patterns of inflammation (e.g., erythema, wheals, eczema). These entities are described independently. The main manifestation of CoU is a wheal, angioedema, or both. Eczema can be the sole manifestation of PCD. Pruritus is almost always present as it is the hallmark symptom. But urticaria and eczema can many times be induced by the same trigger being present simultaneously or consecutively.[1] Our clinical experience suggest that CoU and PCD can be suffered simultaneously by the same patient induced by the same trigger. CoU and PCD encompass CUS.

Staging the Severity of CUS

CUS has been classified in four stages (Tables 3.1 and 3.2). 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 sensations. When CoU is present, it shows as itchy wheals that are usually strictly limited to contact areas and that disappear within a few hours without residual lesions. PCD typically affects the hands (especially the fingertips) and sometimes extends to the wrists and arms. Chronic paronychia with redness and swelling of the proximal nail fold after handling food [2] and natural rubber latex (NRL) [3] 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-conjunctivitis, orolaryngeal symptoms, or gastrointestinal dysfunctions. Internal organs may be involved in CUS patients, depending upon the allergen or preexisting conditions such as atopic dermatitis.[4,5] Either through contact or in the case of a volatile allergen, rhino-conjunctivitis 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.[6] The severity of this multisystemic disease has been reported by Von Krogh and Maibach.[7] Finally, in stage 4, anaphylactic or anaphylactoid reactions may occur as the most severe type of CUS manifestation. CoU can be life-threatening: certain substances, such as latex protein, can induce anaphylaxis and even death.

Oral allergy syndrome can be considered as a special form of CUS localized in mouth and throat. Usually its symptoms are immediate after oral contact with the food involved. They include oropharyngeal pruritus (itching of mouth, palate, and throat); angioedema of lips, tongue, and palate; and hoarseness. The oral syndrome can be accompanied by gastrointestinal reactions and systemic involvement showing urticaria, rhinitis, asthma, or even anaphylaxis.

Definition and Behavior of the Cutaneous Lesions Involved in CUS

Urticaria and Angioedema: Symptoms of CoU

Urticaria is defined by its primary lesion, which is called a wheal or hive. This lesion is characterized by three major features: transient edema of the dermal tissue, a surrounding reflex erythema, and intense pruritus or itch at the same time.[8] Clinically, these three typical features are as follows. Central swelling of variable size, almost

invariably surrounded by a reflex erythema, and associated with itching or sometimes burning sensation. The wheal has a fleeting nature and the skin returns to its normal appearance usually within 1–24 hours.[9] Angioedema is characterized by a sudden, pronounced erythematous or skin-colored swelling of the lower dermis and subcutis with frequent involvement below the mucous membranes. Sometimes it is painful rather than an itching and frequently is involved below the mucous membranes. Its resolution takes up 72 hours. According with the latest consensus classification of chronic urticaria published, CoU belongs to the group of inducible urticarias [9] (Table 3.3).

TABLE 3.1

Definition of the Cutaneous Manifestations Involved in Stage I Contact Urticaria Syndrome

Contact urticaria
Immediate contact dermatitis (chemicals, proteins, protein contact dermatitis)
Itching, tingling, or burning sensation

- Contact urticaria refers to a wheal and flare reaction following external contact with a substance, and usually appears within 30 minutes and clears completely within hours without residual signs of irritation
- Dermatitis refers to tiny vesicles that rapidly appear after external contact with a substance; in some cases, it can be demonstrated only on slightly or previously affected skin and can be part of the mechanism responsible for chronic eczema

TABLE 3.2

Stages of Contact Urticaria Syndrome

Stage 1	Localized urticaria (redness and swelling) Immediate contact dermatitis (eczema, protein contact dermatitis) Itching, tingling, or burning sensation
Stage 2	Generalized urticaria
Stage 3	Bronchial asthma (wheezing) Rhinitis, conjunctivitis (runny nose, watery eyes) Orolaryngeal symptoms (lip swelling, hoarseness, difficulty swallowing) Gastrointestinal symptoms (nausea, vomiting, diarrhea, cramps)
Stage 4	Anaphylactic or anaphylactoid reaction (shock)

TABLE 3.3

Classification of Chronic Urticaria Subtypes (Presenting Wheals, Angioedema, or Both)

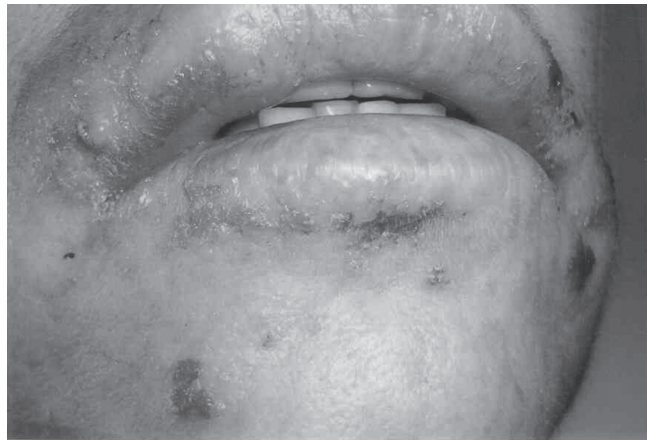
Chronic Urticaria Subtypes	
Chronic Spontaneous Urticaria	**Inducible Urticaria**
Spontaneous appearance of wheals, angioedema, or both ≥6 weeks from known or unknown causes	Physical urticarias Symptomatic dermographism[a] Cold urticaria[b] Delayed pressure urticaria[c] Solar urticaria Heat urticaria[d] Vibratory angioedema Cholinergic urticaria Contact urticaria Aquagenic urticaria

Source: Zuberbier T, Asero R, Bindslev-Jensen C et al. *Allergy*, Apr. 30, 2014, doi: 10.1111/all.12313
[a]Also called urticaria factitia or dermographic urticaria.
[b]Also called cold contact urticaria.
[c]Also called pressure urticaria.
[d]Also called heat contact urticaria.

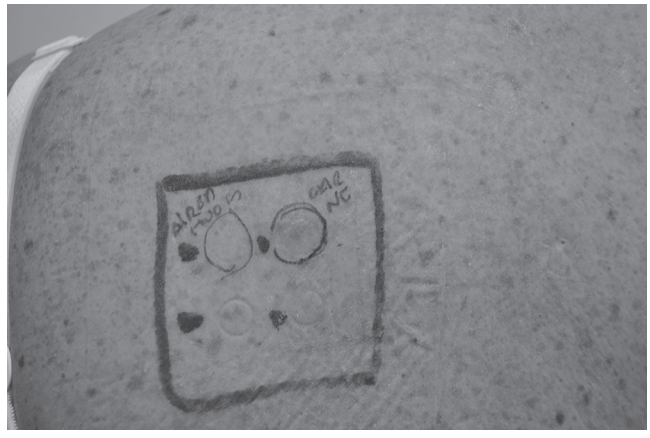
CoU is characterized by a local immediate and/or delayed urticarial reaction, with swelling and redness at sites of epidermal or transdermal contact with certain agents. Generalized cutaneous reactions, rhinitis, asthma, or anaphylactic reactions may be associated. CoU differs therefore from other types of urticaria by the route of access of the antigen or the noxious agent to the body. It penetrates transepidermally, whereas the more common mode of absorption of urticarial substances is transmucosal via the respiratory or gastrointestinal tract. 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.[10]

The basic clinical appearance of the primary lesion of CoU does not differ from that of other types of urticaria. Depending of the type of contactant, the wheal can present different aspects. Linearly arranged wheals are habitually caused by plant nettles. Punctate wheals arise exactly at 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. Burning of the lips can occur when patients react to food (Figure 3.1).

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 hours, the swelling disappears. Redness can persist as long as 6 hours. Exceptional whealing can persist for more than 24 hours. CoU can reappear



(a)



(b)

FIGURE 3.1 CoU and PCD by mango fruit. (a) Contact wheals and angioedema appeared immediately after contact with mango fruit. Two days after, the deep swelling evolved into desquamation and a crusted epidermis. (b) Positive occlusive patch test with mango fruit; a positive prick by prick was also observed.

after 4–5 hours. This dual whealing response has been demonstrated experimentally in the ears of BALB/mice and in humans.[11] Delayed onset of CoU has also been described after repeated applications of the trigger substance.[12] The time course and intensity of CoU lesions differ depending on the nature of the eliciting agent. This variability may also be due to differences in the reactivity of the cells, which secrete the vasoactive amines or the sensitivity of the target tissue to the mediators or chemical released.

Dermatitis and Eczema: Symptoms of PCD

Contact dermatitis is an inflammatory skin reaction to direct contact with noxious agents in the environment. A diagnosis of contact dermatitis requires a correct history, physical examination, and cutaneous skin testing. Although an eczematous reaction is the most commonly encountered adverse reaction to contact substances, other clinical manifestation can also be induced (Table 3.4; Figure 3.2).

TABLE 3.4

Clinical Response to Contact Substances: Patterns of Cutaneous Reactions that Can Be Induced by Contact with the Skin through an Allergic or Irritant Mechanism

- Eczema
- Erosions
- Ulcerations
- Urticaria
- Erythema multiforme
- Purpura
- Lichenoid eruptions
- Exanthemas
- Erythroderma
- Allergic contact granuloma
- Lymphocytoma
- Sarcoidal reactions
- Toxic epidermal necrolysis
- Pigmented contact dermatitis
- Contact leukoderma
- Nodular lesions
- Photosensitive reactions
- Generalized symptoms
- Contact urticaria may become anaphylaxis

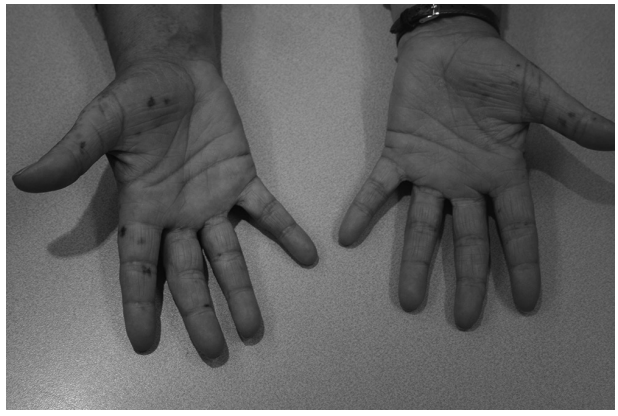


FIGURE 3.2 Hyperpigmentation sequelae of chronic exposure to latex in a patient who only showed a positive prick test to latex and suffered for years with chronic hand eczema. This patient worked in a condom factory.

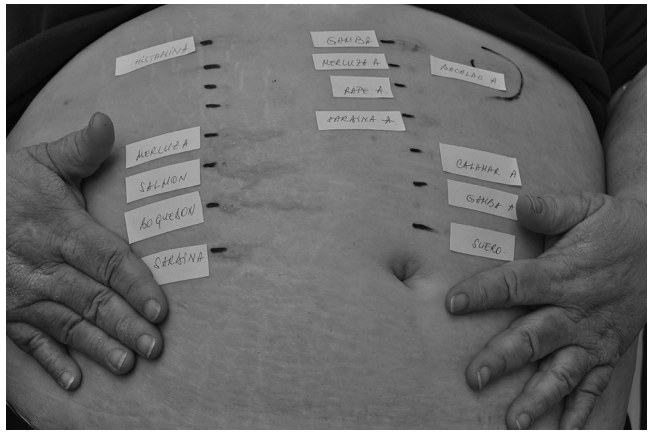


FIGURE 3.3 Chronic eczema induced by common contact with different crustaceans and fish involving both hands in a fish vendor. Positive prick by prick demonstrated which fish was responsible for the disease.

Pruritus is the hallmark symptom of contact dermatitis. Spongiosis of the epidermis is the histological hallmark of acute eczematous reactions. Clinically, the confluence of spongiosis leads to vesicles and even bullae. The vesicle is the elemental lesion of eczema. It is preceded by erythema and dermal thickening and because of scratching the crusts appear. The vesicular response is associated with acute contact dermatitis. Once contact dermatitis relapses, the skin became acanthotic and, macroscopically, the chronic eczema shows a lichenified skin and characteristic painful fissures. The features of chronic dermatitis are pruritus, lichenification, erythema, scaling, fissures, and excoriation (Figure 3.3).

A vesicular or bullous reaction may be seen in allergic and irritant reactions and cannot be used to distinguish between these two types of dermatitis. Few differences between irritant and allergic dermatitis have been described based on the characteristics of the response to an occluded patch test. Minimal itching occurs when a primary irritant is occluded and placed on the skin. The response shows erythema and slight infiltration strictly limited to the area of the patch. Strong irritants may produce bullous or pustular reaction limited to the occluded area. When occlusive testing is done with a substance that induces a cellular immune reaction, the response is pruritic, infiltrated, papular, or vesicular beyond the rim of the occluding ring.[13]

Protein contact with the skin can induce immunological CoU with PCD. Proteins can be responsible for chronic and recurrent eczema. It may be manifested just as a fingertip dermatitis or extend to the hands, wrists, and arms. A urticarial or vesicular exacerbation can be seen in a few minutes after contact with the causal agent, especially on previously affected skin. Some cases of chronic paronychia were considered a variation of PCD, with redness and swelling of the proximal nail fold (e.g., after handling food or NRL). As for CoU, extracutaneous symptoms can appear as rhino-conjunctivitis or asthma and even anaphylaxis. Abdominal pain, diarrhea, and oral allergy syndrome may occasionally develop when the allergen comes in contact with the oropharyngeal mucosa.[14]

Diagnostic Tools Useful to Make an Etiological Diagnosis of CUS

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 measurements of specific IgE in serum are useful for some proteins. A basophil activation test is based on the demonstration of CD63 expression after exposure to allergens by flow cytometry. It can be interesting when rare allergens are studied but specific IgE antibodies are not available. It was useful for chicken meat studied by Gonzalez-Muñoz et al.[15]

The simplest cutaneous provocation test for immunologic CoU (ICoU), nonimmunologic CoU, 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 3 × 3 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 an edema and/or erythema typical of CoU or tiny intraepidermal spongiotic vesicles typical of acute eczema. An immunological and nonimmunological contact reaction usually appears within 15–20 minutes, with the nonimmunological reaction lasting 45–60 minutes. ICoU can also show a delayed onset, although this is rare. Open testing is generally negative unless the substance is applied on damaged or eczematous skin, where it may cause a vesicular reaction.

When the open test results are negative, "prick testing" of suspected allergens is often the method of choice for immediate contact reactions. Skin prick test with fresh material or commercial reagents is the gold standard. The principle of the prick test relies on bringing a small volume of allergen (approximately 5–10 nL) into contact with mast cells by puncturing the skin with a lancet. When a prick by prick is done with the same lancet, the fresh material is pricked and immediately after the skin is punctured (Figure 3.4). A positive reaction is assessed after 15–20 minutes. The diameter of the classical wheal and flare reaction of the skin is measured. The released mediators, mainly histamine, are only present in the wheal. The flare reaction is neuronally mediated.

Sometimes a "rubbing test," gentle rubbing with the material on intact or lesional skin, might be indicated if an open test is negative. A "scratch test" or "chamber scratch test" (contact with a small aluminum chamber for 15 minutes) are less standardized than the prick test, but are useful when a nonstandard allergen must be studied. It carries a higher risk of false-positive reactions and lacks sensitivity compared with the prick test.

For both prick, prick by prick, and rubbing and scratch tests, histamine hydrochloride serves as the positive control and aqueous sodium hydroxide as the negative reference.

A proposed scheduled protocol with consecutive tests has been proposed to study immediate contact skin reactions (Figure 3.5).

When other than cutaneous organs are involved, it is important to begin ICoU testing with a much diluted allergen concentration and to use serial dilutions to minimize allergen exposure. When testing with poorly or nonstandardized substances, control tests should be assessed on at least 20 people to avoid false-positive interpretation. Nonsteroidal anti-inflammatory drugs and antihistamines should be avoided because of the risk of false-negative results. Following the recommended protocol is important for minimizing 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.[16–18]

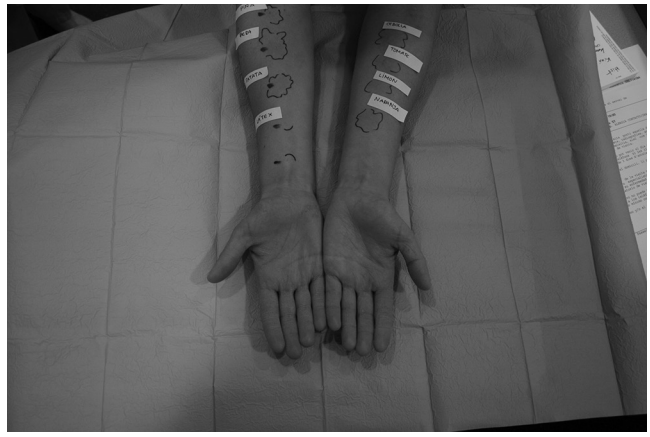


FIGURE 3.4 CoU and PCD by fruits and vegetables. Dermatitis is present in the right palm. Prick by latex was negative; nevertheless, the prick by prick with different fruits and vegetables showed an immediate positive reaction. The patient worked as a fruit vendor but obtained the right to change her work.

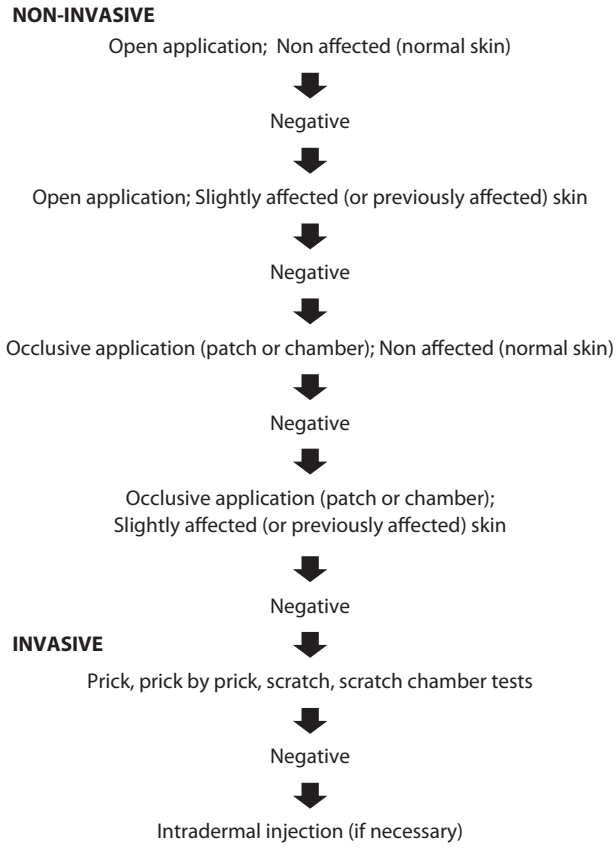


FIGURE 3.5 A scheduled protocol with consecutive tests has been proposed to study immediate contact skin reactions.

Treatment and Prevention of CUS

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. Discovering the responsible agent is required to identify the correct avoidance of the eliciting trigger. Avoidance of further exposure will improve occupational contact dermatitis and CoU. Primary and secondary prevention are highly recommended as necessary common guidelines to prevent well-known occupational risks such as latex allergy.[19]

Considering their good safety profile, second-generation antihistamines must be considered the preferred first-line symptomatic treatment for most CoU reactions. 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.

Conclusion and Comments

How CUS is expressed clinically will be reviewed in different chapters of this book. Specific characteristics regarding lesions morphology, location symptoms, and course will be discussed. The nature of the substance involved, the source of exposure, the frequency of exposure, or the occupational relevance will influence the acute or chronic morphology as well as the predominant lesion involved. Based on the clinical history,

the type of reaction, the substance involved, and protein or low-molecular-weight molecule, a specific protocol should be designed for each patient. Individual study for each patient with cutaneous immediate reactions is a challenge and an opportunity to increase our knowledge.

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4

Mast Cell Biology and Its Role in the Immediate Skin Contact Reactions

Marcus Maurer, Frank Siebenhaar, Oliver Schmetzer, and Martin Metz

Introduction

The mechanisms underlying immediate contact skin reactions are only partially understood, especially regarding nonimmunologic contact urticaria (CoU) and protein contact dermatitis (PCD). Each trigger substance has its own mechanism or mechanisms of action.

Nonimmunologic CoU is due to vasogenic mediators without the involvement of immunological processes. The pathogenesis of immunological CoU reflects a type I hypersensitivity reaction, mediated by allergen-specific immunoglobin E (IgE) in a previously sensitized individual. Skin challenge involves allergen penetration through the epidermis, IgE binding on mast cells (MCs), their degranulation, and subsequent release of histamine and other vasoactive substances such as prostaglandins, leukotrienes, and kinins (Figure 4.1).

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. 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.

In this chapter, we will focus on the characteristics involved in immunological immediate skin reactions, especially in CoU. The mast cell's role is thoroughly discussed.

Type I: Allergic Reactions of the Skin

Cutaneous type I allergic reactions are induced by allergen-activated MCs.[1] Skin MCs express the high-affinity IgE receptor, FcεRI. Upon sensitization to environmental allergens, IgE to these allergens is produced, circulated, and bound to FcεRI on cutaneous MCs.[2] Allergen reexposure of the skin results in its binding by MC FcεRI–bound IgE, polymerization of the FcεRI, and the release of preformed mediators, such as histamine, as well as the production and secretion of *de novo* synthesized lipid mediators and cytokines.[3] These MC mediators bind to their receptors on skin target cells, including vascular endothelial cells and skin nerves, which results in their activation and inflammatory responses such as vasodilation and extravasation.[4,5] These mechanisms are responsible for the signs and symptoms of early-phase allergic reactions of the skin (i.e., wheals and angioedema, erythema, and pruritus).

Cutaneous MCs

Cutaneous MCs are the key effector cells of type I allergic skin reactions. Teleologically, skin MCs are part of the innate immune system and responsible for defense responses.[6,7] MCs are found in high numbers in organs that interface with the environment, including the skin, where they are critically involved in detecting pathogens and other threats and inducing protective responses against them.[8]

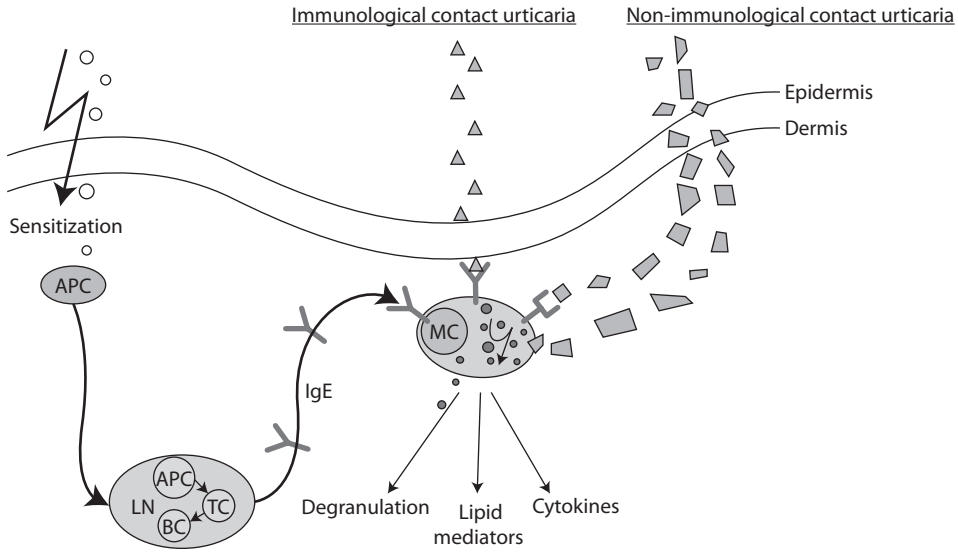

FIGURE 4.1 Immunological and non-immunological contact urticaria. (APC = antigen presenting cell, LN = lymph node, TC = T-cell, BC = B-cell, MC = mast cell)

Development, Differentiation, Distribution, and Morphology

Skin MCs are derived from CD34-positive stem cells in the bone marrow. Committed progenitors are released into the circulation and recruited into the skin and other peripheral tissues, where they differentiate to mature MCs under the influence of local growth factors.[9,10] The key factor in this process is stem cell factor (SCF), which binds to the MC membrane receptor KIT. Interleukin (IL)-3, IL-4, and IL-9 also contribute to MC differentiation.[11] In the human skin, MCs are preferentially found in the vicinity of sensory nerves, hair follicles, and blood vessels. The number of cutaneous MCs is highest in the papillary dermis, where up to 20% of the skin cells are MCs. No MCs are found in the epidermis under physiological conditions. MC numbers are highest in the skin of the face and the hands and feet and lowest in the skin of the abdomen and the back [12] (Figure 4.2). These patterns of distribution may reflect the need for higher numbers of MCs in skin layers and skin regions at increased risk of bacterial infection and exposure to other environmental threats. They also explain, at least in part, why the face and the extremities are commonly affected in patients with inflammatory skin conditions. The number of MCs in healthy human skin does not show substantial changes during the host's lifetime, and skin MC numbers are similar in men and women. Skin MC numbers increase during chronic inflammatory conditions, including atopic dermatitis and chronic spontaneous urticaria.[13,14]

Human skin MCs are readily detectable by Giemsa and toluidine blue staining in routine histology, but difficult or impossible to see in hematoxylin and eosin-stained sections. Giemsa and toluidine blue-stained MCs show multiple metachromic cytoplasmic granules, a hallmark feature of connective tissue MCs. Skin MCs can also be visualized by immunohistochemistry with antibodies against FcεRI, KIT, and tryptase. MCs are among the largest cells of the skin with a diameter of up to 20 μm.

Human MCs are traditionally categorized by their expression of tryptase, chymase, or both proteases as MC_T (tryptase-positive), MC_C (chymase positive), and MC_{TC} (tryptase and chymase-positive). MC_{TC} exhibit tryptase, chymase, and carboxypeptidase; MC_T cells contain only tryptase; and MC_C cells contain chymase and carboxypeptidase, but not tryptase. The vast majority of MCs in human skin are of the MC_{TC} type. In contrast, most mucosal MCs in the airways and gastrointestinal tract are of the MC_T subtype.[15,16]

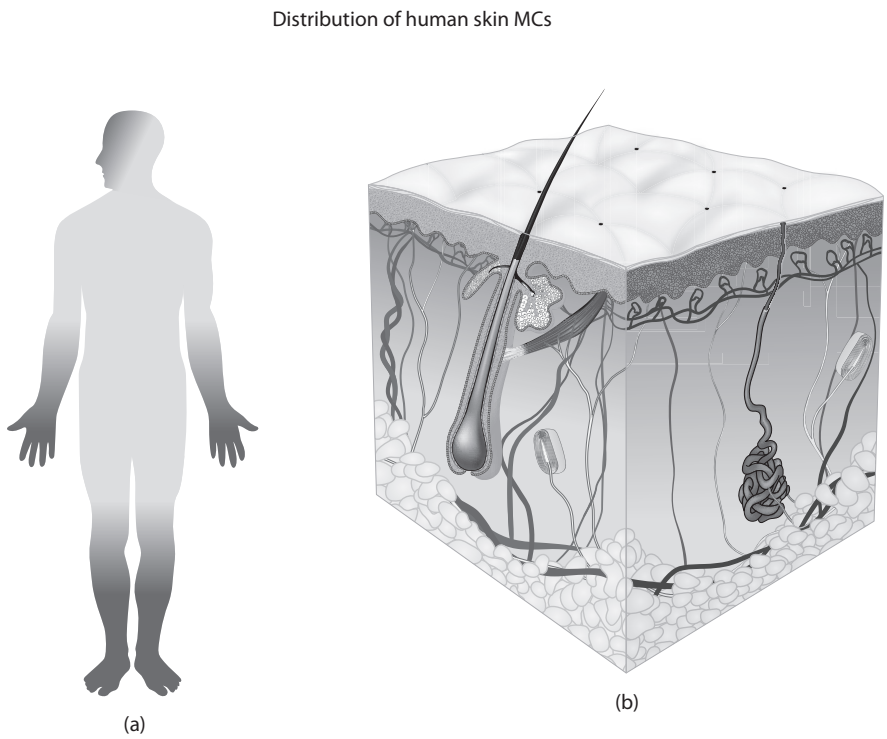

FIGURE 4.2 Humans exhibit distinct patterns of distribution of skin mast cells. (a) Mast cell numbers are increased in peripheral skin sites such as the hands, the feet, and the face. (b) Also, mast cell numbers decrease within the skin with the highest numbers present below the epidermis and a gradient towards the subcutis.

Receptors and activation

Skin MCs express a large array of membrane receptors that bind activators or inhibitors, exogenous or endogenous ligands, and that differ in their structure (e.g., G protein–coupled or ion channel–coupled) and the responses they induce (e.g., differentiation, degranulation, migration, apoptosis, proliferation, cytokine production; Figure 4.3). The most important receptor for type I allergic reactions of the skin is FcεRI. Other important skin MC receptors include the SCF receptor KIT, G protein–coupled neuropeptide and complement receptors, as well as Toll-like receptors (TLRs).[4,8,17,18]

FcεRI, the high-affinity IgE receptor, is expressed by MCs, basophils, monocytes/macrophages, eosinophils, and dendritic cells. In MCs and basophils, the FcεRI is a tetramer, with one α- und β-chain each and two γ-chains. All other FcεRI-positive cell types express trimeric receptors (one α- and two γ-chains). FcεRI binds IgE via its α-chain. The β-chain and the γ-chains are important for the transduction and modulation of MC cellular responses after FcεRI-activation.[2,3]

FcεRI

FcεRI does not bind immunoglobulins other than IgE, and only one IgE is bound by each receptor. The affinity of FcεRI for IgE is very high (disassociation constant = 10^{-10}/M), which is why IgE remains bound to its receptor for several days. The tissue half-life of IgE is even longer, up to several weeks, because IgE that dissociates from its receptor can bind to other FcεRIs or even the same FcεRI after dissociation from the receptor.[19]

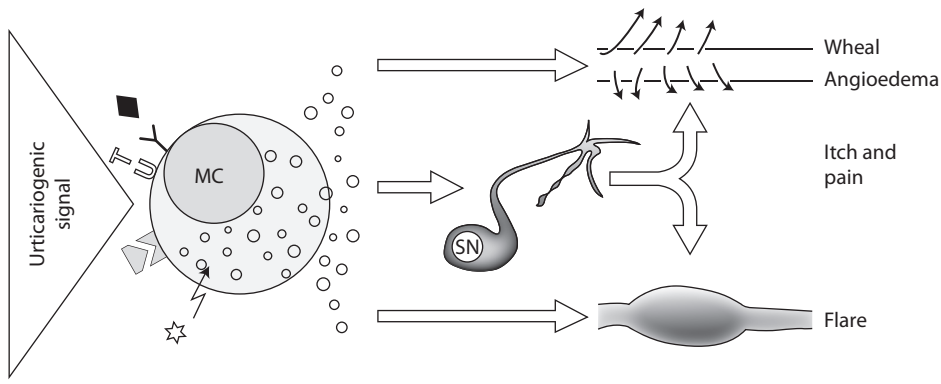

FIGURE 4.3 Mechanisms of the induction of signs and symptoms of contact urticaria (MC = mast cell, SN = sensory nerve). Activation of skin mast cells by urticariogenic signals, either allergens or non-immunological activators, results in the degranulation of mast cells and the release of mediators. This activates skin nerves which mediate pruritus and contribute to vasodilation in extravasation. Mast cell mediators also directly activate blood vessels to increase extravasation and blood flow (vasodilation, flare).

The binding of monomeric IgE to FcεRI on skin MCs has a number of different and important effects, including the upregulation of FcεRI expression (i.e., an increase in FcεRI numbers on skin MC membranes). The reason for this is that IgE stabilizes FcεRI by binding to its α-chain, which inhibits FcεRI internalization and degradation. Monomeric IgE also increases FcεRI production and shuttling to the MC membrane. Importantly, the binding of IgE to FcεRI can also result in the production of cytokines. In addition, monomeric IgE can promote MC differentiation and increase MC responses to activating signals. The binding of monomeric IgE does not result in MC degranulation. For this, FcεRI cross-linking is required (i.e. two or more FcεRIs need to dimerize to induce degranulation). The extent of MC degranulation is linked to the number of FcεRIs cross-linked. In other words, the higher the numbers of FcεRIs that aggregate on the membrane of MCs, the higher the number of MC granules released. Skin MCs express several thousands to hundreds of thousands FcεRIs under physiological conditions. Aggregation of as few as a couple of hundred FcεRIs is sufficient to induce MC degranulation. [2,3,9]

The sensitization to type I allergens (i.e. the production of specific IgE to these allergens) results in the circulation of allergen-specific IgE. Of the five immunoglobulin subtypes, IgE has the shortest half-life (1–3 days) and lowest concentration in the serum. IgE is predominantly located in tissues including the skin. It is produced by lymph node and tissue plasma cells when allergen is taken up by antigen-presenting cells and processed fragments are presented to Th2 cells in the context of major histocompatibility complex class II. This leads to the expression of IL-4 and IL-13 and the induction of class switching to IgE production. Plasma cell-derived IgE then binds to its receptors, the low-affinity IgE receptor (FcεRII; CD23) expressed on the surface of B cells, and other hematopoietic cells or its high-affinity receptor, FcεRI. IgE binds to FcεRI via its Fc region. The recognition and binding of its specific allergen via the Fab region of FcεRI-bound IgEs results in FcεRI polymerization and the induction of complex signal transduction processes. First, the tyrosine kinase Lyn recruits the tyrosine kinase Syk by the phosphorylation of activating domains of the FcεRI-β and -γ chains. Syk, after phosphorylation and activation by Lyn, then activates distinct and interacting signal transduction pathways that result in the degranulation of MCs as well as the production of lipid mediators and the generation of cytokines. FcεRI-induced MC degranulation requires an increase in intracellular calcium concentrations, which is facilitated by its release from cytoplasmic stores as well as by the activation of membrane calcium channels. The production of lipid mediators, which involves the liberation of arachidonic acid from MC membrane phospholipids by phospholipase A2, is brought about by the phosphorylation of ERK1/2. The *de novo* synthesis and release of cytokines from FcεRI-activated MCs is regulated by multiple signal transduction pathways that involve ERK and JNK-dependent mechanisms.[2,3,20]

Skin MCs can also be activated via FcεRI independently of IgE binding to environmental allergens. MC degranulation by activation of FcεRI is also induced by IgG antibodies directed to IgE (IgG–anti-IgE), IgE cross-linking by superantigens, IgE binding of multivalent autoantigens (autoallergens), and autoantibodies directed against the α-chain of FcεRI. These mechanisms are thought to be pathogenetically relevant in several chronic inflammatory skin conditions.[21,22] For example, IgE to thyroperoxidase or double-stranded DNA has recently been shown in subgroups of patients with chronic spontaneous urticarial.[23] Also, patients with rheumatoid arthritis can express IgE to citrullinated proteins, and IgE against the bullous pemphigoid autoantigen BP180 is produced by most patients with this blistering skin inflammatory disorder.[24] Chronic spontaneous urticaria patients have also been reported to produce IgG–anti-IgE as well as MC-activating autoantibodies directed to the FcεRI. The beneficial function of FcεRI-mediated activation of skin MCs remains unclear. The results of work in mouse models suggest that IgE-mediated skin MC activation may contribute to improved host responses to parasites and venoms from poisonous animals.[25,26]

The degranulation of skin MCs does not usually result in cell death. MCs can recycle and resynthesize membrane components and products and undergo multiple cycles of degranulation and regranulation. Following degranulation, MCs begin to generate new cytoplasmic granules after several hours. Skin MCs are refractory to activation during this regranulation process, and MC-dependent skin inflammatory reactions cannot be induced or are markedly diminished during that time. After the completion of regranulation, several days after degranulation, skin MCs are ready to be activated again and can produce normal allergic skin reactions.

KIT (CD117)

KIT (CD117), the receptor for SCF, is expressed by bone marrow cells and downregulated during the ontogenesis of all bone marrow-derived cells except MCs. In healthy skin, detectable levels of KIT are only seen in MCs and melanocytes. Binding of SCF to KIT on skin MCs results in KIT dimerization and the activation of multiple signal transduction pathways that overlap, in part, with those of FcεRI. The activation of MCs via KIT is essential for their development and survival and results in mediator release, proliferation, differentiation, chemotaxis, and their priming for other activating signals.[15]

G Protein–Coupled Receptors

G protein–coupled receptors are expressed in skin MCs. Many different G protein–coupled receptors and their ligands can activate or inhibit MCs. Ligands of the most important activating receptors of this class include neuropeptides such as substance P, the complement components C3a und C5a, and prostaglandin E2 und leukotriene C4.[15,27]

Toll-Like Receptors

TLRs recognize and bind parasites, bacteria, and viruses. Human MCs express almost all of the 10 known TLRs. The activation of skin MCs via TLRs does not typically induce degranulation, but rather the *de novo* production of cytokines and priming of the cells to other activating signals. TLR expression and activation of skin MCs is important for MC-mediated protective responses to pathogens.[8,28]

Mediators

Skin MCs produce and release a large array of mediators. MC-derived mediators are traditionally grouped in three groups: 1) Preformed mediators stored in cytoplasmic granules. They include histamine, heparin, and other proteoglycans as well as tryptase, chymase, and other proteases. 2) Arachidonic acid-derived lipid mediators produced immediately after activation such as prostaglandins, leukotrienes, and platelet-activating factor. 3) *De novo* synthesized cytokines, chemokines, and growth factors.

Preformed MC Mediators

The most important preformed MC mediator for type I allergic reactions is histamine. In healthy skin, MCs are the only cells that make relevant amounts of histamine. MC histamine is produced by the decarboxylation of histidine via histidine decarboxylase. Skin MCs can also take up exogenous histamine, which they store, together with self-produced histamine, in their cytoplasmic granules. There, histamine is stabilized by heparin and released by degranulation after activation via FcεRI or other signals. In addition to FcεRI-induced degranulation, or so-called anaphylactic degranulation, histamine can also be released from MC granules by alternative forms of degranulation. MCs have been shown to undergo piecemeal degranulation, which involves the intracellular fusion of cytoplasmic granules with each other and with the cell membrane. The amounts of histamine and other mediators released during piecemeal degranulation are smaller than those released during anaphylactic degranulation. Skin MC piecemeal degranulation, unlike anaphylactic degranulation, is not a key feature of type I allergic skin responses. The purpose of piecemeal degranulation and the release of mediators during this process remain unclear but is thought to serve homeostatic functions.[13,29]

Histamine released from skin MCs is rapidly degraded by enzymatic digestion unless it binds to histamine receptors. The four known histamine receptors [30] are all expressed in human skin. In type I allergic skin reactions, the effects of histamine are mediated primarily by its activation of H1 receptors, and to a lesser extent by its action on H2 and H4 receptors. The H1 receptor is a transmembrane G protein–coupled receptor, and binding of histamine to the H1 receptor results in the downstream activation of various pathways that involve the signal transduction molecules cyclic AMP, cyclic GMP, calcium, the nuclear factor kappa B, and others. The H1 receptor, as with other histamine receptors, exhibits spontaneous activity (constitutive activity) in the absence of histamine. The binding of histamine to H1 receptor is inhibited by H1 antihistamines. In addition to inhibiting histamine binding, H1 antihistamines result in the stabilization of the receptor in its inactive form, thereby downregulating its constitutive activity. H1 antihistamines are, therefore, inverse agonists. Histamine exerts its proinflammatory H1 receptor–mediated activity by dilating cutaneous arterioles, which results in increased skin blood flow and erythema, and by increasing the extravasation in postcapillary venules, which causes whealing and the development of angioedema and promotes the recruitment of proinflammatory cells from the circulation such as neutrophils, eosinophils, basophils and others.[29,31,32]

Heparin is the most important matrix proteoglycan of human skin MC cytoplasmic granules, where it binds histamine, acid hydrolases, neutral proteases, and cytokines. Upon degranulation, heparin regulates the release and thereby the function of these mediators from the granule matrix. In addition, heparin regulates coagulation, complement activation, and cytokine production, and it promotes the migration and proliferation of endothelial cells.

The neutral proteases tryptase, chymase, and carboxypeptidase account for up to half of the protein content of human skin MCs. Tryptase is produced by the vast majority of human MCs, and MCs are the only cells that produce relevant amounts of this protease. Human skin MCs express α- and β-tryptase as well as membrane-bound γ-tryptase. Under physiological conditions, α-tryptase, which is constitutively released from MCs, accounts for most of the tryptase detectable in the serum. In MC granules, β-tryptase is bound to heparin and loss of heparin binding upon degranulation results in its activation. Tryptase released from human MCs results in the activation of smooth muscle cells, the recruitment of neutrophils, the synthesis of collagen in fibroblasts, and the activation of matrix metalloproteases.[6.32]

Lipid Mediators

The activation of phospholipase A2 in activated MCs leads to the conversion of phosphatidylcholine to arachidonic acid and the subsequent generation of lipid mediators including leukotrienes, prostaglandins, thromboxane, prostacyclins, and platelet-activating factor. Conversion of arachidonic acid to LTA4 by 5-lipoxygenase results in the production of LTB4 and/or LTC4, the most important MC leukotriene, as well as LTD4 and LTE4. The cysteinyl leukotrienes LTC4, LTD4, and LTE4 are proinflammatory and induce skin inflammation via their receptor-mediated effects on smooth muscle cells and endothelial cells. Intracutaneous injections of LTC4 in nanomolar concentrations produce vasodilation (erythema) and extravasation (wheal) that last for several hours.[13,33]

Conversion of arachidonic acid to prostaglandin (PG) H2 by cyclooxygenase 1 and 2 leads to the production of PGD2, PGE2, and PGF2 and of prostacyclin and thromboxane A2. IgE-activated MCs produce primarily PGD2, which is released minutes after MC activation.

Cytokines and Chemokines

Cytokines and chemokines that promote, inhibit, or modulate inflammation are released by activated human skin MCs. Among these mediators, the most important are IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, tumor necrosis factor, transforming growth factor-β, eotaxin, and CCL5. Cytokines and chemokines are produced *de novo* in MCs, hours to several days after their activation. Some cytokines such as tumor necrosis factor, IL-5, and vascular endothelial growth factor are transported to the cytoplasmic granules of MCs and stored there. This allows for their immediate release upon MC activation.

Skin Mast Cell Functions

Skin MCs are mostly known for their pivotal role in the induction of type I allergic skin reactions and their key function as drivers of skin allergic disorders such as atopic dermatitis and urticaria, especially in immunological CoU. Skin MCs are also implicated in nonallergic chronic inflammatory skin conditions such as psoriasis and autoimmune dermatoses. Recently, mouse models have shown that skin MCs also have important functions in protective skin responses to bacteria, wounding, and envenomations.[34–36]

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5

Oral Allergy Syndrome

Pascale Mathelier-Fusade

Oral allergy syndrome (OAS) has been recognized as a presentation of food allergy for more 70 years but remains a challenge for allergists because of conflicting definitions and the clinical and immunologic complexities.

Definition

Clinically, OAS is characterized by oral mucosal symptoms that may involve itching, stinging pain, edema of the lips, tongue, palate, and pharynx with a sudden onset. OAS may be occasionally accompanied by itching of the ear and feeling of tightness of the throat. Typically these symptoms appear within minutes after fruit and vegetable ingestion and resolve in less than 30 minutes. It is a presentation of food allergy provoked by exposure to specific food allergens.[1]

OAS may represent the most common food allergy in adults, and its relationship with atopic disease and allergic rhinitis is close. If the prevalence of allergic rhinitis is estimated between 10% and 30% in adults and affects up to 40% of children, the prevalence of OAS has yet to be determined.[2] In 1970, Anderson et al. published the first OAS prevalence based on specific fruits involved and their correlation with aeroallergens.[3] The authors asked 2067 patients about symptomatic oral pruritus to either generalized or specific fruits (melon and banana). The results showed that 4.3% of all patients and 6.2% of those with pollinosis described OAS symptoms. All 90 patients complaining of oral pruritus after eating melons (cantaloupe, watermelon, honeydew melon) and banana were also sensitive to ragweed. In 1982, Eriksson et al. questioned 600 adults and pediatric patients with documented allergic rhinitis (positive skin prick tests [SPTs] or radioallergosorbent test [RAST] test results) regarding their tolerance of various foods.[4] OAS was found in 70% of birch pollen–allergic patients and only in 20% of individuals allergic to grass pollen or mugwort. As for the Ma et al. survey, allergists answering on their management of OAS estimated the syndrome's prevalence to be 5% in children and 8% in adult patients with no specific pollen allergies. The authors explained the lower prevalence compared with earlier research with both physician underdiagnoses and patient underreporting.[5] More likely, it is possible that the prevalence cannot be performed because of controversy about the very definition of OAS.

The first observation of OAS was published in 1942 by Tuft and Blumstein.[6] These authors discussed clinical observations of four adult patients who presented with itching of the soft palate and swelling of mucous membranes after eating fresh peaches, apples, bananas, and melons, but did not react to cooked or canned fruits. Tuft and Blumstein noticed that at the same time these patients suffered from "hay fever." Tuft and Blumstein established the immunologic correlation between the oral-pharyngeal symptoms and raw fruits when they used freshly extracted fruit juices to do SPTs that yielded positive reactions. Then Juhlin-Dannfelt was the first in 1948 to report the association between hypersensitivity to fruits and vegetables and allergy to birch pollen.[7] This connection between fruit and vegetable hypersensitivity and pollen allergy was confirmed by Hannuksela and Lathi in 1977, who reported that 152 (66%) of 230 atopic patients allergic to birch pollen complained of itching, tingling, or edema of the lips and tongue and hoarseness or irritation of the throat when eating raw fruits and vegetables such as apple, potato, carrot, tomato, celery, and parsnip. Positive results on scratch chamber tests with suspected fresh fruits and vegetables were seen in 36% of the 230 patients. Only seven of 158 (4%) atopic patients who were not allergic to birch pollen had positive skin test reactions to any of the fruits and vegetables tested.[8]

The controversy began in 1987 when Amlot et al. extended the clinical definition of OAS. They reported allergic symptoms in 80 patients induced by eating a food yielding a positive skin test; the symptoms were primarily oral mucosal symptoms that occasionally spread to the entire body as OAS.[9] In the study, the authors noted one subgroup of patients in whom approximately half described only typical oral symptoms and the other half described initial oral symptoms that chronologically progressed to include gastrointestinal manifestations (nausea, vomiting, abdominal pain, and diarrhea), urticaria, or angioedema, and more rarely severe anaphylaxis. Amlot et al. coined an extensive definition of OAS. But they did not mention whether the patients had pollinosis, and the causative foods included shellfish, fish, and eggs. Some authors such as Ortolani contended that OAS should be exclusively confined to the oral cavity, and any extraoral or systemic manifestations should result in a diagnosis of food anaphylaxis.[10] Indeed, he reported in 1988 on 262 pollinosis patients who developed symptoms localized only to the oral mucosa and caused by the ingestion of fruits and vegetables.[11,12]

But in 1994, Liccardi et al. reported oral symptoms without generalized symptoms caused by the ingestion of eggs or egg-containing foods in a patient without pollinosis as OAS.[13] In response to this, Kelso stated that the condition might have been usual egg allergy rather than OAS, but Liccardi argued that no generalized symptom was observed on any of the confirmation challenge tests using egg.[14]

To avoid such confusion related to the term OAS, some authors recommended to use the more specific terms such as "pollen-food allergy" or "pollen-food allergy syndromes" (PFS) for food allergy because of a cross-reaction between pollen antigen and fruit or vegetable antigen has been called the more specific terms.[15,16]

Immunologic Mechanism

It was already noted in the early reports that a pollen-allergic patient usually reacted not only to one but many fruits and vegetables from different botanical groups. Andersen et al. observed the first antigenic correlation among birch, apple, potato, and hazelnut using the cross-line immunoelectrophoresis technique. After confirming an immunologic identity between hazelnut and birch, the authors also recognized a shared "affinity precipitate" between birch and both apple and potato.[17] In 2000, Kazemi-Shirazi et al. confirmed this theory by combining multiple food and pollen antigens in quantitative RAST and immunoblot inhibition assays. They identified that food-specific immunoglobulin E (IgE) epitopes in OAS patients resembled pollen antigens and they concluded that the pollen allergens themselves may be responsible for the elicitation and maintenance of oral allergy symptoms, tying together the longstanding clinical correlation through cross-reactive allergens.[18]

The most common form of food allergy is mediated by IgE antibodies and reflects an immediate type ("type 1 hypersensitivity") reaction characterized by acute onset of symptoms after ingestion or inhalation of food. IgE-mediated food allergy is further classified into primary (class 1) and secondary (class 2) food allergy (Table 5.1). This distinction is based on clinical appearance, the predominantly affected group of patients (children or adults), disease-eliciting food allergens, and the underlying immune mechanism. Primary (class 1) or "true" food allergy starts in early life and often represents the first manifestation of the atopic syndrome. The most common foods involved are cow's milk, hen's egg, peanut, fish, and wheat. Allergens contained in these foods do not only elicit allergic symptoms in the gastrointestinal tract but may induce or influence urticaria, atopic dermatitis, and respiratory symptoms (rhinitis, asthma, cough). With few exceptions, most children outgrow class 1 food allergy within the first 10 years of life.

The mechanism of OAS food allergy is unique and is called class 2 food allergy. This form of food allergy describes allergic reactions to foods in mainly adolescent or adult individuals with established respiratory pollen allergy such as birch, grass, ragweed, or mugwort.[19] OAS is believed to be the immunological cross-reactivity consequence between respiratory allergens and structurally related proteins in the respective foods. In other words, OAS is caused by IgE cross-reactivity between prior aeroallergen sensitization and plant-derived proteins. The recognition of these homologous proteins in foods by IgE antibodies specific for respiratory allergens induces clinical symptoms.

Food allergens that induce OAS rapidly dissolve in the oral cavity and are readily broken down by digestive enzymes such as those in gastric juice. This is why these food allergens are different from known food allergens that are resistant to digestive enzymes and induce sensitization via the intestine. Of the different groups of

TABLE 5.1

Characteristics of Class 1 and 2 Food Allergies

	Class 1	Class 2
Sensitization to allergens	Gastrointestinal tract	Respiratory exposure
Age of peak prevalence	Early childhood	After school age
Symptoms	Rapid onset of gastrointestinal (nausea, vomiting, abdominal pain, diarrhea), cutaneous (urticaria, angioedema), respiratory (cough, difficulty to breath, asthma, rhinitis), or systemic symptoms	Mild pruritus, tingling, and/or angioedema of the lips, palate, tongue, or oropharynx; occasionally, sensation of tightness in the throat Rarely systemic symptoms
Typical food	Egg, milk, peanut, wheat, fish	Fruit, vegetable
Stability in presence of heat, acid, and proteases	Yes	No
Diagnosis	Clinical history Positive SPT ± RAST Oral challenge positive on double-blind food-challenge test	Clinical history Positive SPT Oral challenge–positive with fresh food, negative with cooked food
Treatment	Elimination diet	Elimination diet Possibility to eat cooked fruits and vegetables

pollen-related food allergens responsible for causing OAS, the largest group is perhaps the pathogenesis-related (PR) proteins.

In Europe, more than 70% of patients with birch pollinosis are allergic to pollen-related food allergens such as apple, cherry, and hazelnut. Major allergens responsible for these symptoms belong to a group exhibiting high-level homology with Bet v1 that belongs to the PR-10 protein family. PR-10 proteins are naturally formed in higher order plants in response to fungal or bacterial infections or to various stresses such as drought, flooding, freezing temperatures, ultraviolet-B light, and mechanical injury.[20] Although biologically serving to help protect these plants against their respective environmental stimuli, in humans PR proteins may become clinically relevant when an IgE antibody against a PR protein such as an aeroallergen cross reacts with a similar PR protein from different plant or food source, resulting in oral allergy symptoms. Even if the Bet v 1 is the major birch tree pollen (*Betula verrucosa*) and the key member of the PR-10 family of PR proteins, other members of this protein family have been identified in different foods such as Mal d 1 in apple, Pru p 1 in peach, Pru ar 1 in apricot, Pru av 1 in cherry, Pyr c 1 in pear, Cor a 1 in hazelnut, Api g 1 in celery, Dau c 1 in carrot, Gly m 4 in soybean, Vig r 1 in mung bean, Ara h 8 in peanut, and Act d 8 in kiwi and Jackfruit.[21–24] Apple, cherry, apricot, peach, and pear are members of the Rosaceae fruits, and carrot, celery, and hazelnut belong to the botanic Apiaceae family (Tables 5.2 and 5.3).

Resistance to gastrointestinal degradation and heat treatment is an important characteristic of food allergens, and the PR-10 proteins family is known to be unstable to both heating and digestion.[25] Indeed, simulated gastrointestinal degradation of Mal d 1, Api g 1, and Cor a 1 revealed in different studies that these proteins were completely fragmented within a few minutes of exposure to pepsin, the most prominent gastric protease.[26–28] This proteolytic degradation of Bet-v 1 homologous food allergens into small fragments leads to the loss of their IgE-binding capacity; most IgE epitopes of Bet v 1 are conformational epitopes depending on their tertiary protein structure.[29–31] The rapid and complete degradation of Bet v 1–homologous food allergens explains why systemic IgE-mediated reactions rarely occur after consumption of birch pollen-related foods. At the site of contact with fresh foods (i.e., the oral mucosa), local IgE-mediated immediate allergic reactions are induced by intact food allergens. After swallowing Bet v 1-related food, allergens are rapidly degraded in the stomach and cannot be absorbed into the blood steam and are unable to induce IgE-mediated effector cell activation. As a consequence, systemic allergic reactions to birch pollen–related foods are rare. Nevertheless, more severe reactions with severe systemic symptoms have been observed with PR-10-related antigens of celery (Api g 1), apple (Mal d 1), and soybean (Gly m 4).[32] One of the hypotheses is that a birch pollen–allergic individual drinking

TABLE 5.2

Major Fruits and Vegetables Reported to Show Cross-Reactivity with Pollen

Pollen	Food
Birch	Rosacea (apple, pear, sweet cherry, peach, plum, apricot, almond), Apiaceae (celery, carrot), Solanaceae (potato, tomato), Actinidiaceae (kiwifruit), Betulaceae (hazelnut), Anacardiaceae (mango), chili pepper, etc.
Mugwort	Apiaceae (celery, carrot), Anacardiaceae (mango), spice, etc.
Grass	Cucurbitaceae (melon, watermelon), Solanaceae (tomato, potato), Actinidiaceae (kiwifruit), Rutaceae (orange), Fabaceae (peanut), etc.
Ragweed	Cucurbitaceae (melon, watermelon, cantaloupe, zucchini, cucumber), Musaceae (banana), etc.
Plane	Betulaceae (hazelnut), Rosaceae (apple), lettuce, corn, Fabaceae (peanut, chickpea)
Japanese cedar	Solanaceae (tomato)

TABLE 5.3

PR-10 Protein: Major Fruits/Vegetables Allergens

Food	PR-10 Protein
Apple	Mal d 1
Apricot	Pru ar 1
Carrot	Dau c 1
Celery	Api g 1
Cherry	Pru av 1
Hazelnut	Cor a 1
Kiwi	Act d 8
Mung bean	Vig r 1
Peanut	Ara h 8
Pear	Pyr c 1
Potato	Sol t 1
Raspberry	Rub l 1
Soybean	Gly m 4
Strawberry	Fra a 1

fresh soy milk or freshly prepared smoothies with apple and/or carrot rapidly on a relatively empty stomach of can raise the gastric pH value and prevent immediate pepsinolysis of food allergens.

Exposure to high temperatures destructs the three-dimensional structure of recombinant Bet v 1-related food antigens and reduces their capacities to bind IgE and consequently affects the IgE-mediated effector cell activation. This biochemical behavior explains why only fresh fruits and vegetables typically induce immediate allergic reaction, whereas the same foods are tolerated by birch pollen–allergic patients if they are cooked.

Although the PR-10 family of PR proteins is the largest contributor to OAS, not all patients with OAS are sensitized to birch and not all causative foods contain Bet v 1-type proteins. Food allergens belonging to the lipid transfer protein (LTP) family have been also reported in a wide variety of fruits, vegetables, and pollen [33,34] (Table 5.3). LTPs are essential to transfer phospholipids from liposomes to mitochondria and are also antifungal and antimicrobial agents helping plant defense. They belong to the PR-14 family and exhibit an antigenicity resistant to heating or digestive enzymes.[35] LTPs are major allergens implicated in Rosaceae fruit allergies in patients in Southern Europe not used to birch tree pollen. Furthermore, they can cause fruit allergy even without pollinosis, and the symptoms are not only OAS but also can be severe food anaphylaxis.[36,37] Therefore, they are presently considered to be non-pollen-related allergens (class 1 food allergy) that act by intestinal sensitization. However, there are data that suggest that LTP is also responsible for food allergy associated with pollinosis (class 2 food allergy) in some patients. LTPs are most often clinically found as pan-allergens in the Rosaceae family such as Pru p 3 in peach and Pru ar 3 in apricot but also in cherry, apple, carrot, barley, carrot, wheat, rice, broccoli, onion, and grapevine. (Table 5.4).

TABLE 5.4

LTP: Major Fruits/Vegetables Allergens Belonging to PR-14

Food	LTP Protein
Apple	Mal d 3
Apricot	Pru ar 3
Asparagus	Aspa o 1
Cabbage	Bra o 3
Cherry	Pru av 3
English walnut	Jug r 3
European plum	Pru d 3
Grape	Vit v 1
Hazelnut	Cor a 8
Lemon	Cit l 3
Lettuce	Lac s 1
Maize	Zea m 14
Orange	Cit s 3
Peach	Pru p 3
Strawberry	Fra a 3
Tomato	Lyc e 3

Profilin is considered to be an allergen involved in a wide range of cross-reactivities among plants. They are 12- to 15-kDa, monomeric, actin-binding protein found in eucaryote cells and probably mediate membrane–cytoskeleton interaction.[25,38] Patients sensitized with profilin react with a variety of plants and foods, and this cross-reactivity between plants and pollens is considered to be due to a structural similarity rather than similarity at the amino acid sequence level. Profilin is involved in the mugwort-celery-spice syndrome, grass pollen-celery-carrot syndrome, and tree pollen-hazelnut syndrome. Profilin has also other homologous proteins in apple, pear (Pyr c 4), carrot (Dau c 4), celery (Api g 4), potato, and tomato [39] (Table 5.5). Similar to PR-10 proteins, profilins are generally considered to be labile and easily degraded by gastric digestion, resulting in typical OAS.[40]. However, there has been a partially heat-stabile profilin identified in a profilin-mediated systemic reaction to zucchini and a report of a profilin-mediated anaphylactic reaction to lychee fruit.[41,42]

The observed differences in terms of thermal processing stability and proteolysis between LTPs on the one hand and PR-10 proteins/profilins on the other hand may partly explain both the subset of anaphylactic patients according to the OAS definition of Amlot et al. and justification to separate OAS's oropharyngeal symptoms from extraoral food anaphylaxis.

Diagnosis

The allergic reaction in OAS normally occurs immediately as soon as the fruit, vegetable, or nut is in contact with the oral mucosa. The symptoms may start after a few minutes, affecting almost exclusively the anatomical regions that are in contact with the food.

Overall, it is under control quickly and spontaneously in 15–30 minutes and it is not usually severe. This is the most frequent clinical presentation of OAS. However, there are cases that are more severe with systemic symptoms that run on from oropharyngeal symptoms. The oropharynx symptoms include tingling, irritation, and/or swelling of the oropharynx, edemas of the oral mucosal, itching lips, palate, tongue, and oropharynx. Extraoral symptoms are generally localized on the face and neck with hives, itching of the ears, runny nose, periorbital edema, retractions without respiratory obstruction, and sneezing. Severe systemic symptoms such as abdominal pain, nausea, vomiting, diarrhea, cough, asthma, generalized urticaria, and even in isolated cases anaphylactic shock have been also described. OAS seems more frequent in females and may occur any part of the year, but is often worsened in pollination period.[43]

TABLE 5.5

Profilin Proteins: Major Fruits/Vegetables Allergens

Food	Profilin Protein
Apple	Mal d 4
Banana	Mus xp 1
Bell pepper	Cap a 2
Carrot	Dau c 4
Celery	Api g 4
Hazelnut	Cor a 2
Lychee	Lit c 1
Muskmelon	Cuc m 2
Peach	Pru p 4
Peanut	Ara h 5
Pear	Pyr c 4
Pineapple	Ana c 1
Soybean	Gly m 3
Sweet cherry	Pru av 4
Sweet orange	Cit s 2
Tomato	Lyc e 1

So diagnosis of OAS is based on medical history of pollinic allergies and contact with the food-provoking them. The difficulty is sometimes to identify patients at risk of systemic reactions including anaphylaxis.[44,45]

The "gold standard" test for food allergies is the double-blind, placebo-controlled food challenge (DBPCFC). It is used for traditional food allergy (class 1) and many would agree for diagnosing OAS as well. Nevertheless, in a study comparing OAS history with DBPCFC, Rodriguez et al. demonstrated that of 53 patients with a history of OAS to melon, only 25 (47%) had a positive response to an open food challenge and of those, only 17 (68%) had positive DBPCFC results.[46] For that reason, some authors advocated that a careful clinical history is sufficient to diagnose OAS and may better reflect true disease.[47,48] They argued that some blinding processes may modify the natural oral contact with fresh foods if excipient and taste disguise are used or if food is in pills. Supporting this idea, Anhoej et al. found that a good clinical history of OAS to apple had negative and positive predictive values of 100% and 92%, respectively, when compared with an open food challenge.[49] As a result, some studies compare the sensitivity and specificity of diagnosis testing using clinical history as the gold standard.

To help physicians and improve diagnosis of OAS and more specifically of PFS, studies have tried to elaborate standardized "PFS diagnostic questionnaires." First developed in the United Kingdom and then revised using information on the characteristics of PFS in other European populations, these diagnostic questionnaires are a practical tool that enable rapid identification of subjects with PFS.[50]

The skin tests to determine immediate hypersensitivity are essential to complement the clinical diagnosis of OAS. Skin prick testing is conventionally used to investigate immediate-type hypersensitivity to allergens in patients with rhinoconjunctivitis, contact urticaria, asthma, atopic eczema, and suspected food allergy. SPTs are performed on the forearm or the back. The technique used for skin prick testing involves puncturing the skin with a calibrated lancet (1 mm) held vertically and introducing a small quantity of allergen. All patients undergoing an SPT should also have a positive histamine control and negative diluent (saline) control test. An itchy wheal should develop at the histamine puncture site within 10 minutes. The maximum or mean diameter of the wheals to various allergens should be read at 15 minutes. A wheal of 3 mm or more in diameter is generally considered to represent a positive response (indicating sensitization to the allergen). The negative control is important because it excludes the presence of dermographism, which if present makes the tests difficult to interpret. The relevance of an SPT should be always interpreted in the context of the patient's history. Indeed, positive results can occur in people without symptoms and, similarly, false-negative results may occur. SPTs to commercial allergens are

generally considered safe, but intramuscular adrenaline should be available and full resuscitation facilities are needed when tests are carried out with other allergens such as drugs or fresh foods. In food allergy, sensitivity and specificity of commercial SPTs (CSPTs) are highly variable. Indeed, CSPTs may have sensitivities ranging from 87.5% for potato to 0% for peach. This wide variation may be due to the inadvertent denaturation of the OAS antigens, such as PR-10 proteins, during commercial processing. Furthermore, when compared with fresh fruit SPTs (FFSPT) in OAS, FFSPT yielded better sensitivity and specificity in diagnosis [47] (Table 5.6). This observation was particularly relevant for apple, orange, carrot, celery, cherry, and peach and confirmed in others studies. [49,51] Although most studies are focused on foods related the PR-10 protein family, OAS may be also be due to monosensitization to profilin or LTP. Asero et al. showed in 2008 that 30% of patients sensitized to grass pollen had skin reactivity to date palm profilin (Pho d 2) and 57% of profilin reactors had food allergy. The large majority of profilin-allergic patients reported OAS as the only food-induced symptom.[52] In addition, food allergy may occur via sensitization toward different proteins. The same Asero R demonstrated that among 96 subjects with tomato allergy, 36%, 8%, 28%, 18%, 8%, and 1% of patients were sensitized to PR-10, profilin, both PR-10 and profilin, LTP alone, LTP plus PR-10 or profilin, and genuine tomato allergens, respectively. Consequently, the differentiation between PR-10 proteins, profilin, and LTPs in OAS with SPT can help to evaluate risk levels.[53]

Specific IgE testing is another useful method used to diagnose OAS. IgE serum antibodies can be analyzed via radioimmunoassay, enzyme-linked immunosorbent test or chemiluminescence or RAST. Detection of specific IgE against food uses protein extracts and now natural or recombinant purified allergens. Compared with FFSPT, RAST in patients with a clinical history of OAS were comparable for peanut, hazelnut, and pea, whereas RAST was superior for walnut. However, FFSPT remained superior for sensitivity for apple, orange, tomato, carrot, cherry, celery, and peach.[47] A more recent study compared FFSPT with ImmunoCAP in patients with OAS to melons. This study showed positive predictive values of FFSPT versus ImmunoCAP comparable at 42% and 44% and negative predictive values at 77% and 70%, respectively.[46] Because of the risk of misinterpretation in case of positivity, skin testing and IgE testing should be interpreted only in combination with clinical history.

TABLE 5.6

Sensitivity and Specificity Comparison of CSPTs and FFSPTs for Oral Food Allergy

	SPT: Sensitivity,%	
Food	**CSPT**	**FFSPT**
Apple	2	82
Peanut	67	12
Orange	27	67
Carrot	80	100
Tomato	25	75
Hazelnut	22	41
Pea	75	62
	SPT: specificity,%	
Food	**CSPT**	**FFSPT**
Apple	65	100
Peanut	93	46
Orange	73	97
Carrot	42	65
Tomato	61	79
Hazelnut	80	85
Pea	50	40

Source: Ortolani C, Ispano M, Pastorello EA et al. *J Allergy Clin Immunol.* 1999;83:683–690.

Component-resolved diagnosis (CRD) is a new instrument to manage IgE-mediated allergy. In contrast to the traditional specific IgE assays, CRD does not rely on the whole extract (potentially ill-defined mixtures that contain relevant and irrelevant components) from native allergens but it quantifies single purified or recombinant components specifc IgE antibodies.[54–57] Briefly, CRD establishes individual sensitization profiles in a single measurement. This technique has largely been studied within class 1 food allergy, examining associations with anaphylactic severity and distinguishing anaphylaxis from asymptomatic sensitization. Testing OAS patients for PR-10 versus LTP components is also helpful to distinguish patients limited to oral symptoms from those who may develop a systemic reaction.[58] More recently, the CRD concept has been extended to multiplex testing with more than 100 components on microarrays.[59–61] However, in a recent study, Ebo et al. showed that CRD offered no advantage over conventional quantification of r mal d1 sIgE for discriminating between sensitization and a real allergy in the diagnosis of apple-mediated OAS in birch pollen allergy.[62]

The basophil activation test (BAT) is another test that determines the percentage of activated basophils that expressed the CD63 marker after in vitro stimulation by different antigens. BAT has been reported to be more sensitive or specific than SPT or RAST/fluorescent enzyme immunoassay for allergy to drugs, latex, and venoms. In food allergy and, more specifically in OAS, few studies have been published. In 2003, the authors compared the CD63-based BAT in the diagnosis of allergy to carrot, celery, and hazelnut with SPTs and measurement of allergen-specific IgE.[63] SPTs with native carrot, celery, and hazelnut showed sensitivities of 100%, 100%, and 90%, and specificities of 80%, 80%, and 90%. In contrast, sensitivity of allergen-specific IgE and the BAT for carrot, celery, and hazelnut was 80% versus 85%, 70% versus 85%, and 80% versus 90%, with corresponding specificities of 80% versus 85%, 80% versus 80%, and 95% versus 90%. In another study, Ebo et al. compared patients with birch pollen allergy and a history of apple-mediated OAS (OAS^+), patients with birch allergic without OAS (OAS^-), and healthy controls without birch pollen allergy and OAS. Comparison between OAS^+ subjects and healthy controls showed sensitivities and specificities of 96% and 100% for apple IgE and 88% and 100% for the apple SPT, respectively. In a separate analysis between OAS^+ and OAS^- subjects, specificities decreased to 30% for apple IgE and to 80% for the apple skin test, respectively, and BAT reached a sensitivity of 88% and a specificity of 75%.[64]

Treatment

Clinical and immunological observations provide strong evidence that OAS is the consequence of cross-reactivity between pollen proteins and food proteins. Most of the time, OAS symptoms resolve spontaneously in a few minutes after ingestion and patients did not always mention them. One of the explanations is that these patients are often atopic patients who take antihistamines for allergic rhinitis or pruritus and antihistamines might partially relieve symptoms of OAS. In principle, foods that cause OAS should be avoided, but pollen-associated foods are often edible when heated. Therefore, the unnecessary elimination of foods should be avoided through close evaluation of the history of allergy from cooked foods. Indeed, LTPs may cause severe symptoms and some pollen-related foods such as celery or soybean may lead to systemic reactions even if they belong to the PR-l0 proteins. Therefore, in case of emergency, patients with a history systemic or anaphylaxis should carry a portable epinephrine injection kit and antihistamines with a medical certificate.

Because OAS is believed to be initiated by a primary aeroallergen sensitization, the role of immunotherapy has been evaluated as a potential specific therapy. Thus, one would assume that successful subcutaneous allergen-specific immunotherapy (SIT) of pollen allergy might concomitantly cure pollen-related food allergy. SIT is a series of continuous administrations of increasing doses of allergen extracts to the allergic patient to induce clinical tolerance. It is currently the only causative treatment for IgE-mediated allergy that results in long-term clinical tolerance to allergens. SIT induces high levels of allergen-specific IgG4 antibodies which are considered as "blocking" antibodies because they compete with IgE for allergen-binding.[65–67] Thus, SIT with birch pollen has been proven efficient for the treatment of birch pollinosis.[68–70] However, the clinical benefit of SIT with birch pollen on birch pollen-related food allergy is still debated. Whereas a few studies have described that patients improved their clinical symptoms to birch pollen-related foods after birch pollen SIT, [71–73] others have reported limited curative effects of birch pollen SIT on birch pollen-related food allergy, and some patients even developed allergic reactions to foods during the course of therapy.[74–76] In the end, the majority

of clinicians observe that only approximately 30% of birch pollen–allergic patients undergoing birch pollen SIT concomitantly improve birch pollen-related food allergy.

Sublingual immunotherapy (SLIT) has been demonstrated to be an effective and safe alternative for conventional subcutaneous SIT of birch pollen allergy.[77–79] Similar to subcutaneous immunotherapy, SLIT induces allergen-specific IgG4 antibodies.[80,81] Speculating that sublingual administration directly at the site of food-induced allergic symptoms instead of subcutaneous injections might improve the therapeutic benefit on birch pollen-related food allergy, the effects of SLIT with birch pollen extract on apple allergy in birch pollen–allergic individuals was evaluated in 2007.[82] After one year of treatment, all the patients were considered successfully treated for their respiratory symptoms. However, only very few of the nine patients concomitantly improved allergic reactions to apple in double-blind placebo-controlled food challenges. Surprisingly, all patients developed increased Bet v 1-specific IgG4 antibody levels after 1 year of SLIT but Mal d 1-specific IgG4 antibody levels did not increase significantly in parallel. So treatment with pollen does not effectively induce food-reactive IgG4 antibodies in every patient. Therefore, authors proposed that vaccines for the treatment of pollen-related food allergy should contain the disease-eliciting food allergens. This approach would have the advantage to treat both pollen allergy and food-related allergy.

On the other hand, a first randomized, double-blind, placebo-controlled study in 2005 demonstrated significant increases in tolerance to hazelnut after sublingual administration of hazelnut extract.[83] Tolerance induction was accompanied by increased IgG4 antibody after immunotherapy in only the active group. Thus, SLIT with Bet v 1-associated food allergens may be a promising approach for treatment of birch pollen-related food allergy.

Furthermore, recent developments in the treatment of food allergy (class 1) suggest oral immunotherapy (OIT) with the disease-eliciting food as an interesting option.[84] Indeed, results from a double-blind, placebo-controlled study in peanut-allergic children demonstrated OIT with peanut-induced desensitization and concurrent immune modulation.[85] In contrast to the placebo group, the actively treated OIT group showed significant reductions in skin prick reactivity to peanut and significant increases in peanut-specific IgG4 antibodies. In OAS, the first studies show similar results.[86] Kopac et al. induced local oral tolerance in 17 patients with a clear history of birch pollen rhinoconjunctivitis and associated OAS to apple. Patients should consume daily increasing small amounts of apple. When the whole apple was tolerated without symptoms, the subject continued eating at least three apples per week to maintain tolerance. Seventeen patients (63%) reached the maintenance dose after an average time interval of 20 weeks.[87] Fernandez-Rivas et al. used Pru p 3, the peach lipid transfer protein, for SLIT in patients with peach allergy. After 6 months of SLIT, the active group tolerated a significantly higher amount of peach (three- to ninefold). Local reactions were restricted to the oral cavity and no serious adverse events were reported.[88]

Conclusion

OAS is an interesting allergy induced by foods in sensitive patients. After more than 70 years and many controversies, recombinant allergens are going to explain the different clinical presentations of OAS. New techniques extend the scope of biologic tests but should never substitute for physician approach. Beside food eviction and symptomatic treatment in case of severe OAS, food immunotherapy and food tolerance induction are promising treatments.

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Atopic Diathesis and Contact Urticaria Syndrome

M. Braire-Bourrel, F. Augey, F. Bérard, and J.F. Nicolas

Atopic diseases and contact urticaria (CoU) are both frequent conditions. However, there are very few studies on this topic and the link between atopy and CoU has been rarely investigated. In the present work, we first define atopy, then we review the literature on atopy and urticaria, especially CoU, and finally we focus on the mechanisms by which molecules in contact with the skin could induce urticaria (i.e., a wheal and flare reaction). The main conclusion of this work is that atopy promotes immunoglobulin E (IgE)-mediated CoU; however, its involvement in nonimmunological CoU is still unknown and remains to be addressed.

Atopic Diathesis

Atopy describes the personal/familial tendency to become sensitized and produce IgE antibodies to common environmental proteins.[1] Atopic patients have therefore positive skin prick tests and/or circulating serum IgE to several (and at least one) pneumallergens and/or trophallergens, [2] and this defines "atopic diathesis."

Atopic patients may eventually develop clinical symptoms affecting the skin and/or mucosae that are in daily contact with pneumallergens/trophallergens. The classical atopic "career" starts during early childhood with atopic eczema/dermatitis. Some children may concomitantly develop asthma, whereas their skin lesions improve or completely disappear. Later on, symptoms of allergic rhinitis/conjunctivitis with persistent asthma may emerge. This successive development of atopic diseases defines the "atopic march."[1]

There is considerable evidence that the prevalence of atopic diseases is increasing.[3] In the United States, asthma affects 20 million people, whereas allergic rhinitis affects 20–40 million people, and atopic eczema/dermatitis about 15%–20% of the childhood population.[3]

Atopy and Chronic Urticaria

Chronic urticaria (CU) is not an allergic disease, but rather an inflammatory skin disorder mediated by the chronic activation of mast cells. Although the pathophysiology of CU is still unknown, the current paradigm postulates that patients' mast cells are persistently activated and therefore show activation thresholds lower than those of mast cells from non-CU patients. This results in an apparent fragility of mast cells that can be fully activated by several nonspecific factors that are unable to induce urticaria flares in normal individuals (e.g., physical/chemical triggers, drugs, infections, psychological stress).[4] Exposition of patients to these factors will precipitate or aggravate CU flares.

There are two main factors that may explain the chronic activation of mast cells in CU patients: autoimmunity and atopy.

- Autoimmune CU affects 30%–50% of the patients who produce agonistic autoantibodies directed to mast cell surface molecules especially to IgE and to the IgE receptors (e.g., FcεRI). These autoantibodies activate mast cells and induce urticaria as shown by positive autologous serum skin tests. Patients often also have autoantibodies against thyroid antigens and may suffer from other skin autoimmune diseases (e.g., vitiligo, alopecia areata).[5]

- Atopic CU affects roughly the same proportion of patients as autoimmune CU. Indeed, several clinical reports have highlighted an overrepresentation of atopy in CU.[6] Autoimmunity and atopy can coexist in the same patient. Atopy seems also to promote acute urticaria, whatever the mechanism (i.e., allergic or nonallergic).[6–8] In atopic CU, mast cells may be chronically activated by the presence of minute amounts of allergens that are permanently absorbed through the skin and mucosae and reach the skin mast cells through the blood. The quantity of allergens able to bind specific IgE molecules may condition the activation level of mast cells and their subsequent ability to degranulate upon additional triggering factors.

Thus, atopy seems to be a risk factor for CU. But is this also true for CoU?

Atopy and Immediate Contact Reaction, CoU, and Protein Contact Dermatitis

Are atopic patients more prone to CoU than nonatopic patients? If we accept the hypothesis that mast cells of atopic patients are preactivated by daily exposure to environmental allergens, then atopic patients should be more susceptible to CoU. The 1985 study by Elpern et al. supports this hypothesis by showing that respectively 46%/44% of Hawaiian patients with CoU had a personal/familial history of atopy versus 21% of personal atopy in the control group.[9] To our knowledge, no other study has addressed this question in recent years.

Figure 6.1 summarizes our current hypotheses on the pathophysiology of the two forms of CoU: immunological CoU (ICoU) and nonimmunological CoU (NICoU) contact urticaria.

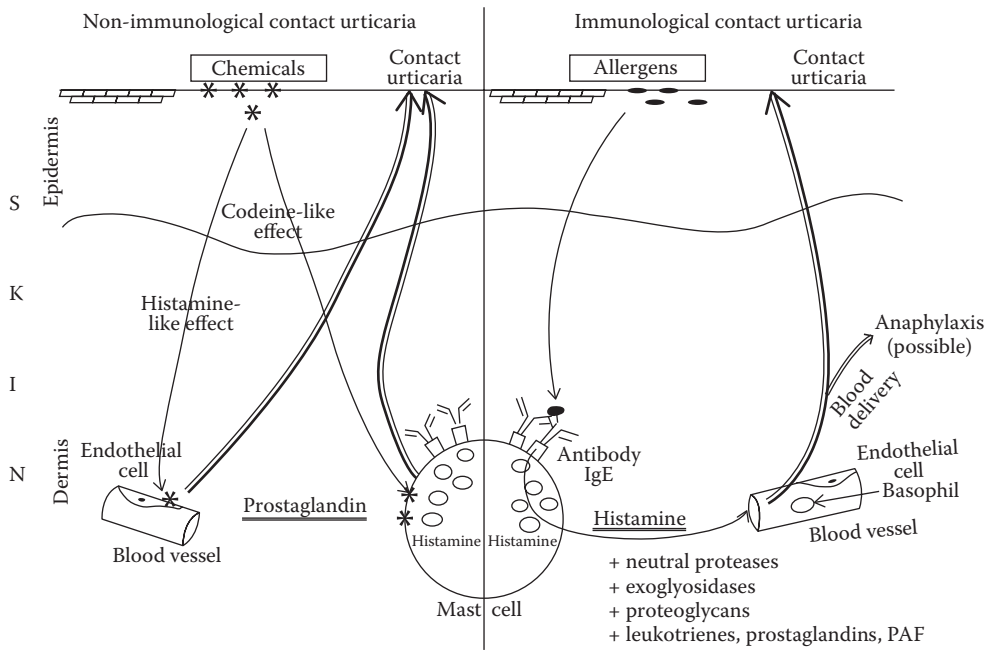

FIGURE 6.1 Proposed pathophysiology of CoU. Non-immunological contact urticaria: chemicals are the main triggers. They penetrate the skin and target mast cells and endothelial cells, which produce prostaglandins and to a lesser extent histamine and probably other (still unknown) vasoactive molecules. This is followed by endothelial cell activation, leading to vasodilation (erythema) and increased vascular permeability (dermal edema). Immunological contact urticaria: allergens (or haptens) are the triggering substances. After penetration through the skin, they interact with IgE bound on the mast cell surface, inducing a type I allergic reaction. Histamine is the main mediator of endothelial cell activation.

ICoU and Atopy

ICoU is a type I hypersensitivity immunological reaction that requires previous sensitization of the patient, which means that he or she has already been exposed to the causative allergen and has produced specific IgE antibodies. The subsequent contacts with the allergen induce mast cell activation and release of histamine, neutral proteases, exoglycosidases, and proteoglycans. The allergen–IgE reaction also leads to the synthesis of leukotrienes, prostaglandins, and platelet-activating factor by the activated mast cells. This results in a wheal-and-flare reaction at the skin site in contact with the allergen, which exceptionally triggers anaphylaxis if a high number of mastocytes is activated.[10]

The ICoU allergens are mostly proteins (including, for example, food allergens) but may be non-protein chemicals such as drugs responsible for CoU in IgE allergic patients (e.g., ICoU to penicillins in allergic health care professionals).

Atopic patients are predisposed to ICU. Several clinical observations indicate that CoU to environmental allergens develops frequently in atopic patients.[12] For example, during prick tests to pneumallergens, positive tests (i.e., urticaria lesions) may develop on adjacent unpricked skin of sensitized atopic patients. Besides, atopy is a well-known risk factor for ICoU to natural rubber latex, food, or animal stuffs; ammonium persulfate is a nonimmunologic trigger of CoU.[11,12] Foods are a very common cause of ICoU in everyday life. Raw fruit and vegetables such as apples, carrots, and tomatoes are frequent culprits. The term "oral allergy syndrome" has been coined to describe the ICoU of the oropharyngeal mucosa following food intake in IgE-sensitized food-allergic patients.[13]

Atopic Dermatitis Patients Are More Frequently Affected by ICoU: The Example of Protein Contact Dermatitis

The higher frequency of ICoU in atopic patients may not only be related to their propensity for IgE sensitization, but also to the coexistence/presence of eczema. For sensitization to occur via the cutaneous route, proteins of high molecular weight must be absorbed through the skin.[14] This is less likely to occur in healthy/intact skin. Eczema is associated with a defect in the epidermal barrier that exists in lesional and nonlesional skin and may allow the penetration of proteins through the epidermis where they can interact with Langerhans cells, a key point of sensitization [15] into the dermis where they can activate IgE-sensitized mast cells.

Protein contact dermatitis is an occupational skin inflammation occurring in atopic dermatitis patients who manipulate food (e.g., meat for butchers) and who are IgE-sensitized. The symptoms associate CoU, which starts a few minutes after the skin contact with food, followed by an eczematous reaction a few hours/days after the contact.[11]

Nonimmunological Contact Urticaria and Atopy

To our knowledge there is no data about nonimmunological CoU (NICoU) and atopy. NICoU is the most common type of immediate contact reaction and occurs without prior sensitization. NICoU can be induced by several physical and organic chemical triggers. Physical triggers include cold, heat, and pressure, which provoke typical CoU reactions. However, these clinical forms of urticaria are generally considered "physical" and not "contact" urticarial.

Substances responsible for NICoU are commonly encountered in our environment: preservatives, fragrances, and flavoring in cosmetics, toiletries, topical drugs, and foodstuffs. These are usually low-molecular-weight chemicals easily crossing the skin barrier. Most substances are aldehydes or weak acids or their salts, but acidity itself is not essential. A minor change in the structure of a substance may greatly alter its capacity to produce a NICoU reaction.[16] Examples include benzoic acid, sorbic acid, and cinnamaldehyde. At usual concentrations, they have been shown to elicit contact reactions.[13] The NICoU edematous reaction usually appears within minutes to an hour and disappears within an hour, but erythema may last for six hours after contact with the eliciting substance.[10] Men seem to react more readily than women.[16] The symptoms vary depending on the substance, concentration, and site of exposure, with vehicle, mode of exposure, usually remaining localized in the contact area. Generalized urticaria rarely seen in ICoU is exceptional in NICoU. Studies using experimentally induced

NICoU showed marked variation in susceptibility to NICoU agents depending on the anatomic site. The most sensitive area is the face, followed by (in decreasing order) antecubital fossa, upper back, upper arm, volar forearm, and lower back.[10]

The mechanism of NICoU depends on the triggering factor and involves the production of vasogenic mediators.[13] It was previously assumed this was the result of histamine release from mast cells; however, antihistamines are not very efficient in physical NICoU and do not inhibit reactions to common NICoU chemical agents such as dimethyl sulfoxide, benzoic acid, cinnamic acid, cinnamic aldehyde, or methyl nicotinate. In contrast, these common NICoU agents can be inhibited by acetylsalicylic acid and nonsteroidal anti-inflammatory drugs both orally and topically, suggesting the role of prostaglandins.[10] The duration of inhibition by systemic acetylsalicylic acid may be up to four days. Experimental data have confirmed that there is a release of prostaglandin D2 without concomitant histamine release following topical application of sorbic acid, benzoic acid, and cinnamic aldehyde.

Ultraviolet A and B irradiation inhibit the NICoU reaction for at least 2 weeks.[10] Psoralen + ultraviolet A treatment also has an inhibitory effect on NICoU reaction. This inhibition also affects areas of the skin sheltered from irradiation, suggesting a systemic effect and the possibility that substances other than prostaglandins are involved in NICoU.

The role of cutaneous nerves has been studied using capsaicin able to block the release of substance P and other active peptides from the axons of unmyelinated C fibers of sensory nerves. Capsaicin pretreatment does not impair NICoU from benzoic acid and methyl nicotinate, but does inhibit the flare of histamine prick tests. Local anesthesia has shown a slight inhibitory effect on the NICoU reaction.[10]

In summary, prostaglandins rather than histamines are now considered to be the main mediator of NICoU reactions. Other, yet-uncharacterized vasoactive molecules are involved. But their cellular sources (mast cells, endothelial cells, macrophages, and others) are so far not identified.

Clinical Study on CoU in Atopic and Nonatopic Patients

As stated previously, there is no epidemiological or clinical data of NICoU in atopic patients and no previous study has addressed the susceptibility of atopic patients to react to NICoU triggers. To have more information on this topic, we set up a small clinical study in 81 consecutive patients who received pneumallergen skin prick tests during an allergological work-up. We used histamine and codeine as NICoU triggers because they both induce urticaria through non-IgE mechanisms. Histamine and codeine were applied as open tests (i.e., they were not pricked) as a complement to the usual list of allergens and controls performed during skin prick tests to pneumallergens. The study aimed to test for qualitative and/or quantitative differences in the results of open tests to histamine and codeine between atopic versus nonatopic patients.

Methods

We included 81 patients having prick tests for pneumallergens in the Allergy and Clinical Immunology Unit, Hospital Lyon-Sud, Pierre-Bénite, France, between February and August 2013. We included all the patients having prick tests for pneumallergens, whatever their medical history. The patients had the standard battery of pneumallergen prick tests including prick tests with histamine and codeine (positive controls) and with saline serum (negative control) on their forearms. In addition, they also had open tests with histamine, codeine, and saline serum on the proximal part of the same forearm.

Results

We divided the patients into two groups: (1) 50 patients were defined as atopic because they had at least one positive pneumallergen prick test and (2) 31 patients who were nonatopic because they had no positive pneumallergen prick test (Table 6.1). We then analyzed the results of prick tests and open tests with histamine and codeine for both groups.

TABLE 6.1

Clinical Study: Results of Histamine and Codeine Skin Tests

	Atopic Patients	Nonatopic Patients
Number of patients	50	31
Prick tests		
Histamine		
Number of positive tests	49	31
Positive tests' average diameter (papule/erythema, mm)	14/29	13/28
Codeine		
Number of positive tests	48	30
Positive tests' average diameter (papule/erythema, mm)	9/24	15/25
Open tests		
Histamine		
Number of positive tests	6	4
Positive tests' average diameter (papule/erythema, mm)	7/22	6/28
Codeine		
Number of positive tests	0	0

Histamine prick tests were interpretable and positive in 49/50 atopic patients and in the 31 nonatopic patients, with similar mean diameters of papule and erythema: 14/29 mm and 13/28 mm, respectively.

Codeine prick tests were interpretable and positive in 48 atopic patients and in 30 nonatopic patients, with mean diameters of papule and erythema of 9/24 mm and 15/25 mm, respectively.

Histamine open tests were positive for 6/50 atopic patients, with a papule average diameter of 7 mm and an erythema of 22 mm; they were positive for 4/31 nonatopic patients, with a papule average diameter equal to 6 mm and an erythema equal to 28 mm.

There were no positive codeine open tests among the atopic and nonatopic patients tested in this study.

The frequency and the size of histamine and codeine skin tests (prick tests and open tests) were similar between the two groups of patients whether the patients were atopic or not. If we focus on histamine and codeine open tests, six of the 50 atopic patients (12%) had positive histamine open test; three of the 31 nonatopic patients (13%) had positive histamine open test. None of the 81 patients had a positive codeine open test.

Discussion

Our clinical study aimed to test for differences between atopic and nonatopic subjects in their skin response to histamine and codeine able to induce CoU when applied onto the skin without pricking. We did not find any difference between the two groups of patients, suggesting that atopic patients are not prone to NICoU. However, we experienced a major methodological problem during the study because open tests to histamine were positive in only a minority of patients (10/81), whereas open tests to codeine were negative in all 81 patients. Because the prick tests with the two chemicals were positive in almost all patients, this suggests that the amount of codeine and, to a lesser extent, of histamine able to penetrate the epidermis was too low to provide efficient mast cell (codeine) and endothelial cell (histamine) activation. Therefore, more studies need to be performed on the ability of atopic patients to develop CoU to classical NICoU triggers.

Conclusion

Atopy is an increasing problem all over the world. Some striking information found by the literature review on CoU is the rarity of studies addressing the pathophysiology of the disease, which is probably explained by

the lack of experimental models of CU. Clinical evidence and recent studies indicate that atopy predisposes to CU and that atopic patients are also more prone to ICoU. However, the role of atopy in NICoU remains to be clarified.

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7

Proteins as Trigger Factors of Immediate Skin Contact Reactions

Paolo Daniele Pigatto and Rossano Hermes Valsecchi

Introduction

Contact urticaria has been reported following skin contact with a multitude of substances ranging from simple chemicals to macromolecules. Its prevalence among the general population is unknown, but it may be a relatively common and underrecognized phenomenon.

Nonimmunological (irritant) causes typically elicit mild localized reactions, which clear within hours. Such agents can be found widely in food, cosmetics, and medicaments. The lower diagnostic end point for nonimmunological contact urticaria has been the subject of debate, which makes interpretation of the literature difficult.

Immunological (allergic) contact urticaria is due to immediate-type hypersensitivity and occurs most commonly in atopic individuals. It is mediated primarily by histamine, and may be associated with systemic and potentially life-threatening symptoms. Natural rubber latex is one of the most important causes today, and the recent "epidemic" of latex protein allergy has helped draw attention to this subject. Immunological contact urticaria to animal or vegetable matter may occasionally affect those who handle food and those in other occupations such as agricultural and veterinary workers. This may be associated with development of a protein contact dermatitis. Immunologic contact urticaria reactions are considered immediate immunoglobulin E (IgE)-mediated reactions that may spread beyond the site of contact and progress to generalized urticaria. Severe immunologic contact urticaria may lead to anaphylactic shock. This can happen, for example, as a result of contact with protein aptens with natural rubber latex. Typically, latex gloves cause a wheal and flare reaction at the site of contact but can generalize to anaphylaxis.

The latex is a milky liquid which is obtained from the *Hevea brasiliensis* tree that is widespread in Malaysia, Indonesia, and Thailand. Imported from Central America by early explorers in the 15th century, the *Hevea brasiliensis* became an industrial product in the late 18th century. The use of latex in ancient Mesoamerica is documented since 1600 BC. The oldest articles in natural rubber come from Veracruz (Mexico) and are 12 rubber balls.[1] In 1813, Adam Elias von Siebold initially suggested the use of latex gloves to reduce the risk of infections; in 1852, a French company created the first catalog of anatomical latex gloves.[2]

The first pair of rubber gloves for surgical use was produced in 1890 by the Goodyear Rubber Company that, in 1839, had discovered the "cure," a process that used sulfur to stabilize and make more effective the elastic properties of natural rubber.[2] Essential constituents of the latex follow.

- Rubber particles (spherical droplets of chains of cis-1, 4 polyisoprene wrapped in a layer of phospholipoprotein). In 1989, two important proteins were identified and sequenced for the synthesis of cis-1, 4 polyisoprene: the prenyltransferase (38 kDa) that catalyzes the summation of the isoprene units, and the rubber elongation factor (14.6 KDa), a cofactor necessary for the activity of cis-prenyltransferase.
- Major luteoid bodies (important for latex clotting and constituents of 20%–25% of the volume) are hevein (4.7 kDa) and pre-hevein (20 kDa).

- Particles of Frey Wyssling (representing 3% of the latex volume), whose role has not yet been fully clarified.
- Cytosol consisting of carbohydrates, organic acids, amino acids, and proteins, which is important for the synthesis of isoprene.[3]

The latex is therefore composed for 65% water, 33% polyisoprene, 2% resin and 1.8% protein.

Understanding the production process of the latex glove is important to be able to interpret the allergy that can result. The steps of the technological cycle include: collection, centrifugation, coagulation, vulcanization, and adding the powder as a lubricant. Because freshly collected latex rapidly undergoes coagulation on exposure to air, deterioration, and bacterial contamination, it is therefore necessary to add preservatives and anticoagulants such as ammonia. Subsequently accelerators are added, including antiozonants, antioxidants, emulsifiers, stabilizers, dyes, biocides, retarders, fragrances, and elasticizers. An important role is played by accelerators that control the degree, consistency, and completeness of the process of vulcanization (thiuram, carbamates, mercaptobenzothiazole). To better understand the problem of latex allergy from a clinical point of view, it is appropriate to focus on the definition, allergens, clinical and predisposing factors, latex cross-reactivity, diagnosis, prevention, and therapy.

Definition

The allergy to latex is characterized by the presence of latex-specific IgE antibodies and clinical symptoms consisting of an IgE-mediated reaction against products of natural rubber. It should be emphasized that patients with laboratory data that indicate the presence of latex-specific IgE without clinical relevance may have cross-reactive antibodies of no clinical significance. On the other hand, patients with anaphylactoid manifestations but without evidence of specific IgE to the latex may simply be responsive to other environmental allergens. For a correct definition of latex allergy, it is necessary to detect the presence of specific IgE (by in vivo and/or in vitro testing) and its clinical symptoms.[4]

Specific Allergens

Over the past 20–25 years, several latex allergens have been cloned and sequenced, whereas others were only partially characterized.[5] The first methods of immunoblotting and inhibition have been largely replaced by methods of molecular biology. Substantial progress in molecular and immunological characterization of allergens of latex to "recombinant production" that allows gathering of a large amount of molecules that are perfectly reproducible has been obtained by "recombinant allergens" [6] that have made it possible to study and better understand the molecular basis of these immunological reactions. There are currently 13 allergens of latex, labeled Hev b1 to Hev b13, that are better identified and characterized (Table 7.1). The latex contains approximately 250 polypeptides, 56 of which have been identified as allergens, and the molecular weight of these proteins 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 lead to a selective enrichment of chemical and heat-resistant proteins that may be denatured or complexed in new antigenic specificity.

Hev b1 (or rubber elongation factor) is a specific latex allergen with a molecular weight of 14.6 kDa: specific IgE antibodies to this antigen are present in 30% of health care workers with latex allergy.[7] Hev b1 and Hev b3 seem to be the major allergens for children with congenital anomalies and latex allergy, along with Hev b7.[8] Allergens such as Hev b 7, 8, 9, 10, 11, 12, and 13 must be taken into account in possible latex–fruit cross-reactivity [9] or latex/pollen-plants.[10]

Recently, Hev b7 has been identified as the third specific allergen in spina bifida. On the other hand, there are children with an allergy to latex without spina bifida or without a history of surgery, in which the most significant allergens are prohevein (Hev b 6.1) and hevein (Hev b 6.2). These children may have been exposed to natural rubber products for nonmedical products, such as elastic bandages, balloons, or rubber toys.[11]

The process of sensitization to latex can occur by dermal, mucosal, parenteral, or aerosol exposure.[12]

TABLE 7.1

Latex Allergens

Allergen	Molecular Weight (KDa)	Name	Physiological Role
Hev b1	14.6	Rubber elongation factor	Rubber biosynthesis
Hev b2	35.1	Beta-1,3-glucanase	Defense protein
Hev b3	22.3	Small rubber particles	Rubber biosynthesis
Hev b4	50–57	Microhelix	Defense protein
Hev b5	16	Acid protein from serum C	
Hev b6.01	20	Prohevein	Defense protein
Hev b6.02	4.7	Hevein	(Latex coagulation)
Hev b6.03	14	Prohevein	C-terminal domain
Hev b7.01	42.9	Chips-like proteins	Defense protein
Hev b7.02			Rubber biosynthesis inhibitor
Hev b8	13.9	Profilin-latex P	Structural protein
Hev b9	47.7	Latex enolase	Enzyme
Hev b10	26	Mn superoxide dismutase	Antioxidant
Hev b11	33	Endochitinase cl. 1	Defense protein
Hev b12	9	Lipid-transferase protein	Defense protein
Hev b13	42.9	Protein primary nodule	Enzyme

Clinical manifestations

Allergic reactions to rubber involve immunoreactions of type I and type IV according to the classification of Gell and Coombs (Table 7.2).

The type I immunoreaction is an antibody IgE-mediated clinical manifestation that may include: asthma, rhinitis, rhinoconjunctivitis, urticaria, nausea, abdominal pain, hypotension, or anaphylaxis. These clinical manifestations are divided in five different stages (Table 7.3).

Urticaria is undoubtedly the most common clinical manifestation of hypersensitivity to latex and reflects an IgE-mediated reaction. The wheals may appear not only in contact with the primary contact but on the whole skin (Figures 7.1 through 7.3). In children, latex allergy can be detected by symptoms such as itching, erythema, and moderate labial edema after contact with a pacifier or rubber balloons, or during the first experience at the dentist office.

Anaphylaxis is the most severe clinical form of hypersensitivity to latex proteins, characterized by a combination of cutaneous, respiratory, and cardiovascular diseases.

The interval between exposure and onset of symptoms is short, and in some cases there are prodromal symptoms whereas others are serious ab initio. Intraoperative anaphylaxis is an extremely serious allergic reaction to latex and sometimes remains unrecognized, being confused with adverse reactions to other drugs administered during anesthesia.[13]

Latex can also become an aeroallergen; in fact, rhinoconjunctivitis and asthma may be due by latex allergens complexed with a starch powder used as a lubricant. The proteins of the latex adhere to the starch powder creating a protein polysaccharide, and, after inhalation, can cause acute inflammation of bronchi and lung. Investigations conducted in several hospitals has shown concentrations of aggregated latex dust particles significantly elevated [14]; without correct ventilation, the data were even higher. The first contact with latex you can have is in the delivery room where babies are exposed through the skin and/or mucous membranes to latex gloves from midwives, nurses, and doctors. Even premature babies are at high risk for possible exposure to latex in the sections devoted to them because of bottles and rubber teats.[11] Recent evidence, however, documented a trend in the reduction of latex allergy cases of as a result of the substitution of latex gloves with latex-free vinyl gloves together with the creation of latex-free pathways in various hospitals.[15]

TABLE 7.2

Allergy to Rubber

Type of Reaction	Clinical Factor	Immunological Mechanism	Diagnosis	Causal Factors
Immediate (type I)	Hives Asthma Angioedema Rhinoconjunctivitis	IgE-mediated	Prick test, RAST	Latex allergens
Delayed (type IV)	Eczema	T lymphocytes	Patch test	Rubber additives

TABLE 7.3

Latex Allergy: Clinical Stages of Type I Reactions

Stage I	Localized urticaria at the site of contact
Stage II	Generalized urticaria with angioedema
Stage III	Urticaria associated with asthma, rhinitis, conjunctivitis, and gastrointestinal symptoms
Stage IV	Urticaria with anaphylaxis
Stage V	Chronic asthma and permanent lung injury

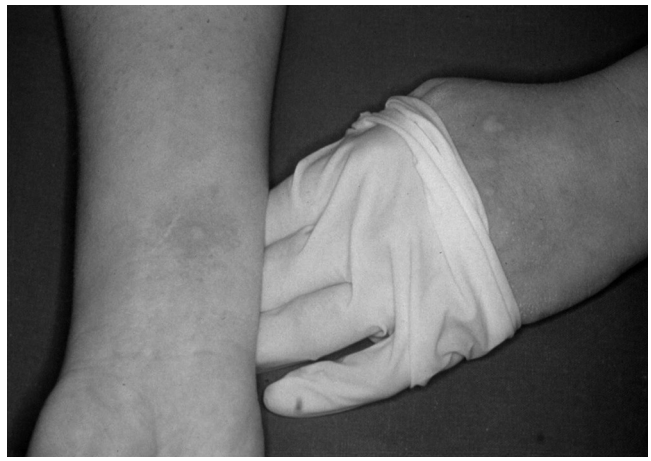

FIGURE 7.1 Contact urticaria: latex glove.

An allergy to natural rubber has been a serious problem since the 1970s, when the demand for latex gloves was definitely increased. During the past decade, there has been a slowdown in reports of new cases that is due to adoption of low-protein and powder-free gloves.

In the general population, it is estimated that the prevalence of latex allergy is less than 1%. There are groups at risk for hypersensitivity to latex in which the prevalence of allergy is higher: health care professionals,[16] workers in the rubber industry,[17] hairdressers,[18] veterinarians,[19] patients with spina bifida or other congenital anomalies, particularly of the urogenital tract, and atopic patients.[10] In the general pediatric population, the prevalence of latex allergy is estimated to be 0.2%–0.8%. Although this prevalence is low, there are groups of patients at high risk for the development of latex-specific IgE antibodies: 72% of young patients with spina bifida, 20.8% of atopic children, and two-thirds of children with bladder problems are sensitized to latex.[20] Repeated exposure to natural rubber during each surgical procedure for orthopedic defects or neurological and urological maneuvers such as catheterization are seen as the main causes for latex protein sensitization in children with spina bifida. In these patients, the risk of intraoperative anaphylaxis to latex is 500 times higher than in the general population.[21] It was also noted that 30%–80% of children sensitized to latex are atopic.

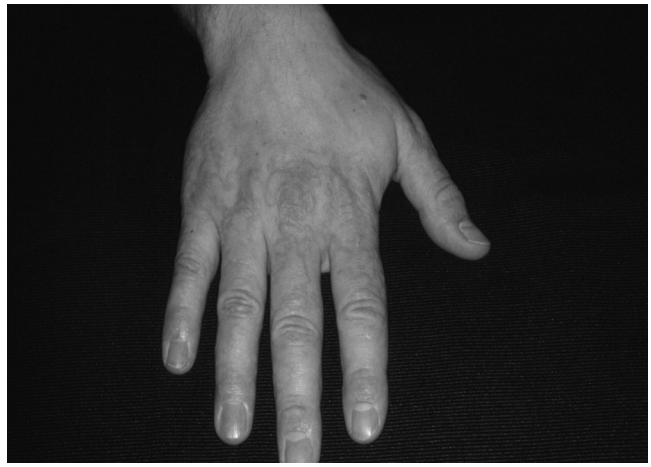

FIGURE 7.2 Hives in the primary contact.

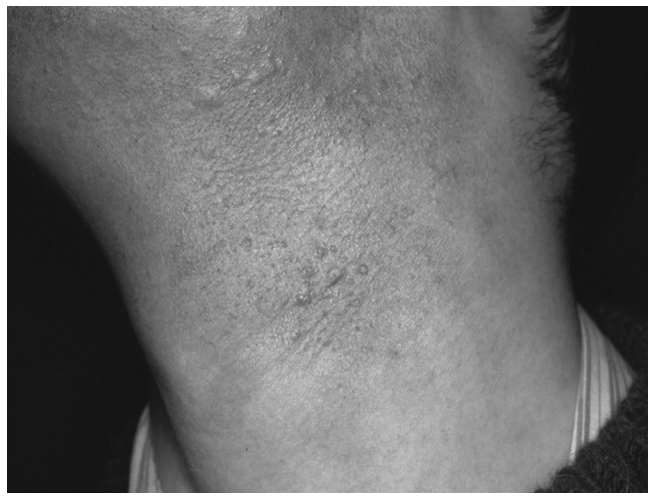

FIGURE 7.3 Hives in a distant location from the original contact of latex.

Young patients with other congenital anomalies require, on several occasions, similar surgery, but do not show the same increase in sensitization to latex.[22] The exact mechanism that competes with immunoallergic children with spina bifida is not entirely clear. It has been suggested as a possible cause in an alteration in the immunological response: among the substances that are released during the immunoallergic reaction are cytokines that modulate the intensity and duration of the reaction itself. It is well known that fetuses, compared with children and adults, have a different cytokine secretion in response to certain infections: the fetus has a predominance of Th2 cells that protects it from maternal immunological responses. This predominance favors particular immunoallergic reactions. During the first weeks of life, there is a switch with a predominance of Th1 cells. Such a switch, however, does not occur in all patients, causing a particular reactivity toward some proteins including those of the latex. Failure of "tuning" from Th2 to Th1 is mostly due to a combination of genetic and environmental factors, and this may occur in children with spina bifida.[15]

Atopy and repeated exposure to allergens in natural rubber through multiple surgical procedures are important conditions for the development of latex-specific IgE isotype antibodie.

In adult patients with chronic renal failure, the prevalence of allergy to latex seems to be equal to 1%, thus comparable to that of the general adult population.[23]

The type IV immunoreactions are caused mainly by contact with chemicals used in the process of manufacturing or sterilization of natural rubber and the most frequent manifestation is contact dermatitis.

The allergic contact dermatitis is the result of a delayed hypersensitivity reaction caused mainly by additives with power accelerator, antioxidant, and curatives added to natural rubber during the machining process.[24]

Irritant contact eczema is a common reaction to rubber products, in particular gloves, characterized by dry, itchy, sometimes burning, cracking skin located mostly at the ends of the fingers. Contact eczema can develop within minutes or hours after exposure and, in the case of latex, repeated exposure may lead to true allergic reactions.

Latex and Cross-Reactivity

Possible cross-reactions are well known: latex–fruit and latex–plant/pollen syndrome. *Hevea brasiliensis* is botanically related to many tropical and subtropical plants and fruit and specific IgEs were observed in children allergic to latex, particularly papaya, mango, avocado, banana, chestnut, passion fruit, fig, melon, kiwi, pineapple, peach, apricot, and tomato. It is worth mentioning that allergy to fruits, vegetables, and legumes usually appears after the second year of life, when most of these foods are introduced into the diet. The allergy to foods is, therefore, a dynamic problem in the function of age. Avocado, for example, is the fruit that is most frequently involved in the latex–fruit syndrome because of a close relationship between avocado and latex related from an endochitinase class 1 pro-protein (MW 31000).[9] The same antigenic epitope was found in the chestnut and banana. These proteins, highlighted in some plants such as potato and tomato (Sol t 1) are delegated to the "defense," which relates to the possible cross-reaction.[25] With regard to clinical manifestations, the latex–fruit syndrome is expressed in approximately 50% of cases with systemic reactions; the remaining 50% is distributed between urticaria, angioedema, and oral allergy syndrome. These percentages may vary depending on the consumption of various foods in different geographical areas. The chestnut allergy, for example, is diagnosed less frequently in Germany than in Spain and Italy. Finally, there are cross-reactions with latex–pollen and plants; for example, natural rubber shares some antigenic epitopes with the pollen of grasses, composite, and birch.

Prevention

Latex, used in the production of numerous tools used in health care (gloves, face mask, intubation tubes, catheters, and adhesive electrodes) and domestic products (balls, pacifiers, helmets, masks pool, and adhesives), is almost a ubiquitous allergen to which everyone is exposed from the early age. Latex objects thus constitute a potential source of awareness for susceptible individuals and a possible danger for sensitized persons.

The prevention of allergy and, consequently, the management of the allergic patient, require knowledge of epidemiological data, the definition of a correct diagnostic procedure, and the availability of information and adequate tools to prevent exposure or, at least, to reduce the adverse effects. These aspects must necessarily be reconnected to different risk groups of pediatric age such as children with a malformation of the neural tube, abnormalities of the genitourinary tract (bladder exstrophy), neurogenic bladder, or anorectal anomalies (anal atresia). Repeated surgery, especially in the first months of life when the predominant Th2 response and atopic diathesis are significant risk factors, is also observed in the general pediatric population.[26]

The prevention of latex allergy is based on primary prevention to implement, where possible, the substitution of latex object with synthetic devices (chloroprene, nitrile, poly-isopropene, polyurethane) or with the adoption of powder-free latex gloves: these interventions reduce by more than 100 times the concentration of airborne allergens (Table 7.4). In the early 1980s, there was a significant increase in the use of latex gloves that caused an increase in production without an adjustment of products, at least initially, to specific quality standards. Latex gloves such as "surgical" and "consultation" containing powder lubricant with a high content of rubber additives (accelerators, vulcanizing agents) and latex proteins were available on the market. In the second half of the 1980s, as a result of the increased signaling of latex allergy, quality of the products grew because of the attention of the

TABLE 7.4

Latex Device in Use at the Emergency Department and Their Replacements

Device	Constituent	Replacement
Gloves	Latex	Synthetic polymers
Facial masks made of black rubber	Latex	PVC[a]
Balls	Latex	PVC/neoprene
Bracelets with different sizes	Latex	Canvas cover
Infusion fittings	Latex	PVC
Syringes with black rubber piston	Latex	PVC piston
Ambu bag	Latex	PVC/neoprene

[a]polyvinyl chloride

glove manufacturers and health care industry. Besides the improvement of production techniques, a replacement of the internal lubricant was obtained, initially consisting of deproteinized talc (magnesium silicate or oxide) with cornstarch. Finally, in the 1990s came the spread of gloves with synthetic polymers (vinyl, nitrile, neoprene, and other materials). The current scientific guidelines now almost universally shared, indicate a preference in which it is still considered necessary to use powder-free latex-free gloves that are low in protein.[27]

Another important aspect of prevention is to identify susceptible individuals to allergy to latex. The questions aimed to investigate a possible allergy should become routine in the history performed by the physician (e.g., swelling itching of the lips during dental examination or inflating balloons, swelling or tingling in the hands, runny nose, sneezing, cough, wheezing or wheezing after contact with latex objects; adverse reactions in the case of anesthesia, invasive surgeries.). From time to time should a possible association with swelling or itching of the lips after ingestion of certain foods (banana, kiwi, avocado, chestnut, or tomatoes) should be investigated.

The precautionary use of latex-free artifacts must encompass children with spina bifida or abnormalities of the urogenital tract. In children with spina bifida, in fact, given the high risk for latex allergy, exposure from birth should be completely avoided. For these children and those who have been subjected to numerous surgical procedures, control allergy must be initiated early, especially before new invasive procedures. In high-risk children who undergo surgery or instrumentation use, implementing a test is also indicated in the presence of negative history (identification of sensitive subjects).

With regard to subjects with known sensitization, prevention is aimed at avoiding the onset of symptoms (cutaneous, respiratory, systemic): artifacts in contact with latex, ingestion of cross-reacting foods, or interventions/health procedures that involve contact with latex (secondary prevention).[28] In the management of allergic children, parents need to be aware about the products, foods, and situations that can trigger allergic reactions; how to take preventive action, and the urgency of providing them with necessary items (e.g., lists, gloves, drugs).

Preventive measures must be brought to the attention (even involving the pediatrician) of the centers where the child is (e.g., kindergartens, schools, holiday centers). Any invasive procedures or those involving mucosal contact (on sensitized or high risk allergic children) must be carried out with latex-free tools and methods. In general, in the management of an allergic population, the diagnosis must be certified to prevent incongruous exposures.

Diagnosis

The current diagnostic algorithm for allergy to latex includes a thorough anamnesis, in vivo skin tests, the request for latex-specific IgE, and, if necessary, a provocation test with a latex glove.

A history collection as complete as possible is of crucial importance. It is important to indicate allergy to natural rubber in any clinical manifestation—such as rhinitis, conjunctivitis, urticaria, angioedema, asthma, or anaphylaxis—occurring after exposure to natural rubber products or in the course of surgical procedures as well as immediate reactions consequent to ingestion of cross-reacting foods with latex. The history is particularly relevant in high-risk individuals.

FIGURE 7.4 Prick tests with eluate: pomphoid reaction with pseudopodia.

In Vitro Tests

Latex-specific IgE antibodies can be searched using the CAP-radioallergosorbent test (CAP-RAST), Ala-STAT fluorescent enzyme immunoassay, and Hy-TEC. In vitro testing is the most used CAP-RAST; its sensitivity is 78% and specificity about 90%. Ala-STAT and CAP-RAST can produce a 25% false-negative result and Hy-TEC, 27% false positives. Recently, the Food and Drug Administration approved another in vitro method, Immunolite 2000 3 g Allergy. This test showed a higher sensitivity than the previous ones, while showing false negativity of 15% compared with a skin test.[29]

In Vivo Test

A suggestive clinical history of hypersensitivity to latex should be comforted by the skin test (prick test). Bearing in mind that the source for allergy test is always a *Hevea brasiliensis* milky extract, it is necessary to consider several variables that may affect the protein content and then allergens present in the extract: the mode of collection, storage, and processing. The proportion between proteins of the collection phase and the final phase is very different; this applies both to standardized extracts of trade and for eluate, which is achieved by immersing 1 g of the suspect glove in 5 mL of saline solution for 20 minutes; after removing the solution is diluted to 1/1000, 1/100, and 1/10 (Figure 7.4). In Europe, standardized extracts of trade are Stallergenes (France), ALK-Abelló (Spain), and Lofarma (Italy).

A diagnostic algorithm for children with spina bifida suggests that the positive anamnesis for clinical manifestations after contact with natural rubber products is sufficient for the diagnosis of latex allergy. The tests are needed if children are asymptomatic (preferably the skin test). The presence of risk factors such as atopy and repeated surgical procedures is sufficient to consider these sensitized patients. The provocation test is generally considered the definitive test although reproducibility, standardization, and criteria for positivity of the challenge are sometimes weak. In any case, a challenge test with latex should not be proposed in children.

Therapy

Patients with a known allergy to latex should avoid exposure, even if the product is in alternative material (vinyl or neoprene). Patients who have to undergo surgical procedures requiring frequent latex-free material should be closely monitored. The high prevalence of latex allergy in risk groups not only justifies but requires a prompt prophylaxis to prevent contact with natural rubber. Children who belong to such groups and those already sensitized

should be treated in a latex-free environment, especially during the induction of anesthesia and surgery. In particular, infants with spina bifida should be cared for in a latex-free course from the first hours of life.

A therapy of primary care includes:

Antihistamine (cetirizine 2.5–10 mg desloratadine 1.25–5 mg);

Prednisone 1–2 mg/kg betamethasone 0.1–0.2 mg/kg; and

Self-injectable epinephrine (e.g., Fast Jekt).

Immunotherapy may be useful in patients with clinical manifestations in which removal from latex is difficult or impossible. On the basis of studies and current clinical evidence, it can be said that the latex immunotherapy may be a viable therapeutic strategy, whereas pointing out that some clinical trials highlight the potential risk of adverse events.[30] The recombinant DNA technology has led to a better immunological characterization and a more fine knowledge of latex allergen immunotherapy that is a prelude to more selective and secure uses.

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8

Chemical Compounds as Trigger Factors of Immediate Contact Skin Reactions

Elena Giménez-Arnau

Introduction

Immediate contact skin reactions manifest as contact urticaria (CoU), contact urticaria syndrome (CUS), and protein contact dermatitis (PCD). These pathologies are characterized by the immediate skin development of itchy flares, wheals, and/or dermatitis, following external contact with a substance.[1]

CoU usually appears within 30 minutes and clears completely within hours, without residual signs of irritation. Fisher defined it in 1973, even though this phenomenon had been recognized for many years.[2] CoU is a very frequent pathology, and an ever-expanding list of causes, substances ranging from simple chemicals to macromolecules, has been reported. Mostly proteins (molecular weight 10,000 Da to several hundred thousands), but also chemical compounds of low molecular weight (LMW) (<1,000 Da) are involved. The present chapter will focus mainly on these LMW chemical compounds.

To review the LMW chemical agents responsible for immediate contact skin symptoms, it is first necessary to be reminded of the defined categories of CoU according to the underlying mechanism(s) involved. Basically, CoU is classified as nonimmunological or immunological. A third category exists for reactions with mixed features or undetermined pathomechanisms.[3]

Nonimmunological CoU (NICoU) is the most common form of the disease, occurring without prior exposure to an eliciting substance, which means without previous sensitization. Substances inducing NICoU are frequently encountered in our environment as preservatives, fragrances, and flavorings in cosmetics, toiletries, topical medicaments, and foodstuffs.[4,5] The pathogenesis is not clearly understood, but it appears to involve the release of vasogenic mediators without involvement of immunological processes. Because of the lack of response to antihistamines and the positive response to acetylsalicylic acid and nonsteroidal anti-inflammatory drugs, it has been proposed that the physiopathology involves prostaglandin release from the epidermis rather than histamine release from the mast cells, as previously assumed.[6,7]

On the other hand, immunologic CoU (ICoU) is a type I hypersensitivity reaction, mediated by allergen-specific immunoglobulin E (IgE) in previously sensitized individuals.[3] In this case, the release of histamine is the major mechanism of action seen. The mechanism following skin challenge includes allergen penetration through the epidermis, binding to IgE on mast cells, causing degranulation and release of histamine and other vasoactive substances such as prostaglandins, leukotrienes, and kinins.[8] Again, many causes have been documented as causing ICoU. Many are plant or animal proteins.[9] However, many LMW chemicals including drugs, biocides and preservatives, metals, or industrial compounds can also produce ICoU. Finally, a third category exists for substances that show mixed features of NICoU and ICoU, or where the mechanism remains unclear. The bleaching agent ammonium persulfate is a classic example. Although the clinical picture looks like an IgE-mediated reaction, such antibodies against ammonium persulfate have not been identified.[5,10] However, this third category is much less common and will not be discussed further here.

Tables 8.1 and 8.2 list the most reported LMW chemical agents producing immediate nonimmunologic and immunologic skin reactions.[1,11]

TABLE 8.1

Chemical Compounds Reported as Triggering Immediate Contact Reactions and NICoU [1,11]

Fragrances, Cosmetics	Biocides, Preservatives	Drugs	Other
α-amyl cinnamic aldehyde[a]	Alcohols (amyl, ethyl, propyl, isopropyl, benzyl)[b]	Acetylsalicylic acid[b]	Acetic acid[b]
Anisyl alcohol	Benzoic acid	Aminophenazone[b]	Butylhydroxytoluol[b]
Balsam of Peru	Bronopol	Amoxicillin[b]	Chloroform
Benzaldehyde	Camphor	Benzocaine[b]	Diethylfumarate[b]
Benzophenone	Chlorocresol	Capsaicin	Dimethylammonium chloride[b]
Cassia oil	Formaldehyde	Chlorpromazine[b]	Dimethyl sulfoxide
Cetyl alcohol (emulsifier)[b]	Imidazolidinyl urea	Dinitrochlorobenzene[b]	Fumaric acid[b]
Cinnamic acid	Kathon CG	Ketoprofen[b]	Panthenol[b] (hair product)
Cinnamic alcohol[a]	2-phenoxyethanol[b]	Lidocaine[b]	Polypropylene[b]
Cinnamic aldehyde[a]	Polyethyleneglycol[b]	Nicotinic acid esters	Trichloroethanol[b]
Cinnamon oil[b]	Sodium benzoate	Pilocarpine[b]	Turpentine (plant derivative)
Coumarin	Sorbic acid	Propyphenazone[b]	Vinyl pyridine[b]
Eugenol[a]		Promethazine[b]	Xylene[b]
Geraniol[a]		Steroids[b]	*Metals:*
Hydroxycitronellal[a]			Aluminum[b]
Isoeugenol[a]			Copper[b]
Menthol			Gold[b]
Propylene glycol			Palladium[b]
Pyrrolidone carboxylate			Rhodium
Resorcinol			Ruthenium
Stearyl alcohol (emulsifier)[b]			Tin
Vanillin			Zinc

[a]Constituent of the Fragrance Mix I.

[b]Immediate contact reaction, unclassified nonimmunological/immunological.

Chemicals and Nonimmunological Reactions

Chemical compounds mainly described as triggering immediate contact reactions and NICoU are listed in Table 8.1. Many of these chemicals are used in fragrances, in cosmetic products, as biocides or preservatives, and as drugs or topical medications. However, there are also other miscellaneous chemicals and metals responsible for these reactions. Most individuals react to these substances with local erythema and/or edema within 45 minutes after application, albeit with widely varying intensities of skin reaction.[12]

Fragrances and Cosmetics Ingredients

NICoU reactions to fragrances and to cosmetics ingredients are well known.[13] NICoU has been reported, for example, to some of the constituents of the Fragrance Mix I (FMI), and to Balsam of Peru.[14] However, clinical relevance must be carefully examined because individuals may develop simple NICoU or CoU associated with delayed hypersensitivity. Indeed, the components of the FMI (alfa-amyl cinnamic aldehyde, cinnamic aldehyde, cinnamic alcohol, eugenol, isoeugenol, geraniol, hydroxycitronellal, and oak moss) are potent skin sensitizers responsible for delayed-type allergic contact dermatitis. Actually, FMI, developed in the late 1970s, and Fragrance Mix II developed in 2005, are the most valuable screening tools for the detection of delayed hypersensitivity to fragrances.[15,16]

Safford et al. conducted a study on 20 patients positive to the FMI in 48 hours and classified the FMI ingredients according to the decreasing ability to induce CoU as follows: cinnamic aldehyde, cinnamic alcohol, isoeugenol, hydroxycitronellal, and geraniol.[17] Cinnamic aldehyde and cinnamic alcohol were the strongest urticaria inducers for nonallergic patients. CoU from cinnamic aldehyde has been reported by several authors,[4] leading even to anaphylaxis.[18] Among the many components of Balsam of Peru, cinnamic aldehyde

TABLE 8.2

Chemical Compounds Reported as Triggering Immunological Immediate Contact Reactions/ICoU [1,11]

Fragrances, Cosmetics	Biocides, Preservatives	Drugs	Other
Allantoin[a]	Ammonia	Aescin[a]	Acetyl acetone
Polysorbates (emulsifier)[a]	Butylated-hydroxytoluene[a]	Albendazole	Acid anhydrides
Sorbitan monolaurate (emulsifier)[a]	Chloramine	Ampicillin	Acrylic acid[a]
	Chlorhexidine	Azithromycin	Acrylic monomers
Sorbitan monostearate (emulsifier)[a]	Chlorocresol	Bacitracin	Aliphatic polyamide
	Formaldehyde	Benzoyl peroxide	*p*-aminodiphenylamine (dye)
Sorbitan sesquiolate (emulsifier)[a]	Mercurochrome	Cephalosporins	Aminothiazole[a]
	Parabens[a]	Cisplatin	Aziridine
Wool alcohol	Phenyl mercuric acetate	Chloramphenicol	Basic blue 99 (hair dye)
	Phenyl mercuric propionate	Diphenylcyclopropenone	Benzonitrile
	Sodium hypochlorite	Donepezil	Bisphenol A
		Gentamycin	Carbamates
		Iodochlorhydroxyquin	Chlorothalonil
		Levopromazine	Colophony (plant derivative)
		Lindane	Diethyltoluoamine
		Mechlorethamine	Dibutylphthalate
		Methimazole	Di-(2-ethylhexyl) phthalate
		Mezlocillin	Diphenylmethane-4,4′-diisocyanate
		Neomycin	
		Penicillins	Epoxy resins
		Pentamidine isothionate	Formaldehyde resin
		Phenotiazides	Methyl ethyl ketone
		Pyrazolones	Monoamylamine
		Rifamycin	Nylon
		Streptomycin	*p*-phenylenediamine (hair dye)
		Sulbactam	*Metals:*
		Virginiamycin	Chromium
			Cobalt
			Iridium
			Mercury[a]
			Nickel
			Platinum salts (cisplatin)

[a]Described as (non-clear evidence).

is described as the strongest agent inducing NICoU, followed by cinnamic acid, benzoic acid, and benzaldehyde.[19] Cinnamic aldehyde is the main component of cassia oil (approximately 90%) and cinnamon bark oil (approximately 75%). It is also the main component of artificial cinnamon oil. Smaller quantities are found in many other essential oils. In nature, the *trans*-isomer is predominant. It is a yellowish liquid with a characteristic spicy odor, strongly reminiscent of cinnamon. Being an unsaturated aldehyde, it undergoes many reactions including hydrogenation to cinnamic alcohol. Its oxidation occurs readily on exposure to air, yielding cinnamic acid. Cinnamic acid has been also used in perfumery, as a flavoring ingredient in pharmaceutical preparations, and in food products. Forsbeck and Skog found CoU from cinnamic acid 5% in petrolatum in three of five patients with immediate skin reactions to Balsam of Peru.[19]

The unsaturated terpene alcohol geraniol, a colorless liquid with a flowery rose-like odor, gave a patch test reaction after 20 minutes of application in a woman suffering from recurring edema in the lips and neck. The test with a perfume containing geraniol gave generalized urticaria.[20] CUS at stage IV has been reported in the case of people applying sunscreen and self-tanning products, with benzophenone-3 the major cause.[21] Benzophenone-3, also named oxybenzone, is often incorporated into sunscreen formulations to offer enhanced ultraviolet A protection because its absorption spectrum extends to less than 350 nm. In toothpaste and in a make-up remover, menthol, belonging to the family of monoterpenols, was described as the reason for urticaria

reactions, as was cephalgia in a woman placed in a context of generalized urticaria.[22] Symptoms disappeared with total eviction of menthol.

Biocides and Preservatives

Many compounds used as preservatives, such as imidazolidinyl urea, bronopol, and sorbic acid, have been shown to induce positive reactions at patch test after 45 minutes in a population of 50 patients.[23] CoU from sorbic acid is however thought to be rare, and only a few reports can be found in the literature. Some authors described that creams and shampoos containing sorbic acid caused erythema, slight itching, and edema sometimes.[24,25] As with sorbic acid, benzoic acid is a natural preservative, having antibacterial and antifungal properties. Present also in Balsam of Peru, it induced CoU at 5% in patients with immediate contact reactions to Balsam of Peru.[19] It has also been commonly used as a preservative in acidic food products. Thus, it was reported in a published study that benzoic and sorbic acid could elicit NICoU at concentrations in use in salad dressing in 18 of 20 school children.[26]

In the case of free formaldehyde, for which bactericidal and fungicidal properties confer it a place of choice for preservation of cosmetics, its use has been reduced because of the bad press it has received as an irritant, sensitizer, and potential carcinogen.[27] Formaldehyde is known to be a strong, ubiquitous skin sensitizer, including from noncosmetic sources of contact. Because of this, exposure to formaldehyde in the European Union is subject to restrictions. Free formaldehyde may be used as a preservative in all cosmetic products (maximum authorized concentration 0.2%, except 0.1% in products for oral hygiene) except aerosol cosmetics. Annex VI of the Cosmetics Directive 76/768 EEC further stipulates that all finished products containing formaldehyde or substances that release formaldehyde must be labeled with the warning "contains formaldehyde" if the concentration of free formaldehyde in the finished product exceeds 0.05%.[28] As an alternative, chemical compounds that slowly release formaldehyde in the presence of water and under usage conditions, the so-called formaldehyde releasers, are commonly employed as preservatives in cosmetics (water-based preparations) instead of free formaldehyde. Examples are bronopol and imidazolidinyl urea. Unfortunately, many formaldehyde releasers used in cosmetics are also skin sensitizers because of released formaldehyde but also to reactive intermediates other than formaldehyde that could be involved in the formation of the hapten-protein antigenic complex, a key step of the sensitization process, and thus explaining their sensitizing potential per se.[29] Even if it is a strong sensitizer, reported immediate reactions to formaldehyde are mainly classified as NICoU because they seem not to be mediated by IgE.[30] However, there is still no consensus in the reports that have appeared as to whether the mechanism is immunological or nonimmunological.[31]

CoU to other biocides such as *p*-chloro-*m*-cresol, benzyl alcohol, 2-phenoxyethanol, and polyethylene glycols, used as preservatives in a wide number of cosmetics and topical preparations, has also been reported.[32–35] CoU from alcohols was reviewed in the 1990s, with cases classified as nonimmunological and some as immunological based on open skin tests.[36]

Drugs

Many drugs can also provoke immediate skin reactions. They include mainly antibiotics, because direct contact with nurses and health care personnel during their preparation, or employees during the production in the pharmaceutical industry. Penicillins and cephalosporins are the most incriminated. All of them seem to have an immunological physiopathology and will be discussed later. For most of the other drugs reported, observed immediate contact reactions cannot be definitely classified as nonimmunological or immunological. Often, skin tests do not allow distinguishing between an IgE-dependent reaction and a nonspecific histamine release, and research of specific IgEs by using the radioallergosorbent test (RAST) is only available for some drugs. One example is lidocaine. It is a common amino amide-type local anesthetic applied topically, and the most important class 1B antiarrhythmic drug applied intravenously. An immediate positive patch test and prick test demonstrated its involvement in the simultaneous presence of CoU and allergic contact dermatitis in the same

patient.[37,38] Ketoprofen, an important cause of photocontact dermatitis, has also been described as responsible for CoU.[39] Other immediate reactions have been observed in personnel of psychiatry services during the manipulation of phenothiazines, antipsychotic drugs related to the thiazine class of heterocyclic compounds, such as chlorpromazine and promethazine.[40]

To end this section, among the many professional areas where case reports of CoU have been reported, workers of pharmaceutical and chemical industries are of considerable concern. They are in contact with highly reactive substances (some listed in Table 8.1) used for synthesis, for example, that have been also described as inducers of immediate skin reactions.

The pathogenesis of NICoU to all of these chemicals is not clearly defined. Different urticariogens may act by different mechanisms. For example, dimethyl sulfoxide can both damage blood vessels and cause mast cell degranulation. However, antihistamines do not inhibit reactions to dimethyl sulfoxide and other NICoU-triggering agents, whereas acetylsalicylic acid and nonsteroidal anti-inflammatory drugs do, both orally and topically, suggesting a role for prostaglandins.[6,7,41] Release of prostaglandin D_2 without concomitant histamine release has been shown, for instance, following topical application of sorbic acid and benzoic acid.[42,43]

Chemicals and Immunological Reactions

ICoU is an immediate type I hypersensitivity reaction, occurring in patients who have specific IgE against the agent(s) eliciting CoU. ICoU needs sensitization, and will appear after repeated contacts. It is more frequent in people with previous atopic symptoms. The allergen reacts with the IgE at the surface of mast cells and basophils and provokes the release of histamine and other vasoactive substances, except in rare cases where IgG or IgM have been incriminated. The consequences are potentially more serious than for NICoU because reactions may not remain localized to the area of contact, and generalized urticaria, or even involvement of organs such as the respiratory and gastrointestinal tract may follow, and end with anaphylactic shock. The most common agents inducing ICoU are food proteins (animal or vegetal), animal proteins, and natural rubber latex, and have been largely reviewed.[9,44] However, chemicals of LMW can also induce ICoU and are listed in Table 8.2. They are very often present in drugs, cosmetics,[45] and industrial preparations. There are extensive lists of proteins and chemicals reported as causing ICoU, only a part of them being reported as occupational.[3,11,44] Most publications about CoU concern case reports or little series and epidemiological studies are scarce. However, some data indicate that ICoU is not rare, although frequently underestimated.

Diagnosis of occupational CoU is based on the patient's previous medical history, chronology, and description of skin symptoms. With exception to substances inducing NICoU, skin tests are generally necessary for diagnosis. An order of skin investigations for evaluation of immediate responses has been suggested.[3,46] Skin prick tests with fresh material or commercial reagents is the gold standard diagnostic test.[8] But the ultimate evidence corroborating that a compound is responsible for ICoU is the measurement of specific IgE in the serum of the patient by the RAST test whenever possible. The RAST is a radioimmunoassay test to detect specific IgE antibodies to a suspected or known agent (protein, chemical compound) responsible for ICoU. The patient's serum is incubated with the agent bound to a solid phase, and the amount of specific IgE recognizing and binding to the agent is quantified with radiolabelled anti-IgE.[47] Determination of specific IgE by RAST will confirm type I hypersensitivity, but their ordinary detection is restricted to some compounds, particularly when they are nonproteinaceous. In this section, some examples reported in the literature are given.

Evidence on IgE-Mediated Urticaria to LMW Compounds: Reported Examples

Biocides and Preservatives

Chloramine is commonly used as a sterilizer, disinfectant, and chemical reagent. It has been described as an occupational hazard for pharmaceutical workers, nurses, and cleaners. Goossens et al. reported the first case of immediate positive epicutaneous tests to chloramine powder solutions used by a nurse.[48] All skin tests

performed on the patient were suspicious of an immediate-type reaction. The immunological nature of the clinical manifestations was investigated by RAST on serum of the patient. High levels of IgE antibodies to chloramine were found, those previously bound to human serum albumin (HSA). The clinical manifestation on the patient was confirmed by radioimmunoassay and classified as a stage 3 CoU syndrome. Chloramine is often confused with chloramine-T because both are employed as sterilizer, antiseptic, and disinfectant agents. However, they are two different chemicals. Chloramine-T is an *N*-chlorinated deprotonated sulfonamide, a white powder, compared with chloramine, which is a simple monochlorinated amine (NH_2Cl) that is a colorless liquid usually handled as a diluted aqueous solution. Allergic asthma caused by chloramine-T is well known and the reactions are IgE-mediated. Kramps et al. were able to demonstrate the presence of specific IgE antibodies in the serum of asthmatic chloramine-T allergic patients.[49] However, skin symptoms of IgE-dependent CoU have also been reported in the case of a hospital bath attendant in Finland. The performed RAST to chloramine-T showed specific IgE antibodies with values being defined as positive.[50]

Chlorhexidine, a cationic chlorophenyl-biguanide, is also an effective antiseptic and disinfectant that can trigger IgE-mediated type I hypersensitivity reactions in sensitized individuals.[51] Many health care workers are exposed to hand washes containing chlorhexidine. In the United Kingdom, four cases of occupational IgE-mediated allergy to chlorhexidine were identified, the diagnosis being made on an appropriate clinical history with positive serum-specific IgE to chlorhexidine and/or positive skin prick testing.[52]

Interestingly, formaldehyde, described already in the previous NICoU section, is a primary skin sensitizer inducing allergic contact dermatitis also suspected to induce ICoU. There have been few reports on allergy to formaldehyde associated with IgE, and single cases of formaldehyde-specific IgE-mediated urticaria exist in the literature.[53] Thus, formaldehyde should probably be classified as a substance that shows mixed features of NICoU and ICoU because the mechanism remains unclear.

Drugs

Antibiotics are very often associated to ICoU, such as penicillin.[54] Allergic reactions are estimated to occur in approximately 2% of patients treated with penicillin. Most of these are maculopapular or urticarial rashes. Severe reactions to penicillin such as anaphylaxis can occur and are potentially life-threatening. Penicillin belongs to the β-lactam group of antibiotics. All penicillin antibiotics contain a common nucleus (6-aminopenicillanic acid) composed of a β-lactam ring and a thiazolidine ring; this complex connected to a side chain. An intact β-lactam ring is necessary for bactericidal activity, and the side chain determines the spectrum of antibacterial activity, the susceptibility to destruction when exposed to acids and β-lactamases, and pharmacokinetics properties. Penicillin is a hapten and becomes immunogenic only when it binds to a protein. The β-lactam ring covalently binds to lysine residues of proteins and forms the penicilloyl group, known as the "major determinant" because it is the major penicillin metabolic product. Penicillin metabolites also form disulfide bonds with sulfhydryl groups of cysteine, producing the "minor determinants," so-called because they are formed in smaller quantities. Thus, immediate allergic reactions to penicillin are mediated through IgE antibodies against either the major or minor determinants or both.

Based on this, penicillin skin testing techniques have been developed demonstrating the presence or absence of specific IgE antibodies against major and minor penicillin determinants. The use of benzylpenicilloyl-poly-L-lysine can test IgE antibodies against major determinants. Histamine is used as a positive control, and saline is used as a negative control. Skin detection of serum IgE specific for major penicillin determinants has a high positive predictive value but fails to identify patients with penicillin allergy. It has been suggested that, ideally, skin testing to major and minor penicillin determinants would improve diagnosis. Methods of preparation of reagents for minor determinants have been published, and penicillin G has been used as a partial source of minor determinants. Today, alternatives to benzylpenicilloyl-poly-L-lysine and minor determinant mixtures are commercially available for skin testing.[55] Penicillin skin testing is believed to be safe if done properly, although severe reactions such as anaphylaxis have been reported, produced because of violation of the test protocols such as doing intracutaneous testing without first doing prick testing.

Concerning the RAST and the enzyme-linked immunosorbent assay, they detect IgE antibodies to the major penicillin determinant only, with a sensitivity of approximately 80%.[56]

The immunologic responses to different determinants of benzylpenicillin, amoxicillin, and ampicillin have been also reported by using these methodologies.[57] One study reported that the sensitization rate by skin prick and intradermal tests to benzylpenicilloyl-poly-L-lysine and a mixture of minor antigenic determinants was 12% in 83 asymptomatic Turkish nurses.[58] Prick and intradermal penicillin sensitivity tests reported rates of 22% for benzylpenicilloyl-poly-L-lysine, 21% for minor determinant mixture, 43% for amoxicillin, and 33% for ampicillin in patients with a clinical history of urticaria and/or anaphylaxis.[59]

After penicillins, cephalosporins are the most important β-lactams inducing IgE-mediated reactions. Responses may be selective or cross-react with common β-lactam determinants. Unlike determinants derived from benzylpenicillin, cephalosporin allergenic determinants have not been well-identified but it is possible to monitor serum-specific IgEs. In a cross-reactivity study conducted with a group of Italian subjects who had immediate allergic reactions to one or more cephalosporins (ceftriaxone, cefotaxime, ceftazidime, cefuroxime), IgE evaluation was performed by skin tests and RASTs with the responsible drugs as well as to classic penicillin determinants.[60] Prick and intradermal tests were performed with penicilloyl-polylysine, minor determinant mixture, penicillin G, ampicillin, amoxicillin, and with the cephalosporins. RAST used benzylpenicilloyl-polylysine, amoxicilloyl, ampicilloyl-polylysine, and the cephalosporin conjugated to polylysine. The results suggested that a small percentage of cephalosporin-allergic subjects reacted to penicillin determinants, and most had positive results to determinants generated only by cephalosporins. In a more recent study, the prevalence and risk factors of sensitization to cephalosporin was evaluated in a total of 161 health care workers. The enzyme-linked immunosorbent assay measured serum-specific IgE antibodies to conjugates of three cephalosporins and HSA. Sensitization rates determined by this technique were 17.4% for any cephalosporin, 10.4% for cefotiam, 6.8% for ceftriaxone, and 3.7% for ceftizoxime.[61]

To mention other drugs involved in immediate skin reactions, a case of CoU and anaphylaxis reaction after administration of powder containing clioquinol and bacitracin was described,[62] as were immediate hypersensitivity reactions presumably IgE mediated to pyrazolones.[63]

Other Chemicals

In the plastic industry, workers are in contact with highly reacting chemicals. Cyclic acid anhydrides are synthetic highly reactive LMW compounds widely used as curing agents for epoxy resins and in the production of polyester resins. Commonly used anhydrides are phthalic anhydride, tetrahydrophthalic anhydride, methyl tetrahydrophthalic anhydride, hexahydrophthalic anhydride, methyl hexahydrophthalic anhydride, maleic anhydride, and trimellitic anhydride. Cyclic acid anhydrides often cause allergic respiratory diseases, and in the literature only single case reports of CoU of a few patients were found. However, recently, occupational CoU has been described by a Finnish study as workers may be exposed in powder or liquid form during manufacturing processes.[64] Data are presented for 21 subjects who had been diagnosed with occupational CoU because of exposure to organic acid anhydrides and examined during 1990–2006. Prick tests with HSA-acid anhydrides conjugates, RAST determination of specific IgE and open application tests were used for the diagnosis. The majority of the patients had been exposed to an epoxy resin containing methyl hexahydrophthalic anhydride. Specific IgE results were in line with the prick tests and the large reaction was seen for the acid anhydride the patient had been exposed to. Phthalic anhydride IgE was positive in 19 of 20 patients. The authors concluded that CoU to these compounds may be more common than previously believed, as first shown by a previous Finnish study with two patients.[65]

Another important constituent of epoxy resins that has been incriminated as producing immediate reactions is bisphenol A, for which specific IgE were demonstrated as the cause.[66] Similar studies have been reported for another known respiratory allergen, diphenylmethane-4,4′-diisocyanate,[67,68] and for acrylates such as 2-ethylhexyl acrylate, acrylic acid, cyanoacrylates, and methyl methacrylate.[69]

CoU to permanent hair dyes such as *para*-phenylenediamine, which is a very well-known skin sensitizer, is almost exclusively reported in consumers, but has also been described in a beautician.[70,71] Other chemical compounds of LMW reported as inducing ICoU are aliphatic polyamides,[72] methyl ethyl ketone, widely used as solvent in plastic manufacture,[73] and monoamylamine,[74] a vehicle ingredient of topical medicaments.

Finally, metals and metallic salts can also cause occupational CoU. Aluminum,[75] chromium, cobalt,[76] iridium salts,[77] nickel,[75,78] platinum salts, and rhodium have been reported. Among them, platinum salts are important

allergens in the catalyst industry; clinical manifestations may involve both the respiratory system and the skin. [79,80] In some cases, an immunological mechanism with specific IgE is demonstrated.[78,81] A RAST was developed, for example, for the measurement of IgE antibodies specific to platinum chloride complexes in sensitized workers.[82]

Conclusion

Numerous LMW chemical compounds may cause CoU, and many of these are encountered in everyday life. Skin clinical manifestations of immediate contact reactions can be expressed as urticaria and/or dermatitis. Both manifestations can be developed by the same patient and can be induced by the same compound simultaneously. Establishing a diagnosis of ICoU is therefore important in order to confirm the need for allergen avoidance and in view of the potentially life-threatening nature of this pathology. Substances responsible for immediate contact skin reactions may be classified by molecular weight, mechanism of action, and occupational relevance. Cosmetics, plants, vegetables, and food are still the most common agents responsible for new cases of CoU. However, detailed chemical and biological studies continue to be necessary to determine the how and why and the behavior that provides immunological signs.

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9

Nonimmunological Contact Urticaria

Vincent Cunanan and Arto Lahti

Definitions, Concepts, and Symptoms

Nonimmunologic contact urticaria (NICoU) and other nonimmunologic immediate contact reactions (NIICRs) of the skin comprise a group of inflammatory reactions that appear within minutes to an hour after contact with the eliciting substance and usually disappear within a few hours. These reactions can also be called immediate-type irritancy. NIICRs occur without previous sensitization in most exposed individuals, and they are the most common type of immediate contact reaction.[1]

Symptoms of NIICRs are heterogeneous, and the intensity of the reaction typically varies depending on the concentration, the vehicle, the skin area exposed, the mode of exposure, and the substance itself.[2] Itching, tingling, or burning accompanied by erythema is the weakest type of reaction. Sometimes only local sensations without and visible change in the skin are reported. The redness is usually follicular at first and then spreads to cover the whole application site. A local wheal and flare suggest a contact urticaria reaction. Generalized urticaria after contact with NICoU agents is a rare phenomenon but has been reported more often after contact with agents eliciting immunologic immunoglobulin E–mediated contact urticaria. Repeated applications of NICoU agents may cause eczematous reactions. Quickly appearing microvesicles are frequently seen after contact with food products in protein contact dermatitis, which can be caused by nonimmunologic (irritant) or immunologic (allergic) mechanisms.[3,4] In NICoU reactions, the symptoms usually appear and remain in the contact area. In addition to local skin symptoms, other organs are occasionally involved, causing conjunctivitis, rhinitis, an asthmatic attack, or anaphylactic shock. This is called the contact urticaria syndrome, and it mostly involves immunologic mechanisms.[5] In some cases, NICoU reactions on appear on slightly affected skin and can be part of the mechanism responsible for the maintenance of chronic eczemas.

The use of the terms *immediate contact reaction*, *contact urticaria*, *immediate-type irritancy*, *contact urticaria syndrome*, *protein contact dermatitis*, and *atopic contact dermatitis* vary in the literature. Immediate contact reaction is the broadest concept, which covers both immunologic (allergic) and nonimmunologic (irritant) reactions, but does not say anything about the appearance of the reaction. Contact urticaria can be allergic or irritant. The redness of skin appearing within tens of minutes after contact with the eliciting substance cannot be regarded as contact urticaria unless at least some people have urticarial reactions at the application site. Protein contact dermatitis is caused by proteins or proteinaceous materials, and it means allergic or irritant dermatitis, which has characteristic features of acute or chronic eczema [1] Atopic contact dermatitis is a historical term and means an immediate-type (immunoglobulin E–mediated) allergic contact reaction in an atopic person.[6] It is included in the concept of allergic protein contact dermatitis (Table 9.1).

TABLE 9.1

Definitions and Terms

Immediate contact reaction	Immunologic (allergic) or nonimmunologic (irritant), urticarial or non-urticarial reactions. Does not define the appearance of the reaction.
Contact urticaria	Allergic and nonallergic urticarial reactions.
Immediate-type irritancy	Nonallergic urticarial or non-urticarial reactions.
Protein contact dermatitis	Allergic or nonallergic eczematous reactions caused by proteins or proteinaceous material.

Mechanisms of NIICRs

The mechanisms of NIICRs, similarly to other irritant reactions, are not well understood. It was previously assumed that substances eliciting NIICRs result in nonspecific histamine release from mast cells. However, it has been shown that the H_1-antihistamines hydroxyzine and terfenadine do not inhibit reactions to benzoic acid, cinnamic acid, cinnamaldehyde, methyl nicotinate, or dimethyl sulfoxide, though they inhibit reactions to histamine in prick tests.[2,7] These results suggest that histamine is not the main mediator in NIICRs to these well-known urticants.

The NIICRs to benzoic acid, cinnamic acid, cinnamaldehyde, methyl nicotinate, and diethyl fumarate can be inhibited by peroral acetylsalicylic acid and indomethacin [8,9] and by a topical application of diclofenac or naproxen gels.[10] The duration of inhibition by a single dose of acetylsalicylic acid can be as long as 4 days.[11] The mechanism by which nonsteroidal anti-inflammatory drugs inhibit NIICRs in human skin has not been defined, but it is probably ascribable to the inhibition of prostaglandin metabolism. This hypothesis appears to be valid, as topical application benzoic acid and sorbic acid have been shown to increase prostaglandin D_2 production by mast cells without the usually complementary histamine release.[12] Prostaglandin D_2 acts as a vasodilator [13] and is likely the mediator of erythema in these NIICRs.

The role of skin nerves in NIICRs has been studied using capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide), which is known to induce a release of bioactive peptides, such as substance P, from the axons of unmyelinated C-fibers of sensory nerves. Pretreatment of the skin with capsaicin inhibits erythema reactions in histamine prick tests,[14] but does not inhibit either erythema or edema elicited by benzoic acid or methyl nicotinate.[15] This suggests that NIICRs are not a type of neurogenic inflammation of the skin to these model substances. Topical anesthesia inhibits erythema reactions to histamine, benzoic acid, and methyl nicotinate, but it is not known whether the inhibitory effect is due to the influence on the sensory nerves only or whether the anesthetic also affects other cell types or regulatory mechanisms of immediate-type skin inflammation.[15]

Exposure to ultraviolet (UV) B and A light can inhibit NIICRs to benzoic acid and methyl nicotinate. The inhibition lasts for at least 2 weeks [16] The reactions on nonirradiated skin sites also decrease, suggesting the possibility that UV irradiation may have "systemic effects."[17] The mechanism of UV inhibition is not known, but it does not seem to be due to thickening of the stratum corneum, as has been speculated.[18]

Molecular structure is important for the irritant properties of a NIICR agent. Pyridine carboxaldehyde (PCA) has three isomers, 2-, 3-, and 4-PCA, depending on the position of the aldehyde group on the pyridine ring. It turns out that 3-PCA is a strong and 2-PCA a weak irritant in both human and animal skin (guinea pig ear swelling test). As previously mentioned, prostaglandin D_2 is a purported mediator of some NIICRs. Nicotinic acid, commonly known as niacin, has been demonstrated to produce cutaneous vasodilation—commonly known as niacin flush—via release of prostaglandin D_2.[13] Nicotinic acid is closely related to 3-pyridinecarboxaldehyde, with the difference being the carbonylic functional group at the 3 position of the pyridine ring (carboxylic acid versus aldehyde). A slight change in the molecular structure of a chemical may substantially alter its capacity to produce NIICRs.[19]

Table 9.2 describes some compounds that have been shown to elicit NIICRs.

TABLE 9.2

Examples of compounds known to elicit NIICRs [28]

Cinnamaldehyde	Benzoic acid
Cinnamic acid	Methyl nicotinate
3-pyridinecarboxaldehyde (strong)	2-pyridinecarboxaldehyde (weak)
Diethyl fumarate	Dimethyl sulfoxide (DMSO)
Glycolic acid [30]	Sorbic acid
Benzaldehyde	Menthol
Vanillin	Anisyl alcohol
Eugenol	Chloroform

Animal Testing Methods

Animal test methods for determining NllCRs are needed to screen for putative agents and to clarify their mechanisms. At the moment, the guinea pig ear-swelling test is the best animal test available for studying NIICRs.[20,21] A positive reaction in the guinea pig ear lobe comprises erythema and edema. Quantification of the edema by measuring the change in ear thickness is an accurate, quick, and reproducible method. Similar to human skin, the swelling response in the guinea pig ear lobe depends on the concentration of the eliciting substance. The maximal response is a roughly 100% increase in ear thickness and it appears 40–50 minutes after the application, depending on the vehicle.

A decrease in reactivity to NIICR agents is noticed after reapplication on the following day.[22] This tachyphylaxis phenomenon is not specific to the substance that produces it, and reactivity to other agents also decreases. The length of the refractory period is four days for methyl nicotinate, eight days for diethyl fumarate and cinnamaldehyde, and 16 days for benzoic acid, cinnamic acid, and dimethyl sulfoxide.

The guinea pig ear lobe resembles human skin in many respects, including the morphology of the reaction, the timing of the maximal response, the concentrations of the eliciting substances needed to produce the reaction, the tachyphylaxis phenomenon, and the lack of an inhibitory effect of antihistamines on the NlICRs.

Human Testing Methods

Special tests for NIICRs are needed, because these reactions are not seen in ordinary tests for irritancy and contact allergy. The most frequently used tests are the open test and the chamber test.

In the open test, 0.1 mL of the test substance is spread on a 3- × 3-cm area of the skin of the upper back, on the extensor aspect of the upper arm, or on the forearm. There are marked differences between skin sites in the reactivity to NIICR substances. The face, especially the cheek, the antecubital space, the upper back, the upper arm, the volar forearm, the lower back, and the leg constitute a rough order of decreasing reactivity.[1,18,23] A 10-µL dose to a 1- × 1-cm area is often used if a greater number of substances are to be tested at the same time. Petrolatum and water were the most often used vehicles 15 years ago.[1] but it has been shown that the use of alcohol vehicles and the addition of propylene glycol to the vehicle enhance the sensitivity of the test to detect marginal immediate irritant reactions.[24,25] The test is usually read at 20, 40, and 60 minutes to see the maximal response. In visual grading, scores for the erythema and edema components of the reaction (+ weak, ++ moderate, +++ strong) have been used,[24] but objective measurement of erythema using chroma meters and laser Doppler flowmeters is strongly suggested.[9,26] The test is usually performed on normal-looking skin, but it is sometimes useful to test suspected irritants on slightly or previously affected skin areas or on skin sites suggested by the patient's history. For example, if an immediate irritant reaction to a cosmetic cream has appeared on the face, we may see nothing if the test is performed on the back, but the reaction can be elicited by reapplication to the previously affected skin of the face. Repeated open tests on the same test site may be needed to detect weak immediate irritant reactions.[27] In a use test, the suspected product or substance is used in the same way as it was when the symptoms appeared.

The chamber test is a routine method of patch testing for contact allergy, but it can also be used to study NIICRs, The test substances are applied in small aluminum chambers (Finn Chamber, Epitest Ltd, Hyrylä, Finland) and fixed to the skin with porous acrylic tape. The occlusion time is 15 minutes and the test is read at 20, 40, and 60 minutes. Occlusion enhances percutaneous penetration and may increase the sensitivity of the test. The advantage of the chamber test is that a smaller skin area is needed than in the open test.[2,28]

The concentration of a NIICR agent needed in a skin test may be difficult to define, as it is in case tests with classical, delayed-type irritants; therefore, dilution series are recommended. They make it possible to determine the threshold irritant concentration for that particular patient and skin area. Examples of the concentrations often used in dilution series in alcohol vehicles are 250, 125, 62, and 31 mM for benzoic acid and 50, 10, 2, and 0.5 mM for methyl nicotinate.[7,29,30]

It is known that oral [9] and topical [10] nonsteroidal anti-inflammatory drugs efficiently suppress NIICRs and may therefore cause false-negative results in testing. The minimum refractory period is three days.[11] Tanned skin has decreased reactivity to NIICR agents,[16] and both UVB and UVA irradiation suppresses these reactions for two to three weeks.[16,17] Skin sites that are washed repeatedly may have a lowered threshold for immediate irritancy to NIICR agents.[29] The importance of the selection of the test site and the testing method has already been mentioned. These sources of false results should be kept in mind when tests for immediate irritancy are performed and the results of such tests are interpreted.

Conclusion

NICoU and other NIICRs of the skin shows urticaria, eczema, or both that are itchy, appear within minutes to an hour after contact with the eliciting substance, and usually disappear within a few hours. NIICRs occur without previous sensitization and are the most common type of immediate contact reaction. Of its pathomechanism, low-molecular-weight substances are involved through the prostaglandin metabolism. Further research is required.

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10

Immunologic Contact Urticaria

Antti Lauerma

Contact urticaria (CoU) is an important skin disease. The symptoms experienced in CoU range from local itch to systemic anaphylaxis. The common factor in urticaria is the release of inflammatory mediators from cutaneous mast cells, such as histamine, cytokines, and chemokines, which causes pruritus and swelling of the skin tissue.[1]

CoU presents as two different entities: immunologic CoU (ICoU) and nonimmunologic CoU (NICoU). They are separate in their mechanisms and etiology, and some differences in their clinical pictures may be seen. The most important distinguishing factor is the role of immunologic memory in these diseases. ICoU occurs only in patients sensitized previously to the causative agent, whereas NICoU does not require immunologic memory and may occur in any person. Because of these differences, the diagnostic procedures in patients differ. This chapter will focus on ICoU, especially its mechanisms.

Mechanisms of ICoU

ICoU is mediated through immunoglobulin E (IgE) antibodies that identify molecules entering the body through skin and perceived as foreign. IgE antibody-mediated reactions are most commonly seen in atopics. The discovery of IgE was much later than the discovery of other immunoglobulin subclasses. In 1921, Praunitz and Kustner discovered a transferable tissue-sensing factor in serum that was able to transfer reactivity from human to human. This was the first evidence for existence of a factor for hypersensitivity reactions. Four decades after, in 1967, it was identified as an immunoglobulin subclass IgE by Johansen in Sweden and Ishizakas in the United States.

IgE is present only at very low levels in blood or extracellular fluid, but is bound specifically and avidly to the high-affinity receptors FcεRI on the surface of circulating basophils and mast cells, which are located beneath the skin and mucosa and along the blood vessels in connective tissue. These cells can produce and release several potent mediators after antigen interaction with a small number of surface-bound IgE molecules. The enormous amplification power of the IgE antibody system not only provides an important defence mechanism against parasites, but also is responsible for a number of allergic clinical disorders.

IgE synthesis by B cells requires at least two signals. The first signal is delivered by a cytokine, interleukin-4 or interleukin-13, and is responsible for the choice of the isotype. The second signal is typically delivered upon engagement of CD40 on B cells by the CD40 ligand expressed on T cells, and results in switching and production of IgE. The CD23/CD21 pair also plays a role in the generation of IgE. The CD23 molecule is positively and negatively regulated by factors that increase or decrease IgE production, respectively. IgE is produced by plasma cells in lymph nodes draining the site of antigen exposure and also at the site of allergic reaction, typically mucosal tissue or the skin.

Type I hypersensitivity reactions are allergic reactions resulting from the production of IgE against external antigens. IgE is mainly localized in tissues, where it is tightly bound to the surface of mast cells, basophils, or antigen-presenting cells through high-affinity receptors (FcεRI). Binding of antigen to IgE cross-links these receptors, causing the release of mast cell mediators such as histamine, lipid mediators, and cytokines. On the other hand, the low-affinity receptors for IgE (FcεRII, known also as CD23), expressed on B cells, monocytes, and dendritic cells, have their biological role unclear at present.

IgE-mediated activation of mast cells orchestrates inflammatory cascade that is amplified by the recruitment of eosinophils, Th2 cells, basophils, and B cells. The physiological function of this reaction is a defense against parasite infection. However, in an allergic reaction, both acute and chronic inflammatory reactions that are triggered by mast cells have important pathophysiological consequences. These include an increase of vascular permeability, amplification of Th2 response, involvement in eosinophil maturation and activation, smooth muscle contraction, stimulation of mucus production, and attraction of eosinophils, basophils, and Th2 cells. These effects depend on mast cell–secreted proteins. Also, structural cells at the site of allergen exposure, such as epithelial cells, fibroblasts, vascular cells, and airway smooth muscle cells, are important sources of inflammatory mediators and participate in allergic responses.

Allergic inflammation can be divided into early events, called early-phase reactions or immediate reactions, which is characterized by short-lived mediators including histamine, and late-phase reactions, which involve leukotrienes, cytokines, chemokines, and the recruitment and activation of eosinophils, basophils, and antigen-specific T cells. Immediate reactions are induced within seconds to about 30 minutes of allergen challenge, and late-phase reactions occur within several to 24 hours.

Immediate reactions (type I hypersensitivity reactions) are mediated by secreted mediators released by tissue mast cells. In sensitized individuals, these mast cells already have allergen-specific IgE bound to their surface FcεRI. Mast cell degranulation begins within seconds of antigen binding, releasing an array of preformed and newly generated inflammatory mediators. The secretions of preformed mediators occur when the membrane of cytoplasmic granules fuses with the plasma membrane of the mast cell in a process called degranulation. This exocytosis releases granule contents to the external environment, including histamine, proteoglycans (heparin), proteases (tryptase), enzymes, growth factors, and cytokines. The signs and symptoms vary according to the site of the reaction and can include vasodilation, increased vascular permeability, constriction of bronchial smooth muscle, and increased mucus secretion. Also basophils can mediate these early phase reaction since they also express the FcεRI.

The molecule causing reactions has to penetrate epidermal layers, including the stratum corneum, as well as basement membrane, before it attaches to IgE bound on mast cell surfaces in the dermis (Figure 10.1). The responsible molecules have to have sufficient size and peptide structures to be able to bind to IgE. Therefore the most usual molecules causing ICoU are proteins or large-molecule-size polypeptides. Smaller peptides or chemicals have to bind to a carrier protein to be able to trigger an immune response. After the responsible molecule binds to the IgE on a mast cell, the cell releases inflammatory mediators, including histamine, cytokines, and

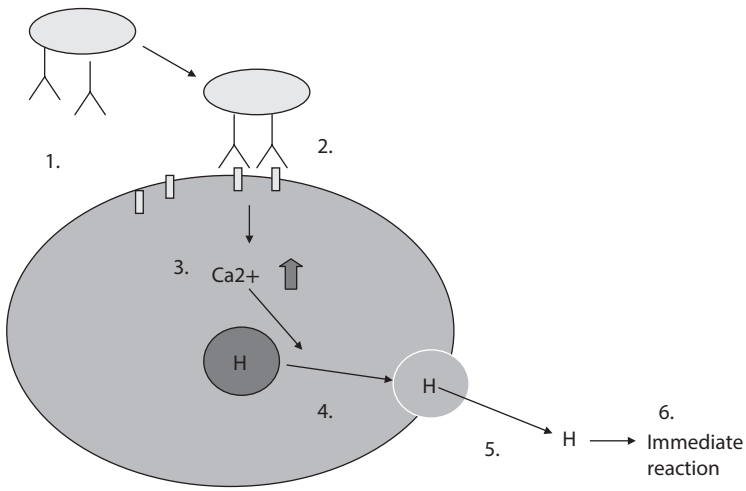

FIGURE 10.1 Immediate allergic reaction. (1) Protein bound with IgE arrives to tissue. (2) IgE bound to protein binds to at least two FcεRI receptors on mast cell. (3) Binding induces rise of intracellular Ca++.

chemokines, which cause itching, inflammation, and swelling in the skin. The swelling is seen as edema, the principal feature of urticaria.

The late-phase reaction occurs between three and nine hours after antigen challenge and is caused by the continued synthesis and release of inflammatory mediators, which are released more slowly than preformed mediators by mast cells. These newly synthesized mediators are cytokines, chemokines, and growth factors. Late-phase reactions are coordinated in part by certain long-term consequences of the mediators released by activated mast cells during early-phase reactions and in part by antigen specific T cells. Late-phase reactions do not develop in all sensitized individuals and, in some patients, there may be no clear clinical separation between the end of the early phase and the onset of the late phase. In the skin, Th2 type cells, and later also Th1 type cells, granulocytes (eosinophils, neutrophils, and basophils), and monocytes are recruited during late-phase reactions. Although mast cells account for the early response to allergen in the skin and airways, it is not clear how important they are for the development of late-phase responses and for the chronic allergic inflammation.[2]

Animal Models for ICoU

Rabbits sensitized with natural rubber latex show wheal-and-flare responses when prick tested. Therefore it could be that such animals can be used as animal models for ICoU to study its pathogenesis and possible medications to it. However, whether open application could be sufficient for ICU in this model as the rate of cutaneous penetration of natural ruber latex proteins has not been studied or established. Also, mice exposed to natural rubber latex have elevated IgE levels and eosinophilia.[3] Other proteins, such as ovalbumin, that are able to cause type I IgE-mediated reactions, should be studied to see if they could be used in a similar manner. CoU can be allergic, IgE-mediated (i.e., ICoU) or nonallergic (i.e., NICoU). ICoU is a relatively common skin disease, but still more rare than, for example, allergic contact dermatitis. ICoU is mediated through IgE antibodies that identify molecules entering the body through the skin and perceive them as foreign. IgE antibody-mediated reactions are most commonly seen in atopics.

Anhydrides cause asthmatic-like symptoms in people that have been exposed to them. The immunologic reactions in experimental animals and patients feature anaphylactic (type I), complement-mediated (type II), antibody complex–mediated (type III), and cell-mediated (type IV) reactions. Nonimmunologic (irritant) reactions may also participate, possibly due to degradation of trimellitic anhydride (TMA) to trimellitic acid. TMA causes skin reactions if sensitization is done through skin contact. The skin reactions appear in two phases, both immediate and delayed, implying that type I and IV reactions are involved. Sensitization of experimental animals can be done through airways or alternatively through skin. Cutaneous sensitization seems to induce both immediate and delayed skin reactions when a TMA-sensitized animal encounters the chemical next time.

In mice sensitized to TMA, a first immediate-type reaction resulting from reapplication is seen at one hour after dosing and a second delayed-type swelling reaction is seen at 24 hours. A dose-dependent swelling is also seen in nonsensitized animals, which can be caused by trimellitic acid, a hydrolization product of TMA. Such reactions could possibly be a form of NICoU.

Mice sensitized to topical TMA can be used for study of topical immunomodulating drugs. In one study, an antihistamine suppressed early, a glucocorticoid suppressed both early and delayed, and a nonsteroidal anti-inflammatory drug enhanced early skin reaction, in line with the clinical findings seen in patients in practice when these medications have been given in atopic IgE-mediated diseases.[4]

When BALB/C mice are repeatedly sensitized for up to 48 hours with strong contact allergen 2,4,6-trinitro-1-chlorobenzene, an immediate-type reaction kinetic emerges at the expense of the more typical delayed-type response to this contact allergen. Such a reaction kinetic shift coincided with an increase of the number of mast cells in the skin area used for sensitization and elicitation. Antigen-specific IgE was also seen, and the reactions were related to the increased number of mast cells on the site of application used.

The causative factors of ICoU are usually animal and plant proteins, and quite rarely, chemicals. Common agents causing ICoU include animal epithelia, fur and excretions, natural rubber latex, cooking powders and dairy, spices, plant foods, eggs, meat, and decorative plants.

Causative Factors of ICoU

Natural rubber latex is very well-studied cause of CoU and other IgE-mediated allergies, such as anaphylaxis. The structure, allergenicity and cross-reactivity of its allergens have been characterized. The most usual cause is medical gloves made from natural rubber latex. The allergens have systematic names starting with Hev; the most common allergen is hevein b 5.[5]

The content of allergens differs between different gloves. In the studies, allergenicity of different gloves was studied and published, which resulted in a reduction of latex protein allergen content in gloves. In study by Palosuo's group in Finland,[6] methods based on immunoelectrophoresis and immunoblotting, skin prick tests in latex-allergic volunteers and human IgE-based inhibition assays determining "total" allergenic content were compared. The study yielded reliable results on relative allergenicity of latex glove brands. This work resulted in decreased allergenicity of natural rubber latex gloves globally.[6] Removal of powder from gloves has also reduced their allergenicity. Furthermore, advisories against usage of highly allergenic gloves, and introduction of alternative nonlatex gloves for medical usage were undertaken. As a result, natural rubber latex allergy has decreased in health care profession and others.[7]

Immunotherapy to latex may be of importance, especially in patients at risk of having surgery in emergency settings. Studies using subcutaneous immunotherapy were done, but serious side effects, including anaphylaxis, have hampered this approach. Introduction of sublingual immunotherapy has been an advancement in latex immunotherapy and the side effect profile is more favorable than in subcutaneous immunotherapy. In most studies with latex sublingual immunotherapy, a positive result has been achieved in latex tolerance induction.

A subgroup of latex-allergic patients also have allergies to some plants, especially freshly consumed fruits. This matter is of importance because sensitization to latex itself has decreased and many reactions are actually cross-reactions from plants to latex, not vice versa. The latex–fruit syndrome includes plants such as bell pepper, potato, avocado, banana, kiwi, peach, tomato, and chestnut. Defense proteins shared by plants have especially been shown to be of importance.[8]

Among plants, common causes of allergy are *ficus benjamina*, yucca plant, dragon trees, ceriman, and Paul flower. Common decorative plants causing CoU include tulips and chrysanthemums. Also dry flowers, such as *Limonium tatarium*, may cause occupational CoU among florists and flower sellers. Mugwort, a common respiratory allergen, may also be part of dry flower bundles sold in flower shops. Salads as composite plants may cause CoU, especially for garden and kitchen workers. Other possible causes include carrots, tomatoes, shiitake mushrooms, ginger, onions, and garlic. Among animals, among others, fish are capable of causing ICoU. It is also possible to have ICoU to human proteins transmitted from another person, including those in semen and sweat. Same agents may also cause allergic rhinitis, asthma, and conjunctivitis.

Some chemicals are capable of causing ICoU. Among these are anhydrides that are used as hardeners for epoxy resins. Persulphates used for hair bleaching may cause CoU. Some antimicrobial compounds, chloramine-T and chlorhexidine gluconate, formaldehyde, aldehyde releasers, epoxy resins, isocyanates, paraphenylene diamine, and reactive coloring agents may rarely cause ICoU, as well as other IgE-mediated reactions.

Conclusion

ICoU is mediated through IgE antibodies. IgE is mainly localized in tissues, where it is tightly bound to the surface of mast cells, basophils, and antigen-presenting cells through high-affinity receptors (FcεRI). ICoU can be prevented by avoiding the eliciting factor.[9] Possible future treatments may include immunotherapy.[10,11]

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11

Immunoglobulin E: Pathogenic Relevance in Urticaria and Eczema

Maria Estela Martinez-Escala, Eduardo Rozas-Muñoz, and Ana M. Giménez-Arnau

Introduction

The term *allergy* is used to describe clinical illnesses produced by excessive immune responses to otherwise innocuous allergens. An allergen is a type of protein or low-molecular-weight chemical that comes from the environment. This specific immune response is mediated by both innate (mast cell, basophil, eosinophil, and dendritic cell) and adaptive (T- and B-cell lymphocyte) immune systems.

The innate immune system is characterized as generating a quick response after its encounter with the pathogen (antigen or allergen), whereas the adaptive immune system has a specialized response, amplifying it after repeated exposures to the same pathogen. During development, T-cell lymphocyte maturation is mediated by cytokines and cell–cell interaction. There are two important types of T-cell lymphocytes regarding cell-surface markers: 1) $CD4^+$, also called helper T cells (Th) (60%–70%) and 2) $CD8^+$, also called suppressor T cells (30%–40%). Depending on the type of cytokine produced, Th cells differentiate into type 1 (Th1), type 2 (Th2), and the newly identified subsets, Th17 and Th22.[1,2] Whereas interleukins (IL) 4 and 13 are cytokines that induce a Th2 balance, IL-2 and interferon-γ (IFN-γ) induce Th1 environment. Th2 cells stimulate immunoglobulin (Ig) E production by B cells. The balance of these stimulatory and inhibitory activities of the Th1 and Th2 is believed to determine an individual's propensity to develop allergic disorders or atopy. The predominance of Th1 or Th2 response in each individual has been demonstrated to be influenced by environmental factors as well as by genetic predisposition by particular population.[3] In fact, children from allergic parents are more susceptible to develop allergic disorders.[4,5] On the other hand, Th17 and Th22 cells have been described in the context of asthma, where the neutrophil is predominant in the infiltrate, and in non-IgE-related atopic eczema as well as in chronic phases of atopic eczema.[2,6]

B-cell development and differentiation are driven by T cells, cytokines, and antigen interaction. By this regulation, B cells differentiate into memory B cells and plasma cells ready to secrete immunoglobulins. Immunoglobulins are protein molecules composed of two identical polypeptide heavy (H) chains and two identical polypeptide light (L) chains, covalently linked by disulfide bonds. The H chains have three or four constant (C) domains (defined as a conserved part of a protein that has its own independent structure and function) and one variable (V) domain (Figure 11.1). The L chains have one C domain and one V domain. The V domains of the H and L chains together form a pair of identical antigen-binding sites and, with the adjacent C domains, make up the antibody-binding fragment. The remaining C domains of the H chains together form the crystallizable fragment (Fc), which binds to receptor of effector cells. There are five isotypes of immunoglobulins determined by the Fc fragment; IgG (γ), IgA (α), IgM (μ), IgD (δ), and IgE (ε). IgG has four subtypes (IgG1, IgG2, IgG3, and IgG4) and IgA has two (IgA1 and IgA2). IgM is the first immunoglobulin produced, and after repeated antigenic exposure a switching of Fc from IgM to IgG, IgA or IgE is induced (isotype switching). IgE is the most important antibody involved in allergic response.

The allergic response is then a hypersensitivity reaction (excessive immune response) mediated by mast cell and/or basophil degranulation (innate immune system), which occurs after predisposed individuals are repeatedly exposed to allergens, also considered a sensitization.

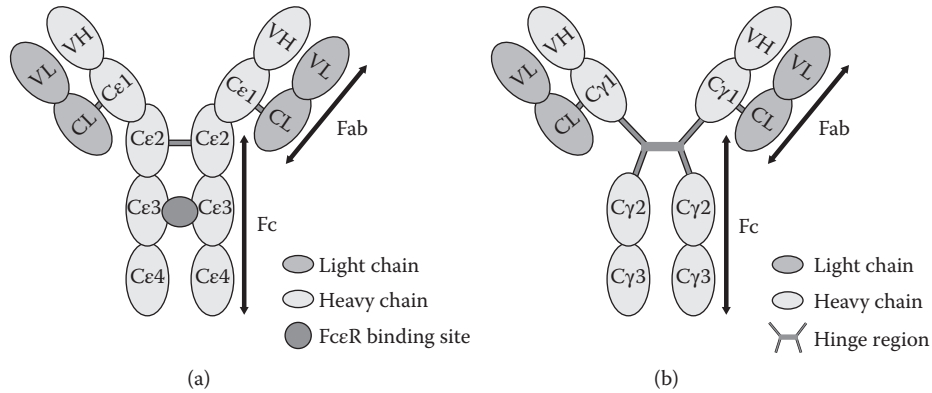

FIGURE 11.1 Comparison of IgE structure with IgG. IgE (a) is a 190-kD glycoprotein and IgG (b) is 150-kD glycoprotein with two identical heavy chains and two identical light chains. The Cε3–Cε4 are equivalent to Cγ2–Cγ3 domains of IgG, and the pair Cε2 is equivalent to the flexible hinge region of IgG.

Gell and Coombs described four types of hypersensitivity reactions [7]: 1) type I, immediate hypersensitivity classically considered IgE-mediated; 2) type II, cytotoxic antibody–mediated (IgG, IgM); 3) type III, immune complex (IgG, IgM); and 4) type IV, the best example of delayed hypersensitivity (T cell–mediated). Type I and type IV are discussed more thoroughly here as both are related with urticarial and eczematous reactions. Type I is an IgE-mediated hypersensitivity reaction, in which a release of mast cell and/or basophil mediators is induced after pathogen (allergen) exposure, creating an immediate and delayed (4–8 hours) response. Symptoms related to this response are rhinitis, acute urticaria and/or angioedema, conjunctivitis, bronchospasm, and anaphylaxis (in generalized responses). Delayed hypersensitivity reaction (type IV) is induced by sensitized T $CD4^+$ cells. Contact dermatitis is a good example of this category. It has also been demonstrated that other inflammatory and immune cells such as Langerhans cells, dendritic cells, and cytokines such as IFN-γ, IL-1, and tumor necrosis factor-α increase intensity of type IV response. This type of immune response seems to play also a central role in autoimmune disease.[1]

Contact urticaria syndrome (CUS), which includes contact urticaria (CoU) and protein contact dermatitis (PCD), requires special consideration. This condition is characterized by the immediate development of skin reactions mainly consisting of wheals and/or eczema after skin-directed contact of trigger proteins or low-molecular-weight chemicals. Patients suffering from CUS may develop either CoU or PCD in which urticaria and eczema can be induced by the same trigger factor and can occasionally be present in the same patient. Two different types of mechanisms have been explained for CoU patients: nonimmunological and immunological. Patients may develop lesions by nonimmunological mechanisms in which direct releases of vasogenic mediators are induced without immunological (IgE) involvement. A previous sensitization is not required in these cases. Otherwise, an IgE-mediated hypersensitivity reaction (type I) can induce weals, eczema, systemic involvement, and even anaphylaxis requiring a period of sensitization. Mechanism-inducing PCD may be explained by a combination of types I and IV hypersensitivity reaction, supported by positive immediate response to open patch test and prick test and also a maintained eczema when using the delayed patch test. Thus, it is speculated that PCD is an eczematous IgE-mediated reaction to proteins.[8]

What is the role of IgE in urticaria and eczema, separately? What is the role of IgE in urticaria and eczema presenting in the same patient? What is the role of IgE specifically in chronic urticaria? Why do patients with chronic urticaria show a moderate increase of IgE levels? Does IgE play any role in the chronicity of atopic dermatitis? Most likely, even more questions might come up to readers.

This chapter summarizes the pathogenic role of IgE in urticaria (acute and chronic) as well as in eczema (atopic dermatitis, and PCD), separately and even presenting together in the same patient. To better understand this, IgE and its receptors are first introduced in a simple manner to describe their function and IgE regulation within allergic response.

IgE

IgE was the fifth and the last human antibody described in 1968 by Drs. Kimishige and Teruko Ishizaka.[9,10] As with IgG, IgE is exclusive to mammals, and both immunoglobulins derive from an ancestral IgY.[11] IgY division favored a functional specialization of each Ig; IgG has an opsonization effector mechanism and IgE induces a hypersensitivity reaction as protection against parasitic infection. The decreasing of prevalence of parasitic infection in Western lifestyles involves IgE having a major role in allergic disease.

IgE is a 190-kD glycoprotein that shares the same basic molecular architecture of the others antibodies, with two identical H chains and two identical L chains formed by their C and V domains (Figure 11.1). IgE has four C domains in its H chain, compared with IgG, which has three. The presence of one more domain in the H chain gives a peculiar characteristic to IgE. The pair of C domains localized in the third and fourth positions of IgE (Cε3–Cε4) are considered equivalent to the second and third C domains of IgG (Cγ2–Cγ3); thus, the second C domains (Cε2) of IgE are equivalent to the flexible hinge region of IgG.[11] The Cε2 domain plays an important role in the stability of the complex between IgE and its high-affinity receptor (FcεRI) on surface cells, creating a permanent binding of IgE to its receptor with a long life of two to three weeks, whereas IgG is linked to its receptor for only hours.[12]

IgE can be found in two forms, as a soluble molecule or as a membrane form. The membrane form binds to cytoplasmic membrane by an additional domain present in each H chain (extracellular membrane proximal domain) of the IgE, between the Cε4 domain and the transmembrane sequence. The binding site to the high-affinity receptor of the membrane form of IgE is still accessible for the FcεRI expressed on other surface cells.[11]

IgE is the least abundant antibody class in serum, because most of it is sequestered in tissues. Its half-life is about two to three days compared with IgG, but increases when IgE is complexed to its receptor (Table 11.1). In a lifetime, IgE levels increase from birth and peak between 16 to 19 years of age.[13]

The elevated IgE serum (>100 IU/mL) is not confined to allergic diseases, and can also be found in parasitic disease (*Schistosoma mansoni, Trichinella spiralis, Strongyloides* sp.), primary immunodeficiency syndromes (hyper-IgE syndrome, Omenn syndrome, T-cell immunodeficiency, Wiskott-Aldrich syndrome) and in other conditions (Table 11.2).

TABLE 11.1

Comparison of IgE and IgG

	IgE	**IgG1**
Structure	4 Cε	3 Cγ
Serum concentration (mg/mL)	0.00015	10
Half-life (days)	3	20
Half-life when complexed with its receptors	21 days	Hours

TABLE 11.2

Factors and Conditions That Can Be Associated with Increased IgE Levels[84]

Factors	Male gender, African-American race, poverty, tobacco smoker, alcohol drinker
Infectious diseases	Parasitic infections, HIV infection, *Mycobacterium tuberculosis*, cytomegalovirus, Epstein-Barr virus, candidosis
Atopic diseases	Allergic bronchopulmonary aspergillosis, allergic fungal sinusitis, extrinsic topic dermatitis, allergic asthma, allergic rhinitis
Immunodeficiencies	Hyper-IgE syndrome, Wiskott-Aldrich syndrome, Netherton disease, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome, Omenn syndrome, DiGeorge syndrome
Inflammatory diseases	Churg-Strauss vasculitis, Kimura disease, IgG4-related disease[85]
Neoplasm	Hodgkin lymphoma, IgE myeloma, mycosis fungoides[86]
Others	Cystic fibrosis, nephrotic syndrome, bullous pemphigoid, bone marrow transplantation

The presence of Th2 bias in primary immunodeficiencies results in the production of extremely high levels of IgE (50,000 U/mL) without allergic symptoms.[14–18] It is the supposed that these IgEs are of low affinity to environmental allergens and that weak cross-linking may not induce mast cell degranulation. The process in which the V domain increases the affinity to environmental allergens (somatic hypermutation) is linked to the class switch recombination process (isotype switching).[19] Two different pathways are described to generate low- and high-affinity IgE to the allergens. Although low-affinity IgE is generated through a direct class switch from IgM to IgE ($\mu \rightarrow \varepsilon$), high-affinity IgE is generated through intermediary phase (IgG) to achieve affinity maturation (from $\mu \rightarrow \gamma \rightarrow \varepsilon$).[18]

IgE Receptors

Two IgE receptors are described regarding their affinity with the immunoglobulin (Table 11.3); FcεRI, the high-affinity receptor, and FcεRII, the low-affinity receptor.

FcεRI structurally belongs to the immunoglobulin superfamily (Figure 11.2a). It is abundant in mast cells and basophil membranes as a tetramer ($\alpha\beta\gamma_2$), and less expressed in Langerhans cells, monocytes, platelets, and eosinophil membranes as a trimer ($\alpha\gamma_2$). Serum IgE influences in FcεRI cell-surface expression and is related to the total number of FcεRI per cell.[20] As stated previously, IgE can remain bound to FcεRI for three weeks,[21,22] and this union stabilizes the receptor expression on the cell surface.[23–25] The humanized anti-IgE antibody (omalizumab) has helped elucidate the interplay between both FcεRI and IgE.[24,26,27] The main effector function of FcεRI is the allergic response, characterized by mast cell degranulation and lipid mediator synthesis. FcεRI is expressed on monocytes, eosinophils, and Langerhans, dendritic, and mast cells in tissues. When the antigen is captured by the IgE, it is presented to the Th cells [28–30] and then carried to the peripheral lymph nodes to initiate the immune response.[11,31]

FcεRII, also named CD23, is considered the low-affinity receptor (Figure 11.2b). It structurally corresponds to the C-type (calcium-dependent) lectin superfamily and is characterized by a three-lectin "head" domain that binds to IgE and a helical coiled-coil "stalk" region that binds to cytoplasmic membranes through the intracellular N-terminal portion. It is misnamed as a low-affinity receptor because its affinity with a single lectin domain is low; however, when IgE binds to the trimer, its affinity approaches that of the

TABLE 11.3

IgE Receptors

	FcεRI	**FcεRII (CD23)**
	High-Affinity IgE Receptor	**Low-Affinity IgE Receptor**
Structure	Immunoglobulin superfamily	C-type (calcium-dependent) lectin superfamily
Subtypes	Heterotetramer ($\alpha\beta\gamma_2$), heterotrimer ($\alpha\gamma_2$)	CD23a[a] CD23b[a]
Type of cells expressed	Abundant in: mast cells and basophils membranes (heterotetramer) Lower levels: Langerhans cell, monocyte, platelet and eosinophils (heterotrimer)	CD23a: antigen-activated B cells CD23b: wide range of cells induced by IL-4
Co-ligands	—	CR2 (CD21), CR3 (CD18-CD11b), CR4 (CD18-CD11c), vitronectin, $\alpha\beta$-integrin
Association constant (Ka) (M^{-1})	10^{10}	10^7 one lectin domain 10^9 three-lectin domain
Functions	Effector response in allergic and parasitic disease antigen presentation	IgE homeostasis induced by CD23 and CD23 fragments Antigen presentation

[a]Both differ by the first six to seven amino acids.

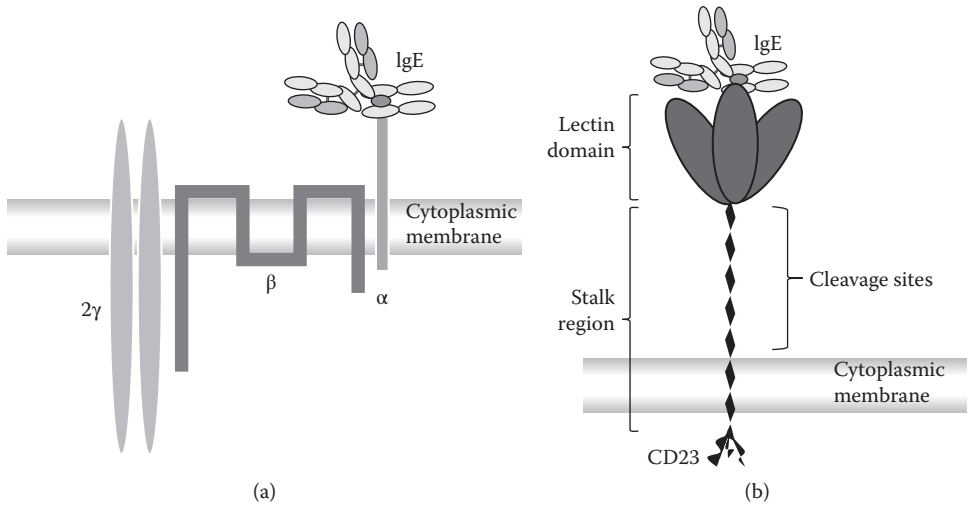

FIGURE 11.2 IgE receptor structure. (a) A high-affinity receptor, or FcεRI. It can be expressed as tetramer with 2γ subunits, 1β, and 1α (as it is represented), usually on the surface of effector cells (basophil and mast cell) or as a trimer with 2γ subunits and 1α on antigen-presenting cells (Langerhans cell). (b) Low-affinity receptor, or CD23, is composed of three head lectin domains and a stalk region that binds to the cell surface. Soluble CD23 is released by the cleavage of the stalk region.

high-affinity receptor.[11] The N-terminal intracellular sequence can differ in their first seven (CD23a) or six (CD23b) amino acids, which determines in which cells will be expressed. CD23a is basically restricted to B cells and corresponds to the major regulator of IgE levels. Thereby, IgE levels become stabilized by binding IgE to CD23 on B cells as it induces negative feedback signals for IgE synthesis. Consequently, when IgE levels are high, the CD23 molecules are occupied by the IgEs decreasing the IgE synthesis. On the other hand, when IgE levels are low, CD23 molecules are mostly unoccupied and therefore enhance IgE synthesis.[11,32,33]

A soluble CD23 fragment can be generated by the proteolysis on the stalk region (between lectin domain and cytoplasmic membrane) of the CD23 molecule, and this may have opposite effects on the regulation (homeostasis) of IgE regarding CD23 membrane-bound form.[34] By cleaving CD23, the IgE production may become up-regulated from lack of feedback inhibition by the IgE-CD23 engagement on B cells. Proteolysis of the stalk region can be induced by endogenous proteases (ADAM 10, a disintegrin and metalloproteinase 10),[35–37] but also by many allergens that can be enzymatically active (e.g., Der p I, *Dermatophagoides pteronyssinus*) and release CD23 fragments,[38] therefore up-regulating the IgE synthesis. CD23 has also a role in antigen presentation in B cells. It binds to human leukocyte antigen (HLA)-DR in B-cells membrane and undergoes endocytosis and recycling [39] (see IgE functions in allergic response). CD21 is one of the most important cofactors of CD23, and because it is expressed in B cells, follicular dendritic cells, activated T cells, and basophils, when pairing with CD23 it shows an important involvement in the allergic response. It is well known its role in B-cell survival and the specification of IgE.[40]

IgE Functions in Allergic Response

IgE has mainly two different functions in allergic response (Figure 11.3). It is involved in the allergen presentation and induces immediate hypersensitivity reaction (type I) by mast cells/basophil degranulation and lipid mediator synthesis.

IgE mediates the allergen presentation to Langerhans, dendritic, and B cells by both IgE receptors, FcεRI and CD23. IgE binds to trimeric form of FcεRI of Langerhans and dendritic cells. The allergen is then captured and they either migrate to a lymph node or remain in the tissue where they present to the Th cells.[41] B-cell allergen

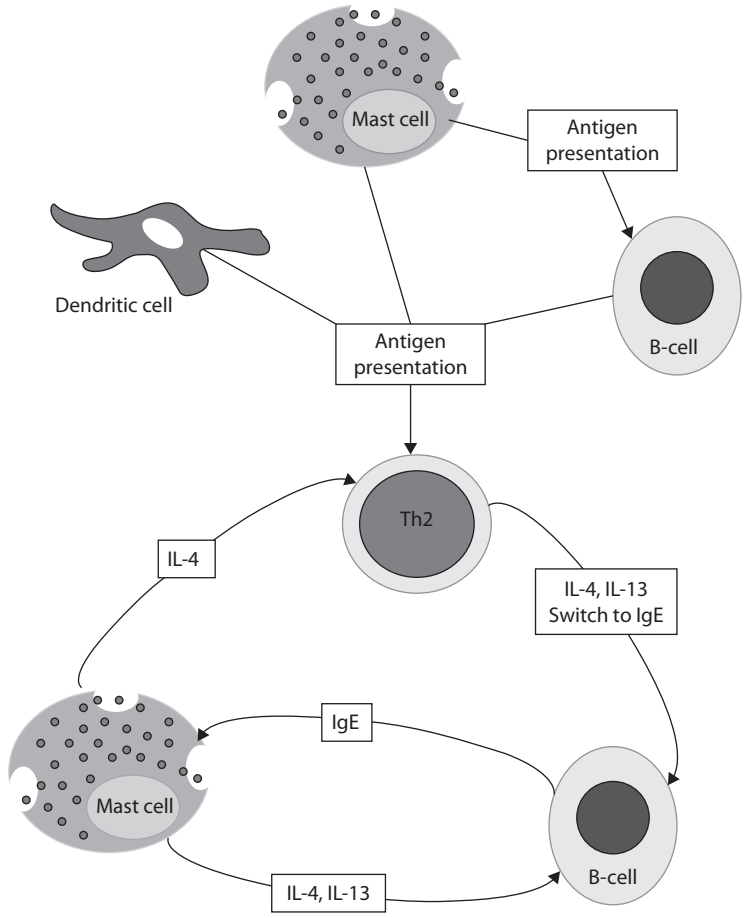

FIGURE 11.3 IgE network in allergic response. Langerhans cells, dendritic cells, mast cells, and B cells induce antigen cell presentation to a Th2 cell. The latter, by the release of IL-4 and IL-13, induces a class switch recombination to IgE on activated B cells. Mast cells, by itself, can mediate antigen cell presentation to B and T cells in addition to Th2 differentiation and encourage B cells to produce more IgE by IL-4 secretion.

presentation might be mediated by a B-cell receptor or by CD23 receptor in activated B cells. Allergen presentation via a B-cell receptor is limited to B cells that specifically synthesized antibodies against a specific allergen, and interacts with cognate T cells. By the expression of CD23 in the B-cell membrane surface and of CD23 with HLA-DR, the allergen-IgE-CD23 complex is engulfed in endosomes and produces allergen-derived peptides. These allergen-derived peptides are loaded onto HLA-DR molecules on a B-cell surface membrane and are presented to Th cells.[42] This can be an explanation of the amplification of immune response to a single allergen and to unrelated allergens, called the *epitope-spreading phenomena* because different epitopes (peptides) from the same allergen are presented to Th cells that might have similarities with other epitopes from other allergens. Thus, this is a positive feedback mechanism that can enhance allergic sensitization.[11]

After allergen presentation, IgE enhances immediate hypersensitivity reaction, which is characterized by an "early phase" and "late phase." The early phase of the allergic reaction is induced after the IgE binds to an antigen and its receptor, FcεRI, by mast cell (in tissue localized reaction) or basophil (in peripheral blood) degranulation and lipid mediator synthesis. The local effects induced are local vascular permeability, arteriolar dilation that increases cutaneous blood flow, increases loss of intravascular fluid from postcapillary venules

TABLE 11.4

Cytokines Involved in IgE Regulation

	Released By	Function
IL-4	Predominantly Th2, NK 1.1$^+$, mast cells, basophils, and eosinophils	Induces IgE synthesis, differentiation to Th2 phenotype, and increases CD23, MHCII, and IL-4R expression on B-cell surface
IL-13	Th2 cells, mast cells, NK cells	Induces IgE synthesis, increases CD23, MHCII, and IL-4R expression on B-cell surface
IL-5	T cells, mast cells	Increases IL-4-dependent IgE synthesis
IFN-γ	T cells, NK cells	Inhibits IL-4-dependent IgE synthesis

Note: NK, natural killer.

to produce erythema, and other effects such as itching from stimulation of cutaneous sensory nerves by histamines. The chemokines and cytokines delivered in the early phase initiate the late phase, which starts hours later (4–8 hours) and involves the recruitment and activation of inflammatory cells at the sensitive sites.[11] Both phases, early and late, are IgE-mediated.[43] IL-4 and IL-13, both released in the early phase, stimulate B cells to produce more IgE, replenishing the IgE consumed in the degranulation.[44] Mast cells and basophils also decrease their thresholds for degranulation because of IL-4.[31,45–48] A summary of the cytokines involved in IgE regulation is presented in Table 11.4.[22]

Allergy and Autoallergy

IgE-binding antigens have typically been related with external antigens (typically called allergen), such as aeroallergens and food allergens (Figure 11.4). According to the size of those antigens, the allergic response can be clinically different. Small aeroallergens usually induce asthma, whereas larger ones can induce rhinitis or

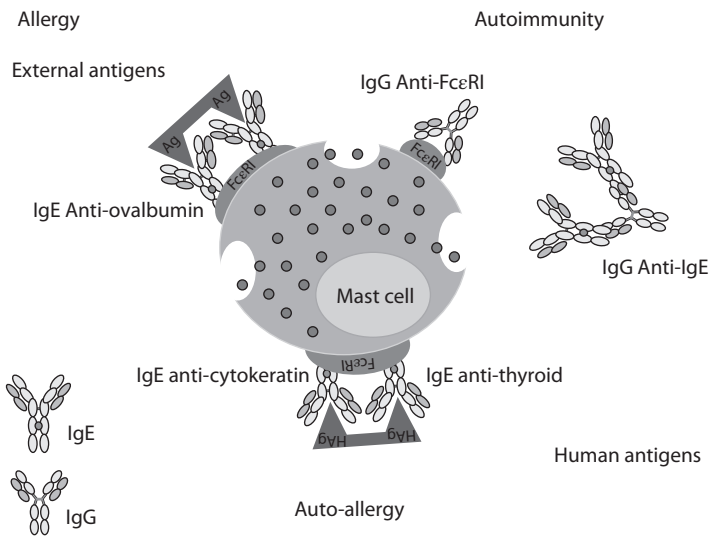

FIGURE 11.4 Allergy, autoimmunity, and autoallergy phenomena. IgE mediates allergic reaction when it cross-links to an environmental allergen. Autoimmunity is mediated by an IgG (subtype 1 or 3) that targets FcεRI or IgE, for instance in chronic urticaria. Autoallergy is mediated by an IgE that target autoantigens (e.g., cytokeratins [83] in eczema, thyrosin peroxidase [68] in patients with chronic urticaria) and induces an allergic reaction by cross-linking to FcεRI.

conjunctivitis. Food allergens can also induce type I or type IV hypersensitivity reactions as anaphylaxis or CUS. The ability of an allergen to induce an allergic response, also called allergenicity, is defined by two properties: 1) the potential to induce symptoms by cross-linking of membrane-bound allergen-specific IgE on effector cells (positive skin test in sensitized patients) and 2) the potential to induce allergen-specific IgE antibodies through a B-cell isotype switches (IL-4, IL-13).[49] For instance, the consumption of apple can induce allergic symptoms in those patients who are allergic to peach or birch pollinosis; however, rarely will it induce specific IgE antibodies against apple proteins.[50]

It has been demonstrated that allergens have revealed striking structural and immunological similarities with human proteins. Valenta et al. demonstrated that 12 of 20 sera from atopic patients who demonstrated pronounced skin lesions contained IgE autoantibodies,[51] compared with those that suffer from allergic rhinoconjunctivitis [52] who failed to display serum IgE autoreactivity. This may explain why certain atopic patients manifest symptoms, most frequently limited to the skin, without allergen exposure and why they have a chronic course of disease. The term *autoallergy* or *autoreactivity* means the presence of IgE against autoantigens that induce an allergic response. The autoallergens characterized represent mainly intracellular proteins, but some of them could be detected as IgE immunocomplexes circulating in the sera of such sensitized subjects.

Role of IgE in Urticaria

Urticaria is defined as the presence of wheal associated or not to angioedema. The wheals show an evanescent nature and disappear in less than 24 hours, but angioedema might last longer, even 72 hours. Both urticaria and angioedema are consequences of skin mast cell activation and its subsequent release of histamine and other proinflammatory mediators. What differentiates acute and chronic urticaria is the course of disease, considered chronic when it is longer than 6 weeks.[53]

Acute urticaria can be triggered by multiple factors: allergens (type I hypersensitivity reaction), acute infections (hepatitis virus B and C, *Streptococcus* sp., *Anisakis*), and histamine-releasing factors such as some drugs (nonsteroidal anti-inflammatory drugs, opioids, polymyxin, vancomycin) or certain foods (e.g., tomato, alcohol). However, in 50% of cases, the triggering factor cannot be determined.[53] The type I hypersensitivity reaction is an IgE-mediated allergy that can be clinically manifested by a wide variety of symptoms, ranging from mild symptoms to anaphylaxis reaction. It is characterized by the presence of a specific IgE that binds to an environmental allergen; this can be demonstrated by skin prick test or immunoassay of serum antigen-specific IgE. Increased concentrations of serum antigen-specific IgE and the size of the skin prick test wheal are generally associated with increased likelihood of a clinical reaction, but they are never predictive of reaction severity.[54–60] The most frequent allergens related to this type I hypersensitivity reaction of acute urticaria are food (e.g., peanuts, peach), drugs (e.g., penicillin), as well as, other proteins also involved in CUS (e.g., latex, seafood).[8,61,62]

Chronic spontaneous urticaria is referred as an autoimmune disease in 45% of patients. Those patients are characterized by a positive basophil activation test, measured by CD63 expression [63] (where patients' serum competes with healthy controls' basophils; it is considered the gold standard) or a positive autologous serum skin test [64] (ASST; patient's serum is intradermally injected; less sensitive). It has been demonstrated that those patients present IgG (subtypes 1 and 3) autoantibodies against FcεRI (30%–40%) or IgE (5%–10%). IgE in chronic urticaria plays a completely different role compared with acute urticaria and eczema (see the following section). Although in acute urticaria and eczema IgE induces an allergic response by cross-linking to an antigen, mast cell, and FcεRI, in chronic urticaria patients, it acts as a target for IgG autoantibodies as well as its receptor, FcεRI. The interaction between IgG autoantibodies and the receptor seems to induce mast cell degranulation and wheal formation, probably with complement involvement.[65,66] It is known that 50% of patients with chronic urticaria exhibited significant levels of total IgE (>100 IU/mL) as compared with healthy controls (13%),[67] but common or uncommon environment allergens are rarely found to be the cause. Moreover, patients with chronic urticaria also suffer from other autoimmune diseases, especially thyroid autoimmune disorders such as Hashimoto thyroiditis.[68–70] Autoallergy phenomena have also been demonstrated. An autoantibody IgE type against thyroid peroxidase (TPO) was first described in 1999 [71] in a patient affected by chronic urticaria and Hashimoto thyroiditis. Afterward, the presence of IgE anti-TPO could not be demonstrated in a large group of patients until 2011, when high levels

(>5.50 IU/mL) of IgE anti-TPO were detected in 54.5% of chronic urticaria patients (259 of 478 patients). In this study, patients with higher levels of IgG anti-TPO also showed higher levels of IgE anti-TPO. There were no differences between age, gender, duration of disease, total serum IgE, and positive ASST.[68] A high percentage of patients with positive IgE anti-TPO show a negative ASST. This could explain a possible etiology in a certain number of patients from those 54.5% that were classified as having chronic spontaneous urticaria with a negative ASST.

Role of IgE in Eczema

Eczema is an inflammatory skin disorder that shares multiple etiological factors (e.g., irritants, allergens). Allergic eczema includes atopic dermatitis induced by food and/or aeroallergens (extrinsic type), allergic contact dermatitis, and CUS. It corresponds to a T-cell–mediated immune reaction (type IV) that in its chronic form is a dynamic nature of the disease mechanism over time, from the initial to chronic phases. In early phases of atopic dermatitis, a Th2 milieu of predominantly IL-4, IL-5, and IL-13 is responsible for the initiation of allergic inflammation, whereas Th1 as well as Th17 and Th22 cells predominate in chronic phases of the disease in which IFN-γ is mostly involved.[2] Then, the Th2 environment present in the early phases favors an IgE synthesis, compared with nonallergic eczema (total serum IgE <100–200 kU/L and no known sensitization). The latter has different findings on the skin compared with allergic eczema (Table 11.5), which include lower levels of expression of FcεRI on epidermal dendritic cells and less abundant interleukins favoring IgE synthesis.

It has been demonstrated that the level of total IgE is associated with the severity of atopic eczema and prognosis in patients with extrinsic atopic dermatitis.[72–74] Specific IgE to aeroallergens or food allergens, as in IgE-mediated urticaria, can be determined by skin prick test or by in vitro test. However, those techniques do not accurately measure the specific IgE that is actually involved in inducing eczematous lesions, as, for instance, a skin prick test corresponds to a type I hypersensitivity reaction (wheal formation). The development of an "atopy patch test" (defined as a variant of the patch test) has allowed the ability to induce eczematous lesions by aeroallergens and less successfully by food allergens. It was first used to diagnose in 1989 [75] and is based on T-cell-specific response to the application of allergens on the healthy skin of the patient's back or forearm.[76] It seems that the combination of a skin prick test, and atopy patch test are needed to accurately know the true allergens that trigger eczematous lesions to patients with extrinsic atopic eczema.[76] When a skin prick test and an atopy patch test are both positive for specific agents, we can establish that those are triggering factors that induce IgE-mediated response; therefore, patients should avoid those factors. Moreover, it allows the prevention of a unnecessarily restrictive diet in patients because those allergens that show positive results with a skin prick test and negative results with an atopy patch test are not required to be avoided. Patients with a positive atopy patch test showing a negative skin prick test and radioallergosorbent test should still be classified as extrinsic atopic dermatitis, despite the fact that it is non-IgE mediated.[76]

Chronic inflammation can be seen in allergic subjects, even in the absence of apparent exposure to known environmental allergens. It can be explained by the involvement of an immune mechanism against self-components (autoallergy). Two observations have led to such hypothesis: 1) the chronic pattern of relapsing-remitting disease is similar to that of other autoimmune diseases and 2) autologous or human components might elicit immediate hypersensitivity reaction in the skin of patients with severe atopic dermatitis.[77] Patients with severe and chronic manifestations of atopy (e.g., atopic dermatitis) have IgE autoantibodies against a wide variety of proteins expressed in histogenetically unrelated human cell types and tissue specimens.[52] This can explain

TABLE 11.5

Skin Findings on Allergic and Nonallergic Eczema [87]

	Allergic Eczema	Nonallergic Eczema
Epidermal dendritic cells	High expression of FcεRI	Lower expression of FcεRI
T cell cytokines	IL-4, IL-5, IL-13, IFN-gamma	<IL-4, IL13 and = IL-5, IFN-gamma
Eosinophils	Eosinophilic granules and promotion of inflammation	Eosinophilic granules and promotion of inflammation

the mixture phenotype of Th1 and Th2 cytokine production that patients with chronic manifestations of atopic dermatitis acquire, as many autoimmune diseases are typically Th1 phenotype, and Th1 predominates in chronic phases of atopic dermatitis. Besides, it has been shown that the levels of IgE autoantibodies are associated with disease severity.[78,79] Nonetheless, no differences in the prevalence of autoreactivity were noted in the two studies that distinguished between patients with allergic eczema and nonallergic eczema (atopic dermatitis patients with low total serum IgE values also displayed strong IgE autoreactivity, and others with extremely high total serum IgE levels failed to react with human proteins).[80,81] As a result, the pathogenic relevance of IgE against autoantigens in atopic eczema is still unclear.[51]

The term CUS was first introduced by Maibach and Johnson [82] for patients who develop immediate inflammatory reactions after contact with eliciting substances. Later on, two entities were included in CUS, being both an extreme manifestation of a spectrum: CoU with predominantly urticarial lesions (type I reaction, when it is immunologically induced) and PCD with predominantly eczematous lesions (type IV reaction). Patient may present with only urticarial lesions or only eczematous lesions or with both. The latter shows that the same allergen can cause types I and IV reactions in the same patient. Similar to atopic eczema, these patients may show a positive skin prick test and patch test, but usually for only a specific agent. Even though it is an IgE-mediated hypersensitivity reaction, the mechanism of combined type I and type IV allergic reactions is not clear.

Conclusions

Allergic disorders are becoming more prevalent in the Western lifestyle, causing chronic symptoms that occasionally can threaten a patient's life. Many insights had been described about this excessive immune response, and the elaboration of new target therapies has produced new knowledge about IgE and its receptors. It is known that IgE plays an important role by itself in allergy; however, multiple functions still need to be elucidated. Moreover, it has been demonstrated that an extensive network is required to induce symptoms and to amplify the immune response to the same allergen, making it clinically severe; or even to other allergens, making the patient able to acquire more allergic disorders (from atopic dermatitis to asthma, the atopy march). In addition, the exact role of the autoimmune phenomena within the allergy disorders seems to increase complexity, favoring the appearance of symptoms in patients even without an allergen exposure. Thus, comprehensive research is needed to develop new target therapies that might interrupt the different pathways downstream or upstream that are involved in allergic response.

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12

Contact Urticaria Syndrome: Diagnostic Tools and Test Procedures

Charlotte G. Mortz and Klaus E. Andersen

Introduction

Contact urticaria syndrome comprises immediate skin contact reactions including contact urticaria and immediate contact dermatitis (protein contact dermatitis). The symptoms can progress to urticaria/angioedema, and beyond the skin to asthma, rhinoconjunctivitis, gastrointestinal symptoms, and full-blown anaphylaxis.

Contact urticaria syndrome was defined as a biological entity in 1975 by Maibach and Johnson.[1] The term *contact urticaria* was introduced by Fisher in 1973,[2] although the phenomenon has been recognized since the 19th century.[3] Contact urticaria refers to a wheal-and-flare reaction after external contact with a substance, usually appearing within 30 minutes and with complete clearing within hours without residual symptoms. The term *protein contact dermatitis* was defined by Hjorth and Roed-Petersen in 1976 [4] as an immediate contact dermatitis induced after skin contact with proteins. The authors described food caterers experiencing itch 10–30 minutes after contact with foods; the itch was followed by erythema and vesicles. Protein contact dermatitis is often seen in chronic hand dermatitis (fingertips) with an acute flare appearing within a few minutes after contact with the causal protein. In a mouse model, histamine has been shown to facilitate the development of eczematous lesions.[5]

The incidence and prevalence of contact urticaria syndrome is not known. However, since 1985, several studies have suggested that contact urticaria syndrome is common in dermatological practice.[6–9] Population-based studies are lacking. In a recent study from Gentofte, Denmark,[10] 372 patients with occupational food-related hand dermatoses were evaluated and 22.0% had protein contact dermatitis and 2.4% contact urticaria. In this, as with other population-based studies, only occupational relevance was discussed.[11–14]

Pathogenesis

Immediate contact reactions can be divided into immunologic and nonimmunologic reactions. The mechanisms in immunological immediate contact reactions are the classical immunoglobulin E (IgE)-mediated reactions, whereas underlying mechanisms of the nonimmunological type are not well understood, as with most other irritant skin reactions.[15] The pathogenesis of nonimmunological contact urticaria is due to the release of vasogenic mediators without the involvement of immunological processes and without previous sensitization. [16] Antihistamines have no inhibitory effect on skin reactions in nonimmunological contact urticaria, but acetylsalicylic acid and nonsteroidal anti-inflammatory drugs inhibit nonimmunologic contact urticaria, suggesting a role for prostaglandins.[17,18]

Symptoms and Clinical Observations

The diseases involved in contact urticaria syndrome were described first in 1975 by Maibach [1,19] and in a review again by Gimenez-Arnau et al.[16] in 2010 describing a four-stage severity level, with stages 1 and 2

including cutaneous reactions only and 3 and 4 progressing to anaphylaxis. The manifestations reflect the potency of the allergen/substance, the dose, and exposure route. Stage 1 reflects local wheal and flare reactions, and eczema with varying degrees of itching, tingling or burning sensations. The wheal and flare of contact urticaria is usually limited to contact areas and disappears within a few hours without residual lesions. Protein contact dermatitis typically affects hands with a damaged skin barrier and preexisting dermatitis, most often the fingertips, and it may extend to the wrist and forearms. Pruritus and aggravated erythema are characteristic features, and it is debated if vesicles can develop. Contact urticaria and protein contact dermatitis can be seen in the same individual. In severe cases, contact urticaria can progress to generalized urticaria, stage 2.

Stages 3 and 4 include extracutaneous symptoms that may also occur as part of a more severe reaction. Stage 3 includes rhinoconjunctivitis, asthma, orolaryngeal symptoms, and gastrointestinal symptoms. Stage 4 is anaphylaxis with symptoms of shock. Latex is one example of a protein that can trigger contact urticaria (phase 1) progressing to full blown anaphylaxis (phase 4). Stage 3 or 4 symptoms may also develop when the protein comes into direct contact with the oral or gastrointestinal mucosa or, for volatile allergens, the respiratory mucosa.

Diagnostic Tools and Stepwise Procedure of Tests

A full medical history including exposure to suspected allergens/substances, symptoms, medications, and other diseases including atopic disease is crucial before deciding the diagnostic algorithm. The diagnostic tools and the diagnostic program have to be individualized for each patient depending on the allergen/substances in question and the medical history, possible concomitant disease, and the clinical symptoms reported after exposure to the suspected culprit. In vivo testing has to be performed under anaphylaxis surveillance as a skin test may trigger anaphylaxis.

First, it is important to evaluate if the reaction is IgE-mediated or nonimmunological in nature. Protein and low-molecular-weight molecules can induce immediate contact reactions in contact urticaria syndrome through an immunological or a nonimmunological pathway. Morphologically, the immunological and nonimmunological contact reactions are indistinguishable.

For latex, food allergens, and certain animal or animal products with suspicion of type I allergic symptoms, the diagnostic tools are shown in Figure 12.1 starting with an in vitro test and/or skin prick test (SPT). If specific IgE measurement/SPT is negative, the next step is a provocation test, often starting with open application on normal skin, proceeding to test on affected skin, and, if negative, to handling of the suspected material according to the exposure history. For irritant or toxic substances, the open application test and other less-validated tests have to be performed directly, as described in Figure 12.2. Again, if negative, a provocation test with handling the substance in question as described in the exposure history is crucial to verify if the substance is responsible for the reaction described in the patient history.

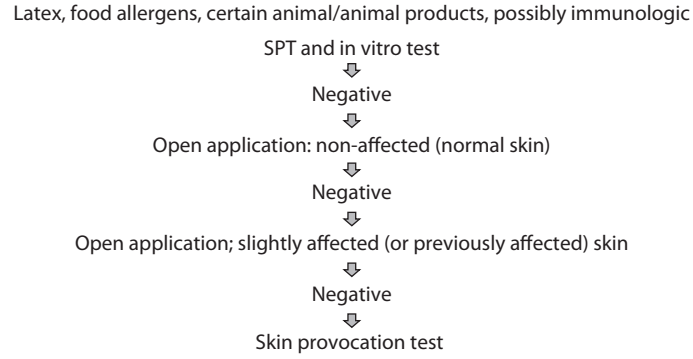

FIGURE 12.1 Suggested protocol.

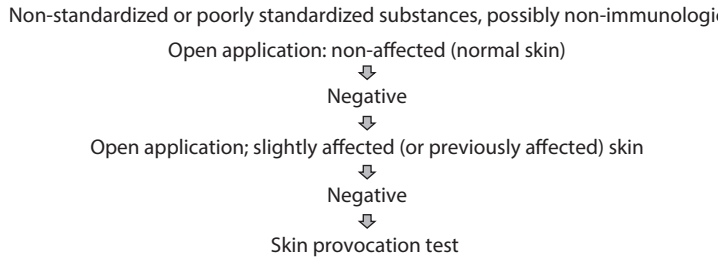

FIGURE 12.2 Suggested protocol.

In Vitro Test

Different in vitro tests exist for measuring specific IgE, such as the Immunocap (Thermo Fisher, Sweden). Specific IgE measurements are available for some of the well-characterized proteins such as latex and some food and animal proteins; however, for many other proteins, measurement of specific IgE is not available for routine use, and in that case a histamine release test [20] or basophil activation test is needed.[21] For latex, it is recommended to start with a latex IgE measurement; if it is positive, together with a clear-cut history, clinical latex allergy is documented.

In Vivo Test

SPT

Testing should always be performed under anaphylaxis surveillance. Anaphylaxis has been reported in rare cases elicited by skin prick tests in highly sensitized individuals.[22,23] An SPT can be performed with latex extract, fresh foods, and selected other proteineous materials to evaluate IgE-mediated reactions.[24] A positive and a negative control must be included.[24] Medications such as an antihistamine must be paused before testing. Testing with fresh food is recommended instead of food extracts to increase sensitivity.[10,25,26] SPT with fresh food has to be performed as a prick-prick test (e.g., prick in the food and then in the skin with the same lancet).[27] In case of poorly standardized test material giving a positive skin test, it is important to test the substance in healthy controls to interpretation of the test results. False-positive reactions may occur. In many patients with occupational exposure, SPTs cannot be performed because of possible irritant or toxic properties of the materials. If an IgE-mediated reaction is suspected, IgE measurements (if possible) or a histamine release test or basophile activation test can be performed. Otherwise the next step is an open application test.

Open Application Test

An open application test is performed by applying the substance on a 3- × 3-cm area of normal skin, either on the upper back or the extensor site of the upper arm, or on the forearm. The recommended amount is 0.1 mL of the test substance.[15]

An immunological or nonimmunological contact reaction usually appears within 15–20 minutes, although the nonimmunological reaction can occur up to 45–60 minutes after application. The test is usually read at 20, 40, and 60 minutes. The skin on the face, neck, back, and extensor sites of the upper extremities react more readily than other parts of the body.[28] If no reaction develops, the test can be repeated on slightly or previously affected skin. Because an open application test on normal skin is often negative, the test is repeated on eczematous skin; if it is still negative, rubbing the substance on intact skin or even eczematous skin can be tried to provoke a reaction.[29] If the case history indicates a severe reaction, the substance has to be diluted, starting with low concentrations. Control tests should be performed on at least 20 people to avoid false-positive

interpretations when testing with poorly or nonstandardized substances. As with SPT, it is important to avoid drugs that can interact with the test results and in nonimmunological contact urticaria, it is also important to stop acetylsalicylic acid and nonsteroidal anti-inflammatory drugs. Again, testing should always be performed under anaphylaxis surveillance.

Provocation Test or Use Test

Provocation tests or use tests are controlled exposure to the allergen/substance under anaphylaxis surveillance; this is the last step if all other tests turn out negative. The provocation test or use test requires the patient to handle the suspected agent as previously handled when symptoms appeared. The test should reflect the clinical situation; for example, a cook handling meat but doing so in a titrated manner starting with low exposure and gradually increasing the exposure to finally reflect the clinical situation. Another example is a clinical suspicion of latex allergy with a negative specific IgE to latex, negative latex SPT, and open application test. The patient should then be gradually exposed first by wearing a latex glove on wet skin on one finger; if no symptoms develop, the provocation test is gradually extended to wearing a glove.

Other Tests

The closed chamber test is a routine technique used for patch testing for contact allergy; it is also used in contact urticaria with occlusion for 15 minutes and reading at 20, 40, and 60 minutes.[15] However, a dilution series is needed because it is difficult to establish the proper test concentration, and control subjects have to be included. Occlusive application on affected skin is also a possibility in selected cases.

The scratch and scratch patch test carry a high risk of false-positive reactions and lack sensitivity compared with SPT.[27, 29] These tests cannot be recommended in clinical settings.

Intradermal testing can be used in selected cases such as suspected reaction to drugs (e.g., antibiotics) together with IgE measurement.[30]

In selected situations, multiple (repeated) applications with a chemical may elicit a delayed-onset contact urticarial as it has been reported for formaldehyde.[31]

Concomitant Sensitization

When evaluating for example food allergy and latex allergy, it is important to consider concomitant reactions to related allergens. In a patient with an allergic reaction to latex protein, reactions to related foods and plants such as banana, kiwi, and *Ficus benjamina* should be evaluated both by history and testing. Pollen sensitization is also important to consider when evaluating allergic reactions to foods to evaluate if the reaction to food is primary or if it is secondary to pollen sensitization (e.g., apple-birch, wheat grass).

Agents Responsible for Immediate Contact Skin Symptoms

The most common causes of immunological contact reactions are food proteins, animal proteins, and natural rubber latex.[15,16] Other common substances are illustrated in Table 12.1; however, the catalog of chemicals and proteins reported is extensive. The substances producing nonimmunologic contact urticaria include benzoic acid, sorbic acid, cinnamic acid, and aldehyde and nicotinic acid esters.[15,16] Other common substances are shown in Table 12.2.

Conclusion

Contact urticaria syndrome can be caused both by immunologic and nonimmunologic reactions, although the clinical picture in contact urticaria and protein contact dermatitis may be the same. A full medical history

TABLE 12.1

Substances Producing Immediate Immunological Contact Reactions

Group	Examples
Animals and animal products	Amnion fluid
	Blood
	Cockroaches
	Dander
	Jellyfish
	Seminal fluid
Foods	Fish
	Fruits
	Grains
	Meat
	Paprika
	Seeds
	Vegetables
	Other animal products (milk, eggs)
Fragrances and flavorings	Myroxylon pereirae
Medicaments	Penicillin
Plants and plant products	Chrysanthemum
	Ficus benjamina
	Lilies
	Tulips
Preservatives and disinfectants	Alcohols
	Chlorhexidine
Miscellaneous	Metals

TABLE 12.2

Substances Producing Immediate Nonimmunological Contact Reactions

Group	Examples
Animals and animal products	Arthropods
	Caterpillars
	Corals
	Jellyfish
	Moths
Foods	Cayenne pepper
	Fish
	Tomato
	Thyme
Fragrances and flavorings	Myroxylon pereirae
	Benzaldehyde
	Cinnamic acid and aldehyde
Medicaments	Alcohols
	Capsaicin
	Nicotinic acid esters
	Tar extracts
Plants and plant products	Nettles
	Sea anemone
Preservatives and disinfectants	Benzoic acid
	Formaldehyde
	Sorbic acid
Miscellaneous	Sulfur

including exposure to suspected allergens/substances, symptoms, medications, and other diseases including atopic disease is crucial before deciding the diagnostic algorithm. The diagnostic tools and the diagnostic program has to be individualized for each patient depending on the allergen/substances in question and the medical history, possible concomitant disease, and the clinical symptoms reported after exposure to the suspected culprit. An algorithm has been suggested.

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13

Molecular Diagnosis in Contact Urticaria Caused by Proteins

Joaquín Sastre

Introduction

The discovery of immunoglobulin E (IgE) in the late 1960s introduced a new tool in allergy diagnosis, and determinations of specific IgE to different allergens were developed soon thereafter. Parallel to the development of new methods to measure specific IgE, there has been a revolution in the field of allergen extracts. In the beginning, crude natural and nonstandardized extracts were used, although in time, the use of standardized extracts with a more precise content of allergenic components improved the diagnostic value of these determinations. The next quantum leap came with the use of purified proteins obtained from natural sources.

Subsequent advances in the field of recombinant allergens, thanks to the application of DNA technology in the late 1980s, led to the development of a new concept in allergy diagnosis: component resolved diagnosis or molecular diagnosis (MD) in allergy.[1] MD is used in allergy to define the allergen sensitization of a patient at the molecular level by measuring specific IgE to purified natural or recombinant allergens, allowing identification of the potential disease-eliciting molecules. Recombinant allergens have also been used in mixture with natural extracts (spiking) to increase test sensitivity. Overall, MD can improve diagnostic accuracy (specificity), distinguish cross-reactivity phenomena from true cosensitization, resolve low-risk markers from high-risk markers (biomarkers), and also improve the indication and selection of suitable allergens for specific immunotherapy. [1,2] Nevertheless, all in vitro test results should be evaluated alongside the clinical history, because allergen sensitization does not necessarily imply clinical responsiveness. Although the use of a large number of allergen components can facilitate these tasks, this approach puts greater demands on the interpretation of the clinician.

This chapter will focus on the clinical utility of the allergenic molecules that are currently commercially available for the diagnosis of contact urticaria (CoU).

Nomenclature and Allergen Components

To begin using allergen components and to properly interpret test results in the clinic, it is worthwhile to learn some of the basics of allergen components and their clinical implications. First, it is important to know the names of the allergen components, including their scientific acronym. Allergenic molecules are named using their Latin family name (genus and species) (e.g., Hev b 1 means allergen 1 from *Hevea brasiliensis*, or latex tree). A number is added to the name to distinguish the various allergens from the same species (e.g., Hev b 5, Hev b 6, or by using decimals, such as Hev b 6.1 in the case of isoforms of Hev b 6). The numbers are assigned to the allergens according to the order in which they are identified. This allergen nomenclature is approved by the World Health Organization and the International Union of Immunological Species (WHO/IUIS) Allergen Nomenclature Subcommittee, a subcommittee charged with developing and maintaining the systematic nomenclature for allergenic proteins). There are different databases of known allergenic proteins that can be accessed (the allergen nomenclature database of the IUIS (http://www.allergen.org), the allergen literature database Allergome (http://www.allergome.org), or the allergen database grouping the allergens into protein families, AllFam (http://www.meduniwien.ac.at/allergens/allfam/).

Second, it is important to understand some properties of allergen components. Almost anything containing proteins can be an allergen source, although it has become clear that most allergens and their components belong to a limited number of protein families [3] (Table 13.1). Each allergen source contains many different allergenic proteins (allergen components). On each allergen component, there are commonly several different epitopes. An

TABLE 13.1

Main Allergenic Proteins

Protein Families	Allergens	Characteristics
Nonspecific lipid transfer proteins (LTP)	Ara h 9 Cor a 8 Pru p 3 Par j 2 Art v 3 Jug r 3	Stable to heat and digestion, causing reactions also to cooked foods. Often associated with systemic and more severe reactions in addition to OAS, and with allergic reactions to fruit and vegetables in southern Europe (not applicable to Par j 2 or Art v 3).
Storage proteins	2S albumins Ara h 2, 6, 7 Ber e 1 Jug r 1 7S albumins Ara h 1 Gly m 5 Jug r 2 Ses i 1 11S albumins Ara h 3 Gly m 6 Cor a 9 Gliadins Tri a 19 Ana o 2 Jug r 4	Found in nuts and seeds. Often stable and heat-resistant proteins causing reactions also to cooked foods.
Pathogenesis-related PR-10 proteins	Bet v 1 Ara h 8 Gly m 4 Cor a 1 Pru p 1 Api g 1.01 Mal d 1 Act d 8 Dau c 1	Heat-labile proteins and cooked foods are often tolerated. They are Bet v 1 homologues and often associated with local symptoms such as OAS and with allergic reactions to fruit and vegetables in northern Europe. May predispose to allergic reactions to Rosaceae fruits, hazelnut, carrot, and celery.
Profilins	Bet v 2 Pru p 4 Mal d 4 Hev b 8 Phl p 12	Actin-binding proteins showing great homology and cross-reactivity even between distantly related species. Sensitization to profilin may give rise to multiple positivity when testing with plants and pollen extracts; however, this has low clinical relevance in most cases. Profilins are associated with OAS.
Thaumatins	Act c 2	Stable proteins. Partial cross-reactivity between thaumatin from pollen (plane), kiwi, peach, cherry, and banana.
CCD	CCD;MuxF3 Ana c 2	Can be used as a marker for sensitization to protein carbohydrate moieties (e.g., pollen, hymenoptera). Seldom associated with clinical symptoms.

TABLE 13.1 (*Continued*)

Main Allergenic Proteins

Protein Families	Allergens	Characteristics
Calcium-binding proteins	Bet v 4 Phl p 7	Highly cross-reactive proteins present in most pollens, but not in plant foods.
Serum albumins	Fel d 2 Can f 3 Bos d 6 Sus PSA Equ c 3	Common proteins present in different biological fluids and solids (e.g., cow's milk, beef, egg, chicken). Sensitization to serum albumins may give rise to reactions to mammalian animals, as well as food reactions to meat and milk.
Parvalbumins	Cyp c 1 Gad c 1	Major allergens in fish. Also a marker for cross-reactivity among different species of fish and amphibians. Parvalbumin proteins are stable to heat and digestion and therefore also cause reactions to cooked foods.
Tropomyosins	Pen a 1 Der p 10 Ani s 3	Actin-binding proteins in muscle fibers. Can be used as a marker for cross-reactivity between crustaceans, mites, cockroach, and nematodes. A marker of food allergy to shellfish.
Lipocalins	Fel d 1 Fel d 4 Can f 1 Can f 2 Equ c 1 Mus m 1	Stable proteins and important allergens in animals. Allergen components belonging to the lipocalin protein family display only limited cross-reactivity between species.

epitope is the actual three-dimensional binding site for the corresponding antibody. There is currently no known structure that is common to all allergen components or epitopes (i.e., there is no common feature that makes a substance an allergen or not). On the one hand, every species contains species-specific allergen epitopes, and antibodies (abs) formed to these structures bind only to the allergen epitopes in that particular species. On the other hand, proteins with similar structures are often present in biologically related species. Abs formed against such protein structures can of course bind to the same or similar structure on a protein from several different species, thereby causing cross-reactivity. Examples of proteins that induce cross-reactivity phenomena are profilin, polcalcins, lipid transfer proteins (LTPs), thaumatins, pathogenic-related protein 10 (PR10), vicilins in the vegetable kingdom, or tropomyosins, serum albumins, parvalbumins, and lipocalins in the animal kingdom. For instance, a patient who is primarily sensitized to grass pollen may also test positive for birch, olive, or latex using a skin prick test (SPT).[4] This cross-reactivity occurs because all these extracts used in SPT contain profilins (rBet v 2, nOle e 2, Hev b 8), which are largely similar to those in grass (e.g., Phl p 12). Sensitization to Hev b 8 (profilin) seems to be clinically irrelevant and not related to clinical latex reactions; in this case, other relevant latex allergens should be tested (Hev b 1, Hev b 5, Hev b 6). Therefore, one of the most important clinical utilities of MD in allergy is its ability to reveal the allergens to which patients are sensitized, including primary or species-specific allergens and markers of cross-reactivity or panallergens. In other words, MD makes it possible to identify whether the sensitization is genuine in nature (primary, species-specific) or if it is due to cross-reactivity to proteins with similar protein structures.

Third, protein stability is another important aspect. Allergens that remain stable to heat and digestion are more likely to cause a severe clinical reaction, whereas heat- and digestion-liable allergens are more likely to be tolerated or only cause milder/local symptoms. Consequently, it is important to know the protein structure of the component and the allergen-protein family to which it belongs as well as its stability to heat and digestion because these features may affect the tolerance of different foods and the degree of severity of clinical reactions.

Some food allergens may be tolerated when consumed raw, whereas others need to be cooked. Some allergens will give rise to clinical reactions ranging from mild to severe, whereas others will cause sensitization without a clinical reaction.

Methods for Measuring Specific IgE to Purified or Recombinant Allergens

IgE to purified or recombinant allergens is usually measured by using a fluorescence enzyme immunoassay. At present, three companies (ImmunoCAP [Thermo Fisher Scientific, Uppsala, Sweden], ImmuLite [Siemens AG, Erlander, Germany], and HyTech [Garden Grove, CA]) offer the possibility of measuring specific IgE to purified or recombinant allergens on singleplex platforms (Figure 13.1). The most extensive catalog of these allergens belongs to Thermo Fisher Scientific. This company offers a unique system that, as of 2013, is able to detect IgE to up to 112 components at the same time. This platform is a microarray-based assay (Immuno Solid phase Allergen Chip [ISAC]), a miniaturized immunoassay platform in which allergen components are immobilized in a microarray.[5] Only 30 μL of serum or plasma is needed, and both capillary and venous blood sampling can be used (Figure 13.2). Using a standard calibration curve, results are reported within a dynamic range of 0.3 to 100 ISU-E (ISAC standardized units), giving a semiquantitative indication of IgE antibody levels. Unlike these, singleplex systems are more quantitative. Because of differences in assay and measurement technology, these ISU-E units differ from kU/L given in ImmunoCAP results and therefore are not interchangeable, although a certain correlation has been observed. Several studies have analyzed the reproducibility of this technique and have made a comparison with other methods of measuring specific IgE. [6–10] Nevertheless, there is a general agreement that the reproducibility of ISAC is acceptable, but special attention is recommended for low specific IgE levels (0.3–1 ISU) in which increased variability has been observed. However, ISAC is not currently recommended for monitoring sensitization but can be useful for diagnostic purposes.

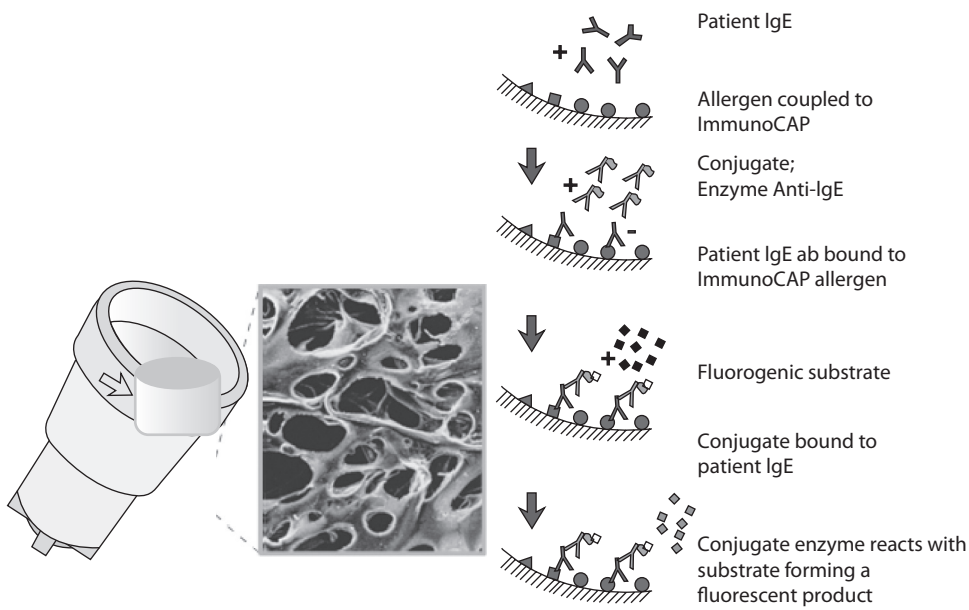

FIGURE 13.1 Illustration of a widely used assay (ImmunoCAP System) for allergen specific IgE quantification. (Courtesy of Thermo Fisher-Scientific.)

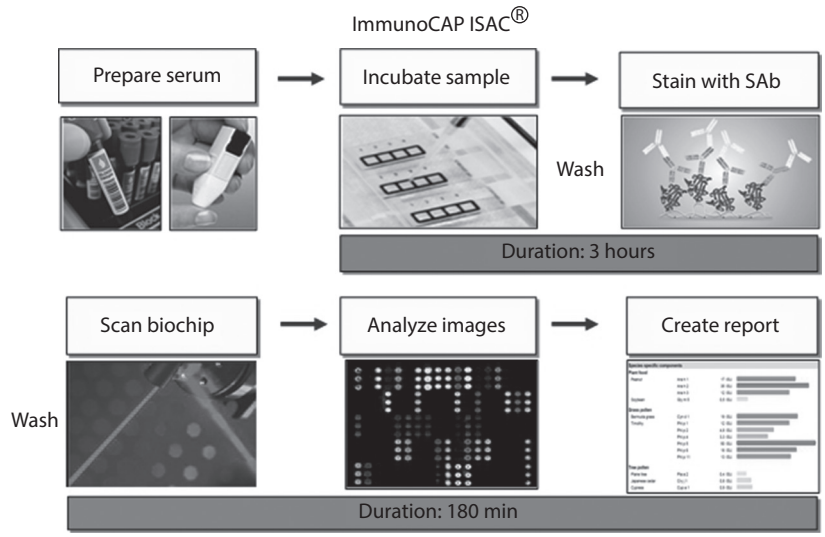

FIGURE 13.2 ISAC methodology in the laboratory. (Courtesy of Thermo Fisher-Scientific.)

Allergens of Interest in Contact Urticaria

Allergens of Animal Origin

Hen's Egg (Gallus domesticus)

Gal d 1 (ovomucoid), Gal d 2 (ovalbumin), Gal d 3 (ovotransferrin/conalbumin), and Gal d 4 (lysozyme) have been identified as the major allergens of egg white.[11] Gal d 5 is present in egg yolk as a livetin protein and in chicken as serum albumin.[12] Although Gal d 1 (ovomucoid) comprises only 10% of the total egg white protein, it has been shown to be the dominant allergen.[11,13] It is very stable against heat and digestion by proteases, and can be allergenic in minute amounts. IgE abs to Gal d 1 is a risk factor for persistent egg allergy, and indicates that neither raw nor cooked egg is tolerated.[11–16]

Cow's Milk (Bos domesticus)

The major allergens of milk are caseins (e.g., Bos d 8), beta-lactoglobulins (e.g., Bos d 5), and alfa- lactoglobulins (e.g., Bos d 4), though allergies to other minor proteins such as bovine serum albumin (e.g., Bos d 6), bovine lactoferrin (Bos d lactoferrin), and immunoglobulins have also been reported.[17,18] Most milk-allergic patients are sensitized to several cow's milk proteins. Conformational epitopes are largely destroyed by high temperatures, and recently it was shown that a majority of milk-allergic children tolerated heated milk.[19] Those children reacting to heated milk had initially higher casein and beta-lactoglobulin IgE levels and were at higher risk for systemic reactions.

Meat Allergy

The α-1,3-galactose (α-Gal) is a sugar structure found on glycoproteins and glycolipids of nonprimate mammals and New World monkeys, but not in humans. IgE abs specific for α-Gal (anti–α-Gal-IgE) are associated with severe allergic symptoms and with delayed-type anaphylaxis to red meat (beef, pork, goat, and deer).[20] α-Gal is also present in cat IgA,[21] on gelatin-containing material, and in cetuximab (cancer drug).[22] It is assumed that sensitization to α-Gal can be induced by tick bites or certain parasite infections.[23]

Bovine serum albumin (e.g., Bos d 6) is a heat-labile allergen present both in milk and beef, which may cause cross-reactivity between different mammalian meat.

Shrimp (Penaeus aztecas, Penaeus indicus, Penaeus monodon, Pandaluseous, *and Others*)

Pen a 1 is a tropomyosin and a major allergen in shrimp.[24] It is detected in approximately 80% of shrimp-allergic patients and Pen a 1 from brown shrimp is regarded as a representative of other shrimp tropomyosins.[25] Tropomyosin has been considered to be responsible for cross-reactivity between crustaceans and other arthropods such as dust mites or cockroach and nematodes.[26] In fact, tropomyosins from dust mites and other arthropods have a shared sequence identity of about 75%–80%. However, recent publications have shown than sensitization to tropomyosins is a good marker of clinical sensitivity to crustaceans but not a marker of sensitization to mites.[25,27] Nevertheless, cross-reactivity between mites and shrimp does exist, but it is due to allergens other than tropomyosins, such as α-actinin and ubiquitin.[28] Therefore, from a pragmatic point of view, in patients with clinical allergic reactions to crustaceans and with positive SPT to mites, determination of markers of specific sensitization to mites is recommended.

Pen m 2, an arginine kinase, Lit v3 from European white shrimp (myosin light chain with high similarity to Bla g 8-cockroach), and Lit v 4 (sarcoplasmic calcium-binding protein) from *Litopenaeus vannamei* are the other allergenic shrimp proteins described.[29,30]

Fish Parvalbumins from Cod (Gadus morhua) *and Carp* (Cyprinus carpio)

Cod Gad c 1 [31] and carp Cyp c 1 [32] are both major fish parvalbumin proteins and are representative markers for fish sensitization in general. Because of the high degree of cross-reactivity between parvalbumins from different species, Gad c 1 and Cyp c 1 are valuable tools in diagnosing patients with fish allergy, but selective epitope recognition in different species may occur.[33] The different expression of parvalbumins across species of fish may explain also lack of cross-reactivity phenomena.[34] Parvalbumins have remarkable stability, which may explain why sensitization can result from ingestion even after cooking, contact, and inhalation of cooking vapor.

Dog (Canis familiaris)

Can f 1, Can f 2, and Can f 5 are specific allergen components indicating primary sensitization.[35,36] Can f 1 is a lipocalin protein and is the most relevant dog allergen. Can f 2 is also a lipocalin protein. Can f 5 is a prostatic kallikrein and has been shown to cross-react with human seminal fluid.[36] Can f 5 is produced by male dogs and responsible for sensitivity in up to 38% of dog-allergic patients [36] (25% in the author's experience). This could explain why some patients sensitized to dog extracts may tolerate female dogs. Can f 3 is the dog serum albumin protein, a cross-reactive component indicating cross-reactions to other bovine serum albumins (e.g., from cat Fel d 2).[37] Many patients are polysensitized to several pet allergens as revealed from using commercial extracts; however, the clinical history is often inconclusive. This may be due in part to cross-reactivity phenomena between allergens contained in different extracts such as serum albumins of cat (Fel d 2), dog (Can f 3), cow, and horse (Equ c 3). Thus, MD may aid in clarifying the relevant sensitization when used in conjunction with clinical history.

Cat (Felis domesticus)

Fel d 1 (uteroglobin) is the major allergen component in cat, indicating primary sensitization. About 60%–90% of patients with cat allergy have IgE abs to Fel d 1.[38] IgE abs to the cat serum albumin Fel d 2 is likely to cross-react with most other mammal albumins, such as dog Can f 3, horse Ecu c 3, pig Sus s PSA, and cow Bos d 6.[37] It can also cause reactions when eating pork (the cat–pork syndrome).[39] Fel d 4 is a lipocalin protein recently shown to cross-react with major allergens from horse Equ c 1, dog, or cow.[40]

Horse (Equus caballus)

Equ c 1, a lipocalin, is considered to be the major allergen of horse dander and has some cross-reactivity with mouse Mus m 1 and cat Fel d 4.[41] Equ c 3 is a serum albumin showing cross-reactivity with other mammals' serum albumins, as mentioned previously.

Mouse (Mus musculus)

Sensitization to mouse Mus m 1 (lipocalin), as an indoor allergen, has been associated with asthma and asthma morbidity in some cities in the United States.[42] Occupational allergy to mouse is fairly common in persons handling experimental animals.

Mites

Numerous house dust allergens have been described (around 23), and it seems that the IgE frequency of individual allergens may show high variability at least in certain populations.[43] The commercially available allergens are rDer f 1 (*Dermatophagoides farinae)*, rDer f 2 (*Dermatophagoides farinae)*, nDer p 1 (*Dermatophagoides pteronyssinus)*, and nDer p 2 (*Dermatophagoides pteronyssinus)* from pyroglyphidae mites, and *rBlo t 5 (Blomia tropicalis)*, rLep d 2, (*Leydugliphus destructor*), and rEur m 2 (*Euroglyphus maynei).* Der p 10 (tropomyosin) is a minor allergen in mite-allergic patients; however, it may still indicate a risk for allergic reactions to shellfish or snail, which can be severe.[27,28]

Parasites Anisakis (Anisakis simplex)

Anisakis is a fish parasite that can cause severe reactions when raw infected fish is eaten or by contact.[44] Allergens Ani s 1 (serine protease inhibitor) and Ani s 4 have demonstrated their utility for diagnosing sensitization to the larvae of the genus Anisakis, but seropositivity for Ani s 1 has a limited diagnostic value in clinically discriminating patients with a history consistent with gastroallergic anisakiasis.[45] Ani s 3 (tropomyosin) [46] is also a major allergen of *Anisakis simplex*, having extensive cross-reactivity with other tropomyosins from nematodes and invertebrates. Other minor allergens are Ani s 5 and Ani s 2 (paramyosin),[47] but are not commercially available.

Allergens of Plant Origin

Peanut (Arachis hypogaea)

IgE abs to Ara h 1, Ara h 2, Ara h 3, Ara h 6, but especially Ara h 2 and Ara h 3, are regarded as a marker for genuine sensitization to peanut.[48] These are stable proteins to heat and digestion and therefore indicate an increased risk for systemic and more severe reactions to peanut. Although clinically rare, sensitization to these peanut components may also give rise to a certain degree of cross-reactivity, especially Ara h 1 to nuts and legumes such as lentil, pea, and Gly m 5 from soybean [49]; Ara h 2 to lupine and tree nuts such as almond and brazil nut [50]; and Ara h 3 to soybean, pea, and tree nuts.[51]

Ara h 8 is a PR 10 protein, a Bet v 1 homologue, and thus a marker for primary sensitization through pollens such as birch and alder. Cross-reactivity with lupine and Gly m 4 from soy bean has also been documented.[48] Ara h 8 is a heat-labile protein; cooked peanuts are therefore often tolerated. Presence of Ara h 9-specific IgE abs is often associated with systemic and more severe reactions in addition to oral allergic syndrome (OAS), especially in southern Europe.[53] Ara h 9 is an LTP, and sensitization in most cases is probably to the result of primary sensitization to peach or other LTP-containing fruits.

Soy Bean (Glycine max)

Gly m 4 belongs to the PR-10 protein family and is a major soy allergen in birch pollen–associated, soy-allergic patients. IgE abs to Gly m 4 is likely from primary sensitization to birch or similar tree pollens and is often associated with mild symptoms.[54] Gly m 4 is also cross-reactive with Ara h 8, and a relevant proportion—about two-thirds—of soy-allergic patients in Europe are associated with peanut and soy allergy.[54] Targeted diagnostic testing with Gly m 4 is strongly recommended in pollen-sensitized patients with suspicion of soy allergy, especially if the soy extract test result is negative. Some Gly m 4-sensitized patients can show low or even negative IgE results with soy extract due to a low Gly m 4 content in the extract.

IgE abs to Gly m 5 and Gly m 6 indicates primary sensitization to soy.[55] Hence, Gly m 5 and Gly m 6 are potential diagnostic markers for severe allergic reactions to soy. Gly m 5 and Ara h1 share sequence homology and so do Gly m 6 and Ara h 3. Serological cross-reactivity between these components has also been shown.

Wheat (Triticium aestivum)

A positive result to wheat-flour extract does not always correlate with clinical symptoms,[56] indicating that in vitro diagnosis of allergy to wheat may be improved by using recombinant wheat-seed allergens.[57] The Tri a aA_TI (alpha-amylase/trypsin inhibitor) protein fractions of raw and cooked wheat are a relevant wheat allergen in food allergy and also play a role in wheat-dependent, exercise-induced anaphylaxis.[58] Positive IgE ab test results to Tri a gliadin indicate primary wheat sensitization with a low risk of pollen cross-reactivity.[59]

The wheat component Tri a 18 (isolectin 1 agglutinin) and the latex component Hev b 6 are known to share sequence homology. In children, IgE abs to omega-5 gliadin (Tri a 19) is associated with a risk of immediate reactions to wheat.[60] High-molecular-weight (HMW) glutenin is also a major wheat allergen and IgE abs to HMW glutenin is associated with wheat-dependent, exercise-induced anaphylaxis.[61]

Other important allergens are the 9-kDa wheat LTP, Tri a 14. Wheat LTP is considered a major allergen only in patients living in southern Europe [62] and also a significant allergen in baker's asthma in the same area. Sensitization to additives, such as enzymes, can also be responsible for contact urticaria in bakers.

Buckwheat (Fagopyrumesculentum)

Buckwheat, a pseudo-cereal, has been recognized as a common food allergen in Asian countries. Fag e 16kD (2S albumin) is a major allergenic protein of buckwheat. Fag e 16kD shows similarities between BW 8-kDa from buckwheat, Ara h 6 from peanuts, and Ric c 1 from castor bean.[63]

Apple and Peach

Because of cross-reactivity within the botanical family Rosaceae, the Mal d 1and Pru p 1 components are good representatives and markers for some stone fruits such as cherry and apricot, among others, and thus not only for apple or peach.[64] Several allergy patterns were found in which the allergen families PR-10, LTP, thaumatins, and profilin were involved. In the western Mediterranean area, allergies to Rosaceae fruits are caused by monosensitization to LTP (Pru p 3), monosensitization to profilin, or cosensitization to both allergens.[65] LTP sensitization is present both in pollinosis and nonpollinosis patients and is associated with peach allergy in particular. On the contrary, monosensitization to PR-10 and, to a lesser degree, cosensitization to profilin and PR-10 is dominant in northern and central Europe, where PR-10 sensitization is primarily associated with concomitant birch pollen and apple allergy. Patients sensitized to profilin are characterized by several concomitant allergies, including grass and other pollens as well as Rosaceae and non-Rosaceae fruits. IgE ab to Pru p 3, an LTP protein, is frequently associated with severe reactions to stone fruits, but also to OAS, [66] whereas sensitization to PR 10 proteins Mal d1 or Pru p 1 and profilin (Pru p 4) is more often associated with OAS symptoms. LTP allergens of the Prunoideae subfamily have a similarity of about 95%, but there is also sequence homology of LTPs of botanically unrelated foods.[67] Recently, a thaumatin-like protein (Pru p 2.0201) has been described as an important allergen in peach-allergic patients from the Mediterranean area.[68] It has partial cross-reactivity with other thaumatin-like proteins from kiwi (Act c 2), apple, cherry, and plane pollen.[69]

Kiwi Fruit (Actidinia deliciosa)

The two main kiwi fruit allergens are actinidin (Act d 1), a thiolprotease, and a thaumatin-like protein (Act d 2).[70,71] The stability of Act d 1 and Act d 2 provides one explanation for the allergenic potency of kiwi fruit. Cross-reactive carbohydrate determinants and thiolproteases that are homologous to Act d 1 are responsible for wheat–kiwi cross-reactivity in some patients.[72] A potential association between respiratory allergy to cereal flour and allergy to kiwi fruit has been demonstrated. In patients with allergic reactions to figs and other tropical fruits (kiwi fruit, papaya, avocado, banana, and pineapple), thiolproteases can mediate, at least in part, this cross-reactivity.[73] A 40-kDa glycoprotein designated as Act d 3.02 and kiwellin (Act d 5) has been described as an important allergens as well.[56] Bet v 1-homologous allergens (PR-10) from green (Act d 8) and gold (Act c 8) kiwi fruit are recognized by birch pollen- or kiwi fruit–allergic patients.[71]

Hazelnut (Corylus avellana)

The main allergens are the Bet v 1 homologue Cor a 1.04, the hazelnut profilin Cor a 2, and LTP Cor a 8.[75] Other molecules that have been investigated in connection with hazelnut allergy are the 11S globulin Cor a 9, the vicilin, Cor a 11, hazelnut oleosin, 2S albumins; and the specific carbohydrate structures, known as cross-reactive carbohydrate determinants (CCDs), for which bromelain has been used as source.[76] Sensitization to Cor a 1.04 is prevalent in the northern regions of Europe and is commonly associated with OAS. On the other hand, sensitization to hazelnut LTP (Cor a 8) is certainly more common in patients from southern Europe,[76]

and these patients can develop either severe or mild allergic reactions to hazelnut. Polysensitization to hazelnut-allergen components is mostly observed in patients with severe symptoms.

Celery (Apium graveolens)

Api g 1, the Bet v 1- PR-10, is the major celery allergen, though profilin (Api g 4) and CCD are also recognized by celery-allergic patients.[77] Api g 1 is more stable to heat than many other PR-10 proteins responsible for cross-reactivity with birch and mugwort pollen, although the structural similarity is less than that of several other PR-10 proteins.

Carrot (Daucus carota)

Dau c 1 -PR-10- is the major carrot allergen and is responsible for cross-reactivity with Bet v 1 from birch pollen. However, in a subgroup of patients with carrot allergy, birch allergens did not inhibit IgE binding to Dau c 1.[78] Profilin (rDau c 4) and CCD are also recognized by carrot-allergic patients. Profilin may be an important allergen in allergy to carrot in birch-free areas, such as the Mediterranean region.[79]

Sesame (Sesamum indicum)

The reactivity of the Ses i 1 (14 kDa, 2S albumin precursor) protein with most of the sera from patients allergic to sesame indicates that it is the major sesame allergen. However, other allergens have seen isolated, such as a 7S vicilin-type globulin; a seed storage protein of sesame and named Ses i 3; another 2S albumin, named Ses i 2 [80]; and olesins named Ses i 4 and Ses i 5.[81]

TABLE 13.2

Commercially Available Purified Natural or Recombinant Allergens and Their Utility in Contact Urticaria

Sources	Allergens of Genuine Sensitization	Allergens with Cross-Reactivity
Animal source		
Hen's egg (*Gallus domesticus*)	Gal d 1, Gal d 2, Gal d 3, Gal d 4	Gal d 5 (serum albumin)
Cow's milk *(Bos domesticus)*	Bos d 4, 5, 6, 8, lactoferrin	Bos d 6 (casein)
Meat	Galactose-α-1,3-galactose (α-Gal) Bos d 6	Galactose-α-1,3-galactose (α-Gal) Bos d 6 (casein)
Shrimp	Pen a 1, Pen m 2, Lit v3, Lit v 4	Pen a 1 (tropomyosin)
Fish	Gad c 1, Cyp c 1	Gad c 1, Cyp c 1 (parvalbumins)
Pet danders		
Cat	Fel d 1 Fel d 4	Fel d 3 (albumin)
Dog	Can f 1, Can f 2, Can f 5	Can f 3 (albumin)
Horse	Equ c 1	Equ c 3 (albumin)
Mouse	Mus m 1	
Mites		
House dust mite pyroglyphidae	Der p 1, Der p 2 Der f 1, Der f 2	Der p 10 (tropomyosin)
Blomia t.	Blo t 5	
Euroglyphus m	Eur m 2	
Lepidoglyphys d	Lep d 2	
Parasites	Ani s 1	Ani s 3 (tropomyosisn)

(*Continued*)

TABLE 13.2 (*Continued*)

Commercially Available Purified Natural or Recombinant Allergens and Their Utility in Contact Urticaria

Sources	Allergens of Genuine Sensitization	Allergens with Cross-Reactivity
Plant source		
Peanut	Ara h 1, Ara h 2, Ara h 3, Ara h 6, Ara h 9,	Ara h 8 (PR 10 protein) Ara h 9 (LTP)
Soybean	Gly m 5, Gly m 6, Gly m 2S	Gly m 4 (PR 10 protein)
Wheat	Tri a aA_TI, Tri a gliadin, Tri a 19, omega-5 gliadin, HMW-glutenin, Tri a 14	Tri a 14 (LTP)
Buckwheat	Fag e 16kD	
Apple		Mal d 1 (PR 10 protein)
Peach	Pru p 3 (LTP)	Pru p 1 (PR 10 protein) Pru p 3 (LTP) Pru p 4 (profilin)
Hazelnut	Cor a 8 Cor a 9	Cor a 1 (PR 10 protein) Cor a 2 (profilin) Cor a 11 (vicilin) Cor a 8 (LTP)
Celery	Api g1	Api g1 (PR 10 protein)
Carrot	Dau c 1	Dau c 1 (PR 10 protein) Dau c 4 (profilin)
Sesame	Ses i 1	Ses i 1 (2S albumin precursor)
Brazil nut	Ber e 1	Ber e 1 (2S albumin)
Walnut	Jug r 1, Jug r 2, Jug r 3, Jug r 4	Jug r 3 (LTP)
Cashew	Ana o 2	
Latex	Hev b 1, Hev b 3, Hev b 5, Hev b 6.01, Hev b 6.02, Hev b 11	Heb v 8 (profilin) Hev b 11 (chitinase)
CCD (carbohydrates determinants)	Ana c 2 (bromelin) and MUXF3	Ana c 2 (bromelin) and MUXF3
Pollen		
Ragweed	Amb a 1	
Mugwort	Art v 1 Art v 3	Art v 3 (LTP)
Parietaria, wall pellitory	Par j 2	Par j 2 (LTP)
Russian thistle or saltwort	Sal k 1	
Goosefoot	Che a 1	
Timothy	Phl p 1 Phl p 5 Phl p 6	Phl p 4 (berberine) Phl p 7 (polcalcin) Phl p 11 (trypsin inhibitor) Phl p 12 (profilin)
Bermuda grass	Cyn d 1	
Alder	Aln g 1	Aln g 1 (PR 10)
Birch	Bet v 1	Bet v 1 (PR10) Bet v 2 (profilin) Bet v 4 (polcalcin)
Olive	Ole e 1 Ole e 7 Ole e 9	
Cypress	Cup a 1	
Plane tree	Pla a 1 Pla a 2	Pla a 3 (LTP)

Nut allergens *are described in Table 13.2.[1,82]*

Latex (*Hevea brasiliensis*)

Specific IgE to latex extract detected using traditional testing is common in individuals without clinical symptoms to latex. Resolving the IgE sensitization into components is a tool to distinguish genuine latex allergy from sensitization to profilin. A profilin component (Hev b 8) is included in traditional extract-based tests; however, it is usually of low clinical relevance. On the other hand, sensitization to Hev b 1, Hev b 3, Hev b 5, and Hev b 6 is associated with primary latex allergy.[83,84]

Latex allergy occurs mostly among individuals exposed to latex in their occupation (e.g., health care workers) or in children exposed to latex early in life, such as those who have undergone multiple operations (e.g., because of spina bifida). Latex allergy was a major health care problem some decades ago, but increased knowledge and awareness has reduced both latex exposure and also the number of latex-allergic patients.

Hev b 1 (rubber elongation factor) is a major latex allergen. Sensitization to Hev b 1 has a high prevalence in children who have had multiple operations and spina bifida (50%–100%), and prevalence is lower among health care workers (10%–50%).[85,86]

Hev b 3 (small rubber particle protein) is a minor latex allergen. Hev b 3 and Hev b 1 are closely related and share stretches of sequence homology, which may explain their cross-reactivity.[87,88]

Hev b 5 (acidic protein) is often associated with occupational latex allergy.[87,88] Hev b 5 has a significant homology with kiwi fruit and potato, which are known to cause allergic reactions in latex-allergic patients.[89]

Hev b 6 (hevein) is a major latex allergen with a prevalence of 70%–90% among latex-allergic patients.[90–94] It is the main sensitizing allergen for health care workers. Hev b 6 is also associated with the so-called latex–fruit syndrome (latex–avocado–kiwi–banana–chestnut).[1] Hev b 6 shares sequence homology with Hev b 11, a chitinase, which may cross-react with chitinases in some exotic fruits.[95]

Hev b 8 (profilin) is not associated with primary latex allergy, and it is a panallergen belonging to the profilin family.[96] Sensitization to profilin may explain serological cross-reactivity with other allergen sources of plant origin and is usually of low clinical relevance.

CCD: Bromelin—MUXF3, Ana c 2

CCD is present in plant and insect glycoproteins (such as honeybees, wasps, and cockroaches), carrying glycans with carbohydrate determinants that do not exist in mammals. CCD is rarely associated with clinical symptoms and can be used to resolve questions on nonsymptomatic sensitizations obtained when testing with allergen extract-based IgE tests.[97] A CCD test could be especially useful in four situations: 1) sensitization to foods of plant origin, 2) sensitization to latex in a pollen-allergic patient without occupational risk factors, 3) in subjects testing positive both for honeybee and for wasp-venom extracts, and 4) in subjects with perennial respiratory symptoms who test positive for cockroach in the absence of demonstrable exposure to cockroach allergens. Ana c 2 (bromelin) and MUXF3 (processed from bromelain and usually coupled to a protein backbone for IgE testing) are both markers for sensitization to CCD.

Pollen Allergens

Increasing the accuracy of diagnosis in pollen-allergic patients is a clinical challenge for specialists, mainly in locations where several pollens coexist. In such cases, it is important for the clinician to know whether a patient is cosensitized to several allergen sources and needs immunotherapy for each or whether the patient is sensitized to several sources because of sensitization to cross-reactive components (e.g., profilins, polcalcins, LTPs, PR10, thaumatin-like proteins) in each of the suspected allergen sources.[98] For instance, a patient who is primarily sensitized to grasses may also test positive for birch, olive, or latex using SPT.[99] This cross-reactivity occurs because all these extracts used in SPT contain profilin (rBet v 2, nOle e 2, Hev b 8), which are largely similar to those in grass (e.g., Phl p 12). MD using recombinants or purified allergens can partially solve this problem and improve the diagnosis of allergy.[98] Table 13.2 contains a summary of the main pollen allergens that are commercially available.

Conclusion

MD for diagnosis purposes in immunologic contact urticaria is useful for improving diagnostic specificity, distinguishing cross-reactivity phenomena from true cosensitization, and resolving low-risk markers from high-risk markers. Most allergens and their components belong to a limited number of protein families. Allergens that remain stable to heat and digestion are more likely to cause a severe clinical reaction. Molecular test for animal, food, plants, or latex allergens are available for diagnosis purposes.

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Conflicts of Interest

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14

Skin Tests and Specific IgE Determinations in the Diagnosis of Contact Urticaria and Respiratory Disease Caused by Low-Molecular-Weight Chemicals

Kristiina Aalto-Korte, Outi Kuuliala, and Eva Helaskoski

Introduction

Low-molecular-weight (LMW) chemicals usually induce delayed cell-mediated type IV contact allergy (i.e., allergic contact dermatitis). Contact urticaria, in turn, is usually caused by proteins, which are large molecules. Some LMW chemicals, however, may induce immediate-type contact reactions (contact urticaria). These chemicals often also cause respiratory symptoms, asthma and rhinitis, and anaphylactic multiorgan symptoms. Concomitant contact urticaria and respiratory diseases are common in occupational settings. Some chemicals induce immunoglobulin E (IgE)-mediated type I allergy, but in most cases the mechanisms are unknown.

Although chemical-induced contact urticaria is indeed rare, it is also probably underdiagnosed. Not all physicians are familiar with the causative agents and symptoms of this rare clinical entity. The symptoms are often mild, limited to areas of skin contact, and of short duration, and people rarely report them to their physician. If patients with chemical-induced respiratory disease are asked specific questions relating to contact urticaria, the answers are often affirmative and lead to the diagnosis of contact urticaria. We must emphasize that although patients often have concomitant respiratory and skin symptoms, these are usually from the simultaneous exposure of each organ, which takes place at the workplace (skin contact leads to contact urticaria and inhalation leads to asthma symptoms), and not to contact urticaria syndrome or another anaphylactic multiorgan entity. True anaphylactic symptoms are rare in occupational settings.

In Finland, persulfates are the most common LMW chemicals causing occupational contact urticaria, followed by organic acid anhydrides. The most significant chemicals that cause occupational asthma are isocyanates, persulphates and cyclic acid anhydrides.

The Finnish Institute of Occupational Health (FIOH) examines patients suspected of having occupational skin diseases and patients with suspected occupational respiratory diseases. 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. We have performed prick tests with protein conjugates of various LMW chemicals for more than 20 years. In this chapter, we present some examples.

FIOH's General Scheme of Diagnostic Tests for Immediate Hypersensitivity Reactions

Contrary to recommendations, at FIOH, prick tests have always been used with rather wide indications as a "screening" method for immediate-type allergy/hypersensitivity. Determination of specific IgE is a practical alternative in primary health care and for patients with severe symptoms. Because FIOH's patients come from all parts of the country, we do not usually have time to wait for the results of specific IgE determination before prick tests. Moreover, the determination of specific IgE is not very useful in terms of LMW chemicals, because commercial assays are available for only a few chemicals. As far as we know, the recommendation of starting

with an open application test in the diagnosis of contact urticaria has never been widely followed in Finland: if we are concerned about systemic reactions, we begin prick tests at very low concentrations. Of course, it is important to reduce the number of tested substances in patients with severe symptoms, concentrate on the most probable candidates for causative agents, and proceed stepwise. The amount of the allergen used in an open test is much larger than the minute amount used in a prick test. Because many patients have concomitant respiratory hypersensitivity to the same allergen, there is a real risk of inducing respiratory or even systemic symptoms from inhalation of the allergen that is applied to the forearm skin, not far from the patient's respiratory zone. Moreover, a prick test usually produces only one wheal, whereas in a strongly positive open application test, a large wheal area appears. We are more afraid of provoking systemic symptoms in an open application test than in a prick test. The amount of the allergen can be further lowered using the prick-prick method as suggested by Hoekstra et al. in the Netherlands.[1] Of course, the rarity of anaphylactic symptoms among our occupational patients has formed our diagnostic policies. The prick test is used as the first diagnostic method in many other countries also.[2–5]

Prick testing allows us to screen a large number of substances at the same time, and the materials for open tests are chosen according to the size of the prick test reaction, the extent of exposure and the symptoms on direct contact. The same skin areas should not be used for open tests and prick tests, because wheals appear in the sites of previous prick tests even several days later. We do not usually perform open application tests on prick test–negative patients. We have, however, sometimes seen urticarial reactions in open application to prick test–negative substances. In such cases, we have suspected nonimmunologic contact urticaria, especially when the reaction has been inhibited by nonsteroidal anti-inflammatory drugs.

When a patient needs both respiratory and skin provocation tests, the open application test (skin challenge) is performed at the end, because we do not want to interfere with the outcome of the respiratory challenges for the abovementioned reasons.

Specific IgE is determined with commercial tests, when possible, and in-house tests; for example, immunospot. However, the significance of these tests is mainly to confirm the diagnosis of immediate hypersensitivity, at least as regards contact urticaria. For occupational respiratory diseases, the role of prick testing is not so important. Respiratory provocations/challenges with LMW chemicals are chiefly performed on the basis of exposure data.

We have no experience with intradermal tests in the diagnosis of LMW chemical-induced hypersensitivity reactions. We avoid this technique because it is demanding to perform the test and interpret the result, and it may also induce systemic reactions.

We have little experience with 15-minute occlusive chamber tests used as such, but urticarial reactions are occasionally seen in routine patch tests, especially with substances that induce nonimmunological contact urticaria. Previously, routine patch tests were sometimes read after 15 minutes, but as this never proved to be very useful, this method hardly exists any longer in our daily diagnostic practice.

Specific inhalation challenge is the principal method used to confirm the diagnosis of occupational asthma and rhinitis at FIOH, but serial peak flow monitoring is also used. Placebo-controlled challenges are performed in challenge chambers as work simulation or nebulization of the occupational agent in the air. These include a 24-hour follow-up for each agent.

Chamber provocation is used to diagnose occupational asthma and rhinitis, but not contact urticaria. However, we have occasionally seen wheals provoked in this challenge test, for example, airborne contact urticaria from acid anhydride (Table 14.1).

Preparation and Characterization of Hapten-Protein Conjugate Antigens

Human serum albumin (HSA) conjugates of chemicals were used for the determination of specific IgE at FIOH in the 1980s. This led to an interest in using HSA conjugates for prick testing.

Hapten-protein conjugates can be synthetized in the laboratory in vitro. HSA has been considered the best carrier for haptens. Serum albumin has shown to be the major protein in plasma that forms adducts in vivo with hexahydrophthalic anhydride, an important cause of occupational chemical-induced asthma.[6] The host response may be hapten-specific or directed against new antigenic determinants formed on the protein carrier.[7]

TABLE 14.1

FIOH's Diagnostic Scheme of Immediate Hypersensitivity Reactions

I. Skin prick test
-Water-based solutions
-In-house HSA conjugates
II. Specific IgE
-Commercial tests (e.g., anhydrides, isocyanates)
-In-house tests (e.g., immunospot)
III. Provocation tests (challenge tests)
-Chamber provocation (asthma or rhinitis)
-Nasal provocation test (rhinitis; only occasionally)
-Open application test (skin provocation; contact urticaria)

Protein conjugates of reactive chemicals for use in immunoassays can be prepared by simply mixing the chemical and the protein in a suitable buffer solution. The chemistry of some haptens may be complex, and it is difficult to anticipate the factors that are important for preparation. For instance, time, temperature, concentration, and pH are factors that influence the structure of the hapten–protein conjugate.

It is also possible to use some coupling agents for linking chemicals containing nucleophilic groups to protein carriers.

To understand the nature of the in vitro synthesized HSA conjugates, they should be characterized immunochemically and physically. The ratio of chemical molecules bound per molecule of carrier protein (hapten density) can be studied. For instance, the optimal conjugates of phthalic anhydride contained an average of 14–16 phthalic anhydride per carrier molecule of HSA.[8]

Skin Prick Test

Because commercial test substances for the investigation of LMW chemicals with prick tests do not exist, only in-house test substances can be used, except for some individual commercial water-diluted preparations intended for patch tests, such as 1% chlorhexidine. Consequently, recommendations for prick testing do not exist either, and usually only a few case reports or smaller patient series are available for guidance.

The technique of prick testing with LMW chemicals does not usually differ from the usual technique with, for example, common environmental inhalant allergens. When patients with anaphylactic symptoms are examined, it is possible to start with the prick-prick technique and proceed to the usual prick test through a drop of allergen solution as suggested by Hoekstra et al.[1] The amount of allergen in the prick-prick method is lower than in a prick test performed with the usual technique.

Some LMW chemicals can be tested as water solutions. Chlorhexidine, chloramine T, ammonium, and potassium persulfates are routinely tested as water dilutions at FIOH. When a patient with strongly suspected LMW chemical-induced contact urticaria is examined, it is worth experimenting with prick tests with their own chemicals as water dilutions. An example is the laboratory chemical (1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, which caused asthma, contact urticaria, and generalized symptoms in a laboratory worker. The chemical was positive when prick tested in water solution at a concentration of 0.1%.[9] Occupationally relevant allergens organic acid anhydrides and isocyanates cannot be tested in water solutions, because in contact with water they immediately form corresponding acids and amines. However, protein conjugates provide a solution to this problem. LMW chemical–HSA conjugates were originally prepared for in-house determinations of specific IgE. Some of them were experimentally used in prick testing. When the initial experiments appeared useful in the clinical investigation of occupational diseases at FIOH, more conjugates were prepared from a large number of occupationally relevant chemicals.

Contact urticaria from organic acid anhydrides is seen relatively often at FIOH. It is caused by IgE-mediated allergy. In a series of 21 contact urticaria patients, the most common anhydride was methyl hexahydrophthalic

anhydride. The patients were prick tested with HSA conjugates of acid anhydrides. The largest noted prick test reaction was often to the acid anhydride the patient had been exposed to. Prick testing with HSA conjugates is a sensitive method for screening immediate allergy, but tests for specific IgE have yielded almost equal results.[10]

The literature contains numerous reports of anaphylactic reactions to chlorhexidine in surgical operations and other medical procedures: wound cleansing, cystoscopy and other endoscopic examinations, urethral catheterization or insertion of chlorhexidine-impregnated central venous catheters, and gynecological examinations. Generalized symptoms usually appear because of its application to wounds or mucous membranes. In Helsinki University Central Hospital, patients displaying positive reactions (≥3 mm) to chlorhexidine were reviewed. Among 1314 patients prick tested with either 1% or 0.5% chlorhexidine gluconate, 33 were positive. Ten patients had had generalized symptoms in connection with surgical operations, but many of them had preceding mild symptoms in the skin and mucosal membranes from local treatment. The size of the prick test reaction was in line with the strength of the most severe symptoms. Small 3- to 4-mm reactions were usually without obvious clinical relevance: many patients with small reactions had not noticed any symptoms from chlorhexidine-containing products or had no known exposure to the chemical.[11] In Denmark, prick testing with 0.5% chlorhexidine digluconate has been used to diagnose immediate chlorhexidine allergy in patients with suspected anaphylaxis during anesthesia, and the results correlate well with determinations of specific IgE to chlorhexidine.[4]

Exposure to persulfates is of relatively high importance.[5] At Helsinki University Central Hospital, seven hairdressers were positive in prick testing with 2% ammonium and potassium persulfates in aqua. Six of them had skin symptoms with or without rhinoconjunctivitis and one had respiratory symptoms without skin symptoms.[12] Although small prick test reactions without clinical significance have been seen,[11] the present literature supports the use of prick testing in the diagnosis of immediate hypersensitivity reactions to chlorhexidine together with assays for specific IgE.[11,13,14]

Chloramine-T is a disinfectant that may cause contact urticaria and allergic contact dermatitis, and also respiratory disease with an IgE-mediated mechanism, especially among health care workers.[15,16] Prick tests with water solutions [15,17] and HSA conjugates have been positive.[15] The present practice at FIOH is to use a water solution of 1% concentration.

Isocyanate CU has been reported only rarely.[18–20] At FIOH, a patient with occupational asthma and urticaria from diphenylmethane-4,4′-diisocyanate (MDI) was positive in prick testing with MDI-HSA conjugate, and specific IgE to MDI and other isocyanates was also detected.[18] In Spain, a patient with similar symptoms had specific IgE to MDI and was also positive to an open application of her own MDI-containing glue diluted to 1% in petrolatum [19]; in Italy, a patient with similar symptoms had specific IgE to MDI and an urticarial reaction to MDI on patch testing at 20 minutes' reading.[20]

HSA conjugates of diglycidyl ether of bisphenol A epoxy resin have been used for prick testing at FIOH. A prick test–positive case with both occupational asthma and contact dermatitis caused by epoxy resin has been reported.[21]

Methacrylates, 2-hydroxyethyl methacrylate, and methyl methacrylate were tested as HSA conjugates for about 20 years at FIOH, but because they yielded no clinically relevant positive results, we no longer test them.

Determination of Specific IgE

Commercial specific IgE determinations are available for only a few LMW chemicals. They include chlorhexidine, chloramine T, formaldehyde, ethylene oxide, isocyanates hexamethylene diisocyanate, toluene diisocyanate and diphenylmethane diisocyanate, and cyclic acid anhydrides maleic anhydride, hexahydrophthalic anhydride, methyltetrahydrophthalic anhydride, phthalic anhydride, and trimellitic anhydride. Medicaments such as beta-lactam antibiotics are also LMW chemicals, but tests for their specific IgE are mainly needed in the diagnosis of drug reactions, and contact urticaria is rarely suspected. Some experimental allergens might also be available.

Contact urticaria from organic acid anhydrides is an IgE-mediated disease. In a series of 21 patients at FIOH, only one did not have specific IgE to any anhydride. Phthalic acid anhydride-specific IgE was tested in 20 of the patients and found to be positive in 19. Thus, this test can be used for screening contact urticaria patients.[10]

Immediate reactions to chlorhexidine seem to be IgE-mediated, and the results of specific IgE determinations and prick tests have a good correlation.[4] Patients with anaphylactic reactions during surgical operations have often had previous mild reactions to chlorhexidine, such as a rash or local swelling at the site of exposure.[4,11] Commercial determinations of chlorhexidine-specific IgE are nowadays available.

In-house methods for the determination of specific IgE are sometimes helpful: at Helsinki University Central Hospital, persulfate-specific IgE was demonstrated with the immunospot method in the sera of two hairdressers with persulfate-induced contact urticaria; one of them was also positive when tested with the radioallergosorbent test method. The immunospot assays were positive only when persulfate-HSA conjugates were used.[12] However, specific IgE cannot be demonstrated in the sera of all patients with immediate hypersensitivity to persulfates.[1,12]

Skin Challenge/Provocation: Single Open Application Test

At FIOH, prick testing is first used for screening, and substances for open application test are chosen according to the size of the prick test reaction, previous symptoms, and extent of the exposure at work. The test substance is applied with a cotton bud to a 5- × 5-cm area on intact healthy skin on the forearm. We perform two to three applications at 20-minute intervals and take readings 20 minutes after each application. A previously affected skin area can also be tested, but we have little experience with this alternative. The test does not need to be positive, as the skin might have healed before the test. The symptoms of contact urticaria are often aggravated by other skin diseases (e.g., irritant contact dermatitis, atopic hand dermatitis). We avoid testing with recently affected skin or eczematous skin areas, and we do not perform rubbing tests. We usually test only prick test–positive substances in open applications, because we want to see the effect of the intact skin barrier to the wheal reaction. In a skin prick test, the skin barrier is passed intentionally, and vigorous rubbing leads to a broken skin barrier—wheals appear immediately after the barrier is visibly broken (i.e., when the red color of the dermis first appears on the rubbed skin area). If the skin barrier is not intact, as in eczematous skin, any prick test–positive substance (e.g. hay pollen test solution in a hay-allergic patient) causes wheals, and it does not help to assess the clinical relevance of a positive prick test.

As regards concentrations used in open application, we have only a few routine practices, and each patient's tests are planned individually. Persulfates (ammonium and potassium persulfate) are tested at a concentration of 5% in water, and the test often provokes a positive reaction in prick test–positive patients.[12] Chlorhexidine in turn did not induce positive open application tests at the Helsinki University Central Hospital even if a relatively high concentration of 5% was used.[11] The literature contains reports of positive results with a 1% concentration.[22] Organic acid anhydrides, which are used as epoxy hardeners in, for example, the electrical industry, must be diluted in nonaqueous material, because they immediately form corresponding acids in the presence of water. We have used 10% dilutions in petrolatum and obtained some positive results, but often a positive result has required the use of the undiluted hardener used at the workplace.[10]

Conclusions

Contact urticaria resulting from LMW chemicals is relatively rare, but often occurs in patients with a chemical-induced respiratory disease. Some chemicals induce IgE-mediated allergy. At FIOH, prick testing is used as the screening method for chemical-induced occupational diseases. Some chemicals can be tested in water solutions, but HSA-hapten conjugates are preferred at FIOH. Prick tests with HSA conjugates are valuable in the diagnosis of immediate acid anhydride allergy, but other chemicals induce immediate skin reactions so rarely that it is difficult to draw any conclusions about the best diagnostic methods. Commercial, specific IgE determinations are available for only a few LMW chemicals. Open application tests are planned individually.

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15

Agricultural Chemicals

Vincent Cunanan, Christopher J. Dannaker, and Howard I. Maibach

Introduction

Working in the agricultural industry typically requires contact with pesticide chemicals, frequently resulting in prolonged and concentrated exposures.[1] Currently, more than 600 active pesticide ingredients are used, yet adequate toxicologic information is available for only approximately 100.[2] The agricultural industry remains the greatest consumer of pesticide chemicals, and, as such, farmers and field workers represent a high-risk population for suffering from toxic or allergic reactions. Agriculture has consistently had the highest rates and numbers of occupational skin diseases reported.[3]

The acute toxic events related to pesticide exposure and issues of long-term carcinogenicity have been the focus of most toxicologic reports.[4–6] Delayed contact allergy commonly occurs from pesticides. Fungicides are implicated as the causative agent much more than insecticides or herbicides.[7,8] There remains, however, a scarcity of reports relating to pesticide-induced contact urticaria.

An operational definition of "pesticide" includes chemicals used for control of fungi, insects, rodents, or weeds. In California, nearly one-third of reported illnesses and injuries from pesticides are associated with skin complaints.[3] Most of these reactions appear to be due to irritation, but allergic contact dermatitis has also been reported.[9] Contact or systemic urticarial reactions to pesticides are not often cited. The paucity of reports may relate to the transitory nature of an urticarial reaction or the lack of association of the adverse reaction with the pesticide exposure. Routine patch testing detects delayed type hypersensitivity but is an incorrect methodology to evaluate contact urticaria.

Common Trigger Agents of Contact Urticaria

Chlorothalonil (tetrachloroisothalonitrile), a fungicide, is one of few pesticides documented to cause contact urticaria and anaphylactoid symptoms.[10,11] Dannaker and Maibach reported an affected nursery worker who experienced facial erythema with edema, accompanied by nasal congestion and chest tightness. Testing with 0.01% chlorothalonil on intact skin resulted in an anaphylactoid reaction within minutes.

Immediate skin testing of controls was negative and the patient's reaction was assumed to be immunologically based. Subsequent negative patch testing of additional controls further supports this deduction.[12] Review of previous reports of contact dermatitis of the delayed type to chlorothalonil, in retrospect, might suggest concomitant contact urticarial symptomatology.[13–15]

N,N-diethyl-*m*-toluamide (DEET) is the most commonly found active ingredient in insect repellants. Developed by the U.S. Army in the mid-1940s, it was initially tested as a pesticide on farms. Vozmediano et al. reported immunologic contact urticaria in a patient as a result of exposure to a particular insect repellant lotion containing DEET. The patient presented with edema and severe pruritic reactions to the application area. The same study also indicated that the patient did not react to other toluamides, such as *N,N*-diethyl-*p*-toluamide.[16] Negative reactions to the *para* isomer of DEET suggest that chemical structure dictates reactivity. Although DEET is no longer used as a pesticide, it is still of concern to those in the agricultural industry because workers may apply insect repellants to protect themselves in their working environment.

Thiuram is a sulfur-containing ectoparasiticide. It is used to protect seeds and crops from damage caused by animals by acting as a deterrent or by fungal diseases by acting as a fungicide.[17] Spiewak described a patient who developed erythematous skin reactions to seed protectants containing up to 32% thiuram. Biopsy of forearm skin showed infiltration of granulocytes into the dermal papilla. Granulocytes, specifically basophils, are thought to be involved in the mechanism behind contact urticaria. The proposed pathomechanism will be discussed later in this chapter.

Zinc diethyldithiocarbamate (ZDC) is used in the process of rubber manufacture and also as an agricultural fungicide and insecticide. Its presence in rubber has been reported to cause immunologic contact urticaria of the hands.[18] Chemically related thiocarbamates may also be potential causes of contact urticaria but have yet to be reported as such. ZDC and other thiocarbamates are used as insecticides (maneb, carbofuran, carbaryl) and were found in one study to be the most frequent cause of delayed type allergic contact dermatitis among farmers with contact dermatitis.[9] It is noteworthy that this class of fungicides, although reported to cause contact urticaria in rubber, has not yet been reported to cause contact urticaria when exposure occurs as an insecticide.

Miscellaneous Pesticides Inducing Contact Urticaria

Veda et al. published the results of a questionnaire-based study of 3717 inhabitants from a rural Japanese district where potential exposure to pesticides was present. Based on this patient-reported questionnaire, 16% reported urticaria-like dermatoses. Of these patients, 21% reported a history of allergic disorders. Poultry farmers had the highest prevalence of allergic symptoms (62%), closely followed by those engaged in raising flowers and tobacco (58%). Of those with allergic symptoms, 12%–38% associated farm work and possible pesticide exposure as exacerbating factors. This study does not, however, definitively establish a link between pesticide exposures and allergic symptoms.[19]

A recent controlled study by Cellini and Offidani evaluated 426 agricultural workers for skin disorders and found a higher prevalence of acute systemic “intoxication” from pesticides (6.8%). Not evaluated was if some of these reactions might have represented cases of contact urticarial.[20]

Assini et al. may have uncovered additional cases of contact urticaria-like systemic reactions to pesticides.[21] The authors describe symptoms of urticaria/angioedema, asthma, and oculorhinitis. Causative pesticides cited included cynoxanil, mancozeb thiophanate, seccatutto, iodine, and paraquat.

Occupational asthma induced by trialkyltin-type fungicides used in carpet manufacture again suggests that an immunologically mediated immediate hypersensitivity reaction can develop from pesticides.[22] Verified cases of pesticide-induced contact urticaria, however, remain rare.

Other chemical exposures among agricultural workers include building materials, such as cement and petroleum products, animal feed and additives, farm animal-related medicaments, grooming supplies, rubber, and livestock waste products.[23] Numerous potential chemical allergens and irritants are necessarily contacted in the course of a farm laborer’s workday. Pesticide applicators, veterinarians, nursery workers, exterminators, and some food handlers may also have potential exposure to agricultural chemicals.

O’Malley and Mathias identified horticultural specialties among all agricultural job titles, reporting the greatest number of claims for chemical exposures. Claims for adverse reactions attributed to plant and food products were also frequent among agricultural workers. This occupational group is recognized to be exposed to a complex range of chemicals (Table 15.1).[23,24]

Erythema, stinging, pruritus without urticaria (suburticariogenic urticaria), eyelid edema, and respiratory complaints may all be presenting signs of the contact urticaria constellation.[25] Contact urticaria may be an explanation for some poorly categorized reactions to pesticides. In addition to cutaneous contact, urticarial symptoms from respiratory pesticide exposure should be considered.

Our present knowledge of contact urticaria to agricultural chemicals, and pesticides in particular, remains deficient. As testing methodology of potential causes of contact urticaria become standardized, conjoined with improved accuracy of physician diagnosis, reports of pesticide-induced contact urticaria will undoubtedly increase.

TABLE 15.1

Causes of Contact Urticaria among Agricultural Workers [30–32]

Animal Products	
Amniotic fluid	Hair
Blood	Saliva
Veterinary Medicaments and Feed Additives	
Ampicillin	Bacitracin
Cephalosporins	Gentamicin
Neomycin	Nitrofuroximine
Penicillin	Streptomycin
Benzocaine[NI,I]	Capsaicin[NI]
Dimethyl sulfoxide (DMSO)[NI]	Balsam of Peru[NI,I]
Menthol	Cinnamic acid[NI]
Cinnamic aldehyde[NI]	Iodine[NI]
Tincture of Benzoin[NI]	Tocopherol
Preservatives and Disinfectants	
Chlorhexidine	Parabens
Chlorocresol[NI,I]	Sodium hypochlorite
Formaldehyde[NI,I]	Crystal Violet (Gentian Violet)
Miscellaneous	
N,N-diethyl-*m*-toluamide (DEET)	Rubber
Epoxy resin	Sulfur dioxide
Grains	Turpentine[NI]
Grain mites	Wood
Insects	Zinc diethyldithiocarbamate (ZDC)

Note: Immunologically mediated (I), unless otherwise specified as nonimmunologically mediated (NI).

Proposed Pathomechanism

Contact urticaria to agrichemicals may be immunological (allergic) or nonimmunological (irritant). The former is thought to be linked with immunoglobulin E-mediated histamine release from basophils. The latter is thought to be linked with histamine release from basophils via an alternate, nonimmune mechanism.[26] A study by Galassi et al. described increased surface expression of the transmembrane protein CD63 on the basophils of a DEET-sensitive patient after exposure to the chemical [27] CD63 is a membrane-associated protein with four hydrophobic transmembrane domains (tetraspanin). It is believed that tetraspanins are present on secretory lysosomes and exosomes. The study also made the connection that in neutrophils—another type of granulated leukocyte—CD63 may be involved in targeting the serine protease neutrophil elastase to the neutrophil's primary secretory granules.[28] Basophils are thought to also contain a type of elastase in its granules.[29] Thus, research could be conducted to determine if elastase in basophils is also targeted to granules with CD63. If so, it is possible to determine if there is concomitant targeting of histamine with elastase to secretory granules.

Conclusion

Agriculture has high rates of occupational skin diseases reported. Although delayed contact allergy commonly occurs from pesticides, few reports describe pesticide-induced contact urticaria. The knowledge of contact urticaria to agricultural chemicals remains deficient. If testing methodology of potential causes of contact urticaria becomes standardized, conjoined with improved accuracy of physician diagnosis the reports of pesticide-induced contact urticaria will increase. Immediate contact skin reactions from chemicals are nowadays underreported.

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16

Animals and Animal Products as Causes of Contact Urticaria and Protein Contact Dermatitis

Päivikki Susitaival

Introduction

Proteins of animal origin constitute a major group of allergens causing contact urticaria (CoU) and protein contact dermatitis (PCD). CoU can be either immunologic (immunoglobulin E [IgE]-mediated) or nonimmunologic, and refers to a wheal-and-flare reaction appearing usually within 30 minutes of contact with the causative agent. The clinical picture of PCD, although IgE-mediated, is chronic contact eczema, but often there are acute phases of pruritus and wheals within minutes of skin contact with the causative animals or animal products. High-risk occupations include workers in the food industry and catering; livestock farmers (especially dairy farming); veterinarians; animal caretakers in veterinary clinics, zoos, and research facilities; researchers; fishermen; and fish and seafood industry workers. The type of animal-based food consumed and diversity and species of animals including sea life and insects vary greatly in different parts of the world. Potentially any proteins of animal origin can be sensitizing.

The prevalence of CoU/PCD caused by animals or animal-derived materials depends on the exposure of the population or occupational group, but little research has been done on this. On the other hand, there are numerous case reports of different animals and animal products causing single cases or small series of CoU or PCD.[1–3] In Finland, physicians are obliged to report suspected or diagnosed occupational diseases and their causes (Finnish Register of Occupational Diseases).[4] In the Finnish Register, half of occupational CoU/PCD has been caused by animal proteins (Table 16.1), and the cases are mostly PCD, although not separated in the register.[4,5] The animal-related causes of CoU/PCD in the Finnish Register of Occupational Diseases during 1990–2011 are listed in Table 16.1. The most common cause by far has been cow dander in dairy farmers or substitute farm workers, but the incidence has decreased because of fewer dairy farms, increased use of protective gloves, and automated milking methods. Also, other animals, including laboratory animals as well as storage mites, have caused few cases of occupational CoU/PCD. Fish (type not specified) have been the most common causes of occupational CoU/PCD related to animal-derived food items in Finland (Table 16.1).[4]

Animal Allergens

The structure and allergenicity of protein allergens of animal origin have been investigated more intensively during the past decade but mostly in the context of respiratory allergy that often coexists with or precedes skin allergy. Most of mammalian, as well as milk and some insect allergens, are lipocalins, three-dimensional structures, which act as transport proteins, among other functions.[6] These are found in animal dander, saliva, and urine, and are also airborne around animals. It has been hypothesized that mammalian lipocalins exhibit 40%–60% homology across species and are in a way at the border of self and non-self. Thus they are not truly foreign to us (which would induce Th1 immunity) or enough homogenous with us (inducing tolerance), but represent weak immunogenic challenge favoring Th2-response and specific IgE production.[7]

Generally, mammalian allergens are needed in high concentrations to induce sensitization, contrary to, for example, arthropod allergens.[8] Adjuvant-like substances may help in lipocalin-sensitization process

TABLE 16.1

Animal-Related Occupational CoU/PCD in Finland in 1990–2000 and 2001–2011, N (% of all animal related), (Finnish Register of Occupational Diseases, Finnish Institute of Occupational Health) [4]

Cause	1990–2000 N (%)	2001–2011 N	All N (%)
Mammals (dander/hair):			
Cow	780	366	1146 (86)
Swine	12	8	20 (1.5)
Rat	5	14	19 (1.4)
Mice	2	3	5
Fox	3	1	4
Horse	2	1	3
Dog	–	2	2
Rabbit	2	–	2
Guinea pig	1	–	1
Human dander/hair	2	–	2
Food items:			
Fish (not specified)	9	27	36 (2.7)
Egg	8	8	16 (1.2)
Meat (not specified)	6	7	13
Crustaceans	2	5	7
Milk	4	2	6
Poultry/fowl	3	–	3
Insects:			
Storage mites	18	6	24 (1.8)
Spiders	–	2	2
Insects (e.g., flour beetle)	2	–	2
Other animal-related material	6	19	25 (1.9)
All animal related (% of all)	**867 (47%)**	**471 (51%)**	**1338 (48%)**
All CoU/PCD	1840	919	2759

Note: CoU, contact urticaria; PCD, protein contact dermatitis.

(pollution, pollens, endotoxins, lipid-binding).[7] The effect of exposure level seems to be bell-shaped for some animal allergens (cat, dog, rat, house-dust mite), intermediate levels being more allergenic and higher levels inducing tolerance.[9–12] In general, the cross-reactivity of allergens from different mammalian species is not believed to be strong, but there are exceptions (e.g., Can f 4 protein in dog dander and 23-kDa protein in cow dander).[13]

Contact allergy to seafood has been studied and documented much less than asthma from seafood. Seafood allergens are mainly high-molecular-weight proteins from shellfish or bony fish. The main bony fish allergen is parvalbumin, fish allergens being mostly different from shellfish allergens. Shellfish include crustaceans—subspecies of *Arthropoda* (e.g., crabs, crayfish, lobsters, prawns) and *Mollusca* (e.g., oysters, mussels, scallops, clams, abalone, squid). Crustaceans are considered to cause the strongest allergic reactions among seafood. The major shellfish allergen and one responsible for cross-reactivity between species (crustaceans, molluscs, dust mites, and other insects) is tropomyosin, but other allergens may play a role such as arginine kinase and myosin light chain.[14–16] Clinical cross-reactivity is often observed among crustaceans and between crustaceans and molluscs (e.g., squid, scallops).[17–20] Some of the allergens are heat-stable (e.g., shrimp tropomyosin), thus preserving their allergenicity after cooking.[21–24] Skin test reactions have been stronger to raw than cooked

fish.[22,25] Fish and shellfish allergens can be found aerosolized in facilities where they are processed, causing airborne CoU.[16,20,24,26,27]

Animals

Data on the prevalence of live animals causing CoU/PCD are scarce. In a study of 1353 California veterinarians, 13% complained of itchy skin rashes occurring within minutes of handling certain animal species.[28] According to the same data, it seems that animal proteins differ in their capacity to cause allergic symptoms, some causing predominantly respiratory symptoms (e.g., cat and horse), but some causing often or mainly skin symptoms (e.g., dog and cow; Figure 16.1).[29]

Some studies have surveyed skin diseases and allergies to animals in veterinarians or farmers.[28,30–32] Most epidemiological studies on immediate allergy from animal contact have been conducted among those working with laboratory animals, and the main interest has been in respiratory symptoms.[33–38] Allergic symptoms to laboratory animals have been reported by 25%–30% of the exposed workers, [37] and the risk of sensitization to animals has been associated with higher exposure levels.[33,39,40] Also, history of atopy, any positive skin prick tests (SPT), allergy to cats or dogs, smoking, and preemployment total IgE >100 kU/L have been identified as risk factors for work-related animal allergy.[31,34,38–41] SPTs to laboratory animals have been positive in 15% to 21% of people who work with animals in laboratories and to cow in 5% to 14% of some surveyed farmer populations.[33–35,38,42–44]

Laboratory animals (rats, mice, guinea pigs, rabbits, hamsters, cats, dogs, frogs) have been reported to cause rashes and CoU.[33,35–38,45–48] Rats and mice have been reported to cause CoU more often than other animals, probably because of their more abundant use. In a study of laboratory animal workers, chamber challenge tests (handling live animals) found equal amounts of positive skin and respiratory reactions to rats/mouse in those with positive SPTs.[38] Rat/mouse exposure has also been reported to cause severe exacerbation of atopic eczema in those allergic to them.[49] Laboratory animal allergy and CoU seem to be more common in people carrying out experiments with animals than in those tending them, possibly because the former involves more direct handling of the animals, their secretions, and internal organs.[37,46] Symptoms are

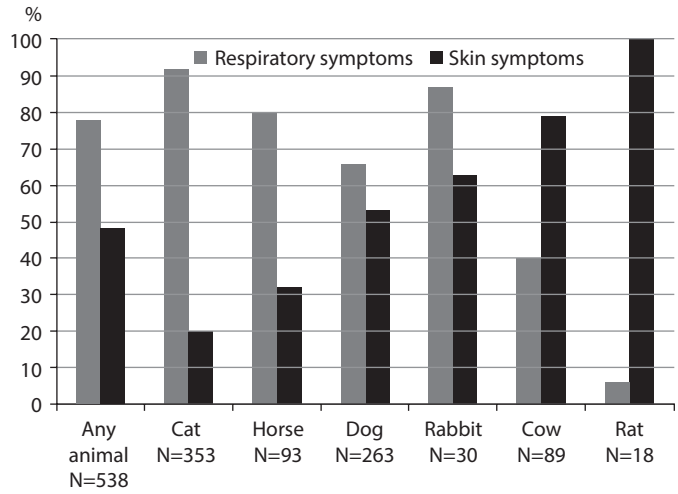

FIGURE 16.1 Skin and respiratory symptoms from common animals in California veterinarians, N = 1353.[29] N is the number of veterinarians reporting respiratory and/or skin symptoms from handling animals. The columns represent the percentage of those reporting the respective symptoms.

often reported on scratched skin, and especially from skin contact with rat/mouse tails and urine.[33,36,39] Up to one-third of those handling rats may get sensitized, and multiple sensitization to different laboratory animals is common.[33,35,36] Handling male rats has been reported to increase the risk of allergy because of higher excretion of urinary proteins.[50] Also, male cats produce more allergens in their excretions; castration reduces the production.[51] Rats seem to cause more severe CoU reactions than mice.[36] Other laboratory animals, for example, guinea pigs, rabbits, and cats, may cause more respiratory symptoms than skin reactions.[29,36,37] Personal protective equipment is often effective in controlling CoU symptoms from laboratory animals.[36]

CoU/PCD or immediate rash from handling cows and/or allergy to cow dander has been reported in both farmers and veterinary surgeons.[28,32,52–61] Immediate skin reactions have been reported by veterinarians also from handling many other animal species, mostly cats and dogs.[28,31,62] Examples of other mammalian species reported to have caused allergic CoU/PCD on contact are giraffe, reindeer, horse, ferret, roe deer, and goat.[43,54,63–66]

The animal organs or fluids, which have been reported to have caused CoU/PCD mostly in veterinary surgeons, their staff, and slaughterhouse workers, include pork and pig gut, bovine and pig blood, bovine amniotic fluid and placenta, cow, horse, dog and cat saliva, dog seminal fluid, and mouse liver.[56,67–79] Contact urticaria from cow's milk is well-known in pediatric allergology, but also dog and mare milk and even human milk have been reported causing CoU/PCD.[80–82]

Insects (cockroaches, locusts, flour beetles, caterpillars, spiders, and storage mites) have also been reported to cause CoU/PCD.[4,83–90] Live fish bait is a common source of allergies.[91–94] PCD/CoU has been reported from several insects and larvae used for fish bait or fish food.[95–99] The common fish parasite (nematode) *Anisakis simplex* has also been reported to cause CoU/PCD, although it more commonly causes bowel symptoms in those eating the fish.[100–102]

Animal-Derived Food Items

In a recent Danish study of 254 cases of occupational food-related hand dermatoses, the most common positive SPT reactions were to fish and shellfish, cod being the most frequent.[3] In the same study, allergy to poultry was more common than to other meats. Most of the positive meat and fish SPT reactions were to fresh and raw foods (prick-prick) rather than commercial extracts.[3] The prevalence of occupational CoU/PCD in seafood-processing workers has been estimated to be somewhere between 3% and 11%, but controlled population studies are lacking.[27] In a study of seafood processing workers, 36% had positive SPTs to at least one seafood allergen, with the most common being crustaceans, but only 6% had symptoms related to work.[103]

There are numerous case reports of animal-derived food materials, from shellfish and fish to meats, other organs, eggs, and milk products, causing CoU/PCD, but hardly any epidemiological studies exist.[1,2] The growing popularity of consuming a variety of seafood products has increased reports of skin reactions among consumers as well as processors of seafood. Shellfish allergies have been reviewed thoroughly in two articles.[15,27] Adverse reactions to seafood can also be caused by contaminants (e.g., parasites, added substances), but are often mediated by the immune system.

Many types of both salt and freshwater fish and shellfish have been reported to cause CoU or PCD in cooks and seafood processors, many of the cases being allergic to several types of shellfish and also bony fish.[25,104–115] Allergy to fish seems to be less common than allergy to shellfish. In many cases, the seafood causing CoU/PCD is well-tolerated as food, but respiratory symptoms often coexist.[22,24,115–118] CoU from fish has also been reported in small children, mostly without systemic symptoms.[22,116, 117] In some children, open skin tests were also positive with cooked fish.[22] Several children got urticaria without other symptoms when exposed to fish aerosols.[116]

CoU/PCD has been also reported in food industry, cooks, and caterers from beef, pork, lamb, horse, roe deer, venison meats, and chicken, with pork being the most common meat reported.[65,104,109,119–125] Also ox, lamb, and calf liver; ox, horse, pig, and lamb blood and dairy products, such as milk and cheese, have been reported causing occupational CoU/PCD.[104,119,122,126–129]

Other Consumer Products

Animal-derived proteins can be found also in other consumer products. Collagens or elastins from bovine and recently more commonly fish origin are used in cosmetics. Bovine collagen and fish elastin in cosmetics have both been reported causing CoU.[130,131]

Non-Immunologic CoU

Caterpillars and occasionally moths may have irritating hairs, spines, venoms, and toxins that may cause non-immunologic urticaria.[132] There are several reports of a southern European pine processionary caterpillar (*Thaumetopoea pityocampa*) causing small epidemics of urticaria reactions also via airborne contamination. [133–135] There is controversy about the mechanism of these reactions, which may also be immunological.[87,136,137] Most species cause mild and self-limiting reactions but occasionally reactions can be severe. Treatment in most cases is symptomatic with prompt removal of the offending hairs.[132]

Diagnosis of Immediate Allergy to Animals or Animal Products

Farmers, veterinarians, and others working with animals may have handled the animals for years before developing skin symptoms. CoU or PCD from animal proteins is often accompanied by respiratory symptoms, which may precede skin symptoms by years.[80,102,138–140] Diagnosis of CoU/PCD should be based on patient history and skin tests: SPTs, specific IgE in blood, and open provocation tests (e.g., rub test) when needed. Skin tests should include possible allergens according to the patient history. If blood tests and SPTs both with commercial series and natural animal materials are negative, the next step would be patch tests with the same materials both for immediate (30 minutes) and delayed (48 and 96 hour) reactions. For allergy to uncommon animal allergens, or other substances with no commercial test materials (such as animal fluids, organs), the diagnostic skin tests can be made with patient-supplied materials (e.g., fresh animal dander/hair). In such cases, attention should be paid to contagious diseases possibly present in fresh materials. In those instances also in vitro, in-house methods, such as enzyme-linked immunosorbent assay or immunospot, can be used to detect immediate allergy to the suspected material.[141]

In case the necessary skin tests cannot be performed or do not reveal the cause, patient history and the effect of skin protection (and provocation) from suspected aggravating factors should help to reach a diagnosis and identify necessary preventive and protective measures.

Conclusions

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 immunologic and nonimmunologic immediate skin reactions. Most common animal-related immediate skin reactions are CoU or PCD from skin contact with domestic or laboratory animals and food items. Contact reactions from food items can also be caused by contaminants, parasites, or added substances. 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.

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17

Contact Urticaria and Eczema from Dental Products

T. Rustemeyer

Introduction

This chapter describes different aspects of occupational contact dermatitis and urticaria from dental products.

The first reports on eczema and urticaria from dental products have been published many decades ago. In this regard, Hensten-Pettersen provided an interesting historical overview.[1] In the first reports of occupationally related dermatoses in dental personnel, local anesthetics, disinfectants, including eugenol, and hand-washing have been identified as the principal causative agents. Several decades later, in the 1950s, methacrylates were introduced in the dental materials market. Within few years, in 1954, Fisher and Woodside [2] described the first cases of occupational contact sensitization to methacrylate monomers in dental personnel. Since then, the number of case reports and studies on occupational contact dermatitis and urticaria from dental products has increased rapidly and numerous chemicals have been identified as causative agents. The rapid developments of new dental products and the subsequent introduction of new chemicals into these products imply a constant update of newly identified allergens and irritants of this field. This chapter will provide an up-to-date overview and give advice on allergological testing.

Incidences

In the last decades of the 20th century, alarming figures of fast-rising incidences of occupational skin diseases in dental personnel were noted.[3–5] The most affected occupational profession was dental technicians. Incidences of skin diseases of about 40% have been reported.[6–9] Based on a Danish cross-sectional questionnaire study among dental technicians, the 1-year prevalence of skin problems on the hands was found to be 43%.[7,10] For dentists, a questionnaire study described a 1-year prevalence of occupationally related skin reactions of 21.4%.[11]

Allergic Contact Dermatitis

As mentioned previously, the incidences of allergic contact dermatitis (ACD) have increased within the past several decades.[4,12] This has resulted in long-lasting sick leaves of affected employees and a dramatic rise of medical care and rehabilitation costs.[3] In dental occupations, the frequency of ACD has been estimated to be about 1%.[8] A more detailed analysis has identified dentists and dental technicians to be most affected. Among dentists, about 4% were found to have serious occupationally relevant allergic reactions.[11] Most common were sensitizations to (di)methacrylates and latex/rubber gloves (each about 2%). Among dental technicians, in general, a similar frequency is considered for (meth)acrylate sensitization. However, within the group of dental technicians with suspected occupational skin disease, ACD was diagnosed in up to 64%.[4,12]

The most allergenic working materials in dental professions were plastics. Among the plastics, especially methacrylates, are the major occupational contact sensitizers.[12–14] But, in the past few years, driven by innovative techniques, more and more multifunctional acrylates and composite resins, including, for example, epoxy resins, have caused occupational ACD in dental personnel (Table 17.1 gives an overview).

TABLE 17.1

Frequent Allergens Causing Contact Dermatitis in Dental Personnel

Plastic monomers (various (meth)acrylates and epoxy resins)
Polymerization initiators
Polymerization inhibitors
Polymerization activators
Disinfectants
Glove ingredients
Metals
Soldering materials

Methacrylates

Fisher and Woodside [2] were the first who described methacrylate sensitization in dental personnel. A few years later, Calnan and Stevenson could identify the methacrylate compound methyl methacrylate as the causing contact allergen.[15] Since then, occupational contact sensitizations to modifications of the (meth)acrylic acid molecule have been published very frequently. In particular, the working group of Lasse Kanerva from Helsinki had a significant contribution to this.[16–19] Still, contact sensitization to methacrylates is the most frequent cause of occupational contact sensitization in dental professions. In particular, dental technicians and dentists are at risk of getting sensitized.[12,20,21] This can be explained by their frequent contacts to chemically highly reactive (meth)acrylate monomers while working with these plastics. The (meth)acrylate monomers are highly volatile. Hence, they can cause not only ACD at the direct skin contact sites, but also airborne allergic contact dermatitis.[22] In dentistry, not only methacrylates are used but also a diversity of acrylate monomers for example in bondings. Hence, sensitizations to both methacrylate and acrylates occurs frequently.[23] In contrast, dental technicians are primarily exposed to methacrylates and, as a consequence, dental technicians are almost exclusively sensitized by methacrylates.[12,24] For dental technicians, the major sensitizers are 2-hydroxyethyl methacrylate (2-HEMA), ethylene glycol dimethacrylate, 2-hydroxypropyl methacrylate, ethyl methacrylate, and methyl methacrylate. Together, these compounds cause up to 50% of all cases of ACD in dental technicians.[12,14,17,23,24] Interestingly, the methacrylate congeners often show multiple positive patch test reactions in a patient. Further immunological analysis has revealed that this is rather a consequence of cross-reactivity than of concomitant sensitizations.[12,16,18,25] The need for constantly improving dental materials with better chemical properties and new application areas is high. Hence, the number of chemical derivatives of the (meth)acrylate molecule grows rapidly. A common property of these new substances is their strong chemical reactivity. Therefore, the risk of introducing new potent allergens in dental professions is high.[26,27] Moreover, sensitization to these new chemical derivatives might be missed by testing traditional (meth)acrylate series.[28] Also the polymerization techniques have been changed. Formerly, heat and cold polymerization techniques have been used. Among them, the content of chemically reactive rest monomers was, in general, higher in cold (meaning polymerization occurs at room temperature) products. Newer polymerization methods, for example, ultraviolet light or self-curing techniques, make use of highly reactive methacrylate congeners. At the beginning of these inventions were molecules such as 2-HEMA, 2-hydroxypropyl methacrylate, and/or ethylene glycol dimethacrylate were introduced into dental materials.[12,29] These exact molecules were later found to be strong contact sensitizers.[24,30–32] In particular, self-curing and ultraviolet light polymerization products have relatively high concentrations of unpolymerized rest monomers in the fresh products.[33,34] Because the freshly cured dental products are cold, they can directly be handled by technicians or dentists. This unprotected skin contact might be the major reason of their increased risk of developing occupational ACD to these methacrylates; in addition, skin areas exposed to polish- and grind-dust, allergic eczematous reactions can occur. Because methacrylates are little volatile molecules, vapors of methacrylates can also cause airborne contact dermatitis.[20,35,36] Methacrylate-induced occupational asthmatic reactions have also been reported.[37,38]

TABLE 17.2

Overview of Additives of (Meth)acrylate Plastics of Dental Materials Causing Allergic Contact Dermatitis

Hydroquinone
Hydroquinone monomethylether
Camphorquinone
Dimethyltoluidine
Triethanolamine
Benzoyl peroxide
Chinacridone B
(Di)amines, various
Benzoates, various

Additives of Dental Plastics

Formulations of plastics contain the reactive polymeric structure forming monomers, sometimes preformed oligomers of polymers, and always additives for regulation of the polymerization process. For (meth)acrylate plastics, these additives are occasionally also occupational relevant contact allergens. In particular, the initiators, accelerators, catalysts, and inhibitors have been identified as such (Table 17.2).

Plastics Other Than (Meth)acrylates

Next to occupational ACD to (meth)acrylates, various other plastic materials have been identified as sources of occupational ACD in dental professions. Although their clinical relevance is still much lower, newly invented plastics are based on composite techniques and, thus, introduce various epoxy and bisphenol-derivatives into dental products. As a consequence, allergic reactions to different epoxy resins, acrylated epoxides and epoxilated acrylates and bisphenol A, such as 2,2-bis(4-[2-hydroxy-3-methacryloxypropoxy]phenyl)-propane, have been documented.[12,39–45]

Metals

Various alloys with noble and un-noble metals are used in dental restorative and orthodontic devices. Because of intense skin contacts to these materials, occupational ACD can occur. Contact sensitization to nickel, palladium, cobalt, chromium, and gold has been reported in dental technicians.[12,20,42,46,47] In addition, in dentists, mercury, as part of the amalgam alloy, is a well-known contact allergen.[48]

Latex Gloves

In the past few decades, sensitization to natural rubber latex proteins has increased rapidly.[49–53] In particular, powdering of natural rubber latex gloves has been shown to increase the risk of sensitization to the latex protein.[54–57] Also, protein-rich gloves have a much higher sensitization risk than gloves with low latex protein content.[58,59] Other sources of contact allergens of glove materials can be preservatives used in gloves [60,61] and polymerization accelerators such as carbamate, thiuram, and mercapto compounds.

Occupational Irritant Contact Dermatitis

Whereas occupational contact sensitizations have been identified as rising threads in dental professions, the risk of developing irritant contact dermatitis (ICD) seems to be better controlled.[62] Thirty to 25 years ago, about half of the dental personnel reported in questionnaires to suffer from occupational hand diseases, the

TABLE 17.3

Common Contact Irritants in Dental Occupations

Wet work
Detergents
Occlusion under gloves
Disinfectants
Plasters
Physical irritation
Grinding
Polish dusts of plasters, metals, ceramics, and plastics

majority of which was probably ICD.[63] The major causing contacts were skin hygienic measures, such as hand-washing and contacts to soap and detergents, contacts to skin disinfectants, or wearing occlusive skin protection gloves.

The most relevant risk factor for the development of ICD was frequent contact to water and wet work.[8,12,64] This can be aggravated by seasonal influences during the cold winter months.[11] Interestingly, plastic monomers, in particular methacrylates, do also have some skin irritative potencies.[64,65] In dentists, latex gloves have caused ICD in 30.1%, as revealed in a questionnaire study.[11] Table 17.3 gives an overview on occupationally relevant contact irritants in dental professions.

Clinical Pictures

The major skin problems in dental personnel are eczematous skin reactions. They are mainly located at direct contact sites, but, at remote sites exposed to aerosols, dust, or vapor, eczema can occur. Occupational ACD frequently starts off at the direct contact sites. Because of the tiny devices that are handled in dentistry with the fingertips, that is where the first symptoms of ACD especially occur. Thus, the principal sites of ACD are the first three fingers.[12,66] But later, the affected sites expand and the lateral and dorsal aspects of the fingers can be involved.[12] In later phases, maybe because of allergen spreading, ACD can occur at distinct sites.[67] Also occupational conjunctivitis associated with methacrylate contact sensitization can occur.[64]

ICD affects mainly the lateral aspects and the dorsum of fingers and the back of both hands. Skin symptoms develop in general slowly. They start off with dry skin, redness, or rash. In later phases, itching and fissures can occur and result in the clinical appearance of chronic ICD.

In case of IgE-mediated sensitization to latex proteins, rapidly developing urticaria-like itchy lesions can occur. They are first located underneath latex gloves, and later spreading to aerosol-exposed skin regions, such as the face and forearms. Clinically relevant can be the change of the clinical appearance, whereas in cases of latex sensitization, the first reactions are urticaria by repeated contacts eczematous reactions occur.[68] But also other allergens can cause occupational urticaria in dental professions. An overview is given in Table 17.4.

TABLE 17.4

Frequent Allergens Causing Contact Urticaria in Dental Personnel

Glove ingredients (latex proteins)
Disinfectants
Soldering materials
Polymerization initiators
Polymerization activators
Plastic monomers (methacrylates)

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18

Contact Urticaria Syndrome Induced by Drugs

Margarida Gonçalo

Introduction

Drugs, as small reactive chemicals, can induce both immunologic and nonimmunologic contact urticaria (CoU) within minutes to 1 hour after cutaneous or mucosae exposure.

All manifestations of contact urticaria syndrome have been induced by drugs: urticaria localized to the area of contact with the offending drug (stage 1), generalized urticaria (stage 2), urticaria with associated systemic symptoms (stage 3), and anaphylaxis (stage 4).[1,2] Moreover, other immediate reactions, such as protein contact type dermatitis and worsening of hand eczema from immediate reactions in an occupational setting have been described with drugs.[3,4] In some cases, both immediate and delayed hypersensitivity mechanisms may be involved, as in a case induced by chlorocresol in the excipient of corticosteroid creams and in occupational airborne disinfectants [5] or as in a case induced by lidocaine.[6]

Topical drugs and dressings, both through their active principles and excipients, can cause contact urticaria when applied on intact skin or, more often, on previously damaged skin.[7,8] Exposure through the semimucosae of the lips or through the conjunctiva, oral, vaginal, or urethral mucosa is more frequently associated with immediate symptoms,[9–11] probably because of the more easy access of the offending drug to dermal mast cells. When exposure occurs through the mucosa, as well as though skin wounds, onset of the urticaria is usually faster compared with application on normal skin, and the reactions are more frequently associated with systemic symptoms, including anaphylaxis, particularly in immunologic cases, mediated by drug-specific immunoglobulin E (IgE).[12,13]

Drugs intended for systemic use (oral or intravenous) can also cause immediate cutaneous contact symptoms upon direct contact or airborne exposure, mainly in an occupational setting.[14–17] Immediate symptoms have also been described with oral drugs, initiated during their transient persistence in the mouth before swallowing; local symptoms of edema of the lips and oral and oropharyngeal mucosae can initiate before progression to a systemic urticaria. Similar reactions can also occur after consort exposure to the oral drug.[18]

Virtually any drug can induce an immediate reaction, but most cases have been described with beta-lactam antibiotics, topical anesthetics, and, more recently with antiseptics such as chlorhexidine (Table 18.1). Published reports of contact urticaria syndrome induced by other drugs represent relatively exceptional cases.

Mechanisms of Immediate Reactions to Drugs

As with other substances causing immediate symptoms, drugs can cause both immune-mediated and, more frequently, nonimmune-mediated contact urticaria syndrome. Drugs intended for skin application are usually small, reactive chemicals that penetrate the epidermis and eventually reach the dermis where they can activate the mechanisms responsible for the immediate symptoms. It is also possible that, as in allergic contact dermatitis, drugs as other sensitizing chemicals activate innate response pathways in keratinocytes and epidermal/dermal dendritic cells with cytokine and chemokine secretion.[19] These pathways, involved in the initiation of the sensitizing phase and the afferent effector phase of allergic contact dermatitis, may also enhance immediate contact reactions to drugs.

TABLE 18.1

Main Drugs Causing Contact Urticaria Syndrome

Antibiotics	**Local anesthetics**
Penicillin,* mezlocillin*	Benzocaine
Ampicillin,* amoxicillin*	Lidocaine/tetracaine peel
Cephalosporins*	Lidocaine and/or prilocaine (EMLA®)
Rifampicin, rifamycin	Mepivacaine, bupivacaine
Chloramphenicol	**Miscellaneous**
Gentamycin, neomycin	Capsaicin
Streptomycin*	Nicotinic acid esters
Bacitracin/Polysporin	Chloroform
Levofloxacin	Dimethylsulfoxide
Sodium fusidate	Tar extracts
Virginiamycin	Tincture of benzoin
Iodochlorhydroxyquin	Dinitrochlorobenzene
Antiseptics, preservatives	Diphenylcyclopropenone
Chlorhexidine*	Pilocarpine
Povidone iodine	Cyclopentolate hydrochloride
Formaldehyde*	Cisplatin*
Phenoxyethanol	Corticosteroids
Benzoic acid	Mechlorethamine
Sorbic acid	Pentamidine isethionate*
Chlorocresol*	Carboxymethylcellulose sodium
NSAIDs	Phenothiazines
Acetylsalicylic acid	Chlorpromazine
Diclofenac	Levopromazine*
Ketoprofen	Promethazine
Etofenamate	Aescin
Pyrazolones	Benzoyl peroxide
Metamizol*	Donepezil*
Aminophenazone	Guanidinium salts*
Propyphenazone	Lindane
	Uranium salts*

*Drug specific IgE has been documented in CoU from these chemicals.

Drugs, as chemicals with pharmacologic activity, may interfere with cutaneous mast cells and induce nonspecific degranulation or may interfere with other neurologic or vascular mediators (prostaglandins/leukotrienes, PAF, substance P, or other neuropeptides) and induce vasodilation, increased vascular permeability, dermal edema, and pruritus. The mechanisms that cause nonimmune-mediated immediate contact reactions induced by drugs have not been studied precisely for most of the drugs.

Similarly to chronic or acute urticaria induced by oral nonsteroidal anti-inflammatory drugs (NSAIDs) where there is an imbalance between prostaglandin 2 and leukotrienes, or by opioids that induce mast cell degranulation, we may suspect that some cases induced by topical exposure to these drugs may depend also on a non–IgE-dependent mechanism.[1,20] This may explain immediate reactions induced by etofenamate, diclofenac, ketoprofen, acetylsalicylic acid, and other topical NSAIDs where specific IgE was not found.[1,21–23] Local anesthetics are also supposed to induce mainly non–IgE-mediated reactions.[24] Benzoic acid and sorbic acid as a preservative in some topical preparations are claimed to induce prostaglandin D2 release, responsible for immediate complaints, and capsaicin can induce immediate symptoms by enhancing the release of substance P from nerve endings.[1] Also, for rifamycin, a non-histamine-dependent mechanism has been claimed [7] and this can also explain an occupational case induced by exposure to the *Cannabis* plant in a forensic institution, where more than one worker had immediate symptoms on exposure.[25]

Drugs can also be specifically recognized by IgE on mast cells, basophils, and, eventually, also by IgE in Langerhans cells and other skin dendritic cells. Drugs very probably combine with proteins (human serum albumin or other serum or skin proteins) previous to IgE recognition.

Drug-specific IgE has been identified in many cases of contact urticaria syndrome induced by beta-lactam antibiotics,[14,18,26,27] bacitracin,[28] chlorhexidine,[9,17,29,30] some topical anesthetics,[31] some NSAIDs,[32] and formaldehyde.[15]

IgE-dependent CoU induced by drugs, as in IgE-mediated CoU induced by other agents, is usually more severe than nonimmunologic reactions, extends beyond the application area, and is more often associated with facial angioedema, oropharyngeal edema, conjunctivitis, and systemic symptoms such as cough, bronchospasm, dyspnea, abdominal cramps, and, in some cases, anaphylaxis with bradycardia and hypotension.[1]

Immediate Skin Reactions from Topical Drugs

Many topical drugs, when used on normal skin or previously damaged skin, have been responsible for contact urticaria syndrome, caused both by the active ingredient or a component of the vehicle.

Some examples of the latter case are induced by preservatives (chlorocresol in topical corticosteroids,[5] benzoic acid and sorbic acid in several topical drugs, 2-phenpoxyethanol in creams and vaccines),[33] by perfumes (cinnamic aldehyde, Balsam of Peru), by guar gum as a constituent of lidocaine gel,[34] by polyethylene glycols or macrogols, present in topical corticosteroids and many other topical or systemic drugs,[35] or by carboxymethylcellulose found in a hydrocolloid dressing.[36]

Some of these immediate reactions manifest only as transient erythema and tingling or pruritus without wheals, resolve in less than 30–60 minutes and therefore they are not usually the object of publications or more detailed study. Most represent a nonimmunological reaction induced by perfumes or preservatives. For instance, in some individuals, antifungal creams containing benzoic acid at higher concentrations (up to 4%) can induce a transient burning or tingling erythema, particularly when used in the groin (personal experience). A fluorine toothpaste containing sodium benzoate was reported to induce transient perioral contact urticaria.[37] Sorbic acid, contained in Thrombocid® ointment, was suspected as the cause of contact urticaria in a patient who developed urticarial lesions on the first application of the ointment on his legs. Thrombocid® ointment induced an immediate patch test reaction in the patient and, also, in three controls studied.[38]

Local anesthetics applied on normal skin, such as benzocaine cream,[39] but mostly creams with lidocaine, have been described as a cause of CoU. Contrasting with its low capacity to induce delayed hypersensitivity reactions,[40] lidocaine has caused contact urticaria in a hemorrhoidal cream [6] and when used in a combination of lidocaine and tetracaine (7% each) [24] or in EMLA® cream, an eutectic mixture of lidocaine and prilocaine at 2.5% each.[41]

Many cases of contact dermatitis, either immediate irritant contact dermatitis with bullae [42] or delayed allergic contact dermatitis, have been published resulting from lidocaine and/or prilocaine in EMLA cream,[43] but, although referred as a frequent side effect, a single case of CoU from EMLA cream with proven immediate hypersensitivity from lidocaine was found in the literature. It refers to a patient who used the cream under occlusion for removal of a nevus and suffered a localized edematous and pruritic but transient (2-hour) reaction, further confirmed by a positive patch test at 20 minutes to lidocaine, with negative patch and prick tests to all the other local anesthetics tested.[41]

In a case in which lidocaine at 7% was applied to the whole face before dermatological laser treatment, immediate erythema and wheals-associated edema of the lips developed, but angioedema did not progress to the tongue and no systemic symptoms were observed.[24]

The caines of amide group, namely lidocaine, mepivacaine, and bupivacaine used more frequently in local anesthesia for cutaneous or dental surgery or for epidural anesthesia also cause localized or more generalized urticaria, although this is also a rare adverse event.[44,45] Moreover, it is not a real contact urticaria syndrome, because the drug is injected into the skin. IgE is seldom involved in CoU to local anesthetics, but it may be advised to study these patients because cross-reactivity usually does not extend to the full group of amides and it is important to find a safe alternative drug for local anesthesia.[45]

Topical antibiotics are often used on skin with barrier defects or even in open wounds or ulcers. This may favor sensitization and/or the effector reaction due to an easier access of the drug to the dermis. Also, in infected or wounded skin, a previous activation of the innate immune system by pathogens and their pathogen-associated molecular patterns, by inflammatory molecules and by danger-associated molecular patterns, may facilitate a specific immune response that will enhance the urticarial reaction.

CoU to topical antibiotics is not frequent, although a few cases have been described and they can be severe. Except for a case with CoU and severe systemic symptoms described for sodium fusidate applied on skin with abrasions in a 16-year-old boy,[8] most published cases of CoU or more severe immediate reactions from topical antibiotics are rather old, like the ones induced by bacitracin and polymyxin B,[28] rifamycin,[7,46] chloramphenicol, gentamycin, streptomycin, neomycin,[39] and virginiamycin.[1]

Topical antiseptics, such as povidone iodine [47,48] and chlorhexidine,[29,49] are particularly involved in immediate symptoms when applied in surgical or other open wounds or in the mucosae.

Immediate reactions have also been described with topical antihistamines such as promethazine, topical NSAIDs such as acetylsalicylic, metamizol, and other pyrazolone compounds,[1,16,50] diclofenac,[23] etofenamate [21] and ketoprofen,[22] and other drugs such as aescin,[51] mostly in isolated cases and dating back to the 1990s. For a more extensive list, see Table 18.1.

Contact Urticaria and Anaphylaxis from Mucosal Exposure to Drugs

Exposure through the mucosae is more often associated with immediate and sometimes severe symptoms, even upon a very discrete exposure to the offending drug. This was shown in the case of a young female, with a previous urticaria from amoxicillin, who developed lip and oropharyngeal edema after kissing her boyfriend who had ingested the drug not long before.[18]

The conjunctiva has been the exposure site for localized or generalized urticaria or even anaphylaxis. A recent case of stage 3 immunologic contact urticaria syndrome developed after the use of eye drops containing levofloxacin, which immediately induced conjunctival hyperemia, sneezing and rhinorrhea, facial edema, and generalized urticaria with dyspnea. It was later confirmed with a positive prick test with the eye drops, but the pure antibiotic was not tested.[11] Because systemic fluoroquinolones, including levofloxacin, can cause IgE-mediated adverse reactions,[52] an IgE-mediated reaction to levofloxacin might explain the exuberance of symptoms in this case after such a small exposure area.

Eye drops containing the mydriatic cyclopentolate hydrochloride applied in a patient before cataract surgery induced a severe immediate localized reaction. Skin tests were positive with the eye drops but the culprit ingredient could not be identified.[53]

The oral mucosae has been the exposure site for cases of CoU induced by anesthetic gels, due both to lidocaine and guar gum in the excipient,[34] to chlorhexidine used in dental endodontic procedures,[49] in a mouth wash,[10] or in a toothpaste [17] and, also, from formaldehyde used in dental procedures.[15]

Exposure of the vaginal mucosae to the chlorhexidine [30] or povidone iodine [48] during gynecological procedures has been associated with generalized urticaria. Chlorhexidine has also been involved in CoU after the insertion of central catheters or intraurethral catheters soaked in this antiseptic [9,12] namely in Instillagel®, which contains both chlorhexidine and lidocaine.[9]

Perioperative urticaria or anaphylaxis can also be a presentation of CoU, mainly by contact with latex, but also by the antiseptics chlorhexidine and povidone iodine,[47] antibiotics rifamycin and bacitracin used for the disinfection of the surgical wound,[30] or by ethylene oxide used for the disinfection of material (masks) to be put in contact with the skin of the patient.[30]

Contact Urticaria to Drugs in Occupational Settings

Occupational CoU from drugs occurs mainly in health care professionals, particularly in nurses, who have to prepare injectable drugs, and nurses and other caregivers who have to smash and handle tablets to give patients. Frequent chronic hand eczema in nurses, from irritation, delayed allergy, or atopic dermatitis, consequently with a disturbed skin barrier, may contribute to an enhanced drug penetration through the epidermis and an easier access to dermal mast cells.

CoU from drugs is rare in the pharmaceutical industry because of the production in closed circuits, and in veterinarians, who have mainly CoU from animals fluids or their fur.[2]

In a recent survey in a Korean hospital, stage 1 CoU and stage 2 CoU were diagnosed, respectively in 8.9% and 0.7% of more than 400 nurses that responded a questionnaire and were observed in consultation.[26]

Most nurses with occupational CoU complain with transient edema or swelling of the hands with pruritus or paresthesia, but lesions on the face, neck, and forearms with generalization of urticaria or systemic symptoms (cough, dyspnea, asthma, rhinorrhea, or abdominal cramps) can also occur, particularly upon airborne exposure to volatile substances or powders of the drug.[14,17] Anaphylaxis has also been described in association with CoU, probably because of airborne exposure and inhalation.[54]

Continuous hand exposure to drugs with immediate symptoms can also induce immediate vesicular reactions, such as protein contact dermatitis, and significantly contribute to the aggravation or maintenance of chronic hand eczema in this occupational setting.[27]

Main drugs responsible for occupational CoU are the antibiotics and, particularly, penicillin, ampicillin, amoxicillin, and the cephalosporins.

Among cephalosporins, many cases of immune-mediated CoU from cefotiam were reported in the 1980s and 1990s in Japan and other Asian countries,[27] although occasional cases have still been studied in recent years.[55] All cases were reported in nurses who developed CoU and systemic symptoms from cefotiam, with some of them becoming sensitized also to other cephalosporins and piperacillin.[26] Most were young female nurses, highly exposed to antibiotics with no protection, some also suffering from hand dermatitis. The high number of CoU cases to cefotiam could be explained by the fact that, during preparation, the powder, which is under vacuum, is liberated and contaminates and irritates the hands, which eventually enhances sensitization.[26]

In recent studies in Asian hospitals that intended to evaluate sensitization rates to beta-lactam antibiotics among nurses and pharmacists, the authors found a high prevalence of sensitization (17.4%) to three cephalosporins (cefotiam, ceftriaxone, and ceftizoxime) diagnosed by the presence of specific IgE. There was a positive correlation with immediate work-related symptoms, including CoU, in the group of sensitized nurses. Most were young females exhibiting a higher frequency of atopic dermatitis and systemic drug allergies.[26]

Apart from antibiotics, other occupational cases in health care workers have been reported. In 2013, three cases from chlorhexidine were reported in nurses working in different wards of a hospital (internal medicine, nephrology, and cardiology) who suffered from "airborne" urticaria and respiratory symptoms.[17]

An isolated case was reported, in 2009, of a nonatopic nurse that crushed donepezil tablets (Aricept®) for a patient with Alzheimer's disease and suffered swelling of the hands and wheals in the forearms.[55]

A rather old case was reported in a nurse who suffered immediate urticarial reactions on exposed areas, exclusively during preparation of cisplatin for oncologic patients. She had positive open tests, read at 40 minutes, to two platinum salts (ammonium tetrachloro and hexachloroplatinate), tests that induced negative reactions in controls, confirming the specific reactivity to platinum salts contained in cisplatinum in this patient.[56]

Diagnosis of Immediate Symptoms Induced by Drugs

The diagnosis of CoU induced by drugs is based mainly on clinical history, which needs a very precise data collection on the timing of events (drug exposure and initiation of symptoms) and the localization of lesions (initial localization and progression).

When the patient has been exposed to a single drug, complementary tests may be important to confirm the etiology, evaluate cross-reactivity to related chemicals,[45] find a safe alternative drug and, eventually, appreciate the participation of drug-specific IgE.

When the urticaria is preceded by exposure to multiple drugs (topical and systemic), it is extremely important to perform complementary tests to have a precise diagnosis and, in the future, avoid the correct drug. Often, in urticaria or anaphylaxis developing during perioperative periods, reactions are incorrectly attributed to systemic drugs as that are the main cause of urticaria in these settings (neuromuscular blockers, antibiotics, anesthetics, opiates, analgesics like metamizol, or radiocontrast media),[29,30] and chlorhexidine used to disinfect the wound can be the cause, as shown in a recent study in which chlorhexidine represented 5% of all cases of perioperative anaphylaxis.[29]

To avoid unnecessary severe reactions upon topical exposure during skin testing, the study of these patients should begin by epicutaneous open testing in normal skin and occlusive patch tests on the forearms with immediate readings (20–30 minutes). If negative, they will be followed by skin prick tests and, if negative, eventually by intracutaneous testing. These tests should be performed in settings where there is easy access to resuscitation measures as, occasionally, even from patch testing, a generalized urticaria can occur, as in cases reported with cefotiam,[57] penicillin or amoxicillin,[14] pyrazolone compounds,[50] or diclofenac.[23] Generalization of urticaria from skin testing, or even anaphylaxis,[23,58] can occur, particularly in the study of severe CoU or anaphylactic reactions.

Many drug allergens are not standardized and commercialized for epicutaneous patch testing. There are even fewer commercialized and standardized allergens for prick or intracutaneous testing.

Topical drugs and dressings can be tested as such in open epicutaneous tests, on the volar forearm, and eventually a puncture with a lancet can be performed across the material applied on the skin.

For prick testing with drugs, dilutions from commercial preparations have to be performed, preferably from intravenous preparations. There is no consensus on the dilutions to be performed, but in the more severe reactions, it is advisable to have higher dilutions and increase the concentration progressively in case of negative tests (10^{-3}, 10^{-2}, 10^{-1}, then pure), or follow concentrations recommended for the study of adverse effects from systemic drugs by the European Society of Contact Dermatitis [59] and European Network for Drug Allergy/European Academy of Allergology and Clinical Immunology study groups.[60]

Results have always to be compared with the positive control (histamine 10 mg/mL) and negative control (saline). According to the guidelines of prick testing, only reactions >3 mm are considered positive.[60] Sensitivity of in vivo testing is usually higher than in vitro tests, but it is important to be aware that some drugs cause nonspecific mast cell degranulation and, consequently, false positive reactions (opioids, NSAIDs). Therefore, in positive results particularly with unknown drugs, skin testing in control patients is mandatory to confirm the specificity of the positive reaction.

Reagents for in vitro testing for specific IgE are commercialized only for a limited number of drugs and excipients, namely beta-lactam antibiotics, chlorhexidine, formaldehyde, ethylene oxide, and gelatin, potentially involved in CoU, and a few others that can cause urticaria upon systemic exposure. Other more sophisticated and nonstandardized techniques can be adapted to detect drug specific IgE, as in recent studies where IgE anti-cefotiam, anti-cefaclor, anti-ceftriaxone, and anti-ceftizoxime combined with human serum albumin were detected by enzyme-linked immunosorbent assay.[54,61]

Basophil activation tests evaluating the degranulation of basophils upon in vitro exposure to the chemical or the increase in basophil expression of CD63 or CD203c evaluated by flow cytometer can be performed in selected laboratories, but these tests are less specific.[62]

Measuring serum tryptase during the acute episode or within the first 2–4 hours after a stage 3 contact urticaria syndrome or anaphylaxis and comparing it with basal values (>24 hours), is a useful complementary test to document mast cell/basophil degranulation.[30]

A controlled exposure to the suspected drug or to safe alternative drugs may be advisable in case when all previous tests were negative.

Conclusion

Topical drugs or, occasionally, systemic drugs that come in contact with the skin or mucosae, may induce CoU, which is certainly very often overlooked. Some reactions are mild and patients do not come to the doctor for them. Moreover, as they all are transient, they are seldom present at the time of consultation or at the time of testing. The doctor often has to believe patients' complaints, which are more and more complemented with photos taken by cell phones during the acute episodes. Although most of the time, the quality of the photos is not brilliant, they may help us understand the type of lesions. Complementary tests (skin tests with immediate readings and, eventually, in vitro tests) are mandatory in certain situations because a precise diagnosis of the culprit drug and a suggestion of alternative safe drugs, can be life-saving.

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19

Contact Urticaria, Dermatitis, and Respiratory Allergy Caused by Enzymes

Monica Stanciu and Denis Sasseville

Introduction

Enzymes are complex proteins or glycoproteins produced by living organisms for the purpose of accelerating biochemical reactions and metabolic processes. These biochemical catalysts act within their host cell, or are secreted outside to assist vital processes such as digestion of food. Early bakers and winemakers were unaware that their products were the result of microbial activity. Louis Pasteur's work on fermentation clearly demonstrated the role of living microorganisms in this process. In reference to the action of such ferments, Wilhelm Kühne in 1877 coined the term "enzyme," meaning "in the yeast." A few years later, Buchner demonstrated the activity of yeast extracts in the absence of living cells. In the following century, the nature, structure, and function of numerous enzymes were elucidated.

Notwithstanding some rare exceptions (e.g., trypsin, chymotrypsin, rennin, papain), enzymes are named by adding the suffix "-ase" to their substrate (i.e., cellulase) or to their function (i.e., peroxidase). The catalytic activity of enzymes greatly reduces the amount of energy and the time needed to carry on a specific biochemical reaction. A little more than 20 enzymes are industrially produced. They are extracted from animal tissues, plants, and microorganisms such as bacteria, fungi, or yeasts. Their industrial applications have flourished because of the ease and low cost of growing their producing microorganisms. Nowadays, protein engineering can modify or create enzymes with increased stability or with activity on new substrates.

Most enzymes are hydrolases that break various chemical bonds with the addition of water.[1] Proteases cleave peptide bonds, glycogenases transform starch into complex or simple sugars, lipases break down fats, and so on. Table 19.1 lists some of the commonly used industrial enzymes, their substrates and their applications.[1–3]

Inasmuch as enzymes are proteins, they can trigger hypersensitivity reactions in the skin or the respiratory tract, including contact urticaria, protein contact dermatitis, angioedema, and asthma. These reactions are often occupational,[4] with a minority of cases occurring from exposure to enzyme-containing household products.

Amylase

Amylases are a family of enzymes that catalyze the breakdown of large polysaccharides into simpler sugars. They were among the first enzymes to be discovered and characterized by Anselme Payen in 1833.[5] Amylases are divided into three groups designated by the Greek letters α, β, and γ.

α-Amylase is found in humans, animals, and insects, predominantly in pancreatic secretions and saliva to help digestion. It is also found in the seed of plants, and is secreted by some bacteria and fungi. α-Amylase hydrolyses the alpha bonds of starch and glycogen, yielding glucose and maltose.[6] Bacterial and fungal α-amylases are widely used as flour additives in the baking industry to enhance carbohydrate fermentation by yeast.[7,8] This speeds up the baking process, increases the rising of the dough, and improves the quality of the bread.[9] Along with proteolytic enzymes, α-amylase is also used in granulate and liquid detergents.[10] The pharmaceutical industry dispenses a porcine pancreatic extract of powdered α-amylase and lipase as an anti-inflammatory or digestive drug.[11–15] Vanhanen et al. report the use of α-amylase, xylanase, and other enzymes in the animal

TABLE 19.1

Industrial Enzymes and Their Applications

Substrate	Enzyme	Industrial Applications
Starch and sugars	α-amylase	Baking and brewing Production of high-fructose syrup Starch processing Laundry detergents Biofuel production Textile industry
	β-amylase	Baking Starch processing
	Amyloglucosidase	Baking and brewing
	Glucanase	Poultry, beverages, and starch processing
	Glucose isomerase	Production of high-fructose syrup
	Invertase	Confectionery
	Lactase	Dairy industry
	Lysozyme	Cheese and wine industry Pharmaceutical industry (sore throat remedies, contact lens solutions, infant formulas, etc.)
	Pectinase	Clarification of fruit juices
	Pullulanase (debranching enzyme)	Production of high-fructose syrup Starch processing Baking and brewing Laundry detergents
Cellulose	Cellulase	Laundry detergents Coffee bean drying Pulp and paper industry Biofuel production
	Xylanase	Baking Wood pulp bleaching Plant fiber degumming Poultry food additive
Proteins	Asparaginase	Pharmaceutical industry (antileukemic medication) Food processing
	Bromelain	Baking and brewing Laundry detergents Dairy industry Meat tenderizing
	Chymotrypsin	Leather processing Pharmaceutical industry Food processing Biomedical laboratories
	Collagenase	Pharmaceutical industry (topical wound debridement)
	DNA polymerase	Molecular biology (polymerase chain reaction)
	Papain	Baking and brewing Laundry detergents Dairy industry Meat tenderizing Contact lenses cleaning Silk refining Leather industry

TABLE 19.1 (*Continued*)

Industrial Enzymes and Their Applications

Substrate	Enzyme	Industrial Applications
	Protease	Baking and brewing Laundry detergents Meat processing
	Rennin (chymosin)	Cheese making
	Streptokinase	Pharmaceutical industry (thrombolysis medication)
	Subtilisin	Laundry detergents
	Trypsin	Leather processing Pharmaceutical industry Food processing Biomedical laboratories
Lipids	Lipase	Cheese making Laundry detergents Paper industry
Hydrogen peroxide	Catalase	Food industry Dairy and cheese industry

feed industry.[16] Other industrial uses of α-amylase include the production of glucose syrup, preparation of alcohol in the brewing industry, and clarification of wine and fruit juice.[3,10]

Contact Urticaria: Falleroni et al., in 1971, published one of the first reported cases of immediate hypersensitivity to α-amylase.[17] Their patient was a 35-year-old homemaker who developed pruritus and moderate chemosis in her left eye after an inadvertent contact with laundry detergent. In the preceding months, she had experienced rhinorrhea and sneezing when doing the laundry. She was prick tested with an aqueous solution of an enzyme mixture present in the detergent as well as with an aqueous solution of nonenzyme portion of the detergent. The enzyme mixture consisted of alkaline protease and α-amylase derived from *Bacillus subtilis* fermentations diluted 1:300,000 in water. The patient had a positive wheal-and-flare reaction to the enzyme mixture, with no delayed reaction. In 1997, Kanerva et al. reported the case of a baker with occupational contact urticaria from fungal but not bacterial amylase.[18] He developed wheals and rhinoconjunctivitis within minutes of direct cutaneous contact with flour. He had positive prick tests and radioallergosorbent tests (RAST) to two fungal α-amylases, but was negative to two bacterial α-amylases. In 2001, Alonso et al. described a 2-year-old boy who developed urticaria and asthma after contact with flour powder at his grandfather's bakery.[19] Prick test and RAST were both positive to α-amylase. His symptoms resolved upon avoidance of contact with flour.

Protein Contact Dermatitis: α-amylase has also been the culprit in a few cases of protein contact dermatitis, especially in bakers. In a review of 27 cases of protein contact dermatitis, Hernandez-Bel et al. identified two patients with hand dermatitis.[20] Both patients were bakers exposed to flour. They both had negative patch tests, but a positive prick test to α-amylase. Morren et al. tested 32 bakers with severe hand eczema and found that seven had positive immediate reaction upon scratch chamber test with α-amylase powder.[21] Two of the seven bakers also had delayed eczematous reactions. Four of these bakers with positive scratch chamber tests where prick tested and developed immediate reactions with dilutions as low as 1:250,000 mg/mL of α-amylase.

γ-amylase, also known as glucoamylase and amyloglucosidase, is used in the baking and brewing industry. In 1998, Kanerva and Vanhanen published a case of occupational protein contact dermatitis from this enzyme.[22] They described a 28-year-old chemical enzyme factory worker who developed hand dermatitis 1 hour after exposure to work products. She had a positive prick test, and a negative patch test to glucoamylase.

Allergic Contact Dermatitis: Cases of delayed hypersensitivity to α-amylase are scarce. In 1987, Schirmer et al. reported a baker with chronic lichenoid dermatitis.[23] Both prick and patch tests were positive with immediate and delayed reactions, respectively. Positive anti–α-amylase IgE antibodies were found in the

patient's serum. The authors concluded to a mixed type I, III, and IV reaction. A Swedish cross-sectional study of 20 factory workers exposed to α-amylase reported an increased incidence of work related rhinitis and dermatitis.[24] Six of the 20 workers had a positive prick test to α-amylase. The dermatitis and "skin symptoms" were not further described in this study. Del Pozo et al. described a 69-year-old patient with a generalized dermatitis after ingestion of digestive tablets.[25] Patch tests showed positive reactions at 48 and 72 hours for amylase, cellulase, and protease. Prick and intradermal tests were negative. This case is among the very few reported in the literature that clearly demonstrate a delayed hypersensitivity to enzymes.

Systemic Involvement: Moreno-Ancillo described a 25-year-old farmer who developed oral angioedema after eating white bread.[7] He had a positive skin prick test to *Aspergillus oryzae* α-amylase as well as elevated anti–α-amylase serum immunoglobulin E (IgE). A food challenge with 5 mg of uncooked α-amylase induced cough and oral angioedema after 10 minutes. A similar case was reported in 1995 of a 29-year-old bakery assistant with urticaria and rhinoconjunctivitis after bread ingestion.[26] She also tested positive to α-amylase on prick testing.

Respiratory Tract Involvement: IgE-mediated asthma is the most common disease associated with occupational and nonoccupational exposure to α-amylase. The most frequent occupational asthma linked to α-amylase exposure is baker's asthma. Respiratory problems in bakers have been described in the 18th century by Ramazzini, and linked to allergy in the beginning on the 20th century.[27] However, it is only in the 1980s that Baur et al. were among the first to link baker's asthma to α-amylase.[8] Among 118 bakers tested, 12 with asthma had a positive RAST to α-amylase, and none in the asymptomatic group. Ten of 12 also had positive skin tests to 0.01 and 0.1 mg/mL dilutions of the enzyme, and four had immediate symptoms upon inhalation of α-amylase. Numerous cases linking α-amylase in flour to baker's asthma have since been published.[15,28–37] In 1998, Houba et al. published an excellent review of occupational asthma in bakery workers.[9] According to this review, 24%–55% of bakers with respiratory symptoms were sensitized to α-amylase. More recent studies focused on the possible transfer of allergen to the family members of bakers. The 2-year-old boy reported by Alonso et al. developed asthma and urticaria after visits to his grandfather's bakery.[19] His sensitization to α-amylase was demonstrated by positive prick test and RAST. In 2012, Tagiyeva et al. studied flour contamination in baker's families [38] and concluded that flour and its allergens (fungal α-amylase, wheat proteins) are transferred into the home environment, with elevated levels of allergens being present in vacuuming dust. This exposure potentially increases the risk of childhood asthma in the baker's family.

It remains to be shown whether bread consumption can trigger asthma in individuals without occupational sensitization to α-amylase. Sander et al. demonstrated that bread crust retains between 0.1% and 20% of the antibody-binding capacity of α-amylase compared to dough, thus maintaining some allergenic potential.[39] This potential was confirmed in 2004 by the case of the farmer who developed oral angioedema without respiratory symptoms after white bread consumption. He didn't have a history of occupational exposure to flour or to α-amylase. His allergy to α-amylase was demonstrated by RAST, prick test, and a positive oral challenge.[7] To date, however, only subjects with previous occupational exposure and sensitization to α-amylase have reported asthmatic attacks after eating bread.[9,26,39,40]

IgE-mediated occupational asthma has occurred from both natural and genetically engineered α-amylases in detergent,[10,18,41–44] pharmaceutical,[12] and biotechnology industries.[45] There are also cases of laboratory workers with occupational asthma and rhinitis from amylase in porcine pancreatic extract.[11,13,14]

Generally not found in animal tissues, β-amylase is present in plant seeds and is produced by bacteria and fungi. Like its close relative α-amylase, it is used in baking as well as in beer brewing and liquor production. Sandiford et al. demonstrated by RAST the allergenicity of β-amylase in barley flour and its potential role in baker's asthma.[46]

In 1988, Baur et al. reported that γ-amylase was a cause of baker's asthma.[47] Quirce et al. published a series of four cases of bakers with asthma who were sensitized to glucoamylase, demonstrated by positive prick tests.[48] Three of the four subjects had early asthma symptoms provoked by specific inhalation challenge with glucoamylase. These subjects were also sensitized to α-amylase and half of them to hemicellulase.

Lysozyme

Lysozyme, or muramidase, is a glycoside hydrolase found in human and animal mucus, tears, and saliva. It is also abundant in avian egg whites. It plays a role in bacterial defense by catalyzing the hydrolysis of mucopolysaccharides in bacterial cell walls.[49] It is used in dairy and cheese making for its antibacterial properties [50] as well as in wine production, baking, and confectionery. Its pharmaceutical uses include sore throat preparations, contact lens solutions, infant formulas, and immunostimulant remedies.[51]

Contact Urticaria: There exist a few reports of lysozyme hypersensitivity from mucocutaneous contact or inhalation. Pichler and Campi reported seven women who developed urticaria or anaphylaxis from mucosal contact with a vaginal suppository containing lysozyme.[52] Three of these patients had a previous history of egg allergy, but the remaining four did not. Five individuals had positive skin tests to lysozyme and all seven had strong T-cell responses to lysozyme in the lymphocyte transformation test. Yagami et al. isolated lysozyme as one of the rubber latex allergens responsible for IgE-mediated urticaria in two patients allergic to latex gloves.[53]

Contact Dermatitis: So far, there have been no published cases of protein or allergic contact dermatitis from lysozyme.

Systemic reactions: Most reported reactions to lysozyme occur after oral ingestion, either from raw eggs, food, or pharmaceuticals containing lysozyme.[50,51,54–57] These reactions range from worsening dermatitis in egg-allergic children to anaphylactic shock.

Respiratory Tract Involvement: Inhaled lysozyme has been linked to IgE-mediated asthma. Bernstein et al. were among the first to publish a case of occupational asthma induced by inhaled egg lysozyme in the pharmaceutical industry.[58] Since the 1990s, additional publications have described occupational asthma in egg-processing facilities, confectionery and baking industry, cheese-manufacturing plants, and in a pharmaceutical industry.[59–65] Santaolalla et al. published in 2002 an interesting case of double sensitization to enzymes.[35] The 25-year-old baker developed rhinoconjunctivitis and asthma at work after using a spraying device for egg mixture. RAST, skin prick test and specific bronchial challenge were positive to lysozyme from the egg mixture and to fungal α-amylase from flour.

Other Starch and Sugar Breakdown Enzymes

Lactase is a digestive system enzyme that breaks down lactose into simpler sugars. Lactase derived from *Aspergillus* species is used in the pharmaceutical industry as a supplement to aid dairy digestion in lactose-intolerant people. Workers manipulating the powdered lactase have developed occupational sensitization to this enzyme.

Protein Contact Dermatitis: In 2007, Laukkanen et al. published the only case of occupational protein contact dermatitis to lactase.[66] Their patient was a 31-year-old nonatopic, non–lactose-intolerant woman who worked in packing lactase supplements derived from *Aspergillus oryzae*. She developed urticarial wheals, dermatitis, and respiratory symptoms following manipulation of the powder. Patch testing [raw enzyme 0.3% and 1% pet, capsule content 30% pet), open application test, prick test (raw enzyme 0.1% and 1%), RAST, chamber challenge test, and lung function tests were all positive to lactase. Her symptoms resolved upon avoidance of the enzyme.

Respiratory Tract Involvement: Muir [67] and Bernstein [68] reported in the late 1990s lactase sensitization in pharmaceutical industry workers who manipulated the enzyme and developed occupational asthma.

Pectinase is an enzyme that breaks down pectin from plant cell walls. It is used in fresh fruit and fruit juice processing. **Glucanase** and **pullulanase** (a subtype of glucanase), additional enzymes that hydrolyze polysaccharides, are also used in the food industry.[69] There are no reports of contact urticaria or dermatitis to these enzymes.

Respiratory Tract Involvement: These enzymes are known to cause occupational asthma. Among others, Sen et al. reported three workers with allergic occupational asthma upon exposure to pectinase and glucanase in fruit salad preparation.[70]

Cellulase and Xylanase

Cellulose, the major constituent of plants, is a polysaccharide consisting of linear chains of repeating glucose molecules. The links between the glucose moieties are slightly different than those found in starch, making cellulose

much more resistant to hydrolysis. Except for herbivores, most animals cannot efficiently break down cellulose because they lack ruminating chambers colonized by symbiotic bacteria that produce cellulase. Hemicelluloses are different polysaccharides, often coexisting with cellulose, present in the cell wall of most plants. These glucans, mannans, xylans and xyloglucans are hydrolyzed by various hemicellulases such as xylanase, produced by bacteria and fungi that feed on plant matter. Both cellulase and xylanase have found many industrial applications, notably in laundry detergents and in the processing of wood pulp.

Contact Urticaria: In 1991, Tarvainen et al. published a case series of four workers employed in enzyme-producing factories who developed contact urticaria on exposed parts of the body that came in contact with cellulase in two cases and xylanase in the other two.[71,72] One worker eventually developed generalized urticaria after exposure to cellulase dust. All patients had positive prick tests with commercial enzymes, diluted in Coca solution, with two subjects reacting to both enzymes. RAST were positive with both enzymes in all subjects. Of note, all four workers also complained of respiratory problems, including rhinitis, hoarseness, cough, and overt asthma. An additional worker was investigated in 1998.[73] He was exposed to cellulase in the production of starch from barley. He developed pruritus and wheals on his arms when exposed to dust in the workplace. His RAST and prick test to cellulase were positive.

Contact Dermatitis: Two of the patients reported by Tarvainen et al. had eczematous lesions located on the dorsum of the hands in one case and on the hands and face for the second patient.[72] Patch tests were performed with serial dilutions (3.3%, 1%, and 0.33%) in petrolatum and water. They were strongly positive to cellulase in one case and xylanase in the second.

Respiratory Tract Involvement: Cellulolytic enzymes have long been known to trigger IgE-mediated airway sensitization. In 1981, Ransom and Shuster reported the cases of a plant pathologist and a coworker in a plant cloning research laboratory who developed rhinitis and asthma from exposure to cellulase powder.[74] The first patient had a strongly positive prick test to cellulase, diluted 1:10 in sterile normal saline. RAST performed on the serum of both workers was also positive. Pulmonary function tests or inhalation challenge were not performed and the outcome of the workers is unknown. Multiple additional cases or case series have since been described, and bakers appear to be at high risk of polysensitization from enzymes and other workplace inhalants.[75–83] The two female patients reported by Losada et al. worked for a pharmaceutical company that produced digestive aids. Both were exposed to cellulase dust and developed work-related rhinitis and asthma. [75] In each case, the diagnosis was established by positive skin prick tests, specific IgE antibodies detected by reverse enzyme immunoassay, and bronchial provocation tests. Five bakers with occupational rhinitis and asthma were similarly investigated and found sensitized to *Aspergillus*-derived α-amylase, whereas four were simultaneously allergic to cellulase.[76] A 46-year-old man suffered from work-related rhinitis and asthma. His task was to maintain the machinery that produced dry enzymes.[77] Skin prick test and RAST were positive for cellulase. A positive inhalation provocation test reproduced his nasal and bronchial symptoms, which were accompanied by severe edema of the pharynx and uvula that lasted a few hours. A 23-year-old textile worker used cellulase powder on a daily basis to remove fuzz from clothes.[79] He eventually developed occupational asthma without rhinitis, and his symptoms were attributed to cellulase from positive prick tests, presence of cellulase-specific IgE antibodies, and reproduction of symptoms by bronchial provocation with cellulase extract. A 48-year-old detergent factory worker developed occupational rhinoconjunctivitis and asthma.[83] Skin prick test and RAST were positive to cellulase, protease, and amylase, whereas bronchial provocation was positive with cellulase.

Xylanase has also caused occupational asthma in bakers, most of the time in the setting of polysensitization. [81,82] A study of German bakers disclosed specific antibodies to xylanase in 14% of cases and to cellulase in 9%, with a high degree of cross reactivity between both enzymes.[84]

Subtilisin

In the early 1960s, the Danish company Novo Industri successfully produced a heat- and alkali-stable proteolytic enzyme obtained through fermentation of *Bacillus subtilis*. Named Alcalase, Maxatase, and Esperase among others, subtilisins soon found applications in the harsh environment of laundry detergents, and by the end of

the decade, half of the detergents sold in Europe and North America were enzyme-laden.[85] In the years that followed, numerous reports described the occurrence of respiratory and cutaneous symptoms from enzymes in laundry detergents, mostly from occupational exposure.

Contact Urticaria: Within hours of cutaneous exposure to liquid enzymes, a 27-year-old atopic man working in an enzyme-producing factory developed hives lasting 1 to 2 hours.[86] Prick test and RAST were strongly positive to *Bacillus subtilis*-derived detergent protease.

Contact Dermatitis: Detergent enzyme dermatitis is primarily of occupational origin. Symptoms are usually mild and easy to control with personal protective equipment and good working hygiene. Some of the workers reported by Flindt complained of skin irritation at the nape of the neck or around the wrists, but patch testing was not performed.[87] Newhouse et al. mention that, in the factory workers that they surveyed, the presenting complaint was an outbreak of fingertip dermatitis among those handling Alcalase powder, whereas some other laborers complained of transient facial erythema.[88] Similarly, McMurrain compiled 110 cases of enzyme dermatitis between 1966 and 1970 in a soap- and detergent-producing plant in the United States.[89] Lesions, described as red, moist, and glistening in appearance involved the palms and fingertips, or the face at points of contact with respirator masks. The incidence of these cases decreased with prevention control measures such as frequent washing of exposed areas and work clothes, as well as the proper use of gloves and protective creams. *B. subtilis*–derived proteolytic enzymes are also used in bakery, as exemplified by the case reported by Smith et al.[90] This 35-year-old baker used to handle the enzyme tablets with his bare hands. He suffered from several episodes of severe palmar dermatitis that resolved after prolonged sick leave. Given negative patch tests with workplace materials that included incremental concentrations of *B. subtilis* protease, a final diagnosis of irritant contact dermatitis was postulated.

A handful of reports describe contact dermatitis in consumers.[91–93] Ducksbury and Dave described 12 housekeepers who developed severe, painful, edematous, and vesicular hand eczema, sometimes within hours of a single exposure to enzyme-containing detergents, or after 7 to 10 days of repeated exposure. Patch testing with a 0.1% dilution of the detergent was negative in every case.[91] A cohort of 13 homemakers developed a similar burning and raw dermatitis on the hands within 1 hour to several days of hand washing clothes with an enzyme-containing detergent.[92] Patch testing was conducted with a 0.5% and a 0.25% solution of the detergent as well as with an identical preparation without enzymes. One-third of the 12 patients tested developed marked erythema and edema under the patch holding the higher concentration of the enzyme detergent. The authors concluded to a severe irritant reaction precipitated by the proteolytic activity of the enzyme. Another report describes 30 patients, adults and children, with hand or widespread dermatitis that the authors attributed to use of enzyme-containing detergents. No investigation was performed and it can only be presumed that resolution followed withdrawal of the offending agent.[93] Zachariae et al. conducted a more convincing study in which they patch tested with Alcalase 79 workers from two detergent enzyme–producing factories, along with 10 control subjects.[94] The workers had experienced dermatitis of the hands, forearms, and face, with some developing lesions in perspiring areas such as the axillae and crural folds. Twelve workers and four controls were tested with serial dilutions of Alcalase. After exclusion of the irritant concentrations, the remainder of the cohort was tested with a 0.01% solution. These tests yielded negative results, thus confirming the irritant nature of the dermatitis caused by this proteolytic enzyme.

Respiratory Tract Involvement: Soon after the introduction of the various subtilisins, it became apparent that they could trigger IgE-mediated immediate sensitization of the upper or lower respiratory tract. The first description is credited to Flindt who reported on 28 workers engaged in the manufacture of detergents who presented with acute breathlessness, cough, or wheezing occurring within minutes to hours of exposure to enzyme dust.[87] Twenty of these individuals had positive prick tests to Alcalase and Maxatase at concentrations of 10 mg/mL and 1 mg/mL, whereas control subjects had negative tests. Pepys et al. further investigated three of these workers with inhalation provocation tests to aerosolized enzymes.[95] These tests demonstrated a bimodal response, characterized by an immediate asthmatic reaction that reversed within one hour, followed by a late attack 4 to 5 hours later. The same year, Wütrich and Ott reported occupational asthma from proteases in laundry detergents in Germany.[96] Additional publications in the 1970s confirmed these early reports, but immunological testing with methods available at the time gave inconclusive results.[88,89,97–102] With the advent of RAST, the presence of specific IgE antibodies to detergent enzymes could be demonstrated, and were found to be present even in asymptomatic

workers.[103] The industry responded to these reports by implementing safety measures to decrease workers' exposure to raw enzyme dust. These include exhaust ventilation and dust control equipment, handling of enzymes through a closed system, protective suits and masks, decontamination showers, and encapsulation of the enzyme in a water-soluble film.[99] These combined measures were generally effective in reducing the percentage of workers who became sensitized or symptomatic. Encapsulation of enzymes, however, was found to be insufficient to prevent sensitization, because 25% of exposed worker in a dry bleach plant developed specific IgE and IgG to Esperase as measured by RAST and enzyme-linked immunosorbent assay, respectively.[104]

Despite preventive measures, occupational respiratory sensitization has not disappeared. In 2000, Vanhanen et al. conducted a cross-sectional survey in a detergent factory. Of 76 workers, 40 were exposed to encapsulated enzyme in manufacturing, packing and maintenance tasks, whereas 36 were affected to unexposed clerical tasks.[105] None of the nonexposed workers was sensitized, but eight workers in the exposed group had symptoms of rhinitis and one had asthma. All had positive RAST and prick tests to various enzymes, mostly proteases. These findings were corroborated by the study of Cullinan et al., who reported an outbreak of occupational asthma in a detergent factory that exclusively used encapsulated enzymes.[43] Of 350 employees, 19% had upper airway symptoms accompanied by enzyme sensitization, whereas lower airway symptoms were present in 16% of sensitized workers. A recent report demonstrates that there is also a risk of sensitization and respiratory disease in workers exposed to liquid enzyme formulations.[41]

Nonoccupational sensitization can also occur in consumers exposed to enzyme-containing detergents. Shapiro and Eisenberg tested 35 asymptomatic homemakers who were using such detergents, and found four with strongly positive intradermal tests to 0.02 ml of a 0.5 mg/mL solution of crystalline Alcalase, including one who reported asthma and rhinitis when using any type of laundry detergent.[99] Belin et al. described three female homemakers with symptoms of asthma, conjunctivitis, and rhinitis when washing clothes with an enzyme-containing detergent.[106] All three had positive prick testing with Alcalase as well as specific IgE demonstrated by RAST and RIST. Falleroni and Schwartz added another case the following year.[17] Their 35-year-old subject developed rhinorrhea, sneezing, and ocular pruritus when using an enzyme detergent, or just walking down the household products aisle at the supermarket. Bernstein's study showed that 25% of 353 highly or moderately allergic male and female patients had positive scratch and intradermal tests with detergent enzymes.[107] Fourteen of those patients complained of respiratory symptoms related with exposure to enzyme detergents. All had positive nasal or bronchial provocation tests and their symptoms abated with avoidance of enzyme products.

Papain and Chymopapain

Papain: This enzyme is a cysteine protease that occurs naturally in papaya (*Carica papaya*). Industrial production involves extraction and purification from the dried latex of the papaya fruit. Papain is widely used as meat tenderizer and beer clarifier, but also finds applications in tissue culture laboratories to dissociate cells. In addition, for the purpose of digesting unwanted proteins or necrotic tissue, it has been incorporated in contact lens cleaning solutions, toothpastes, digestive tablets, cosmetic exfoliating creams, and ulcer care ointments.

Contact Urticaria: A 31-year-old woman suffered six episodes of periorbital angioedema after cleaning her soft contact lenses with a papain-containing cleanser.[1] Thereafter, she complained of ocular pruritus and lacrimation when wearing her contact lenses. Her investigation showed positive skin prick tests to dilutions of 1 mg/mL of papain and chymopapain. These findings were corroborated by positive RAST to both enzymes. The patient of Santucci et al. had repeated episodes of pruritic urticaria involving the fingers, palms, back of the hands, eyelids, and face when she cleaned or wore her soft contact lenses.[2] An open test with 0.1 mL of a 1% dilution of the cleanser produced wheals within 15 minutes. A prick test with a 0.01% solution of pure papain was also strongly positive. Podmore and Storrs investigated 20 patients referred for contact lens intolerance.[3] All were tested to an extensive contact lens components series and to a contact lens solution series. The latter battery of allergens was also used to test for contact urticaria on intact and scratched skin for 30 minutes. Of the six patients who showed immediate reactions, one was positive to papain 1% pet. In 1999, Quiñones et al. presented the case of a worker with contact urticaria coupled with rhinoconjunctivitis and asthma from occupational exposure to papain used to tenderize the meat of squid and octopus.[4] Papain prick test, specific IgE, and nasal challenge test were positive. The two beauticians reported by Soto-Mera et al. developed occupational sensitization to papain tablets, which

they were dissolving in water to facilitate removal of adhesives.[5] Both suffered from contact urticaria, rhinoconjunctivitis and asthma and had positive prick tests and specific IgE antibodies to papain.

Systemic Reactions: A more severely sensitized male worker developed anaphylaxis, characterized by widespread urticaria and angioedema, chest pain, nausea and vomiting, glottic distress, and hematuria.[6] He was making and packing toothpaste and other creams, adding papain powder to the toothpaste. His prick test to papain was strongly positive, and his symptoms cleared with work reassignment. Mansfield and Bowers' atopic patient ate a steak treated with papain meat tenderizer.[7] After 30 minutes, he was rushed to the hospital with generalized itching, angioedema of the extremities and face, and wheezing. Skin prick testing after resolution of the clinical manifestations was positive to the meat tenderizer and to pure papain 0.1, 1.0, and 10 mg/mL.

Contact Dermatitis: an extensive online literature search did not reveal any case of protein or allergic contact dermatitis from papain. In a study by Baur et al., 33 workers were investigated for respiratory symptoms related to papain exposure.[8] Four workers were employed in a spice mill and packed large amounts of papain; others worked in an industrial kitchen and used a papain meat tenderizer or were making digestive aids with papain. Three of the four heavily exposed individuals, who all presented with respiratory symptoms, "exhibited itching and flare reactions on uncovered skin areas." It is unfortunate that the description of the skin lesions was not more complete, but that three of the patients had negative RAST and skin tests whereas one had very weak reactions is in favor of a nonimmunologic mechanism, possibly irritant contact dermatitis from the proteolytic action of the enzyme.

Respiratory Tract Involvement: From the early reports of Osgood and Beecher, it has been known that inhalation of papain powder can trigger asthma attacks.[9,10] Inhalation of papain dust leads to emphysema in experimental animals, probably because of proteolytic digestion of elastic fibers. Gross et al., however, have demonstrated that guinea pigs can become sensitized to inhaled papain and can die from anaphylaxis upon reexposure.[11] Milne and Brand later published the cases of two food technicians who developed acute asthma after inhalation of a fine dust of pulverized papain.[12] Scratch testing with a paste prepared from pure enzyme was positive and was followed by an asthma attack a few hours later in both cases. Flindt published the case of a factory worker who experienced three episodes of acute asthma when papain was being packed in an adjacent room.[13] In his report, Flindt mentions the unfortunate fate of another worker similarly exposed in a different factory who died during an acute asthma attack triggered by inhalation of papain dust. Numerous other reports have since confirmed, by RAST, skin testing, or bronchial or nasal challenge, the highly sensitizing potential of aerosolized papain, especially in the occupational setting.[8,14–20] Of note, 12 of 23 papain-exposed workers in a pharmaceutical plant became sensitized and complained of moderate to severe pulmonary symptoms, whereas 10 of 22 employees in a research laboratory developed rhinoconjunctivitis from papain sensitization.[17,19]

Cross-Reactivity: Quarre et al. investigated three patients known for their immediate hypersensitivity to natural rubber latex and cross-reacting fruits.[21] One patient had experienced angioedema after eating a papaya cake. All three had positive RAST to papain. Vandenplas et al. studied the prevalence of papain allergy in health care workers with and without immediate allergy to latex.[22] Eighteen of 30 latex-allergic individuals had positive prick tests with papain versus one in 148 control workers without latex allergy. Independently of sensitization to *Hevea brasiliensis*, a certain degree of cross-reactivity has been documented between papain and the ornamental plant *Ficus benjamina*, a known cause of allergic rhinitis and asthma.[23,24]

Chymopapain: A proteolytic enzyme closely related to papain and extracted from the same source, chymopapain has found applications in chemonucleolysis to treat herniated discs in the lumbar spine. Injected under local anesthesia, the enzyme dissolves the bulging nucleus pulposus that compresses nerve roots, thus relieving the pain of intractable sciatalgia. The risk of anaphylaxis from chemonucleolysis is estimated at 1%, and the risk of death at 0.14%.[25] In 2003, the sale of Chymodiactin was discontinued in the United States. Sagona et al. demonstrated cross-reactivity between papain and chymopapain.[26] Six patients with positive prick tests to papain also had positive RAST to both papain and chymopapain. The same study showed that 2 weeks after chemonucleolysis, the serum of 12 patients was RAST positive to both enzymes. Hypersensitivity reactions after chymopapain injection can be immediate in patients already sensitized, or can occur 2 to 24 days later, denoting acquisition of hypersensitivity and specific IgE antibodies from the procedure.[27–29] Moneret-Vautrin preoperatively evaluated 700 candidates for chemonucleolysis with a careful history of papain exposure and atopy, and prick testing with chymopapain.[30] Chemonucleolysis was not performed in the 23 patients with positive

tests, whereas the remaining 677 were successfully treated without anaphylaxis. Prick tests after 6 weeks and 6 months after the procedure showed acquired sensitization in 36% of the treated patients.

Bromelain

Bromelain is a sulfhydryl protease present in plants of the Bromeliaceae family, and most commonly extracted from the stems of pineapples (*Ananas comosus*). Its main uses are as a meat tenderizer, beer clarifier, and digestive aid. Claims of anti-inflammatory or antineoplastic activities are largely unproven scientifically.

Contact Urticaria: Our search could not find a report of contact urticaria from bromelain. However, Nettis et al. described generalized urticaria and angioedema, nausea, and diarrhea in a 47-year-old woman.[138] This reaction occurred within 10 minutes of the ingestion of Ananase, bromelain-containing tablets sold as nonsteroidal anti-inflammatory agent. Her investigation showed positive prick test to bromelain and positive RAST for bromelain and papain.

Allergic Contact Dermatitis: Raison-Peyron et al. published what is believed to be the only reported case of allergic contact dermatitis from bromelain.[139] Their patient, a 56-year-old woman, had a 2-month history of cheilitis. She had been using a mouthwash that contained bromelain and sodium bicarbonate. Patch testing was performed with the European standard series, a fragrance series, her own toothpaste, and mouthwash as well as the individual ingredients of the latter. After 3 days, the only positive reaction (++) was to bromelain 2.5% pet. Her lesions cleared with avoidance.

Respiratory Tract Involvement: In 1978, Galleguillos and Rodriguez were credited with the first report of airway sensitization to bromelain.[140] Their two patients, employed by a pharmaceutical laboratory, suffered repeated episodes of asthma and rhinitis triggered by exposure to bromelain dust. One patient who reported similar symptoms when eating pineapples could have been sensitized by ingestion. Both patients showed positive prick tests with bromelin 10 mg/mL and a positive bronchial challenge. In 1979, Baur and Fruhmann investigated a 58-year-old pharmaceutical worker who developed rhinitis and asthma when handling bromelain.[141] RAST and prick tests were strongly positive to bromelain and papain. The inhalation test with a minute amount of bromelain (0.03 mg) resulted in an immediate asthma attack. Oral challenge with pineapple provoked, within 30 to 40 minutes, asthma, nausea, abdominal pain, and diarrhea. The same year, Italian investigators published a series of four cases of occupational asthma from inhalation of bromelain.[142] Austrian authors later published another series of four workers of a blood grouping laboratory who inhaled bromelain powder on a daily basis and who developed occupational asthma.[143] Ingestion of fresh pineapple caused nausea and vomiting in one patient and anaphylaxis in another. All four had bromelain-specific IgE antibodies. Prick testing, performed in three subjects with very dilute solutions of bromelain (0.0001 mg/mL), was strongly positive and caused asthmatic attacks in two of them. The authors then tested 17 additional female workers from the same laboratory and found bromelain-specific IgE antibodies in seven, of whom 4 had respiratory symptoms. These cases emphasize the strong association between bromelain sensitization and occupational exposure, as recently reviewed by Van Kampen.[144]

Cross-Reactions: Because of the close similarity between the two enzymes, cross-reactivity with papain has been repeatedly demonstrated, either by the finding of concurrently positive skin tests to both enzymes in individuals who had been exposed to only one or by RAST inhibition assays.[141,145] Baur also found that wheat and rye flours, as well as grass and birch pollens, exhibit some degree of cross-reactivity with bromelain and papain.[145] In 1997, Tanabe et al. confirmed the cross-reactivity with bromelain in patients allergic to a water-soluble fraction of wheat flour,[146] whereas Pike et al. showed that antibodies prepared in rabbits against the major allergen from ryegrass cross-react with bromelain.[147]

Trypsin and Chymotrypsin

Together with elastase, chymotrypsin and trypsin are serine proteases produced in the pancreas and secreted in the duodenum to catalyze the breakdown of proteins into smaller peptides. Both enzymes are used as dietary supplements for patients with cystic fibrosis, and as topical, oral, nebulized, or injectable anti-inflammatory

agents. They have also found applications in tissue culture and proteomics laboratories, in food processing, in beer brewing and in "bating" leather to make it supple before tanning.

Contact Urticaria: No case report could be found.

Contact Dermatitis: No publication was found.

Systemic Reactions: A 28-year-old graduate student developed rhinoconjunctivitis whenever he was weighing chymotrypsin powder. Intradermal testing with 0.01 mL of a 0.025-mg solution of chymotrypsin produced a strong local reaction, accompanied by signs of anaphylaxis that responded to injected epinephrine and antihistamines.[148] Passive transfer tests in three healthy volunteers gave positive results. A man was treated for epididymitis with repeated intramuscular injections of chymotrypsin. After the seventeenth injection, he developed wheezing and generalized urticaria followed by anaphylactic shock and convulsions.[149] He fortunately recovered with repeated intravenous injections of epinephrine and hydrocortisone succinate. The patient reported by Howell was not so fortunate: he had received a single injection of chymotrypsin after a car accident. Three years later, a second injection was administered after suturing of facial lacerations. Within minutes, he collapsed and became unconscious without discernible pulse and respiration. Aggressive management of his anaphylactic shock was successful, but the patient was left with severe neurologic deficit secondary to cerebral anoxia.[150]

Respiratory Tract Involvement: A research chemist developed severe rhinoconjunctivitis when handling small amounts of crystallized chymotrypsin and trypsin.[151] Intradermal testing was positive with both enzymes, their inactivated forms, and their zymogen precursors. Also tested with these preparations, an asymptomatic worker in the same laboratory showed positive reactions to trypsin. In both cases, inhalation was the postulated route of sensitization.[151] A case of occupational asthma was confirmed by positive intradermal tests and inhalation tests with trypsin in a worker employed in the extraction of this enzyme from bovine and porcine pancreas.[152] Fourteen workers were exposed to airborne trypsin powder in a plant that produced plastic polymer resins.[153] Four of these workers developed occupational asthma, proven to be due to trypsin hypersensitivity by positive scratch tests, inhalation challenge, and passive transfer of IgE antibodies.

Collagenase

Collagenase is a metalloproteinase that specifically degrades various collagens, mostly type I and type III. It is produced in large amounts by some bacteria, notably *Clostridium* species, the microorganisms responsible for gas gangrene. Extracted from *Clostridium histolyticum*, collagenase is a mixture of various proteases that includes clostridiopeptidase A. For many years, it has been used topically for enzymatic wound debridement.[154,155] In 2010, an injectable formulation has received Food and Drug Administration approval for treatment of Dupuytren's contracture.[156] It is currently being studied as a nonsurgical approach in Peyronie's disease.

Contact Urticaria: A PubMed search retrieved no case of contact urticaria from topical exposure to collagenase.

Contact Dermatitis: Four publications describe eight cases of allergic contact dermatitis from exposure to collagenase ointment.[157–160] In each case, the ointment was applied for debridement of leg ulcers. Braun's two patients reacted to the ointment and to collagenase.[157] The patient of Lisi and Brunelli presented an exudative and crusted dermatitis on her legs after treating venous ulcers for 2 months with a collagenase ointment.[159] She subsequently developed widespread autoeczematization that cleared with oral corticosteroids and withdrawal of the ointment. Patch tests were positive with the ointment but negative with its vehicle. Testing with collagenase was not preformed. Foti et al. described four patients with leg ulcers who developed periulcerative eczema after using collagenase ointments.[160] Only one had a strong positive patch test reaction to the ointment, whereas the other three had doubtful reactions. However, all four reacted to clostridiopeptidase A 1% pet. The authors concluded that many cases could be missed if tested with the ointment alone. In a prospective study of 45 patients with chronic wounds, Freise et al. performed patch testing with comprehensive series that included wound care products and dressings.[161] Iruxol N, a collagenase ointment, was positive in three patients.

Respiratory Tract Involvement: A single case report describes the cooccurrence in a laboratory technician of occupational asthma from mouse allergens together with symptoms of rhinoconjunctivitis from exposure to powdered collagenase.[162] Inhalation challenge reproduced the symptoms and specific IgE antibodies were detected to the collagenase that she used in her work.

Rennet

Rennet is a mixture of enzymes secreted in the fourth stomach, or abomasum, of ruminants. Its main constituents are pepsin and rennin, also known as chymosin. Extracted from cattle stomach or produced by microbial fermentation, rennet's main use is to coagulate casein into curds in cheese making. Although natural chymosin and substitutes generated from genetic engineering are used exclusively in the production of cheese, pepsin is also used to prepare protein hydrolysates for the food industry, to remove hair from hides in the leather industry, and, in some immunological assays, to digest the Fc fragment from antibodies.

Contact Urticaria: A PubMed search was unable to retrieve cases of contact urticaria caused by pepsin or chymosin.

Contact Dermatitis: A similar search was also negative for cases of allergic or irritant dermatitis from contact with either enzyme.

Respiratory Tract Involvement: In 1940, Maisel published the first case of rhinitis and asthma caused by pepsin.[163] His patient was a pharmacist who developed respiratory symptoms while weighing powdered pepsin. He had a positive prick test with pepsin 1% in buffered saline. Niinimäki and Saari described a female cheese maker with a 3-year history of shortness of breath caused by a powdered rennet substitute.[164] Scratch tests were positive with Suparen, a rennet from *Endothica parasitica*, but negative to animal rennet from calf stomach. Her symptoms resolved when the powdered rennet was replaced with a liquid one. A quality control supervisor in a pharmaceutical company with a history of asthma experienced worsening of his symptoms when exposed to the dust of pepsin, herbs, and pollens at work.[165] Inhalation challenge with pepsin produced moderate rhinoconjunctivitis and severe asthma after 1 minute. Prick tests, RAST, and RAST-inhibition assays were also positive. The cheese maker described by Añibarro Bausela and Fontela had similar symptoms and was sensitized to both pepsin and lysozyme, but not to chymosin.[166] Jensen et al. studied the prevalence of allergic sensitization in workers of a rennet-producing plant.[167] Thirty-five employees were examined and 12 complained of work-related respiratory symptoms. Skin prick tests were positive in 14 workers, mostly with pepsin-rich rennet. Sensitization was most common among workers handling rennet powder, considered to be strongly allergenic. Van Kampen has recently reviewed the published literature on occupational sensitization to rennet.[16]

Lipase

Lipase is a digestive enzyme that catalyses the hydrolysis of fats. It is found in porcine pancreatic extracts used for digestive remedies, in detergents, and in the production of bread and cheese. An extensive literature search did not find any cases of contact hypersensitivity, immediate or delayed, to lipase.

Respiratory Tract Involvement: Workers exposed to this enzyme in the pharmaceutical and detergent industry have been reported to develop occupational asthma.[83,105,169,170]

Conclusion

Cutaneous contact with enzymes may give rise to irritant reactions, which appear more common with proteolytic enzymes due to their direct effect on epithelial integrity. As well, inhalation of large amounts of proteases can damage the airway and lead to the development of emphysema.[171] More commonly, however, enzymes behave as allergens and are mostly responsible for immediate reactions mediated by specific IgE antibodies. The clinical manifestations can include contact urticaria and protein contact dermatitis, but the upper and lower respiratory tracts are involved much more often, usually from inhalation of airborne dust. The role of atopy in the development of sensitization to enzymes is controversial: a number of publications report a greater frequency of sensitization in atopics,[33,68,97,107,124,133,172] whereas other authors find no such association.[105,143,173] T-cell-mediated allergic contact dermatitis occurs much more rarely, probably because of the large size of the enzyme molecules and poor epidermal penetration. In some of the cases in which a delayed positive patch test reaction was seen, sensitization occurred after the enzyme had been applied to damaged skin. With the exception of those cases in which the enzymatic preparation was used as medication, cutaneous or respiratory sensitization occurs in the occupational setting.

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20

Contact Urticaria Syndrome from Epoxy Resin

Monica Hindsén and Magnus Bruze

Use

Epoxy resin is commonly used. Examples of occupational exposure are components of paints, cement additives for quick bonding, and in manufacturing electrical equipment for enclosing transformers, condensers, and other components in aircraft and other industries for adhesive purposes these application represent mainly occupational exposure.[1–4] Nonoccupational exposure is also common; for example clothes,[5] hairpins,[6] ostomy bags,[7] and nasal cannulae.[8]

Epoxy-Resin System

Epoxy resins are components of an epoxy resin system. Besides epoxy resins there are other components in the epoxy resin system such as curing agents, reactive diluents, modifiers, and additives. The resins and the reactive diluents are epoxy compounds, whereas the other components represent other chemical substances and groups.

Diglycidyl ether of bisphenol A (DGEBA) is the monomer in the most commonly used epoxy resin (Figure 20.1). Diglycidyl ether of bisphenol F is a chemically closely related monomer present in epoxy resins. Examples of monomers in other epoxy resins are diglycidyl ether of tetrabromobisphenol A, tetraglycidyl-4, 4′methylenedianiline, and triglycidyl derivative of paraaminophenol.

Allergic Contact Dermatitis

The most frequent cause of occupational allergic contact dermatitis from epoxy resin is the one based on diglycidyl ether of bisphenol A.[1] This is the reason why such an epoxy resin (based on DGEBA) is included in most baseline patch test series in the world.

Contact dermatitis caused by epoxy resin is often described in the literature.[1–3] Besides contact allergy to epoxy resins, the reactive diluents and curing agents are often contact sensitizers.

Contact Urticaria

Contact urticaria from epoxy compounds has infrequently been reported.[1] The reported cases often represent occupational cases. Maybe the first case with contact urticaria was reported in 1961 when aliphatic polyamide hardeners were reported to generate immediate reactions.[9] Patch testing with epoxy resin was reported to induce a generalized urticarial and asthmatic reaction.[1,10]

A case of occupational contact urticaria from methylhexahydrophthalic and methyl tetrahydrophthalic anhydride has been reported as an immunologic airborne contact urticaria.[11]

Contact urticaria to epoxy resin in an aircraft factory has been reported in a 23-year-old man with a 6-month history of recurrent pruritus and urticarial wheals and sometimes with angioedema.[12] He had positive urticaria reactions at prick testing to epoxy resin (1% pet) and to the reactive diluents phenyl glycidyl ether (0.25% pet) and cresyl glycidyl ether (0.25% pet). He also had specific immunoglobulin E antibodies to epoxy.

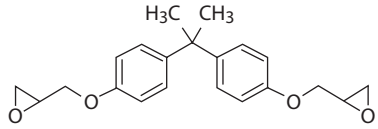

FIGURE 20.1 Diglycidyl ether of bisphenol A.

The acid anhydrides are well-known occupational respiratory allergens.[12] They have been reported to cause contact urticaria in workers in an electronic plant.

Acid anhydrides are widely used in production of alkyd and polyester resins and as curing agents of epoxy resins.[13] Adverse health effects of occupational exposure to several anhydrides have been described including contact urticaria from methylhexahydrophthalic anhydride, methyltetrahydrophthalmic anhydride, and hexahydrophthalic anhydride.

A man worked in a factory that used plastic composite materials in various processes.[14] He developed work-related eczema and half a year later he also developed edema of the lips and eyelids as well as urticarial reactions on other skin areas. Skin prick test with his "own" epoxy resins sealant compound provoked a positive wheal. He also had a positive prick test to DGEBA and the sealing compound in acetone-water (0.1%). A radioallergosorbent test to DGEBA-human serum albumin was negative. DGEBA may also cause asthma.

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21

Contact Urticaria Syndrome from Foods and Food Derivatives

Angèle Soria and Pascale Mathelier-Fusade

Contact urticaria syndrome (CUS) was first defined as a biologic entity in 1975 by Maibach and Johnson.[1] This syndrome is characterized by an immediate development of contact skin reaction that appears after contact with eliciting substances. These cutaneous symptoms can be associated to systemic manifestations.

Definition and Clinical Presentation

Patients suffering CUS most of the time develop contact urticaria. Usually, contact urticaria refers to a wheal-and-flare reaction elicited within 15–20 minutes and is strictly localized to where the offending substance has been in contact. Then the reaction disappears completely within 30–60 minutes without residual symptoms. Sometimes contact urticaria can spread appearing as generalized urticaria and can affect extracutaneous organs (e.g., bronchospasm, rhinoconjunctivitis, abdominal pain, diarrhea, vomiting).[2] More rarely it can be associated to anaphylactic shock. The severity of these symptoms depends on the allergen or preexisting conditions such as atopic dermatitis.[3,4]

Dermatitis/eczema immediately after contact with the trigger substance may be also observed in CUS. Hjorth and Roed-Petersen defined protein contact dermatitis (PCD) in 33 food caterers with hand dermatitis in 1976.[5] The typical clinical presentation consisted in pruritus 10–30 minutes after contact with proteins such as meat, fish, or vegetables and followed a few hours after by erythema and vesiculation. Application of the relevant food to the affected skin resulted in either urticaria or vesiculation.[6]

In PCD, the hands are the most commonly affected site, but lesions can be localized on the tips of the first, second, and third fingers. Other sites may be affected such as wrists, forearms, and face. Extracutaneous manifestations can be also observed (respiratory symptoms, gastrointestinal symptoms) but rarely.[7,8] Chronic paronychia in food handler is considered as a clinical variety of PCD.[9] In this atypical presentation of PCD, patients have an immediate erythemato-edematous or vesicular reaction on the proximal nailfold in contact with the food. The reaction is associated with moderate itching. An association between atopy and PCD occurred in approximatively 50% of the patients. Food handlers, cooks, caterers, bakers, and butchers are at risk from CUS because most of the reported cases are occupational.[10]

Patients suffering from CUS can develop CUS and/or dermatitis/eczema for the same substance and sometimes simultaneously.[11] Severity of CUS manifestations is classified according to the system of Von Krogh and Maibach (Table 21.1).[12] Stage 1 of CUS includes localized contact urticaria, immediate contact dermatitis, and an itching, tingling, or burning sensation. Stage 2 denotes generalized urticaria with or without angioedema. Stage 3 includes extracutaneous symptoms with bronchial asthma, rhinoconjunctivitis, and orolaryngeal and gastrointestinal symptoms; stage 4 is associated with severe anaphylaxis with anaphylactic shock.

TABLE 21.1

Diseases Involved in Contact Urticaria Syndrome

Contact urticaria	Stage 1
Immediate contact dermatitis	
Itch, tingling, or burning sensation	
Urticaria	Stage 2
Bronchial asthma	Stage 3
Rhinoconjunctivitis	
Orolaryngeal symptoms	
Gastrointestinal dysfunction	
Anaphylaxis	Stage 4
Anaphylactoid reaction	

Pathophysiogical Mechanisms

Nonimmunological Contact Urticaria

Two types of contact urticaria exist; a nonimmunological contact urticaria (NICoU) begins with some food contact by a nonsensitized individual, without the involvement of immunological processes. Vasoactive substances such as histamine, leukotrienes, and prostaglandins are released from the mast cell. This form is the most frequently encountered and usually has no systemic effect.

Preservatives, flavoring agents, food additives (benzoic acid, sorbic acid, cinnamic acid cinnamic aldehyde. and Balsam of Peru) are often involved in NICoU.[12,13] An animal model with guinea pig for studies on NICoU was used and showed various concentrations of inducing NICoU agents (i.e., benzoic acid, sorbic acid, cinnamaldehyde, cinnamic acid, methyl nicotinate, and dimethyl sulfoxide). This study showed that all responses were dose-dependent with dermal edema and perivascular infiltrate of eosinophils and lymphocytes.[14] NICoU reaction can be abolished by pretreatment with aspirin, suggesting prostaglandins are in part responsible for these reactions.[15]

Immunological Contact Urticaria

On the other hand, immunological contact urticaria (ICoU) occurs in sensitized patients usually with immunoglobulin E (IgE)-mediated type I hypersensitivity or sometimes with IgG or/and IgM pathways. ICoU occurs after sensitization by cutaneous, oral, or inhalation exposure and is more common in atopic individuals. These reactions are local but can be generalized with systemic symptoms including generalized urticaria, asthma, abdominal pain, rhinitis, and anaphylactic shock.

This specific sensibilization has been demonstrated through the passive transfer of serum from a sensitized individual to a nonsensitized individual with reaction to contact with the allergen; but this test is no longer performed for the diagnosis.

Common inducing ICoU agents are food additives and spices.[16]

A particular form of ICoU is PCD, which is considered to be a combination of immediate type I and delayed type IV allergic hypersensitivity.[17]

Food Responsible for CUS

Food proteins are the most frequent causative proteins involved in CUS. Janssens et al. have classified PCD into four groups; this classification can also apply to CUS.[18]

- Group 1: Fruits, vegetables, spices, plants
- Group 2: Animal proteins: meat (beef, pork, horse, lamb, chicken), fish (cod, herring, salmon) and crustaceans (shrimp, lobster), milk, cheese, saliva, blood, amniotic fluids of animals
- Group 3: Grains such as rye, wheat, barley, oats, corn
- Group 4: Enzymes (amylase)

Table 21.2 provides a list of the food having caused ICoU and NICoU.

TABLE 21.2

Foods Responsible for Immediate Contact Reaction

Meat	**Vegetables**	**Fruits**
Beef	Asparagus	Almond
Calf	Beans	Apple
Chicken	Cabbage	Apricot
Ham	Carrots	Apricot stone
Lamb	Castor bean	Banana
Liver	Celery	Kiwi
Pork	Chamomilla	Litchi
Sausage	Chicory	Lemon
Turkey	Chives	Lemon peel
	Coffee beans	Lime
	Cucumber pickle	Mango
Fish and seafood	Dill	Nuts
Cod	Endive	Orange
Crab	Fungi	Peach
Cuttlefish	Garlic	Peanuts
Frog	Lettuce	Peanuts butter
Herring	Lime	Plum
Lobster	Menthe	Strawberry
Mackerel	Mushrooms	Watermelon
Mullet	Mustard	
Oyster	Onion	**Seeds and grains**
Pilchard	Parsley	Sesame seeds
Plaice	Parsnip	Sunflower seeds
Shrimp	Potato	Buckwheat
	Rice	Flour
Other animal products	Rocket	Maize
Cheese	Runner bean	Malt
Eggs	Rutabaga	Rice
Honey	Salami casing molds	Wheat
Milk	Soybean	Wheat bran
	Stock (*Matthiola incana*)	
	Tomato	
	Winged bean	

Fruits and Vegetables

Raw fruits and vegetables such as apples, carrots, and tomatoes are a common cause of contact urticaria (especially ICoU) in daily life and are more often observed in atopic patients.[19] Most of the time, the same food but cooked does not induce contact urticaria. Preferentially CUS affects the hands, and typical localizations can be observed as with garlic and onion, affecting only the first, third, and fourth fingers of the nondominant hand.[20]

Thus fruits and vegetables represent the most frequent causes of food allergy especially in adults. If CUS is a common cause of food reaction especially in atopy, the most frequent clinical manifestation is oral allergy syndrome (OAS).[21] This syndrome is clinically close to CUS and is characterized by oral mucosal symptoms that may involve itching, stinging pain, and edema of the lips, tongue, palate, and pharynx with a sudden onset. Typically these symptoms appear within minutes after fruit and vegetable ingestion and resolve in less than 30 minutes. The relationship of OAS with atopic disease and allergic rhinitis is close. OAS is believed to be the immunological cross-reactivity consequence between respiratory allergens and structurally related proteins in the respective foods.[22] OAS is caused by IgE cross-reactivity between prior aeroallergen sensitization and plant-derived proteins. The recognition of these homologous proteins in foods by IgE antibodies specific for respiratory allergens induces clinical symptoms.

There are different groups of pollen-related food allergens responsible for causing OAS and the largest group is perhaps the pathogenesis-related proteins. In Europe, more than 70% of patients with birch pollinosis are allergic to pollen-related food allergens such as apple, cherry, and hazelnut. Major allergens responsible for these symptoms belong to a group exhibiting high-level homology with Bet v1. These allergens belong to the pathogenesis-related 10 protein family.[23] Typically only raw fruits and vegetables induce immediate allergic reaction, whereas the same foods are tolerated by birch pollen–allergic patients if the foods are cooked. Food allergens belonging to the lipid transfer protein (LTP) family have been also reported in a wide variety of fruits, vegetables, and pollen.[24,25] LTPs are major allergens implicated in Rosaceae fruit allergies in patients in southern Europe. Furthermore, they can cause fruit allergy even without pollinosis, and the symptoms are not only those of OAS but can be severe food anaphylaxis.[26,27] Typically, immediate allergic reactions with LTPs are observed with raw and cooked fruits and vegetables.

There are similarities between CUS and OAS because homologies between proteins are divided in botanic families. Thus in 2009 Alikhan et al. reported a 48-year-old atopic patient with 10-year history of contact urticaria elicited by vegetables belonging to the Solanaceae (tomato, red bell pepper, green bell pepper, Serrano pepper, jalapeno, pasilla pepper) and Alliaceae (garlic, yellow onion, green onion, leek) families, but not with the Asparagaceae, Asteraceae, Cucurbitaceae, Amaranthaceae, Apiaceae, or Piperaceae botanic families.[28]

Contact urticaria has been also described by a typical clinical presentation of peach allergy that may occur in the absence of any symptoms upon ingestion of the fruit. Curiously isolated contact urticaria is not observed with other Rosaceae fruits (apricot, apple, pear, cherry). This contact urticaria to peaches is associated more frequently with LTP Pru p3 and not with a higher level of peach-specific IgE. Asero notes that in several cases, contact urticaria may precede the onset of food allergy by years.[29] Interestingly, it seems that patients reporting contact urticaria from peaches have no symptoms with nectarines, a fruit botanically very close to the peach. One explanation is that LTP is present in large amounts in peach fuzz and fuzz is totally lacking on the skin of nectarines. So LTP released from peach fuzz might play a relevant role in the pathogenesis of contact urticaria.[30,31]

Animal Proteins

Fish is a common cause of food allergy in adult as well as in children.[32,33] Such reactions usually result from ingestion, as with any other food allergen, with the risk of severe anaphylaxis.[34] In these cases, patients react to heat- and denaturation-resistant allergens. Fish allergy may also emerge in CUS. Interestingly, contact urticaria and PCD are described in individuals having prolonged and repeated skin contact with raw fish; for example, cooks and fishmongers.[35] It appears that in these cases, fish allergy is the result of hypersensitivity to a thermolabile and gastrosensitive allergen and is limited to the contact site, because most of the time there is a good tolerance to fish ingestion.[36] This selectivity of such reactions has been studied by Porcel et al., who described

a 36-year-old woman with contact urticaria from handling raw fish and good tolerance to its ingestion.[37] The in vivo (prick tests) and in vitro (sodium dodecyl sulfate polyacrylamide gel electrophoresis, IgE immunoblot) tests performed with sole, hake, and cod demonstrate a type I hypersensitivity to heat-sensitive fish allergens as the underlying cause of contact urticaria from fish.

PCD and CUS have been reported with anchovy, [38] herring, [5] plaice, [5] cod, [5] mackerel, [39] mullet, [39] pilchard, [39] and isolated contact urticaria caused by IgE-mediated fish allergy exists even in the pediatric age.[40]

Seafood may also induce CUS. Crustaceans (shrimp, lobster) are frequently involved in PCD but contact urticaria with lobster, shrimp, and scallops has been also described.[41] Some cases of PCD to mollusk (i.e., cuttlefish) have been reported.[42]

In 1951, Seeberg reported three patients with PCD from handling meat. They all had relapsing vesicopapular rashes appearing two to 15 hours after contact with the meat. The diagnosis was confirmed by positive prick tests with boiled and raw meats.[43] These prick tests were later negative when the dermatitis had healed. Later, raw meat (beef, pork, lamb, chicken) or other animal parts, such as skin (chicken, turkey], liver (calf, chicken), gut (pig), and blood (cow, pig) have been found to cause either ICoU or NICoU in cooks, kitchen workers, butchers, and slaughterhouse workers.[44–47]

Grain Contact Urticaria

Wheat protein and its derivatives can cause asthma but also PCD, which mainly occurs in bakers. These reactions do not prevent the patient from consuming bread or cakes. Recently Matsuo et al. have identified a wheat 27-kDa allergen, peroxidase, and purple acid phosphatase as candidate allergens for wheat PCD. More recently, contact urticaria to cosmetics containing hydrolyzed wheat protein, produced by hydrolysis of gluten and used in certain cosmetics, has been reported.[48]

Rice is commonly thought to be nonallergenic. In 1992, a case report presented a young woman with hand erythema, eyelid, dyspnea, and cough after throwing raw rice at a wedding. She had never had a reaction from eating cooked rice. Prick testing was positive for rice and corn (episode of generalized acute urticaria after eating polenta six years prior). Scratch testing and use testing were positive for raw rice.[49] A similar case reports contact urticaria, rhinoconjunctivitis, and asthma after handling raw rice.[50,51]

PCD after corn flour or oatmeal exposures with positive handling tests have been also reported.[52–54]

Food Additive Responsible for Contact Urticaria, Contact Urticaria Syndrome, and Clinical Manifestations

Flavoring, Fragrances, and Taste Enhancers

Cinnamon and Derivatives

Cinnamon and its component cinnamic aldehyde are spices used in many products for flavor in toothpastes, mouthwashes, foods, mints, and chewing gums. Cinnamic acid is a metabolic product from cinnamaldehyde and cinnamic alcohol application on skin. Cinnamaldehyde is a more potent skin sensitizer than cinnamic alcohol. Cinnamic alcohol seems to be a prohapten that requires metabolic activation, presumably by oxidoreductase enzymes to produce a hapten: the protein-reactive cinnamaldehyde.[55]

Contact urticaria with cinnamon and its derivatives have been reported, including anaphylaxis, after contact. [56]. Open tests with a cinnamic aldehyde-containing product in patients with CUS and in control subjects may produce immediate erythematous or urticarial responses in all tested individuals, suggesting NICoU. The incidence of positive reactions was shown to depend on site of application, vehicle, concentration, and time of reading.[57] Many reports of delayed-type allergic contact dermatitis with cinnamic aldehyde have been described.[58,59]

A study with high-performance liquid chromatography coupled with mass spectrometry and ultraviolet spectrometry detected the presence in some tomato extracts of coniferyl alcohol and cinnamic alcohol.[60]

Menthol

Menthol (2-isopropyl-5-methyl cyclohexanol) is the active ingredient of peppermint and is used as flavoring in foods, cosmetics, mouth washes, and toothpastes. Contact urticaria to menthol is rare, but several clinical cases with menthol-containing products (i.e., toothpaste, cigarettes, and lozenges) have been reported.[61,62]

Condiments and Spices

Cardamom, caraway, and coriander produce mostly ICoU, and occupational ICoU dermatitis was described with people exposed to many powdered spices. Mucosal edema in children was described because of spices. There are common antigenic determinants in birch pollen and spices like in various fruits and vegetables, which explains the connection between immediate allergy to spices (and ICoU).

Some contact urticaria with coriander was reported, with a negative patch test but a positive prick test; this was considered a PCD.[63,64]

A case of immediate hypersensitivity to sesame in two patients with contact urticaria has been reported.[65]

Two cases of contact urticaria from curcumin were reported, mediated by uncertain mechanism, nonimmunologic or immunologic mechanisms, or both.[66]

Conservatives and Preservative Agents

Benzoic Acid, Sodium Benzoate, and Sorbic Acid

Benzoic acid occurs naturally in some fruits such as cranberries or blueberries. Sodium benzoate is the sodium salt of benzoic acid. Sodium benzoate is widely used to delay yeast spoilage of acidic foods and beverages.

Several clinical reports of adverse reactions to benzoate have been recorded with generalized urticaria and angioedema [67] or perioral contact urticaria from sodium benzoate from a toothpaste.[68] A case of occupational sensitization to benzoic acid was described, with anaphylaxis after eating food containing benzoic acid.[69]

Contact urticaria was observed in 18 of 20 kindergarten children following the intake and accidental perioral application of a mayonnaise salad cream. Twenty-minute patch tests with components of the salad dressing showed positivity with sorbic acid and benzoic acid in some healthy adult controls. A nonspecific contact urticaria has been reported in 5% of general population with sorbic acid. This phenomenon could be only partially blocked by local application of antihistamine before testing; suggesting a nonimmunological mechanism in these contact urticaria cases from sorbic and benzoic acids. Most CUS from conservative agents were a NICoU mechanism.[70]

Exacerbations of chronic or recurrent urticaria were described after ingestion of food additives (i.e., azo dyes, benzoic and sorbic acids, and tartrazine) occurring more frequently in acetylsalicylic acid–sensitive patients than in nonreactors.[16]

Sulfites

Sulfites and derivatives agents (sulphur dioxide, sodium sulfite, sodium bisulfite, sodium metabisulfite) are widely used as preservatives and antioxidant additives in many foods, beverages (sulfur dioxide were encountered especially in wines and beers), and pharmaceutical industries. Various clinical manifestations were described with topical, oral, or parenteral exposure to sulfites occurring a few minutes after ingestion or inhalation (i.e., flushing, urticaria, angioedema, diarrhea, nausea, abdominal pain, bronchospasm, hypotension, and anaphylactic reactions). Metabisulfites are incriminated in urticaria and angioedema reactions, not with contact urticaria.[71]

These reactions have been reported predominantly among patients with asthma; sulfites can cause bronchospasm in 4% of asthmatic patients and 8% of steroid-dependant asthmatic patients.[72] Sulfite-sensitive asthma is more common in adults than in children.[73] Several cases of systemic reactions to sulfites have been reported with IgE-mediated mechanism.[74–76] Few reports of adverse reaction to sulfites concern nonasthmatics. The pathogenesis of sulfite sensitivity is not clear and probably there is more than one mechanism. Metabisulfite and sulfites was considered as irritants, but the pathogenic mechanism of sulfite-induced reactions is unknown; probably, these adverse reactions to sulfites in foods are not immunologic reactions because of the negative results of skin tests with sulfites and derivatives and normal levels of histamine level during acute reactions.[74,77–79] But some authors have reported, in metabisulfite-sensitive patients, positive skin tests, challenge tests, and passive cutaneous transfer tests with metabisulfite, suggesting that some of these reactions might be IgE-mediated.[74]

Parabens

Parabens have been shown to elicit IgE-mediated hypersensitivity reactions with contact dermatitis among workers in the food industry, but no there is report in consumers, even those who are sensitized.[80]

Colorings, Agents, and Dyes

Contact urticaria and CUS with anaphylactic reactions attributed to ingestion of colorings is less common and has been reported with tartrazine, amaranth, sunset yellow, ponceau red, and quinine.[81] The sensitivity of the population to tartrazine had been evaluated between 0.03% and 0.15%.[81] Tartrazine is used in cotton candy, soft drinks, instant puddings, cake mixes, jam, jelly, gelatins, and mustard. In rare cases, tartrazine has been a trigger for urticaria or asthma. Cross-reactivity between tartrazine and acetylsalicylic acid has been suggested, but some studies are inconsistent. A Cochrane meta-analysis reviewed studies linking the synthetic yellow dye tartrazine and asthma; this study concluded the lack of evidence about effect of tartrazine on asthma.[82]

Contact urticaria to natural coloring agents is rare. A case of ICoU with cochineal red A and allura red AC was reported in children with positive open skin tests in red Play-Doh containing food coloring.[83]

Carmine is a common red food coloring obtained from the bodies of cochineal insects; it is used in juices, ice cream, yogurt, and candy. Some cases of adverse reactions to carmine following ingestion have been reported, suggesting an IgE-mediated hypersensitivity. In almost all of the reported cases, the sensitization to carmine was topical exposure (cosmetics or occupational exposure). It is not known whether all individuals with carmine sensitivity induced through topical use are sensitive to the ingestion of carmine in foods, but reactions to carmine ingestion are rare probably from the low use levels of carmine in foods and beverages.[84–87]

Only one anaphylactic reaction to saffron, a yellow food coloring obtained from the flower of *Crocus sativa*, suggesting an IgE-mediated reaction, has been reported as compared with the high use of saffron, which suggests that sensitivity to saffron is extremely rare.[84]

Annatto is a yellowish orange coloring used particularly in cheddar cheese, ice cream, and beverages obtained from the seeds of the tropical tree *Bixa orellana*; a case of anaphylaxis [88] and a case of urticaria/angioedema [89] have been reported.

Diagnosis

Diagnosis of contact urticaria/PCD is based on a full clinical history and skin tests. Patients should be asked about

- Their medical history, especially atopic history.
- Their occupation: some workers are prone to develop CUS with food (such as cooks, bakers, and butchers).
- The list of food handled at home and at work.
- The relationship between the development of the clinical manifestations and the contact with the suspected food and the recurrence of the disease on reexposure to the same substance.

- The site of the lesions (hands+++, fingers, forearms).
- The association to extracutaneous manifestations.

Skin Tests

Skin tests are preferably performed with the suspected fresh or native food. If the patient suffers from severe manifestations (grade 2, 3, or 4), tests will be done with the necessary precautions and resuscitation facilities immediately available. Several steps of testing are recommended.[90,91]

Before testing, antihistamines should be stopped by patients for at least three days, as should skin applications of local corticosteroids. Open application testing can first be performed on intact skin. If no reaction occurs, the testing can be repeated on previously affected or currently mildly affected skin. In case of negative response, prick tests should be performed with fresh material or commercial extracts. Prick tests are the gold standard because open testing is generally negative unless the substance is applied on damaged skin. Positive reactions are observed after 15 to 20 minutes. Sometimes a rubbing test (gentle rubbing with the material) on intact or lesional skin might be indicated. Scratch and scratch-patch testing carry a high risk of false-positive reactions.

In vitro Tests

Specific IgE tests with the suspected food can be performed, but RAST tests are less sensitive than native skin tests. Curiously, although PCD presents clinically as chronic eczema, patch tests are usually negative.

In food allergy, reactions may be species- and organ-specific. So contact urticaria to cod does not imply a reaction to all fishes. Calf's liver may provoke a reaction, whereas chicken liver may not. Chicken meat may provoke a reaction, whereas chicken liver may not. So it is important to test different species of food, raw and cooked, before avoiding them.

No in vitro tests are actually validated for food additive sensitivity; the basophil degranulation tests can be help in such cases. No commercial RASTs for food additives were available.[16]

Challenge Tests

For mucosal or perioral reactions, the oral mucosal test deposits substances on the mucosa; within 20 minutes, swelling of mucosa, lips, or throat were noted, with sometimes rhinitis or conjunctivitis, which are exceptionally generalized reactions with urticaria. Also, oral challenge tests with substances tested given in a capsule and in a double-blind manner can be useful.

Skin test and challenge tests should be performed near people entrained to resuscitation with suitable equipment, taking into account the possibility of systemic reactions.

Treatment

First-line therapy is allergen avoidance after testing. In addition, treatments that inhibit the mastocyte degranulation and effect of mast cell mediators can ameliorate or suppress symptoms. When dermatitis is present, topical steroids can be used and antihistamines are helpful in the management of urticaria. Severe cases of CUS may require a short course of oral steroids or even treatment in an emergency unit.

Conclusion

Food responsible for CUS includes fruits, vegetables, spices, plants, animal proteins, grains, and enzymes. Food proteins are the most frequent causative proteins for contact urticaria and PCD. The diagnosis and the identification of the responsible agent are based on a full clinical history and accurate skin tests. Food additives

responsible for CUS include flavorings, fragrances, taste enhancers, conservatives and preservatives, and colorings agents and dyes. For these substances, the cutaneous provocation tests need to be defined and standardized. Once the diagnosis is done, the avoidance approach is recommended. In most cases, it is necessary to implement occupational preventive measures.

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22

Cosmetic Components Causing Contact Urticaria Syndrome: An Update

Lien Verhulst and An Goossens

Introduction

The term *contact urticaria* (CoU) was introduced by A.A. Fisher in 1973 and refers to a wheal-and-flare reaction after external contact with a substance.[1] CoU is classified as nonimmunologic (type A) and immunologic (type B), and a third category (type C) for reactions with mixed features or for which mechanisms and pathophysiologic features are not well-understood.

Nonimmunological CoU (NICoU) is an immediate contact reaction of the skin without previous sensitization to the agent. The skin lesions are restricted to sites of contact and they rarely cause systemic manifestations. Substances eliciting NICoU do not result in nonspecific histamine release from mast cells because antihistamines cannot inhibit NICoU reactions elicited, for example, by benzoic acid, cinnamic acid, cinnamic aldehyde, methyl nicotinate, or dimethylsulfoxide.[2]

Immunological CoU (ICoU) is probably less frequently seen in clinical practice than NICoU; however, the mechanism is better understood. The pathogenesis of ICoU is identical to other types of immediate hypersensitivity reactions and involves coupling of percutaneously absorbed antigen with specific immunoglobulin E (IgE) molecules on the surface of mast cells. The cutaneous symptoms result from the release of histamine. ICoU is a type I hypersensitivity reaction occurring in a previously sensitized individual.[3]

A classic example for type C CoU used to be ammonium persulfate, which is used as bleaching agent. It has been shown that it may cause IgE-mediated hypersensitivity reaction.[4]

In 1975, contact urticaria syndrome was first defined as a biological entity by Maibach and Johnson; ever since, numerous cases have been reported together with a broad spectrum of clinical manifestations.[5] Immediate reactions usually start within 30 to 60 minutes after cutaneous exposure and clear completely within 24 hours. Delayed-onset CoU appears within 4 to 6 hours. The mechanisms for this delay are unknown, although a slower percutaneous penetration could offer an explanation.[5]

Contact urticaria syndrome manifestations reflect the dose and exposure route of the responsible substance: they can be strictly limited to the contact areas, but other sites may also be affected, and generalized urticaria may be present with involvement of internal organs, depending upon the allergen or preexisting conditions such as atopic dermatitis.

The classical four-step staging of the syndrome remains rational.[6] The local symptoms range from nonspecific symptoms such as itching, tingling, and burning sensation to a wheal-and-flare response restricted to the area of contact (stage 1). Generalized urticaria after local cutaneous contact is not frequently reported (stage 2). Stage 2 also includes angioedema. Extracutaneous manifestations may include the respiratory (bronchial asthma or rhinoconjunctivitis), orolaryngeal, or gastrointestinal tracts (stage 3). Anaphylactic reaction is the most severe stage of this possible multisystemic disease (stage 4). Wakelin et al. suggest that the consequences of NICoU are less serious than for ICoU because reactions may remain localized to the area of contact and there is no involvement of internal organs such as the respiratory or gastrointestinal tract.[7] However, according to Davari and Maibach, even NICoU can be a component of contact urticaria syndrome and cause anaphylactic shock.[8]

The epidemiology of CoU is not easy to determine and the symptoms are easily recognizable when wheal-and-flare reactions are present; however, there is confusion about the milder reactions.[7,9]

We will provide an update of the literature concerning contact urticaria syndrome caused by ingredients present in cosmetic products.

Methods

Research methodology involves different databases: Medline, CDESKPRO, PubMed, and LIMO. A literature review was performed on search terms (contact urticaria syndrome) AND (cosmetics), (contact urticaria syndrome) AND (fragrances), (persulfate) OR (ammonium persulfate) OR (potassium peroxymonosulfate), (contacturticaria OR systemic) AND hair dyes, (IgE OR immediate) AND cosmetics, (contacturticaria) OR (type 1) OR (immediate).

Many of the reported cases, however, often lacked appropriate controls and detailed investigation.

Cosmetic Components Causing Contact Urticaria Syndrome

Cosmetics have been used for millennia to embellish the physical, mental, and spiritual well-being of mankind. Virtually everyone today uses cosmetics in the form of hair products, skin moisturizers, facial makeups, nail products, cleansers, deodorants, and fragrances. Adverse reactions to cosmetics include allergic and irritant contact dermatitis, photosensitivity reactions, depigmentation, and contact urticaria (syndrome); the latter is taken into account in this review [10] (Table 22.1).

TABLE 22.1

Cosmetic Agents Causing ICU, NICoU, and CUS

Products	Reactions	Case Reports
Hair dye products		
Paraphenylenediamine	ICoU, asthma, angioedema	Mavroleon, 1998 [65] Calnan, 1967 [66] Edwards, 1984 [67] Temesvari, 1984 [68] Goldberg and Herman et al., 1987 [13] Fukunaga and Kawagoe et al., 1996 [69] Belton and Chira et al., 1997 [70] Sahoo and Handa et al., 2000 [71] Wong and King, 2003 [72] Birnie, 2007 [73]
Para-aminophenol/ para-methylaminophenol	Anaphylaxis	Nagano and Kanao et al., 1991 [74] Oshima et al., 2001 [11]
Para-toluenediamine	Anaphylaxis	Pasche-Koo and French et al., 1998 [12] Taniguchi and Higashi et al., 2000 [75]
N'N'-bis-(4-aminophenyl)-2,5-diamino-1,4-quinone-diimine (Brandowski's base)	Anaphylaxis	Goldberg and Herman et al., 1987 [13]
Henna	ICoU, conjunctivitis, rhinitis, asthmatic symptoms	Pepys and Hutchcroft et al., 1979 [76] Starr and Yunginger et al., 1982 [77] Cronin, 1979 Majoie and Bruynzeel, 1996 [79]

TABLE 22.1 (*Continued*)

Cosmetic Agents Causing ICU, NICoU, and CUS

Products	Reactions	Case Reports
		Bolhaar and Mulder et al., 2001 [80] Onder and Atahan et al., 2001 [81] Davari and Maibach, 2011 [8]
Basic Blue 99	ICoU, oral and auricular swelling and itching	Wigger and Elsner et al., 1996 [82] Jagtman, 1996 [83] Davari and Maibach, 2011 Nonpublished case (KU Leuven), 2013
Persulfate	NICoU, asthma, anaphylaxis	Calan and Shuster et al., 1963 Brubaker, 1972 Fisher and Dooms-Goossens et al., 1976 Pepys and Hutchcroft et al., 1979 White and Catchpole et al., 1982 Kellett and Beck, 1985 Blainey and Ollier et al., 1986 Pankow and Hein et al., 1989 Schwaiblmair and Baur et al., 1990 Van Joost and Roesyanto, 1991 Parra and Igea et al., 1992 Wrbitzky and Drexler et al., 1995 Yawalker and Helbling et al., 1999 Borelli and Wuthrich, 1999 Perfetti and Galdi et al., 2000 Rodríguez and Gozalo et al., 2001 [95] Aalto-Korte and Mäkinen-Kiljunen, 2003 [4] Babilas and Landthaler et al., 2005 [96] Moscato and Pignatti et al., 2005 [97] Harth and Raulf-Heimsoth et al., 2006 [98] Bregnhøj and Søsted, 2009 [99] Becker and Geier et al., 2010 [100] Hoekstra and Van Der Heide et al., 2012 [101] Hougaard and Menné et al., 2012 [102]
Meta-aminophenol	CUS	Tsunoda and Horiuchi et al., 1993 [103]
Ortho-aminophenol	CUS	Tsunoda and Horiuchi et al., 1993 [103]
2,4-diaminophenoxyethyanol-HCL	Generalized pruritus and erythema, anaphylaxis	Nosbaum and Dupin et al., 2012 [104]
Antimicrobial agents and preservatives		
Chlorhexidine	ICoU, Quincke's edema, dyspnea, anaphylaxis	Ohtoshi and Yamauchi et al., 1986 [105] Okano and Nomura, et al., 1989 [20] Evans, 1992 [106] Torricelli and Wüthrich, 1996 [107]

(*Continued*)

TABLE 22.1 (*Continued*)

Cosmetic Agents Causing ICU, NICoU, and CUS

Products	Reactions	Case Reports
		Thune, 1998 [108] Snellman and Rantanen, 1999 [109] Krautheim and Jermann et al., 2004 [19] Garvey and Krøigaard et al., 2007 [110] Nagendran and Wicking et al., 2009 [111] Silvestri and McEnery-Stonelake, 2013 [18] Wittczak and Dudek et al., 2013 [112]
2-phenoxyethanol (Euxyl-K 400)	ICoU, anaphylaxis	Bohn and Bircher, 2001 [23] Hernández and Ortiz-Frutos et al., 2002 [22] Birnie and English, 2006 [24] Lujan and Hernandez-Machin et al., 2009 [113] Núñez Orjales and Carballas et al., 2010 [21]
Polyaminopropylbiguanide	Anaphylaxis	O Kautz et al., 2012 [25] Nonpublished case (KU Leuven), 2013
P-chloro-m-cresol	Angioedema, hives	Walker and Chalmers et al., 2004 [26]
Sorbic acid	CUNS	Rietschel, 1978 [34]
Sunscreens		
Benzophenone-3	Anaphylaxis	Ramsay and Cohen et al., 1972 [114] Berne and Ros, 1998 [115] Emonet and Pasche-Koo et al., 2001 [116] Yesudian and King et al., 2002 [28] Landers and Law et al., 2003 [27] Bourrain and Amblard et al., 2003 [29] Spijker and Schuttelaar et al., 2008 [30]
Fragrance components		
Balsam of Peru	CUNS	Rudzki and Grzywa, 1976 [117] Forsbeck and Skog, 1977 [118] Temesvári and Soos et al., 1978 [119] Katsarou and Armenaka et al., 1999 [120] Cancian and Fortina et al., 1999 [31] Tanaka and Matsumoto et al., 2004 [121]
Fragrance mix	CUNS	Tanaka and Matsumoto et al., 2004 [121] Temesvári and Németh, 2002 [122] Cancian and Fortina et al., 1999 [31]
Cinnamal	CU type C	Diba and Statham, 2003 [32]
Cassia oil	CUNS	Rudzki and Grzywa, 1976 [117] Rietschel, 1978 [34]
Geraniol	Edema	Yamamoto and Morita et al., 2002 [33]
Toothpaste flavors		
Menthol, mint	ICoU, rhinitis, asthma, anaphylaxis	Holmes and Freeman, 2001 [35] Andersson and Hindsén, 2007 [37] Paiva and Piedade et al., 2010 [36]

TABLE 22.1 (*Continued*)

Cosmetic Agents Causing ICU, NICoU, and CUS

Products	Reactions	Case Reports
Carvone	Angioedema	Hansson and Bergendorff et al., 2011 [38]
Hair glue		
Latex	Anaphylaxis	Cogen and Beezhold, 2002 [39]
Botanically derived cosmetic ingredients		
Chestnut	Anaphylaxis	Seitz and Trautmann, 2011 [49]
Oat	ICoU, oral allergy syndrome	Boussault and Léauté-Labrèze et al., 2007 [41] Vansina and Debilde et al., 2010 [42]
Wheat protein	ICU, Anaphylaxis	Kousa and Strand et al., 1990 [123] Freeman and Lee et al., 1996 [129] Pasche-Koo and Claeys et al., 1996 [124] Niinimäki and Niinimäki et al., 1998 [43] Sanchez- Pérez and Sanz et al., 2000 [125] Varjonen and Petman et al., 2000 [47] Pecquet and Laurière et al., 2002 [48] Laurière and Pecquet et al., 2006 [46] Chinuki and Kaneko et al., 2011 [45]
Protein hydrolysates	CUNS, conjunctivitis, rhinitis, bronchospasm	McFadden and Rycroft et al., 2000 [44] Varjonen and Petman et al., 2000 [47] Pasche-Koo and Claeys et al., 1996 [124] Pecquet and Lauriere et al., 2002 [48] Laurière and Pecquet et al., 2006 [46] Olaiwan and Pecquet et al., 2010 [126] Barrientos and Vazquez et al., 2012 [127]
Soybean	Facial erythema and swelling	Shaffrali and Gawkrodger, 2001 [50]
Sesame	Generalized CUNS, anaphylaxis	Birnbaum and Porr et al., 1997 [52] Smith and Wakelin et al., 1998 [128] Pecquet and Leynadier et al., 1998 [51]
Fish derived elastin	ICoU	Nishida and Tateishi et al., 2012 [53]
Crotein Q (protein hydrolysate)	ICoU, angioedema, bronchospasm	Kousa and Strand et al., 1990 [123] Pasche-Koo and Claeys et al., 1996 [124] Freeman and Lee et al., 1996 [129] Niinimäki and Niinimäki et al., 1998 [43]
Panthenol	CUNS	Schalock and Storrs et al., 2000 [54]
Citrus seed	Anaphylaxis	Glaspole and de Leon et al., 2007 [55]
Chamomile and mango	Oral allergy syndrome, angioedema	Rudzki and Zawisza et al., 1999 [56] Rudzki and Rapiejko et al., 2003 [130]
Tilia cordata (linden) and *M. chamomilla,* banana	Itching and erythema, rhinoconjunctivitis	Subiza et al., 1990 [57] Foti and Nettis et al., 2000 [58] Krakowiak and Krecisz et al., 2004 [59]

(*Continued*)

TABLE 22.1 (*Continued*)

Cosmetic Agents Causing ICU, NICoU, and CUS

Products	Reactions	Case Reports
Permanent makeup and tattoo		
Tattoo ink	Anaphylaxis	Lee-Wong et al., 2009 [60]
Alcohol contact urticaria syndrome	Urticarial papules	Rilliet and Hunziker et al., 1980 [64]
Rouge	CUNS	De Groot and Liem, 1983 [131]
Other cosmetic ingredients		
Glyceryl thioglycolate	Type I, type IV	Engasser et al, 2000 [132]

Note: CUNS, contact urticaria nonspecified.

The Culprits

Hair Dye Chemicals and Bleaches

Constituents of hair dyes are common causes of allergic contact dermatitis in both hairdressers and those who dye their hair, but there are few reports of them causing immediate-type hypersensitivity. The development of anaphylaxis or respiratory symptoms appears to be rare, although such reactions might be underdiagnosed because patients may not relate respiratory symptoms to their skin problem.

Among the causal hair dye ingredients, the following dyes have been reported as inducers of CoU, sometimes with systemic symptoms: the permanent oxidation hair dyes para-phenylenediamine and its derivatives, such as para-aminophenol and para-methylaminophenol,[11] and para-toluenediamine.[12] The reaction seems to occur only after oxidation by H_2O_2 and is partially reversed when the antioxidant sodium sulfite is added to the mix.[12] Goldbert et al. were able to identify the oxidation product of para-phenylenediamine that is causing the reaction: N'N'-bis-(4-aminophenyl)-2,5-diamino-1,4-quinone-diimine.[13]

The natural permanent hair dye henna, derived from the leaves of the shrubs *Lawsonia alba* or *Lawsonia inermis*, also used to stain nails and skin, has caused immediate hypersensitivity as well, with symptoms such as rhinitis, conjunctivitis, sneezing, urticaria, and asthmatic symptoms. IgE-mediated hypersensitivity and a positive prick test from a commercial henna extract were reported.[9] Sensitization mainly occurs through inhalation of henna powder dispersed in the air.[14]

Also direct hair dyes (i.e., Basic blue 99 dye and patent blue dye) have been reported in this regard, mainly through occupational exposure.[8] Figure 22.1 illustrates one of our patients, a female hairdresser, who reported itching on the hands and in both ears, as well as a bad taste in her mouth whenever she applied a temporary hair dye lotion to a client's scalp. Prick testing was positive to the hair dye solution itself, as well as to Basic blue 99 and Basic Brown 17, both present in the causal product.

Persulfate salts are widely used in hair-bleaching formulas: they have a strong oxidizing action that accelerates the bleaching process and also makes the hair more receptive to the dyes, especially the light shades.[4] Nowadays, potassium persulfate is more frequently used than ammonium salt, because the latter has an unpleasant odor.[15] Ammonium persulfate is a low-molecular-weight chemical and is a known cause of urticaria, contact dermatitis, rhinitis, and asthma, the latter mainly by inhalation in an occupational context.[1] Asthmatics seem to be particularly susceptible to develop such reactions.[16] Some studies could demonstrate specific binding of IgE to persulfates by two methods, immunospot and radioallergosorbent test, hence the mechanism of immediate hypersensitivity to persulfates seems to be IgE-mediated at least in some patients.[4] Yawalker et al.

provided evidence that T lymphocytes specific for low molecular compounds such as persulfates may be directly involved in mediating inflammatory processes in the airways, rather than only acting through induction of IgE synthesis in persulfate-triggered occupational asthma.[17]

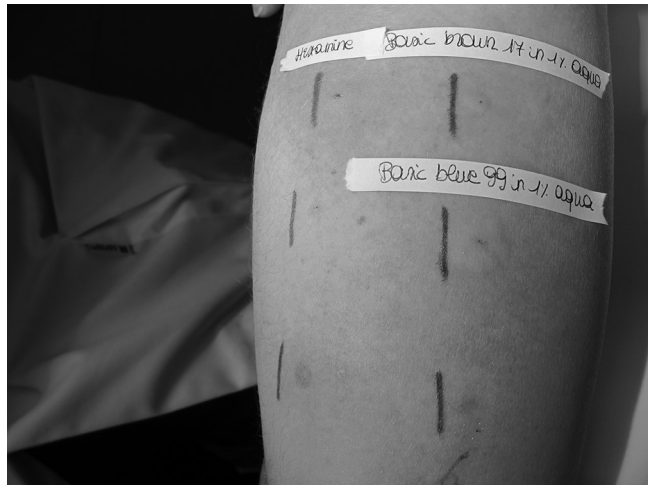

FIGURE 22.1 Immediate type I hypersensitivity reaction including oral and auricular symptoms following contact with a hair lotion. The product and the individual components were tested, resulting in a positive prick test for Basic blue 39 (+++) and Basic brown 17 (++).

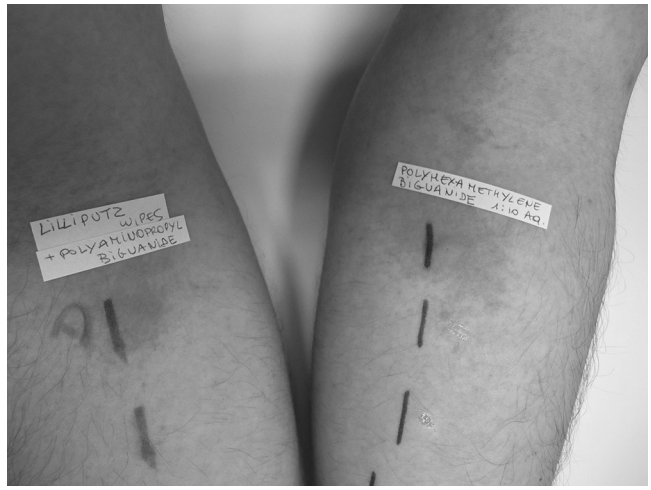

FIGURE 22.2 Immediate type I hypersensitivity reaction to wet wipes. A prick test was performed on the forearm of the patient with fluid from the wet wipes (polyaminopropylbiguanide and polyhexamethylenebiguanide), with a positive urticarial reaction within 15 minutes.

Antimicrobial Agents and Preservatives

Chlorhexidine is a biguanide topical antiseptic and disinfectant with broad antimicrobial efficacy. It is increasingly being used as an aseptic but it is also gaining use as a biocidal ingredient in shampoos, conditioners, hair dyes, sunscreens, toothpastes, mouthwashes (Corsodyl), wet wipes (also for babies), eye creams, antiwrinkle creams, moisturizers, contact lens solutions, and instillation gels for urinary catheters.[18,19] Urticaria following application to intact skin or mucosae, in some cases accompanied by dyspnea, angioedema, syncope, or anaphylaxis has been described [18] via the mucosal route at much lower concentration than elsewhere, generally as low as 0.05%.[19,20]

Phenoxyethanol is commonly used in cosmetics for its antibacterial and antifungal properties. It is increasingly being used in vaccines as a substitute for thiomersal and is also a component of pen inks and, more rarely, ear drops.[21] Reactions to phenoxyethanol have rarely been reported. Three cases of CoU induced by phenoxyethanol in cosmetics have been reported.[22–24] 2-Phenoxyethanol is used as a single agent and in combination with other preservatives such as 1,2-dibromo-2,4-dicyanobutane (Euxyl K 400) and parabens, or in conjunction with quaternary ammonium compounds.[23] The possibility of immunological IgE-mediated reaction could not be confirmed because specific IgE against 2-phenoxyethanol was negative.[22]

Another biguanide antimicrobial agent is polyhexanide or polyaminopropylbiguanide that may partly cross-react with chlorhexidine and that has shown to elicit IgE-mediated reactions from toilet paper [25] and wet wipes, as in a case we have diagnosed recently. This subject reacted positively on prick testing to the wipes and the antimicrobial agent and also had a positive basophil activation test; however, tests with chlorhexidine, another biguanide with which it may partially cross-react, remained negative. Polyhexanide is a poly-biguanide antiseptic, which is widely used, for example, in contact lens solutions, wound dressings, pool cleaners, and in cosmetics [25] (Figure 22.2).

P-chloro-m-cresol is used as a preservative in a wide number of topical preparations and is a rare cause of allergic contact dermatitis and CoU, the mechanism of which remains uncertain.[26]

Sunscreens

Allergic contact dermatitis from sunscreen chemicals has traditionally included CoU, allergic contact dermatitis, and photoallergic contact dermatitis.[27] Benzophenone-3 (2-hydroxy 4-methoxy benzophenone) or oxybenzone is a common ultraviolet A/ultraviolet B sunscreen ingredient known to cause contact and photocontact allergic reactions, which is the reason its presence needs to be labeled on the cosmetic packaging.[28] Because of the recognition of p-aminobenzoic acid (PABA) and its esters as sensitizers, the presence of benzophenones in "PABA-free" sunscreens has become more prevalent.[27] The occurrence of CoU and even contact-mediated anaphylaxis with benzophenone-3 is rare.[28] Bourrain et al. also described photo-induced urticaria to benzophenones.[29] The severity of the clinical reaction depends partly on the amount of skin exposed; therefore, patch testing does not necessary elicit anaphylaxis.[30] Benzophenones are also added to protect against discoloration of cosmetics, textiles, and plastics exposed to sunlight.[28]

Fragrance Components

Balsam of Peru and fragrance mix I (a mixture of eight fragrance components as tested in the baseline series) may act by both immunologic and nonimmunologic mechanisms,[31] with cinnamal, a common ingredient to both, being probably the most important causal ingredient.[32]

CoU caused by fragrances is well known. Yamamoto et al. reported a case of facial edema after applying cosmetic products containing geraniol, a component of the fragrance mix. A 20-minute closed test showed wheal with this product; no delayed hypersensitivity was observed after 24–72 hours. Yamamoto suggests an immunological mechanism because the patient developed widespread urticaria and flare reactions on the face and neck at the 72-hour reading of the patch test.[33] Rietschel describes a patient with immediate hypersensitivity to cassia oil in toothpaste. The same patient revealed CoU sensitivity to sorbic acid, a preservative, in her shampoo.[34]

Toothpaste Flavors

As in the case report of Holmes et al. regarding type I allergy to mint-flavored toothpaste, CoU should be considered in cases of persistent undiagnosed cheilitis, and skin prick tests as well as patch tests should be carried out with suspect contact allergens.[35] IgE-mediated allergy to mint or menthol includes urticaria, rhinitis, asthma, and/or anaphylaxis.[36,37]

R-Carvone is the main substance in spearmint oil, also present in toothpastes; it is the cause of delayed-type allergy resulting in cheilitis, but Hansson et al. also described a case of angioedema of the lips appearing within minutes after contact with toothpaste, with an open test resulting in an immediate and strong reaction to carvone.[38]

Hair Glue

Increasingly popular cosmetic hair alterations, the application of matching hair to the scalp that immediately changes both the length and style of the hair, use latex-containing bonding glues to attach hair to the scalp. This contains high concentrations of soluble latex antigen and may cause IgE-mediated reactions and anaphylaxis. Repeated glue exposure may potentially sensitize consumers.[39] Pumphrey et al. described the recent anaphylactic death of a 28-year-old British fashion designer directly after receiving a hair extension. The victim had a history of nut and inhalant atopy as well as cutaneous IgE reactivity to natural rubber latex.[40] Latex-containing bonding glue is not only used in commercial hair alterations but also in application of artificial eyelashes.[39]

Botanically Derived Cosmetic Ingredients

Emollients and moisturizers are widely used in the therapy of atopic dermatitis, and a recent trend in the cosmetics industry is the use of plant protein derivatives (e.g., from soya, wheat, oat, sesame). Oat proteins, in particular, are used because of their anti-inflammatory, antioxidant, and antipruritic properties. Contact dermatitis to oat protein found in moisturizers has been previously reported in atopics,[41] and a case report of Vansina et al. describes ICoU resulting from an emollient cream because of the oat extract present in it. The diagnosis was confirmed by prick tests and enzyme-linked immunosorbent assay testing. The patient later on also experienced an oral allergy syndrome when eating oatmeal-containing biscuits and bread.[42]

The route of sensitization to proteins can indeed be gastrointestinal, respiratory, and percutaneous, although the penetration of proteins through intact stratum corneum is very low. However, the presence of a damaged or an impaired skin barrier, skin inflammation, and the ability for production of elevated IgE levels in atopic individuals are predisposing factors for sensitization.

Protein hydrolysates of collagen, keratin, elastin, milk, wheat, almond, and silk added to hair conditioners to "repair" broken hair and provide a more voluminous appearance are urticaria culprits as well,[43] capable of producing reactions through a type I mechanism in atopic dermatitis patients in particular.[44]

Moreover, hydrolyzed wheat proteins are widely used in other cosmetic products, of which several cases of immediate-type reactions have been reported in the literature. Wheat contains a variety of proteins (approximately 10%) that can be divided into salt-soluble proteins of albumin and globulin type and salt-insoluble proteins, the latter ones referred to as gluten (gliadins and glutenins)[45,46]; their widespread use in food and nonfood products multiplies the risks of sensitization. New epitopes may appear during the hydrolysis, or the additives used may act as allergens.[47] In the case report of Pecquet et al., gluten-derived products were responsible for immediate hypersensitivity both by cutaneous and oral contact. Although the primary route of sensitization is uncertain, the chronology of reactions in this case favors the cutaneous route.[48] It has been shown that hydrolyzed wheat proteins composed of large polypeptide aggregates possibly induce sensitization to a greater degree than lower molecular weight hydrolyzed wheat proteins.[45]

Most cases of IgE-mediated hypersensitivity to chestnut (*Castanea sativa*), a member of the Fagaceae family, have been attributed to the so-called latex-fruit syndrome, in which ingestion of fruits such as avocado, kiwi, banana, and, more rarely, chestnut leads to urticaria and anaphylaxis in latex-sensitized individuals. This

syndrome is caused by cross-reactivity between class I chitinases with a hevein-like domain such as Mus a 1 (banana), Pers a 1 (avocado), Cas s 5 (chestnut), and Hev b6.02 (late hevein). However, chestnut allergy may occur independently; Cas s 8, a lipid transfer protein, has been identified as the offending allergen. With an increasing number of food proteins being included in so-called natural cosmetics, new cases may appear in the literature, such as, for example, contact anaphylaxis induced by as cosmetic facial peel containing chestnut.[49]

Soybean has many commercial uses, including cosmetics. Shaffrali et al. reported on a patient with delayed-type contact allergy to all dilutions of pure soybean extract, and also an immediate response to the 20% dilution, suggesting a possible type I hypersensitivity reaction. However, the allergen-specific IgE for soybean was negative and the patient had previously eaten soybean without adverse reaction. It has been demonstrated, however, that the radioallergosorbent test may yield a false-negative result in 27% of the cases; hence, a negative IgE-level for soybean does not preclude a diagnosis of type I hypersensitivity.[50]

Reports of immediate allergy and anaphylaxis from ingested sesame seed or sesame oil have been published, the latter being a known contact allergen in topical pharmaceutical products and cosmetics.[51] Despite its wide use, to our knowledge, only two cases of immediate-type reactions induced by cosmetic products have been reported.[51,52]

Also other protein-containing cosmetic ingredients may elicit immediate-type reactions: a patient with a history of respiratory distress when inhaling smoke from grilled fish developed CoU (without systemic symptoms) to a fish-derived elastin-containing cosmetic cream.[53]

A study by Niinimäki et al. demonstrated hydroxypropyl trimonium hydrolyzed collagen (stearyltrimonium hydrocyethyl hydrolyzed collagen, Crotein Q) to be an especially potent cause of immediate skin reactions, with positive prick test reactions to very low concentrations. Furthermore, specific IgE to Crotein Q was found in the studied sera.[43]

Panthenol, the alcohol corresponding to pantothenic acid (vitamin B5) and a component of coenzyme A, is a common additive to many cosmetic products, including as a conditioning agent in hair care products. Panthenol, as a coenzyme constituent derived from β-alanine, could be acting in the same manner as Crotein Q, thus causing CoU, though exceptionally.[54]

Glaspole et al. described a case of anaphylaxis after showering with lemon-impregnated soap. This patient also reported laryngeal edema, generalized urticaria, and asthma symptoms within minutes after ingestion of whole crushed orange juice, citrus seeds, and peanut and tree nuts, which seem to be an unusual clinical phenomenon. It is suggested that it is the citrus seed reactive antibodies that have led to the cross-reactive immune response.[55]

CoU has occurred after use of cosmetics containing chamomile and mango in a patient with a personal history of infantile eczema and oral allergy syndrome, with hypersensitivity to different kinds of fruit.[56]

Eye washing with chamomile tea is a folk remedy used by the general public to treat conjunctivitis and other ocular reactions, but is also found in many cosmetic products. Some cases of contact dermatitis (but not reactions of type I) were reported after its topical applications. Subiza et al. present seven hay fever patients that suffered from conjunctivitis; two of them also had lid angioedema after eye washing with chamomile tea. All presented with positive skin prick tests to the chamomile tea extract. *Matricaria chamomilla* pollens contained in these infusions are the allergens responsible for these reactions.[57]

Foti et al. present a case of a 23-year-old woman who developed eyelid angioedema after applying compresses of chamomile tea to her eyelids. Prick tests showed also strong positive reactions to German chamomile.[58]

Krakowiak et al. reported a case of a cosmetician with recurrent itching and erythematous lesions on the back of her hands and rhinoconjunctivitis due to contact with depilatory wax containing *Tilia cordata* and *Matricaria chamomilla*. Total IgE in this patient was 13 084 IU/mL, and prick tests were positive to flowers of *T. cordata* and *M. chamomilla*.[59]

Permanent Makeup and Tattoos

Tattoos and permanent makeup are increasingly prevalent in Western society and delayed hypersensitivity reactions to tattoo ink are well described in the literature. Lee-Wong et al. reported a case of anaphylaxis to tattoo ink, with an immediate skin reaction to purple and blue ink. The inks used in tattoos are composed of different

pigmented compounds, such as cobalt (blue), manganese (purple), and chromium oxide (green). The inks are suspended in liquid that may include water, ethylene glycol, and other agents. Unfortunately, many tattoo ink manufacturers are not required to print ingredients on their labels, making it difficult to identify the precise agent responsible for the allergic reaction.[60]

Alcohol Urticaria Syndrome

Urticaria-angioneurotic edema after ingestion of alcohol may be due to different agents contained in the beverages, among others, yeast. Cases reported to be due to pure ethanol are rare. Case reports of contact urticaria syndrome from local application of alcohol seem even rarer: 1) Drevets et al. reported a patient who noted diffuse pruritic rash after drinking alcoholic beverages; ethyl applied to the skin provoked an erythematous reaction in about 20 minutes.[61] 2) Fischer et al. observed allergic CoU from ethyl and isopropyl alcohol.[62] 3) Gaul et al. described an urticarial-like dermatitis provoked by ethyl alcohol and stearyl alcohol associated with delayed dermatitis.[63] 4) Rilliet et al. presented a case of alcohol CoU after applying perfume or disinfecting the hands. The immediate reactions with most of the primary alcohols were positive. Passive transfer, using a method corresponding to that of Prausnitz-Küstner, was achieved.[64]

Conclusion

This review confirms that various cosmetic components can cause CoU with or without systemic symptoms, sometimes life-threatening; however, such cases are grossly underdiagnosed and underreported because patients lack awareness. Physicians therefore should continue the search for possible new culprits. Anaphylactic reaction can also be provoked by patch testing with the culprit component, hence precautions remains necessary.

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23

Contact Urticaria Syndrome from Reactive Dyes in Textiles

Marléne Isaksson

Background

The reactive dyes (RDs) play an important role among textile dyes in the dyeing of cellulose fibers such as cotton as well as polyamide, wool, and, to a lesser extent silk, fur, and leather.[1] RDs are water-soluble and sold as powders, granules, or water solutions. They produce bright colors, their application is fast, and their fixation is permanent in natural and synthetic fibers.[2] Therefore they are extensively used and there are an enormous number of commercially available products. The RD molecule contains a color-forming component (chromogen) and a fiber-reactive component that form irreversible covalent bonds with the amino acid residues of cellulosic fibers [3] and with hydroxyl groups in the fiber molecule.[4] Because RDs form strong covalent bonds with the fibers to be dyed, they show excellent fastness to washing if the dyeing process is properly done.[5] There are several RDs with different reactive functional groups to which carrier proteins bind to induce immune responses.[6–8] The color-forming component is usually an azo, anthraquinone, or phthalocyanine derivative. Hydrophilic groups improve the water solubility. According to Elliot and Yeung in 1979,[9] functional groups were not less than 23. Some of these were suitable only for either cellulose fibers or wool and nylon, whereas others could be used for any of these materials. According to another report, only dyes belonging to a minority of the existing reactive groups seemed to have been involved in allergic cases. The groups mostly involved were bromoacrylamide, dichlorotriazine, monochlorotriazine, monochlorodifluoro pyrimidine, vinyl sulfone, fluorotriazine, and pyrazolone. The vinyl sulfone RDs are major causes of occupational asthma (OA) and have one or two vinyl sulfone reactive groups.[1,10,11]

Dyes are referred to either through their trade name or Color Index name, whereas the chemical class and to a greater extent the reactive group not always is known.[1] In a publication from Romano et al. from 1992, an extensive table lists the RDs described until then in the literature as a cause of allergic reactions in humans.[1] Besides RD molecules, commercial reactive dye stuffs also contain several other components to improve their dyeing properties, and many of these may also be sensitizers. In Finland, Estlander tried to patch test with scrapings from a thin-layer chromatography plate in which a RD called Remazol Schwarz B had given 10 spots, but the patch tests were negative.[2]

RDs are not only used in the textile industry but can be found in home dyeing and in fur and leather dyeing.[1,2]

Concerning contact urticaria syndrome (CUS) and RDs, diseases from stages 1 through 4 have been reported.[12]

RDs for dyeing cotton textiles were launched in 1956 by Imperial Chemical Industries Ltd in the United States; the company warned on its packages that the dyes could cause respiratory allergy, [13] but it was not until 1978 that the first report on adverse events from RDs came, when OA and rhinitis was demonstrated in Finland.[4]

Different Types of Hypersensitivity Reactions

An RD can act as a hapten and elicit contact dermatitis,[5] contact urticaria (CoU),[2] urticaria,[1,2,14] rhinorrhea, cough, dyspnea,[15] and asthma.[6,11,16]

Atopy is not considered to be a predisposing factor for RD-induced OA.[14] However, smoking is.[17]

It has been proposed that yellow and orange RDs would be more sensitizing than green and brown ones. [1,10,18]

Asthma

The first cases of work-related asthma from exposure to RDs were reported from Finland. Four cases of immediate-type occupational allergy to these compounds were published in 1978. All the patients had had symptoms of asthma and allergic rhinitis and had been weighing dyes for a minimum of two years. The skin prick tests (SPTs) to the dyes were positive, and nasal and bronchial provocation challenges also produced positive immediate reactions. A high-serum titer of specific immunoglobulin E (IgE) could be demonstrated for three of the dyes by the radioallergosorbent test (RAST). The identification of specific IgE shows that the mechanism of the hypersensitivity is immunological, reactive dyes acting probably as haptens.[4] Since then, many cases have been reported, at least until early 2000. Many reports come from Korea, where the reported prevalences of OA has been 2.5%–5.9% in the 1980s [19] and RDs were among the most frequent causes of OA in Korea until the 1990s.[16]

Early diagnosis and treatment is essential for a good prognosis according to some.[11] Job relocation is often needed as well as inhaled corticosteroids and close follow-ups.[15]

However, in a Korean study, 11 OA patients confirmed by RD bronchial challenge were enrolled in a study; examinations were conducted at four and 14 years after the initial examinations. Reduced lung function at the initial examinations did not recover at the first and second examinations despite cessation of exposure and proper pharmacological treatment. In addition, asthma severity and nonspecific airway hyperresponsiveness (AHR) to methacholine also did not improve. On the contrary, skin reactivity to RDs almost disappeared at the second examinations. The study demonstrated that reduced lung function and asthmatic symptoms persist in RD-induced OA even after long-term exposure avoidance.[11]

In another study the long-term outcomes of RD-induced OA was studied in which methacholine AHR and lung functions were evaluated and compared in 26 patients with RD-induced OA at the time of diagnosis and after complete avoidance of the causative agents. Patients with continued or remitted AHR were further monitored for approximately 10 years. The authors concluded that early diagnosis and avoidance therapy are the most important prognostic factors in RD-induced OA. The AHR and lung function of patients with RD-induced OA can sometimes be recovered steadily and slowly through avoidance measures.[20]

A Korean study examined the relationship between asthma mortality and occupational exposure in the dye industry, including over 66,000 male workers, of which 904 worked in the dye industry. The all-cause mortality in dye industry workers was significantly lower than in the general population, whereas the asthma mortality was significantly higher. Deaths from nonmalignant respiratory diseases were higher in the dye industry workers, but were not statistically significant. Because asthma is a life-threatening disease, special consideration and preventive measures must be taken for workers in the dye industry.[16] Lethal asthma has also been described in the 1980s.[21] For the diagnosis of OA, positive SPTs to the RD in question and detection of IgE specific to the reactive dyes in serum samples are recommended.[7]

Contact Urticaria and Urticaria

Dye-factory workers or workers in dye-related industries that are exposed to RDs may constitute a high-risk group for getting (CoU).[22] Also, generalized urticaria is reported from handling RDs [21,23] in dye-factory workers. There are also several reports in the medical literature.[14] Urticaria or Quincke edema was seen in three of 162 workers in Swedish plants. A positive prick test with RDs was reported in one patient and with standard allergens in another patient.[14] One worker handling RDs suffered from diffuse urticaria and asthma and had an increased level of IgE, and a SPT was positive to a bromoacrylamic dye called Lanasol yellow 4G.[1] In 1988 in Finland, five workers were reported to have occupational eczema, urticaria, and respiratory disease from reactive dyes. They had worked in dye houses or textile plants and been exposed to theses dyes for eight months to four years before symptoms developed. Four patients with eczema were patch test–positive to nine commercial dye powders and two of them to a dye, Remazol Schwarz B. The two patients with respiratory symptoms and/or urticaria were prick test–positive to the aforementioned commercial dye powders. A fifth patient with urticaria and respiratory symptoms reacted positively on prick testing to a dye, Remazol Gold Gelb RNL, but the patch test was negative. Patch testing with 1% pet dilution of commercial dye powder was recommended and for prick testing 1% in distilled water.[2]

Diagnostic Tests

Patch Testing

A Swedish dye manufacturer worker was patch test positive to several RDs and he had hand eczema as well as cough and rhinitis at work.[5] According to Estlander, a 1% pet dilution of commercial dye powder can be used for patch testing. Four patients with eczema were positive to nine commercial RDs. Organic tests are of no use in screening for contact allergy to RDs.[2] Another case had a positive patch test to a RD even though he never had any dermatitis. The test was performed with 1% dilution of the RD in normal saline. This patient got urticaria when challenged with the RD in an exposure chamber.[1] The same was seen in another worker in Sweden.[24] Another group patch tested with RDs diluted 1% in water.[14]

Prick Testing

The SPT can be used for screening, diagnosing, and monitoring OA from RDs.[15] There are various recipes for the preparation of dye solution for use in the SPT. According to some, the dye powder can be diluted at 1% in distilled water or at 10 mg/mL.[5] Others have dissolved 10 mg of a RD in 1 mL of modified Coca solution containing 50% sterile glycerine and used this for SPTs. Others have used extracts of RDs 10 mg/mL.[15] In another article, RDs were diluted in saline-glycerol to a final concentration of 2 mg/mL; these authors also claimed that unconjugated dyes could be used for the SPT.[14] There is a potential risk of anaphylactic reactions and why such investigations should only be undertaken at clinics with necessary control systems. The SPT can be executed with progressively more concentrated solutions of the RD (e.g., starting with 1:20,000, then 1:2,000, and then 1:200 of a dye solution).[1] Two patients with respiratory symptoms and/or urticaria had a positive SPT to the same dyes as on patch testing. Another patient with respiratory symptoms and urticaria had a positive SPT but a negative patch test.[2] It is also claimed that even in case of low positivity to the SPT, this does not represent a reliable guide as to the level of the bronchial response.[1]

Bronchial Challenge Tests

Bronchial challenge tests performed in an exposure chamber, best for monitoring the level of RD dust concentration, can be dangerous. Extreme care should be taken when this is performed and this challenge should only be performed at specialist clinics and under strict supervision. A wool and cotton dyer handling an RD called Lanasol Yellow 4G, a bromoacrylamic dye, was prick and patch test–positive to the dye. A four-minute exposure through a chamber inhalation challenge to the dye produced a severe anaphylactic reaction with ventilation obstruction; arterial hypotension followed within minutes accompanied by urticaria of the face and upper limbs. Bronchial hyperresponsiveness did not follow. It was suggested that serial challenges be made with increasing concentrations of the dye to prevent serious reactions, even in the case of low positivity to the SPT, as in this case. The patient did not have any signs of contact dermatitis from the dye.[1] Another dye worker's inhalation challenge tests with RD extracts gave significant bronchoconstriction (a 45.6% fall in forced expiratory volume in 1 second from the baseline value) with dyspnea and wheezing 10 minutes after inhaling 10 mg/mL of an RD extract.[15] There are various ways of exposing the patient to the RDs in the chamber. One case is described in which the male patient tips the powder dye from one container to another according to the Pepys et al. method.[25] It is also recommended to dilute the RD powder to a 5%–10% dye-lactose mixture before the provocation to minimize the risk of severe reactions and to perform the bronchial provocation challenge test with lactose powder as the placebo [4] and according to the technique described by Pepys, Pickering, and London.[26]

Detection of Specific IgE to RD-Human Serum Albumin Conjugates in Serum

IgE antibodies specific to the RDs were determined with RAST already in the first four cases of OA described. [4] Since then, positive RASTs have been detected in many RD-exposed patients with work-related rhinitis and asthma.[14] Positive results to the RAST have suggested that airborne dye molecules may act as haptens

and provoke the production of RD-specific IgE antibodies.[14] Conjugates between the RDs and human serum albumin (HSA) can be prepared according to Wass et al.[8] Hence, the detection of specific IgE to RD-HSA conjugate in serum is useful in the diagnosis of this type of allergy.[7] Serum-specific IgE antibodies to RD-HSA conjugates were also measured using an enzyme-linked immunosorbent assay.[27] A vinyl sulfone reactive dye (vRD), which consists of vinyl sulfone reactive groups and a chromogen, can elicit IgE-mediated OA by haptenation. HSA is known as the most reliable carrier protein for the vRD, but the IgE epitopes of vRD-HSA are not well characterized. In a Korean study, the epitope of vRD-HAS-specific IgE were evaluated. The authors concluded that the conformational structure of HSA would be critical for the IgE epitopes during the haptenation process and that both of the chromogen and reactive groups of the vRD would contribute to the formation of the IgE epitope. Their results confirmed the heterogeneity of IgE epitopes in the RD-HSA complex.[27] RAST and RAST inhibition can detect whether there is a cross-reactivity between some RDs.[14]

Summary

RDs are reactive molecules that induce OA, rhinitis, and urticaria in exposed RS workers. Smoking is predisposing. Immunochemical identification of the offending agent awaits clarification (parent component and/or impurity). Diagnosis is based on SPTs and detection of specific IgE and bronchial challenge provocation tests.

Appropriate protective measurements are needed to minimize the exposure in high-risk groups.

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24

Hairdressing Products: Contact Urticaria Syndrome

Parastoo Davari and Howard I. Maibach

Introduction

Hairdressing products are commonly used on a daily basis. A wide variety of hairdressing products containing natural and synthetic compounds is commercially available. However, the product ingredients may not be standardized or fully tested yet[1]; they may cause immediate- or delayed-type reactions. Contact urticaria syndrome presents immediately after direct contact of the urticariogenic substance with the skin. Clinical manifestations are due to immunologic (immunoglobulin E–mediated) or nonimmunologic responses to the offending substance. However, urticarial reactions with unknown mechanisms have been reported. The presentation varies from local wheals, flare, and itching to generalized urticarial reaction, respiratory and gastrointestinal distress, and anaphylactic shock.[2,3]

Prevalence of contact urticaria from hairdressing products is not fully documented, and only case reports and case series have been published. However, hairdressers have been reported among the most common occupation groups diagnosed with contact urticaria.[4] In an Australian study, contact urticaria affected 13 of 106 hairdressers (12%) with occupational skin diseases.[4] Although common sites of contact urticarial reaction are scalp, ears, and neck and face, hands and fingers are more involved in hairdressers. Table 24.1 summarizes hairdressing products and their ingredients that cause contact urticaria syndrome.

Hair Shampoos

Shampoos are frequently used hair products. They are not only cleansing agents, but they are expected to have cosmetic effects as well as improve hair and scalp medical problems such as dandruff. Most shampoos are composed of detergents such as surfactants, conditioning ingredients, and additives.[5] Zirwas and Moennich noted that fragrance, cocamidopropyl betaine, methylchloroisothiazolinone/methylisothiazolinone, formaldehyde releasers, propylene glycol, vitamin E, parabens, benzophenones, iodopropynyl butylcarbamate, and methyldibromo glutaronitrile/phenoxyethanol are the most common type IV allergens in shampoos.[6] Considering their frequent use, they are not frequently reported as a cause of contact urticaria. Low concentration and transient exposure of the potential causative agent could be a reason. Nonimmunologic contact urticaria occurred after application of a shampoo containing sorbic acid.[7] Generalized urticaria and dyspnea were experienced after use of a Tilia (lime) extract shampoo, containing a low concentration of eugenol as well. The patient had an immediate positive test with the shampoo.[8] Benzophenones are also used in cosmetic products; two cases of photoallergic contact urticaria to benzophenone-3 in their cosmetics and shampoos have been reported.[9] A patient experienced recurrent episodes of contact urticaria after use of shampoo and permanent wave solution containing polyvinylpyrrolidone derivatives. Later, she developed generalized urticaria and anaphylactic shock after vaginal application of a polyvinylpyrrolidone solution.[10]

TABLE 24.1

Hairdressing Products Causing Contact Urticaria Syndrome

Etiology	Causative Ingredient	Signs and Symptoms	References
Hair shampoos	Sorbic acid	Urticaria	[7]
	Tilia	Generalized urticaria, face, lip, and mouth edema, and dyspnea	[8]
	Eugenol	Generalized urticaria, face, lip, and mouth edema, and dyspnea	[8]
	Benzophenone-3	Itching and erythema	[9]
	Polyvinylpyrrolidone derivatives	Urticaria	[10]
Hair conditioners	Unknown	Urticaria and angioedema	[12]
	Panthenol	Itching, erythema, and edema	[13]
	Protein hydrolysate: -quaternized collagen hydrolysate	Local and generalized urticaria	[14]
	-Hydroxypropyl trimonium hydrolyzed collagen	Urticarial and periorbital edema	[15,16]
	-Stearyl trimethyl ammonium chloride	Urticaria, rhinoconjunctivitis, cough, wheezing, and dyspnea	[17]
	-Hydrolyzed bovine collagen	Urticaria, rhinoconjunctivitis, cough, wheezing, and dyspnea	[17]
	Banana hair conditioner	Angioedema	[18]
	Egg emulsion	Urticaria	[19]
Hair dyes and bleaches	Unclear	Urticaria, asthma, and anaphylactic shock	[20–22]
	Paraphenylenediamine	Local and generalized urticaria, nausea, vomiting, hypotonia, and anaphylactic shock	[23–30]
	Paratoluenediamine	Urticaria, asthma, abdominal cramps, vomiting, diarrhea, and anaphylactic shock	[31]
	Para-aminophenol and para-methylaminophenol	Generalized urticaria, stridor, and dyspnea	[32]
	2,4-diaminophenoxyethanol-HCl	Generalized urticaria, hypotonia, dyspnea, and vomiting	[33]
	Basic Blue 99	Generalized urticaria, rhinoconjunctivitis, cough, and eyelid swelling	[34,35]
	Henna	Urticaria, rhinoconjunctivitis, and wheezing	[37]
	Senna	Rhinoconjunctivitis and dyspnea	[39]
	Persulfates	Local and generalized urticaria, rhinoconjunctivitis, asthma, sneezing, nausea, edema of eyelids and face, and anaphylactic shock	[38,43–51]
Permanent wave preparations	Polyvinylpyrrolidone derivatives	Urticaria	[10]
	Glyceryl monothioglycolate	Urticaria	[55]

Hair Conditioners

Hair conditioners are used to enhance hair shine, softness, and manageability. Conditioners flatten the hair cuticles and protect the hair cortex from potential environmental damage.[11] Urticaria and systemic reactions from hair conditioners have been observed.[12–19] A case of contact urticaria was reported after use of a conditioner containing panthenol, the alcohol analog of pantothenic acid or vitamin B5.[13] Protein hydrolysates are used in hair products such as conditioners for repairing damaged hair or as volumizers.[15] Kousa et al. reported a case of contact urticaria with a conditioner containing a quaternized collagen hydrolysate.[14] Hydroxypropyl trimonium hydrolyzed collagen induced urticaria and periorbital edema.[15,16] A conditioner containing stearyl trimethyl ammonium chloride and hydrolyzed bovine collagen caused skin and respiratory symptoms.[17] One patient experienced several episodes of angioedema for two years linked to her wearing natural rubber latex gloves and packaging banana hair conditioners. She showed positive prick tests to both natural rubber latex proteins and banana.[18] A hairdresser showed contact urticaria to raw egg in the course of her work. She also had a history of urticarial reactions after eating egg.[19]

Hair Dyes and Bleaches

Hair dyes fall into different categories: permanent, demipermanent, semipermanent, and temporary dyes. In permanent dyes, a reaction between the oxidative dyes such as paraphenylenediamine or paratoluenediamine and hydrogen peroxide is required. The product molecules are large and remain in the cortex. Semipermanent dyes are water-soluble and nonionic and do not require hydrogen peroxide. Temporary dyes are water-soluble and have a large molecular size, which prevents them from passing the cuticle.[11] Urticarial and systemic reactions have been seen with hair dyes and their constituents, including paraphenylenediamine, paratoluenediamine, para-aminophenol, para-methylaminophenol, 2,4-diaminophenoxyethanol-HCl, Basic Blue 99, henna, and senna.[20–39] Patients may experience such reactions after long-term use of the dye without any complications.[20]

Paraphenylenediamine is an organic compound in hair dyes and causes allergic contact dermatitis.[40,41] It can also induce immediate-type reactions varying from local urticaria to allegedly fatal systemic reactions and anaphylactic shock.[23–30] An oxidation product of paraphenylenediamine, N'N'-bis-(4-aminophenyl)-2,5-diamino-l,4-quinone-diimine or Brandowski's base, was the causative agent for contact urticaria.[26]

Recurrent urticaria, gastrointestinal and respiratory distress, and shock from a dye containing paratoluenediamine have been reported. Pasche-Koo et al. found that an oxidation product of paratoluenediamine could be responsible for these reactions.[31] A patient experienced generalized urticaria and respiratory symptoms using a commercial hair dye. Scratch test with the dye ingredients showed positive reactions to para-aminophenol and para-methylaminophenol.[32] An oxidation colorant, 2,4-diaminophenoxyethanol-HCl, which is used in hair dyes, caused immediate-type reactions.[33]

Basic Blue 99 is an aminoketone and a semipermanent dye, and caused generalized urticaria and respiratory symptoms.[34,35]

Natural hair colors are mainly plant derivatives and have become increasingly popular. Henna, senna, and chamomile are such natural hair dyes. Henna is derived from the leaves of *Lawsonia alba*. Skin and respiratory reactions, angioedema, and conjunctivitis from skin contact with henna or inhaling its small powder particles have been reported in hairdressers.[36–38,42] In all those cases, a prick test with henna was positive. However, a negative prick test with the coloring molecule of henna, 2-hydroxy-1, 4-naphtoquinone, may indicate that other compounds are responsible for these reactions.[37] Senna is an herbal remedy and is used in laxatives. It is also a constituent of hair dyes. Occupational asthma, rhinitis, and conjunctivitis have been seen due to exposure to senna and a positive prick test confirmed that senna was the responsible agent.[39]

Hair bleaching is used to lighten hair color. Hydrogen peroxide and ammonia are used to open the cuticles and strip the cortex from eumelanin.[11] Ammonium persulfate, potassium persulfate, and sodium persulfate

are inorganic salts added to hair-bleaching products to accelerate the oxidation reaction. Several cases with immediate-type skin and respiratory reactions have been reported after exposure to persulfates.[38,43–51] The mechanism of the immediate-type reactions to persulfates is unclear. It seems that persulfates induce histamine release through slow mast cell degranulation.[52] It was also shown that these reactions can be immunoglobulin E–mediated in certain patients.[50] However, other studies could not demonstrate specific immunoglobulins to persulfate salts.[53,54]

Permanent Wave Preparations

Recurrent episodes of contact urticaria were reported after use of a permanent wave preparation containing polyvinylpyrrolidone derivatives.[10] A permanent wave solution containing glyceryl monothioglycolate caused urticaria in a hairdresser.[55] Other ingredients such as fragrance and protein hydrolysates in permanent wave preparations may cause contact urticaria.

Fragrance

Fragrance, found in most hair products, is composed of natural and synthetic ingredients. Fragrance is one of the most common causes of contact dermatitis to cosmetics.[56] Immediate contact reactions to fragrance compounds such as fragrance mix have been reported.[57] A shampoo containing lime extract and a low concentration of eugenol caused generalized urticaria and dyspnea.[8]

Other Styling Products

Hair styling products, used to change the texture of hair or to maintain a hair style for a period of time, exist in different forms including sprays, gels, waxes, mousses, lotions, and pomades. Although contact urticaria has not been reported with these hair styling preparations, they contain potential urticariogenic ingredients such as alcohol, acetone, fragrance, vitamins, coloring agents, and preservatives. Katugampola and Statham reviewed the ingredients of 36 hair products and found numerous plant derivatives and nonstandardized ingredients in addition to allergens that had been tested by standard hairdressing series.[1]

Other Products

Rubber gloves are made from concentrated liquid natural rubber latex derived from the plant *Hevea brasiliensis*. Hairdressers use protective gloves to avoid skin contact with irritant and allergic components of hairdressing products. However, immediate-type reactions to latex gloves have been reported.[58] In a study of 302 hairdressers, 10 patients who had itching and swelling of hands after using latex gloves underwent a provocative test with latex gloves, and four hairdressers showed a positive reaction.[59] In another study, five of 41 hairdressers had positive results to chamber scratch test with liquid and/or solid latex or latex gloves.[60] Also, positive prick test reactions to natural rubber latex were found in three of 107 hairdressers.[61] Hairdressers are among the high-risk groups for latex hypersensitivity. Contact urticaria to latex gloves should be considered in hairdressers that experience swelling and itching of the hands and exacerbation of hand dermatitis after wearing latex gloves. Vinyl and nitryl gloves can replace latex gloves to avoid hypersensitivity reactions.[60,62]

Nickel and cobalt are used in hairdressing utensils such as scissors and clips. Chemicals such as ammonium thioglycolate in permanent hair wave solutions can release nickel from the instruments.[63] Cases with immediate-type reactions from nickel in the instruments other than hairdressing utensils have been reported.[64–66] Contact urticaria has also been observed because of cobalt. None of the reactions was due to hairdressing instruments.[67,68]

Hair products contain other agents such as disinfectants. Chlorhexidine is used as a biocidal ingredient in cosmetics and hair care products.[69] It caused immediate-type reactions in other circumstances, not related to hairdressing products.[70,71]

Diagnosis and Test Methods

Taking a comprehensive medical history is crucial in the diagnosis of contact urticaria and distinguishing it from irritant dermatitis, which may resemble its clinical manifestations.[3] Skin testing with the suspected agent and its ingredients should be performed as well. Open test with the offending substance is simple to perform. If the results are negative, prick test is the next step. Although it is less standardized, a scratch test can be useful too. Intradermal testing may cause anaphylactic reactions; thus, it should be reserved until other skin tests are inconclusive and should be done with precautions. Resuscitation equipment should be available during the skin testing process because of the possibility of life-threatening reactions. Also, for the nonstandard substances, similar skin tests should be performed on healthy control individuals to avoid false-positive interpretations.[72]

Conclusion

Considering the regular use of hairdressing products, the incidence of contact urticaria is low. Hair dyes, hair bleaches containing persulfate salts, and hair products containing protein hydrolysates have been the main cause of contact urticaria syndrome. A thorough medical history and skin testing with the causative product and its constituents are helpful in the diagnosis of contact urticaria. Patients with a previous episode of contact urticaria should avoid reusing the offending hair products. For hairdressers with daily exposure to hair dyes and bleaches, it is important to avoid direct skin contact with these products by wearing protective gloves and properly covering the skin of exposed areas such as forearms.

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25

Metals as a Cause of Contact Urticaria Syndrome

Majken G. Hougaard and Jacob P. Thyssen

Introduction

Although there exist an abundance of different metals, most humans are only exposed to a minority of them, and only some cause sensitization. Metals are mainly allergenic as salts and not in their metallic form. Although type IV hypersensitivity reactions such as allergic contact dermatitis (ACD) to metals are well-documented and frequent,[1] type I hypersensitive reactions to metals including contact urticaria, asthma, rhinitis, and anaphylaxis have only occasionally been described and are considered to be rare. Interestingly, some metals are able to cause both type I and type IV hypersensitivity reactions (Table 25.1). In this chapter, we will review contact urticaria reactions to nickel, chromium, aluminum, iridium, platinum, and cobalt. Other metals that can induce asthma will only be discussed briefly.

Contact Urticaria Syndrome and Nickel

Nickel has the atomic number 28, and belongs to the group of transitional metals. Its widespread use in various alloys, coins, cosmetics, jewelry, orthopedic implants, and household utensils promotes frequent skin exposure. Among metals, nickel is considered the primer allergen. It is a well-established cause of ACD [1] and may infrequently play a role in urticaria, asthma, and rhinitis.[2–6]

TABLE 25.1

Metals Capable of Inducing Urticaria and Hypersensitivity Reactions

Metal	Type 1 Reactions (References)	Type 4 Reactions (References)
Nickel	Contact urticaria [2,3,7–11] Asthma [4,5,36,48–50] Rhinitis [6,37]	ACD [1,2] Oral [51]
Chromium	Systemic urticaria [16] Asthma [33,35] Anaphylaxis [16]	ACD [1]
Iridium	Urticaria [27] Rhinitis [27] Asthma [27]	Oral [28][a]
Platinum	Contact urticaria [17,19,24] Asthma [19,20] Rhinitis [19]	ACD [19]
Cobalt	Contact urticaria [32] Generalized urticaria [32] Asthma [32] Anaphylaxis [32]	ACD [30]

[a]The patients reacted to the patch test but did not have ACD.

Note: ACD = allergic contact dermatitis.

Epidemiology

The frequency of type I hypersensitivity to nickel is unknown.

Nickel and Urticaria

Few case reports on urticaria caused by nickel have been published [2,7–11] (Table 25.2). The mechanism behind this is not fully understood, although it has been postulated that nickel may act as a mast cell discharger on a nonimmunological basis.[8] Both individuals with occupational and nonoccupational exposure to nickel are described.

The first case report listed [2] describes a 27-year-old woman who worked with manual grinding of metal castings for 2 years. She had previously suffered from ACD from nickel-containing jewelry. She later developed contact

TABLE 25.2

Case Reports on Contact Urticaria Caused by Nickel

Author	Patient	Symptoms/Disease	Diagnostic Tests	Result
Estlander, 1993 [2]	Woman working with grinding of metal castings	Contact urticaria ACD Asthma Rhinitis	SPT $NiSO_4$ 0.1% and 1% Open test $NiSO_4$ 1% RAST Patch test $NiSO_4$ 2.5% Nasal provocation test $NiSO_4$ 1% Specific inhalation challenge	SPT was positive to 1% $NiSO_4$ Open test positive after 15 minutes RAST showed presence of specific IgE toward $NiSO_4$ Patch test was positive Nasal provocation test was positive with an immediate reaction Specific inhalation challenge was positive with a late reaction
Walsh, 2010 [3]	Woman, dental patient	Contact urticaria on mouth mucosa and skin	Patch test $NiSO_4$ 1%, 3%, and 5%	Patch test was positive for urticaria at all three sites after 20 minutes
Malo, 1982 [7]	Man working in metal plating factory	Contact urticaria Asthma	SPT $NiSO_4$ 1% Specific IgE ($NiSO_4$-RAST) with nickel sulfate Specific inhalation challenge	SPT was positive RAST suggested presence of IgE specific for nickel
Osmundsen, 1980 [8]	Case 1 Woman with occupational and consumer exposure to nickel Case 2 Woman with consumer exposure to nickel	Case 1 Contact urticaria and ACD Case 2 Contact urticaria and ACD	Cases 1 and 2 Patch test $NiSO_4$ 2.5% Chamber prick test $NiSO_4$ 2.5%	Case 1 Patch test was positive on broken skin and negative on normal skin Chamber prick test produced an urticarial reaction after 20 minutes Case 2 Patch test was negative Chamber prick test produced an urticarial reaction after 20 minutes

TABLE 25.2 (*Continued*)

Case Reports on Contact Urticaria Caused by Nickel

Author	Patient	Symptoms/Disease	Diagnostic Tests	Result
Tosti, 1986 [9]	Woman, appendectomy patient	Contact urticaria ACD	SPT $NiSO_4$ 1% Patch test $NiSO_4$ 2.5% Open patch test $NiSO_4$ 5%	SPT was positive Patch test was positive Open patch test was positive after 24 hours
Valsecchi, 1987 [10]	Woman with consumer exposure to nickel	Contact urticaria ACD	Patch test with $NiSO_4$ (ICDRG), 30-minute patch test with nickel sulfate 5% pet	ICDRG patch test was positive for contact dermatitis to nickel sulfate after 48 and 96 hours The 30-minute patch test was positive for urticaria
Helgesen, 1997 [11]	Woman with consumer exposure to nickel	Contact urticaria ACD	SPT $NiSO_4$ 2.5% Patch test (open and closed) $NiSO_4$ 0.01%, 0.1%, and 1%	SPT was positive Open patch test positive on the arm within 10 minutes, negative on the back Closed patch test positive on arm and on the back after one to two hours

urticaria, asthma, and rhinitis at work. The symptoms disappeared on weekends and holidays. Scratch chamber test, open test, specific immunoglobulin E (IgE) determinations (radioallergosorbent test [RAST]), and a RAST inhibition test indicated an IgE-mediated mechanism. A nasal provocation test with nickel sulfate was positive within five minutes. The specific inhalation challenge test with nickel sulfate provoked a late asthmatic reaction.

In the second case report, [3] a 38-year-old woman was referred by her dentist with a history of reacting to dental procedures since childhood. She experienced pain and oral swelling in relation to dental procedures. In addition, direct contact with knives and forks induced pruritus, pain and tingling of the palms within minutes, and swelling and erythema within one hour. She also reacted to phlebotomy. She never had accompanying rhinitis or asthma. She was patch tested with nickel sulfate 1%, 3%, and 5%. Within seconds, she complained of discomfort at the site of the 5% concentration, and after 20 minutes an urticarial reaction had developed at all three sites. After 96 hours, evidence of residual eczema at the site of 5% application was noted.

Another case report [7] described a 28-year old man who worked in a metal plating factory. One year after exposure to nickel, the patient developed an urticarial rash on his arms and legs. The reactions were present only at work and disappeared a few hours after nickel exposure was stopped. The patient had accompanying asthma symptoms. Skin prick testing (SPT) with a routine battery of aeroallergens were negative, but SPT with 10 mg/mL nickel sulfate showed a positive reaction. Eight controls were skin tested with nickel sulfate and showed no immediate reaction. Experimental specific inhalation challenge with nickel sulfate at the same concentration produced a bronchial obstruction typical of an early asthmatic response.

Osmundsen et al. [8] reported two cases of contact urticaria from nickel. The first was a case of a 30-year-old woman working as a cleaner using a bucket with a metal handle. She had eruptions on her hands and fingers and dermatitis on her stomach and wrist corresponding to her watch and metal buttons on her trousers. She was patch tested with the International Contact Dermatitis Research Group (ICDRG) standard series, containing nickel sulfate 2.5%, and a "plastics and glue" series with negative results. A chamber prick test (material applied to a prick on the skin and covered by a Finn chamber) with nickel sulfate 2.5% in pet produced a strong urticarial reaction within 20 minutes. The second case was a 19-year-old woman with eruptions on her hands, wrists, forearms, ears, and neck that she claimed were provoked by metals and plastic. When tested with patch tests for metal and plastics, no reactions occurred. When tested with a 20-minute chamber prick test with nickel sulfate 2.5%, a strong urticarial reaction occurred. In addition, the patient had a strong urticarial reaction to a 20-minute patch test with a piece of a plastic bag.

Tosti et al. [9] described a 24-year-old woman who at age 13 years developed an urticarial reaction and postoperative peritonitis after appendectomy; healing of the abdominal wound had been difficult and lasted 1 month. She had noted immediate swelling and redness on sites of contact with nickel jewelry, and that contact dermatitis would develop one or two days later. SPT with 1% nickel sulfate produced an urticarial wheal within three minutes. This reaction lasted several hours, and the next day, an eczematous reaction (+ +) was present at the test site, clearing four days later. Prick tests with 1% nickel sulfate on 10 patients with positive patch tests to nickel sulfate, were negative. Intradermal tests were performed to exclude sensitivity to antibiotics.

Valsecchi et al. [10] described a 59-year-old woman with urticarial lesions on her hands from touching jewelry. She was tested with the ICDRG standard series and showed a positive test reaction to nickel sulfate at 48 and 96 hours. She also had a 30-minute patch test with nickel sulfate 5% pet performed that produced a strong urticarial reaction.

Helgesen [11] described a 19-year-old woman with concomitant hypersensitivity to nickel and aluminum. When in contact with metal, she experienced erythema, burning, and itching within minutes. A short time after, vesicles and bullae developed, and after a day erosions and ulcerations.

The patient had a positive SPT to nickel sulfate 2.5%. When patch tested with the European standard series, more than half of the testes were positive after two and three days. A simple test with a Norwegian coin on the patient's forearm and back was performed. On the arm, erythema and itching developed after five minutes and, after two days, there were large crusts. On the back, no reaction could be seen after 25 minutes, but after two days the area was crusted and severely itchy.

The patient had open and closed patch tests performed with nickel sulfate 0.01%, 0.1%, and 1% on the forearm and on the back. All tests were positive on the forearm, producing erythema within 10 minutes and crusts after two days. Only the closed test was positive on the back, producing wheals and erosions within two hours.

An open test with aluminum powder in petrolatum was positive after 1 hour on both the back and the forearm. A pressure urticaria test was negative. The patient was diagnosed with contact urticaria to both nickel and aluminum and was treated with antihistamine with excellent results.

This is the only report of contact urticaria to aluminum. Aluminum and its salts are seldom reported to induce contact allergy, [12] except from recent vaccination series.

Contact Urticaria Syndrome and Chromium

Chromium was discovered in 1797 by the French chemist Nicolas Vauquelin. It has the atomic number 24 and belongs to the group of transitional metals. Chromium is the fourth most commonly found metal of the Earth's crust. It is widely used in electroplating processes, metal alloys, tanning of leather, cement, paint, and production of chromate salts. Historically, the most important route of chromium exposure has been occupational exposure to cement. Today, leather products are responsible for the main chromium exposure.[13] Nearly 90% of the global leather production is tanned using chromium sulfates.

Chromium metal is nonallergenic, but chromate salts have been investigated extensively as causative agents in contact dermatitis.[14]

Although chromium has different oxidation states, the trivalent and hexavalent forms are most common. Hexavalent chromium compounds have an increased potential for sensitization compared with the other forms. [15] Chromium is one of the common causes of ACD. Among immediate-type reactions, chromium has been reported to cause systemic urticaria, asthma, and anaphylaxis.[16]

Epidemiology

The frequency of chromium type I hypersensitivity is unknown.

Chromium and Urticaria

A case report from 1986 [16] described a welder with systemic reactions after exposure to chromium. An inhalation challenge test with a solution of $NaCrO_4$ for 25 minutes resulted in a late reaction of systemic urticaria,

angioedema, and severe bronchospasms. A late-onset reaction suggested an immunologic mechanism. SPT, patch test, and in vitro studies did not support a role for a classic IgE-mediated response. A skin biopsy specimen obtained after subsidence of most of the angioedema and wheezing demonstrated findings consistent only with an urticarial eruption, and a specific diagnosis could not be assigned to the lesion.

Contact Urticaria Syndrome and Platinum Group Elements

Platinum, iridium, ruthenium, palladium, osmium, and rhodium are metals that belong to a group called platinum group elements (PGEs). They are placed in the fifth and sixth period in groups 8, 9, and 10 in the periodic table of elements. The PGEs are commonly used in industrial applications and sometimes in jewelry and dental alloys, where catalytic properties, chemical resistance, and surface and weight properties are desired. All PGEs are rare elements of the Earth's crust. Their specific physical and chemical properties have led to the development of some highly sophisticated technical applications, especially in the field of catalysis.[17] Most of the information about the effects of PGEs in humans derives from the occupational exposure in the refinery process.[17]

Platinum has the atomic number 78 in the periodic system. It is a transitional metal, and is placed in the tenth period in the periodic table of elements. It is a highly reactive with partly filled d-shells [2] and easily complexes with donor groups in amino acids to form a complete antigen.[3] The hypersensitivity-eliciting compounds are confined to a very small group of ionic complexes containing reactive halogen ligands. Chlorinated soluble compounds, such as hexachloroplatinic acid ($H_2[PtCl_6]$), its potassium and sodium salts, potassium and sodium tetrachloroplatinate ($K_2[PtCl4]$, $Na_2[PtCl_6]$) represent the most dangerous chemical forms. Platinum is used in catalytic converters, laboratory equipment, electrical contacts and electrodes, platinum resistance thermometers, dentistry equipment, and jewelry. Compounds containing platinum, most notably cisplatin, and carboplatin are also applied in chemotherapy against certain types of cancer. Hypersensitivity to platinum in this setting is uncommon but well recognized in both patients and health care personnel.[18]

Platinum salts have been reported to induce rhinitis, conjunctivitis, asthma, contact urticaria, and less frequently ACD.[17,19–22]

Epidemiology

Platinum salts are highly potent occupational allergens causing asthma, rhinitis, conjunctivitis, and contact urticaria in a high percentage of workers of precious-metal refineries. Cristaudo et al. [17] examined 153 subjects working in a catalyst manufacturing and recycling factory. Fourteen percent had positive SPT to platinum salts, and 1.3% had positive patch test reactions.[17]

In a study [23] on workers in a secondary refinery of precious metals, 15 (14%) of 107 current employees and eight (28%) of 29 former employees who had been terminated from employment because of respiratory symptoms, had positive SPT to platinum salts. The study also showed a strong association between smoking and platinum sensitization.

Platinum salts are the third most frequent cause of occupational asthma and represents 12% of all occupational asthma cases in South Africa.[24]

Between 1988 and 1998, 194 ovarian cancer patients with no prior exposure to platinum salts were evaluated for hypersensitivity reactions to carboplatin. Thirty-two of 194 patients (16%) who were on intravenous carboplatin treatment developed symptoms compatible with a hypersensitivity reaction to carboplatin. Hypersensitivity reactions always occurred after administration of the first four intravenous courses of carboplatin.

Platinum and Urticaria

Few case reports on contact urticaria caused by platinum have been published.[14,19,25]

Santucci and Cristaudo [17,19] consecutively examined 800 patients with SPTs and patch tests to PGEs. The enrolled patients were both occupationally exposed workers in a catalyst plant and nonoccupationally exposed

subjects living in urban areas. In the exposed group, five cases of contact urticaria were observed. Four reported concomitant asthma and one concomitant rhinitis. The workers were skin prick tested with $H_2[PtCl_6]$, $K_2[PtCl_4]$ and $Na_2[PtCl_6]$ at concentrations varying from 10^{-2} to 10^{-8} M. All five patients had positive SPT to one or more platinum salts. No positive SPT reactions were reported in the nonoccupationally exposed group. In addition, two of the patients also had positive patch test reactions even though they did not have dermatitis.

Schena et al. [25] reported a case of occupational contact urticaria to platinum. A nurse from an oncology department developed urticarial reaction on the face, chest, upper limb, and dorsa of the feet when preparing cisplatin-infusion solutions. The lesions disappeared after 2 hours. She never had symptoms at home or when preparing other solutions. An open test with ammonium tetrachloroplatinate 0.25% aq and ammonium hexachloroplatinate 0.1% were both positive.

Contact Urticaria Syndrome and Iridium

Iridium is a silvery-white transitional metal belonging to the PGEs. Iridium is the most corrosion-resistant metal, even at temperatures as high as 2000°C, and only certain molten salts and halogens are corrosive to solid iridium; however, finely divided iridium dust is much more reactive. The main use of iridium is as a hardening agent for platinum alloys. It is also used in dental alloys, where unspecific reaction such as burning and dryness of the mouth; symptoms from the eyes, joints, and muscles; tiredness; and headache have been described.[26]

Among type I hypersensitivity reaction, iridium has been reported to induce urticaria, rhinitis, and asthma.[27]

Epidemiology

During 1990–1996, a study was performed on all patients referred to a dermatology clinic in Sweden with suspected hypersensitivity to dental material.[28] Most patients had no oral mucosal reactions, but suffered from systemic reactions as described previously.[26] From 1990 to 1995, patients were patch tested sporadically with iridium and indium salts, but from 1995 to 1996, the patients were consecutively patch tested. Positive patch test results to iridium were detected in 1% of the patients.

Iridium and Urticaria

Bergman et al. [27] reported the only case of contact urticaria caused by iridium.[27] A man with occupational exposure to iridium chloride developed respiratory tract symptoms and contact urticaria. Application of iridium salt to normal skin produced an urticarial reaction. SPTs with iridium chloride in increasing concentrations was positive to a 5.0×10^{-4}g/mL solution (0.05%) and a scratch test resulted in anaphylaxis. Fourteen controls were skin prick tested with iridium chloride with negative result. Platinum salt allergy was excluded through SPT with hexachloroplatinate solution.

This is the only case description of a patient with a positive SPT to iridium without a simultaneous positive reaction to platinum salts that we have identified. Positive SPT to PGEs usually occur simultaneous with a positive reaction to platinum.[29] This is interpreted as cross-reactivity.

Contact Urticaria Syndrome and Cobalt

Cobalt is a hard, silver-gray metal with the atomic number 27 belonging to the group of transitional metals. It is usually found associated with nickel. Cobalt is primarily used as the metal in the production of hard metal alloys, magnets, and prosthetics. Also, cobalt-based blue pigment has long been used for paints.

Cobalt has been reported to induce ACD, [30] asthma, [31] anaphylaxis, and contact urticaria.[32]

Epidemiology

The frequency of cobalt type I hypersensitivity is unknown.

Cobalt and Urticaria

A case report from 2009 [32] described a 39-year-old nonatopic woman employed as a ceramics decorator. Three months after she started the work, she developed ACD on her hands. Five years later, she also developed generalized urticaria and angioedema of face, lips, and tongue after using a blue paint containing cobalt chloride. She was removed to a different job in the same factory and the symptoms disappeared.

Two years later, the patient was patch tested with the European baseline series, skin prick tested with common aeroallergens, cobalt chloride (1 and 0.1 mg $CoCl_2$/mL), and nickel sulfate (10 and 1 mg $NiSO_4$/mL) dissolved in water. Serum samples were analyzed for metal-specific IgE, and a challenge test with the patient painting pottery using the blue paint was carried out.

The patch test was positive to cobalt chloride and nickel sulfate. The SPT was positive to cobalt chloride. Ten healthy controls had negative SPTs with cobalt chloride. The level of cobalt-specific IgE was 2.97 IU/mL (class 2), whereas chromium- or nickel-specific IgE was not found.

The challenge test was also positive. After 30 minutes of painting, the patient developed the first symptoms of urticaria; the wheals appeared on her hands and forearms, followed by edema of her face, lips, tongue, and hands 20 minutes later. Despite stopping exposure, the patient developed anaphylaxis and was treated with intravenous corticosteroids.

SPT with Metals

Patients with contact urticaria to metals are to be skin prick tested. Table 25.3 summarizes concentrations and solvents used in the previously mentioned reports.

Asthma and Metals

Several metals have been reported to have asthmogenic properties:

Platinum [17]
Iridium [27]
Rhodium [22]
Cobalt [33,34]
Chromium [33,35]
Nickel [36,37]
Manganese [4]
Aluminium [38]
Zinc [39,40]

TABLE 25.3

Skin Prick Testing with Metals

Metal	Concentration/Solvent
Nickel	$NiSO_4$ 1.0–2.5%/aqua
Platinum	$H_2[PtCl_6]$ 0.4%/aqua K_2[PtCl4] 0.4%/aqua $Na_2[PtCl_6]$ 0.4%/aqua
Iridium	$IrCl_3$0.03–1.0%/aqua
Cobalt	$CoCl_2$ 0.01–0.1%/aqua

Recently published data indicate that occupational asthma caused by metals may represent between 0.8% and 6.3% of all diagnosed cases of occupational asthma.[36]

Platinum salts are among the best described causes of metal-induced asthma.[17] Occupational asthma from platinum salts has been reported in refineries and catalyst plants. There is good evidence for an IgE-mediated mechanism in platinum salt asthma.[29]

Occupational asthma has been reported in workers exposed to dust or aerosols containing cobalt. Cobalt-induced asthma is reported in workers exposed to hard metals alloys.[41] Hard metal is an alloy consisting of tungsten (75%–95%) carbide and cobalt (5%–20%) as a matrix and other metals such as nickel, titanium, tantalum, vanadium, and chromium. There is evidence of the formation of specific (IgE) antibodies to protein conjugates of cobalt, suggesting that asthmatic reactions to cobalt are IgE-mediated.[42,43] The asthmatic reactions to cobalt are characterized by late or dual onset [34] and sustained by airway inflammation.[31]

There have been case reports of occupational asthma caused by chromium salts among metal plating factory workers, cement workers, and stainless steel welders.[44] Welders are exposed to several metals and occupational asthma to nickel, chromium, cobalt, and manganese has been reported in this occupational group.[41] Evidence exists of formation of specific (IgE) antibodies to protein-conjugates of nickel and chromium.[7,45] suggesting that asthmatic reaction to nickel and chromium result from IgE-mediated responses.

The occurrence of occupational asthma in potroom workers has been documented in longitudinal [46] and cross-sectional [47] studies. Potroom workers are exposed to a complex mixture of particles and gases. The particles are mainly composed of aluminium oxide, carbon dust, and fluorinated compounds of sodium and aluminium called cryolite. It has been difficult to identify the causal agent of potroom asthma. Fluoride compounds have been suggested to be the major candidates. The reported incidence of potroom asthma varies from 0.06% to 4% of exposed workers per year.[38] The most common clinical presentation of potroom asthma is a late reaction. The underlying mechanism is not fully understood.

In reports [39,40] of asthma in subjects welding galvanized metal, sensitization to zinc was suggested, but the possible presence of other metals such as cobalt, which can be present in galvanized metals, was not investigated.

Asthma from iridium, palladium, and rhodium in workers in the electrochemical industry is rare.

In summary, the pathophysiological mechanisms of metal-induced asthma remain unclear. The role of allergen-specific IgE antibodies is unclear. IgE-specific antibodies to some metals (nickel, chromium, cobalt, platinum) have been identified, but their role in the pathogenesis of metal-induced asthma is not fully confirmed. The role of other mechanisms (i.e., late-type allergic reaction and/or immunotoxic mechanisms) has not been excluded.

Summary

In spite of the frequent exposure to metals, few cases of contact urticaria caused by metals have been reported. It is noteworthy that most reports have not performed simultaneous testing in controls. The metals involved in contact urticaria are all members of the group called transitional metals in the periodic table of elements. Metals are mainly allergenic as salts and not as the metallic form. The mechanism behind contact urticaria caused by metals is unclear, but an IgE-mediated mechanism in indicated because most cases are supported by a positive SPT to the metal. Whether the metals haptenize to form a complete allergen is unknown, but it is a possible explanation.

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26

Skin Allergy Caused by Organic Acid Anhydrides

Riitta Jolanki and Kristiina Aalto-Korte

Introduction

Organic acid anhydrides (OAAs) are cyclic and mostly highly reactive low-molecular-weight chemicals (a molecular weight being 100–500 Da), which are widely used in the chemical industry. OAAs react easily with water and form corresponding acids, which are skin and respiratory irritants. OAAs are well-known for their ability to cause respiratory immunoglobulin E (IgE)-mediated sensitization and occupational rhinoconjunctivitis and asthma. In general, the adverse health effects occur in the use of the compounds as curing agents for epoxy resins.

Chemistry, Properties, and Applications

OAAs are used especially in the production of plasticizing agents, and of alkyd, epoxy, and polyester resins. They were among the very first epoxy curing agents used and remain a major class of epoxy curing agents for heat cure systems when excellent thermal, mechanical, and electrical properties are required. OAAs are the principal curing agents for cycloaliphatic and olefin epoxy resins in electrical casting and potting. OAA cured epoxy resins are also used in, for example, filament-wound epoxy pipes, printed circuit board laminates, mineral-filled composites, and encapsulation applications.[1]

OAAs offer long pot or working life (i.e., the period of time after the addition of curing agents before epoxy-anhydride systems become too viscous to apply satisfactorily). In addition, OAAs exhibit cure with low shrinkage and low exothermic heats of reaction, making them suitable for use in large mass epoxy cures.[1]

Commercially important OAA epoxy curing agents include phthalic anhydride (PA; CAS Chemical Abstract Service [CAS] 85-44-9; Figure 26.1), tetrahydrophthalic anhydride (CAS 85-43-8), methyltetrahydrophthalic anhydride (MTHPA; CAS 26590-20-5), methylhexahydrophthalic anhydride (MHHPA; CAS 25550-51-0 and 19438-60-9), hexahydrophthalic anhydride (HHPA; CAS 85-42-7), methyl himic anhydride (MNA; CAS 25134-21-8), benzophenonetetracarboxylic dianhydride (BTDA CAS 2421-28-5), and tetrachlorophthalic anhydride (TCPA; CAS 117-08-8). Methylated anhydrides, such as MTHPA and MHHPA, are liquids at room temperature and thus easy to handle. Less important OAAs used for epoxy curing agents include trimellitic anhydride (TMA; CAS 552-30-7), maleic anhydride (MA; CAS 108-31-6), chlorendic anhydride (CA; CAS 115-27-5), and dodecenylsuccinic anhydride (DDSA; CAS 25377-73-5).

Exposure

Workers may be exposed to OAAs in powder or liquid form during various manufacturing processes, such as during OAA synthesis or when the anhydrides are used as raw materials for thermosetting plastics. Exposure to OAA fumes is also possible in hot processes, for example, when epoxy resins are hardened, polyester paints are cured, alkyd or polyester painted metal surfaces are welded, or when paints are burned from surfaces.[2]

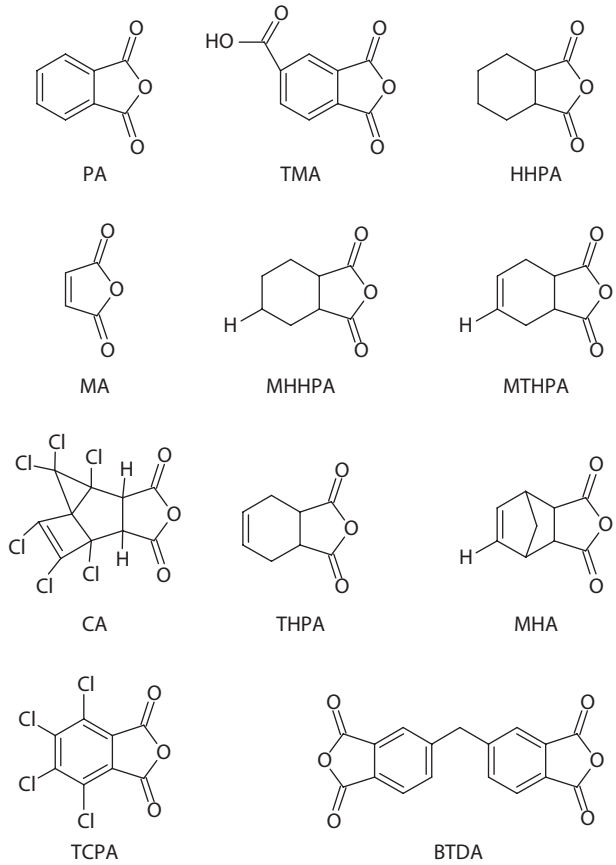

FIGURE 26.1 Chemical structures of common acid anhydrides: phthalic anhydride (PA), trimellitic anhydride (TMA), hexahydrophthalic anhydride (HHPA), maleic anhydride (MA), methylhexahydrophthalic anhydride (MHHPA), methyltetrahydrophthalic anhydride (MTHPA), chlorendic anhydride (CA), tetrahydrophthalic anhydride (THPA), methyl himic anhydride (MHA), tetrachlorophthalic anhydride (TCPA), and benzophenonetetracarboxylic dianhydride (BTDA).

Contact Urticaria

Urticarial reactions in the production of PA were described as early as in the 1950s.[3,4] The first case reports on contact urticaria (CoU) from OAAs describe two patients, one examined in 1978 [5] and the other in 1985,[6] at the Finnish Institute of Occupational Health (FIOH). They worked in the same electrical factory in which condensers were manufactured. The first patient's work involved filling the condensers with a slightly warmed uncured mixture of an epoxy resin, an MHHPA curing agent, an accelerator, and a colorant. Within two months, she developed urticarial eruptions on the face, neck, chest, and arms. After changing jobs, the eruptions disappeared. All patch tests were negative, but open tests with complete filling mixture and undiluted MHHPA on the antecubital area of the arm were positive (small urticaria on the test area). The tests with all other compounds, both mixed and separately applied, were negative. Skin prick tests or radioallergosorbent test (RAST) to MHHPA were not performed. Open tests with the undiluted MHHPA in 12 control patients were negative. The second patient was a maintenance worker.[6] After 10 months' work at the factory, he developed symptoms of CoU on the forehead and also symptoms of rhinitis. Patch tests were negative, but MHHPA at 1% in petrolatum showed considerable irritation. An open test with 100% MHHPA caused an urticarial

reaction in five minutes, which enlarged and became more enduring during the first hour, persisting for eight hours. One percent MHHPA caused a similar (but less intense) reaction in 40 minutes. A scratch chamber test with MHHPA (1%) caused a strong wheal (9-mm diameter) with pseudopodia (histamine hydrochloride 10 mg/mL, 5 mm). RAST to MHHPA was positive, but scratch chamber and RASTs to PA, TMA, and MA were negative. Occupational rhinitis from MHHPA forced the patient to move his worksite to an isolated building, whereupon the symptoms of CoU and rhinitis disappeared. During 1990–2006, an additional 21 patient cases of diagnosed CoU from different OAAs were retrieved from FIOH.[7] Some of the patients had been reported shortly after their diagnosis.[8–11] Twelve of the patients worked in the manufacture of electrical machines as winders, installation workers, electricians, impregnators, or chimney sweeps. All of them were exposed to MHHPA, and one also to HHPA. Other occupational fields included the production of sports equipment (two patients; MTHPA/MHHPA), forestry machines (one patient; CA), capacitors (one patient; MHHPA), polyester resins (one patient; MA), (micro)electronics (two patients; MHHPA or MTHPA), warehouse work (one patient; PA), and plumbing (one patient; PA). The mean exposure time before symptoms was five years. Sixteen of the patients had allergic rhinitis from OAAs and five patients had OAA-induced asthma. Only three patients had CoU as the sole diagnosis without a respiratory disease from OAAs. The 21 CoU cases represented 24% of 87 patients with immediate OAA sensitization diagnosed by skin prick tests during the same period. Three CoU patients reported that CoU was the first symptom and five that CoU rhinitis was the first symptom. In the rest of the cases, CoU and respiratory symptoms had developed simultaneously. Seven of the patients had CoU exclusively on the hands and forearms from handling products containing OAAs. Five patients had experienced urticaria only on the face and neck. Six patients had more widespread symptoms on the bare areas of the skin on the face and upper limbs. In two patients, the symptoms had also spread to covered skin areas. None of the patients had severe generalized urticaria with systemic symptoms. Six of the patients had not handled OAA products themselves but had suffered airborne exposure from processes in an adjacent work environment. Welding fumes represented a specific form of airborne exposure. Two of the patients had been exposed while welding items with a coat of paint containing OAAs. A total of eight (38%) patients had airborne urticaria from OAAs. Skin prick tests were performed with a series of different OAAs that were tested as hapten conjugates of human serum albumin. The prick test results showed a good correlation with occupational exposure: all patients had a positive prick test reaction to the OAA they were exposed to. Concomitant reactions to several OAAs were also common. This could be explained by concomitant exposure (MHHPA epoxy hardeners usually contain traces of HHPA and MTHPA) or cross-reactivity. Specific IgE to some OAAs was determined in all of the patients, but five patients exposed to MHHPA had not been tested for MHHPA-specific IgE. Thus 16 patients were tested for specific IgE to the OAA used in the workplace, and only one of them was negative. The results of the specific IgE correlated well with the exposure and the skin prick test results. Specific IgE to PA was determined in 20 patients and was positive in 19 regardless of which OAA the patient had been exposed to. Therefore this serves as a useful screening method for sensitization to OAAs. Open application tests were performed on 11 of the 21 patients with varying test substances, and gave positive results in all who were tested. A clear positive urticarial response required the use of the undiluted hardener in seven of the nine patients who were tested with their own product.[7] Today at FIOH, the open application test is first performed with a 1% dilution of the hardener in petrolatum, followed by a 10% dilution in petrolatum, and finally by the undiluted curing agent product.

Recent reports from countries other than Finland are sparse: A Spanish refinery worker with CoU from PA [12] and a Japanese electronics worker with airborne CoU from MHHPA [13] have been described.

Allergic Contact Dermatitis

In the literature, there are only a few reports of allergic contact dermatitis from OAAs. Allergic contact dermatitis from epoxy hardener DDSA was reported by Göransson in a laboratory technician with bullous finger dermatitis.[14] The patient's work involved preparing tissue samples for electron microscopy. The embedding material consisted of epoxy resin, two hardeners, and additional chemicals. One of the hardeners was DDSA, and it was the only ingredient that was positive on patch testing at concentrations of 0.5% and 1% in acetone. Fifteen controls were negative.

Motolese et al. [15] reported positive patch test reactions to MA at a concentration of 1% in ethanol in two of 190 workers from five ceramic factories. The test with PA at 1% in petrolatum was negative. MA and PA were specifically used by enamellers and decorators. The authors also reported sensitizations to MA in three other workers from earlier investigations on ceramic workers.

A horizontal boring machine worker examined at FIOH had developed allergic contact dermatitis and rhinitis from MHHPA. Patch testing elicited strong allergic reactions to MHHPA at concentrations of 2%, 1%, and 0.5% in petrolatum, and weak allergic reactions at 0.25% and 0.125%. Skin prick testing with a human-serum-albumin-MHHPA conjugate gave strongly positive reactions, but specific IgE could not be demonstrated in the sera with the RAST method. A respiratory challenge test with MHHPA was negative, but provoked skin symptoms within 15 minutes on the upper arms and at the sites of the patient's previous dermatitis, still persisting 24 hours later.[16]

Since 1998, at FIOH, MHHPA has been included in the specific epoxy compound series at a concentration of 1% in petrolatum, but no other cases of allergic contact dermatitis have been diagnosed, namely, tested on 469 patients yielded no allergic patch test reactions.

In 2002–2007, several nonoccupational cases of allergic contact dermatitis from a phthalic anhydride/trimellitic anhydride/glycols copolymer ingredient present in nail varnish have been reported.[17–19] Unfortunately, the specific component responsible for the contact allergy has not been identified because patch tests were not performed for PA and TMA.

Conclusions

OAAs are well-known respiratory allergens. They have the ability to induce specific IgE-mediated sensitization. CoU from OAAs is rare but occurs particularly in the production of electrical machines. Allergic contact dermatitis has been described even more rarely. Although the symptoms of CoU are often mild and transient, it is important to diagnose immediate sensitization and investigate possible respiratory symptoms.

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27

Immediate Skin Contact Reactions from Plants

Flemming Andersen and Evy Paulsen

Urticaria to plants may be both immunologic and nonimmunologic. Although most cases of contact urticaria from plants are believed to be toxin-mediated rather than involving type I hypersensitivity, the mechanism is often not clarified in the individual case reports, especially in older literature.[1]

This chapter focuses on plants in the surroundings of man, be it as weeds, woods, or ornamentals. For plants used as foodstuffs, please refer to the appropriate chapter.

Nonimmunological Contact Urticaria

Several plant species have developed silicaceous stinging hairs [trichomes) on leafs and stems. When rubbed the trichoma is broken at the tip, thus transforming into a hypodermic needle, injecting the contents of the hair into the skin or mouth of the culprit. Because the hairs contain several toxins including histamine, acetylcholine and 5-hydroxytryptamine, the would-be plant-eater instead of getting a delicious meal gets hives.[1–3]

Plants from the nettle family, Urticaceae, are the worldwide most important causes of nonimmunologic contact urticaria.[4] The archetypical representative of this family is the stinging nettle (*Urtica dioica*) found worldwide except in tropical regions. However, immunological contact urticaria has been reported from small nettle *Urtica urens* as well as stinging nettle *U. dioica*.[5,6]

Being stung by a nettle results in short-lived hives with burning and itching, being stung by members of the genus *Dendrocnide* may result in week-long stabbing pains and even death.[3,7,8] As could be expected, *Dendrocnide* spp. are mostly found in Australia, thus supporting the myth that everything in Australia evolved to kill everything else.

Members of other plant families, such as *Cnidoscolus angustidens*, known as mala mujer (bad woman) are also able to induce nonimmunologic contact urticaria.[3] An overview of the most common plants inducing nonimmunologic contact urticaria is shown in Table 27.1.

Immunological Contact Urticaria and Urticaria by Unclassified Mechanism

In theory, every plant species may induce immunological contact urticaria.[67] The limiting factor is how frequently the plant species is handled; in order to sensitize, a fair amount of handling is necessary. Ornamental plants are probably handled more frequently and intensely than for instance weeds and wood in both occupational and nonoccupational settings. Consequently, immediate hypersensitivity is to be expected, although likely underreported because of the obvious relationship between exposure to a culprit plant and the symptoms. Epidemiological data are scarce. However, Goldberg et al., in their study on the prevalence of positive skin prick tests to pollen of some common flowering ornamentals, found 17% positives among 292 people referred for allergic evaluation, 23% among 44 biology students, and finally 52% among 75 flower growers. The percentages of positives were even higher when only atopic participants were included. Almost half of the flower growers reported mucosal or respiratory symptoms,[11] but ornamental plants may also cause immediate skin reactions: Kanerva et al. listed decorative plants as number six among 15 causes of occupational contact urticaria (and protein contact dermatitis) in 815 cases registered at The Finnish Institute of Occupational Health between 1990 and 1994.[12]

TABLE 27.1

Examples of Plants Causing Immunological Contact Urticaria

Family	Genus	Species	Distribution
Compositae	*Chrysanthemum*	spp.	Worldwide [46]
Euphorbiaceae	*Acidoton*	*urens,* etc.	West Indies Central and South America
	Cnidoscolus	*angustidens, stimulosus urens,* etc.	SE United States and tropical America
Hydrophyllaceae	*Wigandia*	*caracasana, urens,* etc.	Americas
Loasaceae	*Aosa*	spp.	Mainly Brazil
	Blumenbachia	spp.	Temperate South America
	Caiophora	spp.	South America, Andes
	Cevallia	*sinuata*	SW United States and Mexico
	Chichicaste	*grandis*	Columbia to Costa Rica [9]
	Eucnide	spp.	SW United States and Mexico
	Fuertesia	*domingensis*	Hispaniola
	Gronovia	*longiflora, scandens*	Central America
	Huidobria	*chilensis, fruticosa*	Chile
	Loasa	*acanthifolia, acerifolia, argentina, bryoniifolia, longiseta, sclareifolia, tricolor,* etc	Mexico, temperate South America
Urticaceae	*Urtica*	*dioica, urens, pilulifera,* etc.	Worldwide
	Laportea	*canadensis, grossa,* etc.	Mostly tropical, but also North America
	Dendrocnide	*gigas, moroides, photinophylla,* etc.	Mainly Australia

Source: Adapted from Mitchell J C, Rook A. *Botanical Dermatology. Plants and Plant Products Injurious to The Skin.* Vancouver: Greengrass, 1979: p.591.

Note: All plants in this table, except for Chrysanthemum spp., are equipped with nettle hair capable of injecting urticariogens into the skin upon contact.

Contact urticaria has not only been reported to flowering indoor and outdoor ornamentals, but also to indoor foliage plants that rarely bloom as well as shrubs.[13–18] In the following are described ubiquitous ornamental species that are well-known causes of immunological contact urticaria and urticaria of unknown mechanism.

For an overview of examples of plants causing immunological urticaria or urticaria by unknown mechanism, see Tables 27.2 and 27.3.

Indoor Foliage Plants

Weeping Fig (*Ficus benjamina*)

Weeping fig is a tropical tree that is commonly grown as an indoor pot plant in colder climates. It is native to south and southeast Asia and Australia.

The first cases of immediate hypersensitivity to weeping fig were reported in two plant keepers in 1985. They were employees in a plant-leasing firm, and their job was to deliver, water, nourish, clean, and trim various indoor plants at the clients' offices or buildings. The two patients developed rhinoconjunctivitis and, respectively, exacerbation of a preexisting asthma and a nonproductive cough. Prick tests to leaf and twig extracts

TABLE 27.2

Examples of Plants Causing ICU (Predominantly Cultivated Plants)

Family	Botanical Name	Popular Name
Araceae	*Spathiphyllum floribundum*	
	Spathiphyllum wallisii	Spathe flower [13,16,33,42]
Araliaceae	*Hedera helix* cv. "Hester"	Common ivy [37,38]
Asclepiadaceae	*Araujia sericifera*	Moth plant [10]
	Stephanotis floribunda	Madagascar jasmine [41]
Asparagaceae	*Dracaena fragrans*	Corn plant [40]
	Yucca filamentosa Yucca elephantipes	Yucca [34,35]
Cactaceae	*Rhipsalidopsis* hybrids	Easter cactus [49]
	Schlumbergera hybrids	Christmas cactus [48,49]
Caryophyllaceae	*Dianthus caryophyllis*	Carnation [54]
	Gypsophila paniculata	Baby's breath [54]
Commelinaceae	*Tradescantia albifloxa*	Wandering jew [36]
Compositae	*Aster* spp.	Aster [45]
	Chrysanthemum spp.	Chrysanthemums [45]
	Gerbera hybrids	Gerbera [14,41]
	Leucanthemum vulgare	Marguerite [45]
	Solidago virgaurea	Golden rod [45]
Euphorbiaceae	*Euphorbia pulcherrima*	Poinsettia [41]
	Hevea brasiliensis	Pará rubber tree [66]
Liliaceae	*Lilium longiflorum*	Easter lily [53,54]
	Tulipa spp.	Tulip [53,54]
Moraceae	*Ficus benjamina*	Weeping fig [27,28]
	Morus alba	Mulberry [70]
Plumbaginaceae	*Limonium tataricum*	Statice [57]
Rosaceae	*Rosa* spp.	Rose hips [63]
Verbenaceae	*Verbena* hybrid	Verbena [50]
Urticaceae	*Urtica dioica*	Stinging nettle [6]
	Urtica urens	Small nettle [5]

Note: The plants here have been demonstrated to cause IgE-mediated urticaria in susceptible individuals.

were positive and specific immunoglobulin E (IgE) antibodies detected by radioallergosorbent test (RAST), and weeping fig sensitization was thus considered a new occupational disease.[19] The results were confirmed in subsequent studies by the same investigators: plant caretakers, as opposed to gardeners working with the plants in humid greenhouses, composed a high-risk group and the main mode of sensitization was assumed to be inhalation of airborne dust particles containing the allergens from the sap.[20,21] The hypothesis was that 6%–8% of the water taken up by the roots of the plant would diffuse through the leaves, and by osmosis soluble allergens would follow and be deposited on the surface of the leaves after evaporation of the water. When house dust accumulated on leaves subsequently, the allergens would be absorbed by the dust, making them potentially airborne. The theory was supported not only by the previously mentioned differences between sensitization rates of greenhouse gardeners working with weeping fig and plant caretakers, whose work with weeping fig included shaking of the plant to remove dust from the leaves in low-humidity offices, but also that some of the sensitized persons had negative prick test reactions to leaf extract, but positive to dust extract from weeping fig leaves.[21] Furthermore, Bircher et al. later confirmed the presence of weeping fig allergens in house dust.[22] In the light of this mode of sensitization, it is not surprising that mucosal symptoms such as conjunctivitis and rhinitis appear and usually precede asthma.[20] However, Axelsson et al. mention the skin as another possible

TABLE 27.3

Examples of Plants Causing Urticaria by Unknown Mechanisms

Family	Botanical Name	Popular Name
Araceae	*Epipremnum pinnatum*	Pothos, devil's ivy [41]
Asparagaceae	*Yucca aloifolia*	Yucca [16]
Brassicaceae	*Matthiola incana*	Stock [58]
Cactaceae	*Rhipsalidopsis* hybrids	Easter cactus [49]
	Schlumbergera hybrids	Christmas cactus [48,49]
Campanulaceae	*Campanula* spp.	Bellflower [41]
Compositae	*Aster novi-belgii*	Aster [41]
Geraniaceae	*Pelargonium* hybrids	Geranium [41]
Iridaceae	*Iris* hybrid	Iris [1]
Malvaceae	*Hibiscus rosa-sinensis*	Hibiscus [41]
Moraceae	*Ficus pumila*	Creeping fig [41]
Nyctaginaceae	*Bougainvillaea* spp.	Bougainvillea [51]
Proteaceae	*Grevillea juniperina prostrate*	
	Grevillea juniperina trinerva	Grevillea [17]
	Hakea suaveolens	Sweet Hakea [18]
Rosaceae	*Cotoneaster dammeri*	Cotoneaster [59]
	Rosa hybrid	Rose [64]
Rubiaceae	*Gardenia jasminoides*	Gardenia [41]
Verbenaceae	*Verbena elegans* "Cleopatra"	Verbena [50]

Note: Most plants in this category simply have not been tested for mechanism, others such as the cacti may induce both immunological and toxin-mediated urticaria.

contributory route of sensitization because 13 of 18 occupationally sensitized persons reported contact urticaria from contact with the sap of weeping fig.[20] Contact urticaria from occupational exposure to weeping fig was also reported by Kanerva et al.[16] Schmid et al., on the other hand, reported contact urticaria as well as edema of the lips and asthma in a 32-year-old nonatopic male who was sensitized by a weeping fig in his home.[23] An unusual mode of sensitization was described by Sesztak-Greinecker et al.: a 31-year-old atopic male was sensitized to weeping fig by transfer of the allergen to his skin via his pet chameleon, followed by "skin prick" with the animal's sharp allergen-contaminated claws. The chameleon used to climb a big weeping fig plant in the living room and a smaller weeping fig specimen in its vivarium. The patient developed urticarial lesions on contact with the chameleon's claws, but no mucosal symptoms.[24] Anaphylactic reaction to weeping fig has also been reported.[25]

The risk of developing occupational sensitization to weeping fig is high in those taking care of such plants outside greenhouses on a daily basis: 16 of 52 (31%) plant keepers were sensitized.[20] In the same study, another two people with moderate occupational exposure to weeping fig were sensitized, and seven of these 18 persons were atopics, whereas 11 were nonatopic (although four had a family history of atopy).[20]

In another study by the same group, sensitization to weeping fig in subjects less exposed was investigated: 395 consecutive patients referred to an allergy department and 107 office workers from two offices decorated with weeping fig plants were included. Altogether, 13 patients and three office workers were sensitized, and all of them were atopics. On the basis of the detection of specific IgE antibodies to weeping fig, 8% of exposed atopics were sensitized, which makes weeping fig allergy as prevalent as that of the most common mould (*Cladosporium herbarum*) in Sweden. The authors concluded that atopic persons exposed to weeping fig, especially in home surroundings, were at risk of becoming sensitized and the estimated risk figure was 6%.[21] Later, Axelsson reported on four nonatopic people with mucosal symptoms from weeping fig at home and/or at work.[26] Concerning the allergens of weeping fig, Axelsson et al. identified three major and eight minor allergenic components of the sap.[27]

On the basis of reactivity to sera of 24 weeping fig–sensitive people, it was concluded that seven other *Ficus* species contained various amounts of allergens common to weeping fig and thus might be eliciting factors in persons with weeping fig allergy.[28]

In the previously mentioned study on sensitization in less exposed people, one of the patients was sensitized only to leaf extract and not extract of twigs and sap, suggesting the presence of allergens other than the 11 identified in the sap.[21,28] In the same study, a positive prick test to weeping fig was found in many RAST-negative patients, suggesting either low-grade sensitization or, more likely, according to the authors, a nonspecific irritant reaction.[21]

In vitro cross-reactivity between weeping fig latex and natural rubber latex from *Hevea brasiliensis* is well-known, and 25% of patients with clinical latex allergy have IgE antibodies that bind with two proteins in weeping fig latex.[29,30] Focke et al., in their study on cross-reactivity to weeping fig allergens, rubber latex, pollen, and tropical fruits in patients with clinical fig allergy, concluded that allergic reactions to fresh or dried figs (*Ficus carica*) could be a consequence of primary sensitization to the related weeping fig, independent of sensitization to rubber latex allergens.[31]

In another study, positive prick test reactions to weeping fig were associated with positive prick test reactions to not only figs, but also kiwi fruit, papaya, avocado, banana, and pineapple ("Ficus-fruit syndrome"). The cross-reactivity may be partly caused by thiol proteases.[32]

Yucca Species

The genus Yucca of the Asparagaceae family of plants comprises several species used as sturdy houseplants. Yuccas, which are native to Central America, Mexico, the Caribbean, and the southern United States, may grow into a height of 2 m and are therefore suitable for public buildings and large office spaces. Like weeping figs in public places, yuccas may be tended by professional plant caretaker firms. Kanerva et al. reported the first case in an occupational setting: a 33-year-old male plant caretaker developed work-related dermatitis and occasional wheals on hands and forearms and later mucosal symptoms. Prick tests showed positive reactions to mugwort, five different spathe plants, yucca, and weeping fig. Twenty controls tested negative.[33] Another atopic male plant caretaker also developed occupational contact urticaria, and consequently hand dermatitis now and then, and he was sensitized to the same three plants.[16] Prick test to *Yucca aloifolia* leaves was positive in the patient and negative in 20 controls, whereas RAST to the leaves was negative. The authors also reported the results of prick testing with a series of decorative plants in more than 600 patients: 5.8% [37/634] tested positive to *Yucca aloifolia*, making this the third in the ranking of seven plants tested.[16] A third case of occupational sensitization to another yucca species, *Yucca elephantipes*, was reported as a poster presentation at the First World Congress of Work-Related and Environmental Allergy. The patient was a 43-year-old female gardener and caretaker of indoor plants in offices who developed occupational rhinoconjunctivitis as well as intensely itching erythema when touching, among other things, *Yucca elephantipes*. Prick test showed histamine size reactions to both *Y. elephantipes*, weeping fig, and another *Ficus* species, whereas 10 common inhalant allergens, latex, and various fresh food items tested negative. Testing in controls was not performed, but histamine release test was positive to *Y. elephantipes*, weeping fig, and the other *Ficus* species, indicating, although not proving, that the patient had immunological contact urticaria.[34]

Finally, Munno et al. reported a case of nonoccupational sensitization to outdoor *Yucca filamentosa* plants in a nonatopic Italian male. The patient first developed slight angioedema of eyelids, urticaria, and itching of the face when working close to a yucca plant in his garden, and later acute urticaria-angioedema of face and neck accompanied by mucosal symptoms after trimming a yucca plant. He was not examined until 2 years later, when prick by prick test with yucca leaves, but not flowers, elicited strongly positive reactions in the patient and negative reactions in 10 controls. The detection of specific IgE antibodies to yucca leaves suggested true immunological contact urticaria.[35]

In conclusion, although yuccas are low-maintenance houseplants and, in accordance with this, nonoccupational sensitization only has been reported once,[35] plant caretakers may be heavily exposed to yuccas during cleaning procedures, making the risk of developing contact urticaria and other type I allergies not negligible.

Miscellaneous Indoor Ornamental Foliage Plants

Tradescantia species, commonly known as wandering Jew, are popular trailing pot plants. They are native to North America and tropical South America and belong to the Commelinaceae family of plants. Two cases of nonoccupational sensitization in atopics have been reported.[23,36] Schmid et al. described cough and dyspnea in a 41-year-old female when she repotted *T. albiflora* and *T. fluminensis*. When touching the plants, she developed edema of the lips and conjunctivitis. Prick tests with the plants were strongly positive in the patient and negative in five controls.[23] Likewise, in the case reported by Wüthrich and Johansson, a 32-year-old female office employee with perennial rhinoconjunctivitis, and positive prick tests to mugwort and tree pollen and house dust mites, developed itching of the face, throat, and conjunctiva as well as swelling of the lips, dyspnea, and wheezing when repotting *T. albiflora* and *T. fluminensis* plants. Positive prick tests to the leaves of both species, and detection of specific IgE antibodies to *T. albiflora* confirmed the allergic etiology. The rhinitis symptoms disappeared, at least outside the tree pollen season, when the plants were removed from the patient's home and house dust mite avoidance measures were applied.

Later, the relevance of the reactions was further supported by a flare of urticaria and mucosal symptoms after contact with a *T. albiflora* plant at her place of work.[36]

Another popular green pot plant is common ivy (*Hedera helix* cultivars). The genus *Hedera*, which belongs to the Araliaceae family of plants, comprises 15 species, and common ivy is also a common weed distributed worldwide, especially in temperate regions. The first report of an urticarial reaction to common ivy was published in 1975: the patient had positive patch test reaction to the plant and her symptoms cleared after avoidance of contact. Testing for immediate hypersensitivity was not performed, and it is thus possible that the patient had contact allergy only.[37] The first case of contact urticaria to common ivy confirmed by positive prick test and histamine release test occurred in a 45-year-old female gardener with a positive prick test to mugwort as well. One of 10 controls with a positive prick test to mugwort tested positive to common ivy, but the histamine release test was negative.[38] In a Danish questionnaire study, the prevalence of rhinoconjunctivitis and skin symptoms was significantly higher in gardeners working with common ivy and weeping fig on a daily basis as compared with a control group of industrial workers and teachers. Rhinitis and urticaria were significantly more prevalent in gardeners, but because they were not examined or tested, the nature and any possible causal relationship between these symptoms and the plants could not be proved. However, in 84% of the affected patients, the symptoms appeared after they began working with weeping fig and/or common ivy.[39] The group of gardeners working as indoor plant caretakers had higher prevalences of mucosal and skin symptoms as compared with gardeners working with propagation of the plants in nurseries: this is in accordance with the findings of Axelsson et al.[20]

Dracaena species of the Asparagaceae family of plants are also popular large tree-like pot plants. Brito et al. reported a case of nonoccupational sensitization in a 54-year-old Spanish housewife: on several occasions, she developed rhinoconjunctivitis, contact urticaria, and asthma after cleaning a corn plant (*D. fragrans*) at home, sometimes to a degree requiring emergency treatment. Prick tests were positive to *D. fragrans* leaf extract and an extract from a high-volume air sampler placed near the plant as were specific IgE antibodies to the leaf extract, suggesting an IgE-mediated allergy. Prick tests to pollen of *O. europaea*, *A. vulgaris*, and *S. kali* were positive, but specific IgE to the same species were negative in this patient with no personal or family history of atopy.[40] The mechanism of sensitization was suggested to be the dusty environment created by cleaning the leaves, which is similar to that described for weeping fig.[21] In the previously mentioned Finnish study in which more than 600 patients were prick tested with a series of seven decorative houseplants, 26 of 621 [4.2%) had positive reactions to *D. fragrans*, making this number five in the ranking. Based on the case report and the latter results, sensitization would seem to be a risk in persons occupationally involved in caretaking of plants.[16] In accordance with this, a positive prick test reaction to *D. fragrans* stem with RAST class 1 was reported in an atopic plant caretaker who was primarily allergic to spathe flower.[13]

In a Danish study on immediate reactions to plants in gardeners and greenhouse workers, *Epipremnum aureum* (pothos, devil's ivy) and *Ficus pumila* (creeping fig) cultivars elicited contact urticaria and positive prick and/or scratch patch tests, but further laboratory tests to classify the reactions were not performed.[41]

Indoor Flowering Plants

Spathe Flower (*Spathiphyllum wallisii*)

The beautiful white-flowered spathe flower belongs to the Araceae family of plants, and it is native to tropical South America. Immediate type IgE-mediated hypersensitivity causing both contact urticaria and mucosal symptoms has been reported in occupational settings.[13,16,33] The first report described a 22-year-old atopic male plant caretaker with occupational asthma, swelling of eyes, and contact and generalized urticaria.[13] Prick test reactions to spathe flower, pollen, stem, and leaves were positive with pseudopodia, whereas stem and leaf were negative in 20 controls (atopics and nonatopics). RAST was positive (almost class 3] for the flower, whereas bronchial provocation caused contact urticaria on the eye lid and mucosal symptoms from the eyes, nose, pharynx, and larynx, but not the lungs. In IgE immunoblotting, one heavy band was detected at about 14kDa, perhaps identical with profilin.[13] The patient was heavily exposed as he washed, cleaned, and trimmed the plants, and his sensitization developed through skin and/or respiratory exposure within 10 months, making it necessary for him to give up his job. The patient's brother, who had an atopic diathesis with a positive prick test to mugwort, also worked with spathe flower as a plant caretaker in clients' offices, and he developed occupational dermatitis, contact urticaria, and rhinoconjunctivitis.[33] Prick test positivity and specific IgE antibodies class 1–2 to five different spathe flower cultivars were detected and nasal and conjunctival provocation tests with one of the cultivars were positive. The patient also had positive prick test reactions to weeping fig and yucca, but RAST was negative to the former and not tested in the latter. Twenty controls had negative prick test reactions to all three plants. The patient developed local and generalized urticaria when he tried to resume work, and consequently was forced to retrain for a new job.[33] A similar sensitization pattern was reported in a third case. The patient was an atopic 22-year-old male gardener and plant caretaker who was diagnosed with contact urticaria, and consequently occasionally hand dermatitis, from spathe flower, weeping fig, and yucca. Prick tests were positive to all three species, whereas specific IgE antibodies class 2 could only be detected to spathe flower and weeping fig.[16] Finally, a case of nonoccupational sensitization occurred in an atopic female: her symptoms were, however, purely mucosal.[42] Her symptoms worsened when she trimmed the plant, and altogether these reports emphasize the risk of close contact with spathe flower plants in atopics.

Compositae Plants

Autumn-flowering chrysanthemums (*Chrysanthemum* cultivars, formerly described by some authorities as *Dendranthema cultivars*) are among the most popular pot (and garden) plants. In light of this, immediate hypersensitivity is rarely reported and only in occupational settings. Tanaka et al. described positive patch test to juice of chrysanthemum leaves and flowers and positive immediate hypersensitivity reaction in a scratch test to diluted flower juice in a female, nonatopic gardener. The controls were negative and the patient's dermatitis was ascribed to a combination of delayed and immediate hypersensitivity.[43]

Contact urticaria, mucosal symptoms, and asthma to chrysanthemums were reported in two florists by Piriilä et al. and Uter et al., respectively.[44,45] In the latter case, the patient tested positive to pollen of five *Compositae* species, and the detection of specific antibodies to the same pollen, including chrysanthemum, suggested immunological contact urticaria.[45] Conversely, Fischer et al. described a case of nonimmunological contact urticaria to chrysanthemum flowers occurring in a female gardener. The localized skin symptoms, negative RAST, and patch test, but positive rub test and complement-activated C5a cellular antigen stimulation test were in accordance with a nonimmunological reaction.[46]

The flowers of *Gerbera* hybrids obviously contain pollen. Estlander et al. reported a case of occupational contact urticaria and rhinoconjunctivitis in a nonatopic plant molecular biologist who had worked with flowering gerberas for five years.[14] In accordance with a previous Dutch study, prick tests to pollens elicited stronger reactions than those of petals and leaves, and a positive RAST to the gerbera pollen confirmed the allergy.[47] In the Danish study on immediate reactions to plants in gardeners, positive prick, scratch patch, and histamine release tests to gerberas were

found in two people with contact urticaria, mucosal symptoms, and dermatitis.[41] In the same study, *Aster novi-belgii* elicited a positive scratch patch test in a person with contact urticaria, and Uter et al. later confirmed type I sensitization to *Aster* pollen in their patient with occupational contact urticaria, mucosal symptoms, and asthma.[45]

Miscellaneous Indoor Flowering Plants

Schlumbergera and *Rhipsalidopsis* hybrids of the Cactaceae family of plants, known under the colloquial names Christmas and Easter cactus, respectively, are popular flowering pot plants. The first report on occupational contact urticaria and mucosal symptoms from Christmas cacti comprised five female cactus workers who were all atopics. All five had positive prick and histamine-release tests to cactus shoots, and in three of them specific IgE to the plants could be detected by Maxisorp RAST and immunoblotting.[48] However, a subsequent questionnaire study in 84 cactus nursery employees, followed by interview and testing of 63, demonstrated a modest concordance between skin prick test results and basophil histamine-release test/Refix results of 61%. The authors concluded that Christmas and Easter cacti apparently could elicit contact urticaria and rhinoconjunctivitis both by an immunological and a nonimmunological mechanism. Risk factors included personal atopy, duration of exposure, and working with cactus propagation by which top shoots are broken off manually, releasing an aerosol of sap.[49] Cultivated *Verbena* species are used as both container and garden plants. The first verified case of IgE-mediated immediate hypersensitivity was reported by Potter et al.: a 14-year-old atopic boy developed severe urticaria, palpitations, dizziness, and bronchospasm after touching *Verbena* plants (*V. hybrida*) in a garden. Autoradiography of the Western blots of *V. hybrida* leaf extract demonstrated a 62kDa allergen.[50] The other case described in the same report was a 23-year-old female gardener who developed an urticaria-like dermatitis, hand eczema, and later rhinoconjunctivitis and asthma on occupational exposure to *Verbena* plants. Although histamine- release test to *V. elegans* "Cleopatra" was negative, the patient's history with gradually worsening symptoms and positive prick and patch test reactions to *Verbena elegans* suggested the simultaneous occurrence of immediate and delayed hypersensitivity to *Verbena* plants.[50]

Fischer reported a nonoccupational case of sensitization to *Bougainvillea* in 49-year-old nonatopic woman: she developed contact urticaria and shortness of breath when tending her plants and a scratch chamber test with crushed *Bougainvillea* leaves and flowers were positive and negative in 10 controls.[51]

In a Danish gardener study, Madagascar jasmine (*Stephanotis floribunda*) and Christmas star (poinsettia) (*Euphorbia pulcerrima*) elicited positive prick or scratch patch tests, respectively, as well as positive histamine release tests, suggesting possible immunological immediate reactions.[41] In the same study, the following flowering plants elicited contact urticaria and positive prick and/or scratch patch tests: *Hibiscus rosa-sinensis, Pelargonium hybrid* (geranium), *Campanula* species (bellflower), and *Gardenia jasminoides* (gardenia). However, no laboratory tests were performed and the contact urticaria thus could not be classified further.[41]

Cut Flowers

Immediate hypersensitivity to cut flowers seems to occur mainly in occupational settings. Lahti reported the first case of contact urticaria and respiratory symptoms from tulips in a 37-year-old atopic female who owned a florist shop and a funeral parlor.[52] She had positive scratch chamber tests to bulbs and stems of five varieties of tulips and to funeral lily (*Lilium longiflorum*) of the same plant family (Liliaceae). Forty controls tested with one of the tulip varieties had negative reactions. Scratch and prick tests to a water extract of the bulbs of one tulip variety and funeral lily were also positive.[52] Although an allergic etiology was likely, it was not definitely proved. However, later studies have confirmed immunological contact urticaria to both tulips and *Lilium longiflorum*.[44,53,54]

Two cases of sensitization to plants of the family Caryophyllaceae have been published: the first was a 35-year-old atopic male flower supplier who developed IgE-mediated rhinoconjunctivitis and contact urticaria as well as dermatitis to baby's breath (*Gypsophila paniculata*) and carnation (*Dianthus caryophyllus*), the other was a 52-year-old female florist with a history of childhood atopic dermatitis who developed contact urticaria from baby's breath.[44,54]

The extremely popular cut flower Peruvian lily (*Alstroemeria* hybrids) has been reported as a cause of occupational allergy, too: a 34-year-old male florist with a history of perennial allergic rhinitis in childhood developed mucosal and respiratory symptoms as well as contact urticaria/angioedema after removal of stamen from various flowers. Prick test was positive to a pollen extract of Peruvian lily as was a challenge test: one control person tested negative to the former.[55]

Another popular cut flower is statice (*Limonium sinuatum* Miller = *Statice sinuata L.*) of the Plumbaginaceae family of plants. Ueda et al. reported work-related mucosal symptoms in three Japanese statice growers: positive intradermal and provocation tests and the detection of specific IgE antibodies to statice extracts by RAST supported immediate type hypersensitivity.[56] The dried flowers of another *Limonium* species, *L. tataricum*, that is also grown in herbaceous borders, caused occupational contact urticaria, mucosal symptoms, and asthma by a similar mechanism. The floral industry worker was a 27-year-old male with an atopic diathesis, and it was suggested that the dry flowers might create a dust aerosol that sensitized through both inhalation and cutaneous exposure.[57]

Lahti listed iris as a cause of contact urticaria based on references from the nineteenth century.[1] Both chrysanthemum and gerbera hybrids of the Compositae (Asteraceae) family of plants may be used as cut flowers. Immediate hypersensitivity to these is described in the section on flowering indoor plants.

Outdoor Ornamental Plants

In contrast to most of the cases of indoor plant allergy, immediate reactions to outdoor plants occur mostly in amateur gardeners. Galindo et al. reported a case of contact urticaria to stock (*Matthiola incana*) sheaths in an atopic male. Prick and rub tests were positive, and although RAST was negative, an IgE-mediated allergic contact urticaria was suspected.[58] Another flowering garden plant is cotoneaster of the Rosaceae family of plants: one case of contact urticaria with positive rub test (negative in one control person) has been reported by van Ketel.[59] Mitchell and Rook, in their book *Botanical Dermatology,* [60] quote White [61] for citing Cooper who published four cases of urticaria from *Cotoneaster microphylla* in 1900.[62] Incidentally, in a study of 13 workers with work-related respiratory symptoms attributed to rose hip powder, two had urticaria. Both workers had positive prick and enzyme-linked immunosorbent assay tests for rose hip suggesting an IgE-mediated allergy.[63] Another case from the rose family was reported by Kleinhans in 1985: a 48-year-old atopic woman had noticed contact urticaria when she handled roses, and scratch tests were positive to leaf, stem, and the content of a thorn.[64] Furthermore, in a Danish gardener study, one person with contact urticaria had a positive reaction to a "prick" test with rose thorns.[41] Finally, contact urticaria from both *Grevillea juniperina* and *Hakea suaveolens* was reported in the same amateur gardener; however, an urticarial reaction to *G. juniperina* was also seen in two of three controls.[17,18]

The Latex Allergy Epidemic

Pará Rubber Tree (*Hevea brasiliensis*)

The rubber tree is the source of the highest quality latex used in the manufacture of rubber goods and has become the most well-known source of immunological contact urticaria and even anaphylactic reactions. Nutter originally described a case of contact urticaria to rubber confirmed by skin contact with a leaf causing urticaria, [65] soon to be followed by reports of asthma and anaphylactic reactions. Because of the wide spread use of latex products in the health care industry, a veritable latex allergy epidemic rose.[66] Introduction of low-protein powder-free latex gloves combined with education and other preventive measures has substantially reduced the incidence of latex allergy.[67,68]

Testing with Plants

In our experience, the following tests are sufficient. All tests should be controlled using 10–20 nonallergic volunteers to determine whether the reaction is immunological or not.

1. Prick-prick test, in which a lancet is first pricked into the suspected plant and then into the patient's skin is a simple safe and reproducible method.[69]
2. Histamine release test is a robust in vitro assay allowing testing with extracts of plants or plants as is.[70]
3. Use test involves handling a plant part in the same way that caused the urticaria. Precautions must be taken before the challenge, so that an anaphylactic reaction can be handled safely.

Conclusion

IgE-mediated urticaria is commonly induced with cultivated plants, whereas toxic or nonimmunological urticaria is most commonly seen in wild plants. Several species of plants have been reported to cause urticaria by unknown/unclassified mechanisms. The rubber tree is the source of latex used in the manufacture of rubber goods, and has become the most well-known source of immunologic contact urticaria and even anaphylactic reactions. Once again, the clinical history and cutaneous provocation tests help us to make a correct diagnosis. Prick-prick test, histamine release test, or use test are available diagnostic tools. The management of the contact urticaria syndrome induced by plants include the avoidance of exposure to the trigger agent.

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28

Contact Urticaria Caused by Preservatives and Disinfectants

Ryan Toholka and Rosemary Nixon

Introduction

Preservatives and disinfectants are common and well-documented causes of allergic contact dermatitis (ACD), where there are data available indicating incidence and prevalence. In contrast, contact urticaria (CoU) to preservatives and disinfectants is far less common. As a consequence of this, the literature consists almost entirely of case reports with just a few case series, with a notable lack of studies documenting the actual incidence and prevalence of CoU to preservatives and disinfectants.

It is uncertain whether there is an immunological mechanism for CoU caused by preservatives and disinfectants because there is a paucity of specific immunoglobulin E (IgE) antibody tests commercially available and prick testing is not often performed. It is widely accepted that sodium benzoate, benzoic acid, benzyl alcohol, and sorbic acid cause nonimmunologic contact urticaria and formaldehyde, parabens, povidone-iodine, chloramine, and chlorhexidine can cause a type I IgE-mediated hypersensitivity and consequently immunologic contact urticaria. Preservatives and disinfectants may also cause the more generalized reactions of the contact urticaria syndrome (CUS), such as generalized urticaria (stage 2), bronchial asthma, rhinitis, conjunctivitis, oropharyngeal and gastrointestinal symptoms (stage 3), and anaphylaxis (stage 4).[1]

Examples of preservatives and disinfectants not yet documented to cause CoU include methylchloroisothiazolinone, methylisothiazolinone, benzylisothiazolinone, iodopropynyl butylcarbamate, glutardehyde, chloroxylenol, thiomersol, and formaldehyde releasers imidazolidinyl urea, diazolidinyl urea, Quaternium 15, DMDM hydantoin, and bronopol.

Benzalkonium Chloride

Benzalkonium chloride, a quaternary ammonium compound, is found as a preservative in contact lens cleaning solutions, soaps, and skin care products and is used as a disinfectant and impregnated on medical devices to prevent bacterial colonization. Localized CoU has been described to cutaneous contact with a toilet cleaner.[2] Parenteral and mucosal exposure has been documented to result in a generalized urticaria, respiratory compromise, and anaphylaxis. It was used as a preservative in bronchodilator nebulizer solutions; however, it was proven to cause bronchoconstriction in some asthmatic patients [3,4] and a call for its withdrawal from these products occurred in 2001.[5] Whether these effects are related to an IgE-mediated mechanism has not been established.

Bernstein et al. describe a case of combined occupational asthma and localized and generalized CoU to contact with benzalkonium chloride in a toilet cleaner. They could not show benzalkonium chloride-specific IgE antibodies in the serum of this patient.[2]

Benzalkonium chloride in nasal drops,[6] eye drops,[7] nebulizer solution,[8] and a benzalkonium-coated central venous catheter [9] have been documented to cause immediate generalized reactions and anaphylaxis.

Benzoic Acid, Benzyl Alcohol, and Sodium Benzoate

Benzoic acid is a metabolite of benzyl alcohol and sodium benzoate is the sodium salt of benzoic acid. These three related compounds are used as preservatives in a variety of products, such as cosmetics, toothpastes, hair

products, medication preparations, and emollients, and in foods. They are well-recognized to cause nonimmunological CoU and reactions are concentration-dependent.[10] Both oral intake and cutaneous contact of benzyl alcohol, benzoic acid, or sodium benzoate can cause immediate reactions; however, there is a lack of correlation between the two and skin tests should not be used to predict sensitivity to oral intake of these preservatives.[10]

Immediate reactions to the oral ingestion of these preservatives are rare. Nettis et al. investigated 47 patients with a history of urticaria after the ingestion of meals or products containing sodium benzoate, and only one patient had a generalized urticarial reaction to an oral challenge test of 50 mg of sodium benzoate.[11]

Perioral CoU to sodium benzoate in a toothpaste [12] and salad dressing,[13] airborne CoU to sodium benzoate powder at a pharmaceutical manufacturing plant,[14] and CoU to benzyl alcohol in saline soaked wound dressings [15] have been described.

Oral intake of these preservatives may lead to systemic symptoms such as generalized urticaria,[16] rhinitis, [17] and wheeze.[18,19] However these reactions are not believed to be caused by an IgE-mediated mechanism.

Similar to CoU caused by sorbic acid, prostaglandin D2 (PGD2) has been implicated in the mechanism by which benzoic acid causes erythema of the skin, with a rise in PGD2 evident after the topical application of benzoic acid and a subsequent attenuation with pretreatment with aspirin of both the rise in PGD2 and amount of erythema.[20]

Chloramine

Chloramine is commonly used as a disinfectant and sterilizer. It has caused CoU, exacerbated asthma,[21] and triggered anaphylaxis [22] with chloramine-specific IgE antibodies being demonstrated.[21]

CoU to chloramine disinfectant solutions has been reported. A 52-year-old nurse experienced recurrent attacks of eyelid edema, dyspnea, rhinitis, and tingling sensations in both her fingers and mouth when she came in contact with chloramine powder, which was dissolved in water to make a disinfectant solution. An open application test of chloramine produced localized erythema and wheal after 20 minutes, and specific IgE antibodies to chloramine were detected in the serum of this patient with the use of a radioallergosorbent test (RAST).[23] A 48-year-old patient care attendant was described to experience a localized CoU to chloramine-containing disinfectant solutions. Skin prick testing to chloramine was positive, and a RAST test again revealed chloramine-specific IgE antibodies.[24]

Chlorhexidine

Chlorhexidine is commonly used as a skin and mucosal disinfectant and agent to reduce colonization on medical devices such as central venous catheters and in products such as toothpastes, hand washes, cosmetics, and lubricants. Chlorhexidine use in health care is ubiquitous and it can cause both type I immediate allergy and type IV delayed allergy. Although chlorhexidine allergy is rare, it may be underestimated,[25–27] and reports appear to be increasing. There is no prevalence or incidence data; however, the Danish Anaesthesia Allergy Center reports suspected anaphylaxis during anaesthetic procedures was caused by chlorhexidine in four of 36 (11%) cases,[28] and in Wessex, England, seven of 16 (44%) cases.[27]

Chlorhexidine has been shown to cause all of the manifestations of type I allergy, ranging from localized CoU to anaphylaxis. More generalized and life-threatening reactions tend to occur with mucosal or parenteral exposure, whereas contact with intact skin tends to produce localized CoU.[29] An immunologic mechanism has been confirmed with specific IgE to chlorhexidine detected. Ohtoshi et al. first described chlorhexidine-specific IgE antibodies in 1986.[30] Garvey et al. used an immunological assay to detect chlorhexidine-specific IgE in 11 of 12 patients,[31] as did Aalto-Korte et al., in six of 14 patients,[32] with skin test positivity to chlorhexidine.

The literature consists of numerous case reports of type I allergy to chlorhexidine. Localized CoU from chlorhexidine in surgical preparations is described,[33,34] and at our institution, we have seen an operating theater technician with localized CoU and associated dyspnea to a chlorhexidine-containing hand gel (yet to be published). Generalized urticaria from a chlorhexidine mouthwash,[35] surgical site preparation,[36] and disinfectant wash for a gynecological procedure [37] are reported. Anaphylaxis resulting from chlorhexidine has

been caused by the use of surgical site washes,[29] impregnated central venous catheters,[34,38–40] urethral lubricants,[41,42] chlorhexidine bath,[43] a throat lozenge,[44] and a disinfectant cream applied to wounds.[45] Patients with coexistent type I and type IV allergy to chlorhexidine have also been described.[29,33,36]

Chlorocresol

Chlorocresol is used as a preservative in a variety of topical preparations, such as corticosteroid creams and moisturizers and in disinfectants and detergents. Three case reports implicate chlorocresol as a cause of CoU; however, whether this is due to an immunological cause is uncertain.

Walker et al. report a patient who experienced localized CoU to a number of topical medicaments and moisturizers within 30 minutes of application. Patch tests of chlorocresol and her own preparations containing chlorocresol applied for just 30 minutes produced marked urticarial responses.[46]

A woman working in an aviary developed eyelid edema and erythema every time she used two specific disinfectants. Open and skin prick testing to 10%, but not 1%, chlorocresol was positive in this case and negative in 10 controls. This patient also experienced eyelid involvement as well as local reactions to the testing, both with superficial necrosis. Freitas et al. acknowledged that it was unusual on both aspects: for such a high concentration to be required to elicit an urticarial reaction and for superficial necrosis to occur.[47]

A case of simultaneous delayed and immediate hypersensitivity has also been reported. Goncalo et al. report a 35-year-old laboratory worker exposed to chlorocresol in both detergents and corticosteroid creams. Patch testing was positive and the patient was diagnosed with allergic contact dermatitis to chlorocresol, which was present in numerous products. Open and skin prick testing to 1% and 5% chlorocresol were positive after 20 minutes. Ten controls were also tested, all were negative to the 1% formulation, although six were positive to 5%,[48] suspicious for a nonimmunological CoU.

Ethanol

Ethanol is commonly used as a disinfectant, especially in the health care setting. Individuals are also exposed to ethanol orally via the ingestion of alcoholic beverages. Ethanol has rarely been described to cause CoU [49]; however, ingestion is well-documented to have the ability to cause a generalized urticaria [50–52] exacerbate asthma [53] and lead to anaphylaxis.[54,55] It is believed that an immediate-type allergy to the metabolites of ethanol—for example, acetic acid and acetaldehyde—are often responsible for these generalized reactions. Whether IgE antibodies are involved in this mechanism is uncertain.[51,56,57]

Wilkin et al. tested three patients who experienced severe flushing to oral ingestion of alcohol. Patches were applied for five minutes and reviewed at 60 minutes. All three patients had positive erythematous reactions to primary alcohols, including ethanol, and aldehydes. The authors suspected the aldehydes as the primary cause of these reactions.[58] Nakagawa et al. described a patient who developed generalized urticaria and lip edema to alcohol ingestion. This patient had a positive 20-minute closed patch test reaction with wheal and flare to acetic acid.[52] Emonet et al. also found acetic acid to be the cause of generalized urticaria after alcohol ingestion, with positive skin prick testing to 10% acetic acid.[59]

Two cases have been described in the literature of CoU to an ethanol-based hand sanitizer. A 30-year-old nurse described erythema, pruritus, and edema of her hands 20 minutes to 4 hours after using a hand-sanitizing gel. A similar local reaction occurred when she applied perfumes. Drinking alcoholic beverages had caused generalized urticaria, wheeze, and dyspnea requiring hospitalization on one occasion. CoU to ethanol and acetaldehyde was confirmed with patch tests applied for just five minutes.[60] A 44-year-old midwife also reported developing an erythematous rash with the application of an alcohol-based hand sanitizer and perfumes, and described headaches and dizziness from even very small amounts of alcohol ingestion. Positive urticarial reactions occurred at the site of closed patch testing to primary alcohols, including ethanol, within minutes, and progressed to involve her forehead and lumbar regions. A passive transfer test was performed and was indeterminate. No reaction occurred with the application of ethanol initially; however, when the skin was scratched before application of ethanol, a wheal developed.[61]

A late-phase urticarial reaction occurring several hours after alcohol ingestion and the use of an alcohol wipe has been reported. Patch testing resulted in erythema and edema to ethyl alcohol, peaking 9–10 hours after application. A passive transfer test was performed and positive in this case, indicating a possible IgE-mediated mechanism.[62]

Formaldehyde

Formaldehyde, used as a preservative in consumer goods such as skin care products, hair products, cosmetics, cleaning products, medications, materials and textiles, and as a disinfectant, is a common cause of type IV hypersensitivity; however, it can also cause a type I IgE-mediated hypersensitivity resulting in symptoms ranging from CoU to anaphylaxis on rare occasions. More severe reactions tend to occur with mucosal or parenteral exposure, although cutaneous contact has been documented to cause a generalized response. It is also a well-documented cause of asthma.[63]

Most literature concerning generalized urticaria, respiratory compromise, and anaphylaxis to formaldehyde revolves around exposure to formaldehyde-containing disinfectants used for root canals and other dental procedures.[64–67] Orlandini et al. report a patient who became sensitized to formaldehyde via accidental inhalation of formaldehyde vapor. After this event, the patient developed further episodes of respiratory and cardiovascular compromise with exposure to formaldehyde vapor and even developed an immediate reaction on patch testing with 1% formaldehyde, resulting in a local wheal and flare plus decreased respiratory function.[68] Formaldehyde has also been used in the sterilization of hemodialysis machines and a patient undergoing dialysis was documented to have generalized urticaria, bronchospasm, and anaphylaxis as a result of formaldehyde exposure.[69]

Helander described a patient who worked in a factory making leather dresses who developed localized CoU that progressed to a generalized eruption with associated lip swelling on cutaneous contact with formaldehyde in leather.[70] Lindskov also describes a case of localized CoU developing on areas exposed to formaldehyde vapors in a laboratory worker.[71] Another case of localized CoU to formaldehyde vapors was described in a nurse by Torresani et al. This case though was considered to be caused by a nonimmunological mechanism because the patient had multiple physical urticarias and a passive transfer test was negative; however, specific IgE testing was not performed.[72] Specific IgE to formaldehyde has been documented in numerous patients with immediate reactions, confirming an immunological mechanism.[64–66] Although exposure to formaldehyde is common, type I hypersensitivity to formaldehyde is rare, as even at relatively high levels of exposure, formaldehyde rarely evokes the production of specific IgE.[73]

Formaldehyde releasers such as imidazolidinyl urea, diazolidinyl urea, Quaternium 15, DMDM hydantoin, and bronopol have not yet been documented to cause CoU.

O(ortho)-Phenylphenate

One case report exists of a patient who developed CoU to o-phenylphenate found as a preservative in a component of a plaster cast material.[74]

Parabens

Parabens, including butyl, ethyl, methyl, and propyl esters, are used as preservatives in a vast array of products including medicines, cosmetics, and foods. They have been documented to cause localized CoU when applied to the skin, and systemic reactions, including generalized urticaria, bronchospasm, and anaphylaxis when parenterally administered or in contact with mucosal surfaces. An IgE immune-mediated mechanism is suspected.

Henry et al. described the case of a 31-year-old male who had experienced numerous episodes of CoU occurring 15–20 minutes after the use of a variety of skin products. Parabens were a common ingredient of these products and open patch tests to 5% ethylparaben and methylparaben reproduced localized urticarial reactions 30 minutes after application. This man had also experienced a local reaction to a lignocaine injection, with

significant swelling, erythema, and pruritus occurring 20 minutes after injection. This anesthetic contained methylparaben and when a lignocaine injection without methylparaben was used, no reaction occurred. A previous injection of penicillin caused a generalized urticarial response; however, no testing was performed to determine whether this was due to a paraben or the penicillin itself. Passive transfer testing was positive to methylparaben and ethylparaben in two volunteers, suggesting an IgE-mediated mechanism.[75] However, Kokubu et al. were unable to prove an IgE-related mechanism in six patients with suspected allergy to methylparaben or local anaesthetics with the use of an experimental RAST that they had developed.[76]

Anaphylaxis from a rectal lubricant jelly containing methylparaben [77] and three cases of anaphylaxis to a barium enema in which methylparaben was the suspected cause [78–80] are documented.

Nagel et al. describe bronchospasm and generalized pruritus occurring in an asthmatic patient after the intravenous administration of hydrocortisone containing methylparaben and propylparaben. No reaction occurred when hydrocortisone without parabens was administered. Intradermal tests were positive for 0.15% methylparaben, 0.15% ethylparaben, and 0.02% propylparaben. Passive transfer testing was positive for methylparaben and propylparaben, again indicating an immunological mechanism.[81]

(2-)Phenoxyethanol

Phenoxyethanol is a preservative used in consumer and health care products, including vaccines, pen inks, ear drops, shampoos, skin cleansers, moisturizers, sun care products, and topical medicaments. The preservative Euxyl-K 400 also contains 2-phenoxyethanol, in combination with methyldibromoglutaronitrile.

The literature comprises five cases of CoU to phenoxyethanol, but the mechanism of CoU remains uncertain. There are three reports of localized CU; Lujan et al. described localized CoU occurring on the face after application of aftershave containing phenoxyethanol, with confirmatory positive open tests to 1% phenoxyethanol after 20 minutes.[82] Hernandez et al. described localized CoU to emollients, make up, shampoos, and soaps containing phenoxyethanol, with confirmatory patch tests read at 20 minutes and skin prick tests to 1% phenoxyethanol. Skin prick tests to 1% phenoxyethanol were negative in 10 controls.[83] Birnie et al. described localized CoU to a moisturizer and positive scratch test to the moisturizer and phenoxyethanol.[84]

Bohn et al. described a generalized CoU to a body lotion applied in the shower; however, the lotion was likely have been applied in a generalized fashion. Open and skin prick testing to phenoxyethanol was positive in the case and negative in two controls; however, no mention was made if this also caused a generalized eruption. An experimental specific IgE test was performed, but failed to reveal phenoxyethanol-specific IgE antibodies.[85]

Orjales et al. described a patient with flares of hives at the site of contact of a number of products, including moisturizers, sun care products, skin cleansers, shampoos, toothpaste, and a blue ink pen, with associated shortness of breath, rhinorrhea, and light-headedness. Phenoxyethanol was a common ingredient in all of the products causing a reaction, and open testing to 1% phenoxyethanol and skin prick testing to a vaccine containing 5 mg/mL phenoxyethanol were positive. Similar testing was negative in five controls.[86] Given the nature of these reactions, including some generalized symptoms and that testing in controls was negative, an immunological mechanism could be responsible for these immediate reactions; however, no confirmatory testing was done to prove this.

Povidone (Polyvinylpyrrolidone)–Iodine

Anaphylaxis, generalized urticaria, angioedema, bronchoconstriction, and laryngeal edema to the intravenous administration of iodinated contrast media is well recognized; however, the etiology is uncertain, with only rare cases suspected of being true IgE-mediated allergy.[87,88]

The literature suggests that topical iodine does not typically cause an immediate allergic reaction; however, when coupled with povidone, it can. The povidone component is believed to be the cause of such reactions. Povidone is a synthetic polymer that is primarily used as a suspending and dispersing agent and is commonly used as a carrier for iodine in disinfectant solutions.

Generalized urticaria and facial edema in response to topical application of 1 mg/mL povidone-iodine to a wound on a patient's arm was described by Lopez Saez et al. Skin prick testing was positive to the causative disinfectant and povidone; however, it was negative to other iodine containing compounds. Enzyme-linked immunosorbent assay was performed and confirmed the presence of serum-specific IgE to povidone, but not to any of the other iodinated compounds tested.[89] Ronnau et al. performed a dot blot technique demonstrating specific IgE to povidone in the sera of a patient who experienced generalized urticaria, angioedema, and anaphylaxis after the oral administration of an analgesic containing povidone. Scratch testing was positive to povidone and nil other of the analgesic excipients.[90]

Generalized urticaria and anaphylaxis have also been documented to povidone with the oral administration of medicines [91,92] and the use of povidone-iodine disinfectant on broken skin,[93] during surgical procedures, [94] and on mucosal surfaces.[95,96] Immediate allergy developing to povidone-iodine on contact with intact skin has yet to be documented.

Sodium Hypochlorite

Sodium hypochlorite, commonly known as bleach, may be used as a disinfectant solution. It is a strong irritant; however, isolated reports of CoU to sodium hypochlorite exist. The mechanism for the CoU is uncertain.

Hostynek et al. describe a 36-year-old woman who developed an intensely pruritic maculopapular rash to a hypochlorite-containing cleaning product that she spilled on her leg. The rash progressed to involve her trunk and extremities and was associated with teary eyes, dyspnea, and facial edema. There was a history of a previous sensitizing event, and open testing to 1% sodium hypochlorite produced an immediate urticarial reaction. The authors suggest that this could be due to an immunological mechanism given the generalized symptoms; however, no confirmatory testing was performed and the potential of sodium hypochlorite to cause nonimmunologic CoU was evident with four of 10 controls experiencing a wheal-and-flare reaction to open application of 6% sodium hypochlorite.[97]

Caliskan et al. described a 32-year-old female who developed severe lip edema and breathing difficulty after using a sodium hypochlorite irrigation during endodontic treatment. A scratch test to sodium hypochlorite resulted in immediate erythema and edema that began to extend up the patient's arm. She also had a history of breathing difficulties and had developed dermatitis from her hands to elbows with the use of household cleaning agents.[98]

Neering reported on a patient who had experienced intermittent CoU to chlorinated pools and contact with a cleansing agent containing sodium hypochlorite. A scratch test to chlorinated water was strongly positive in this patient, but negative in five controls, and closed patch testing to sodium hypochlorite was strongly positive at three hours.(99)

Sorbic Acid

Sorbic acid is commonly used as a preservative in foods, but may also be used in personal care products such as topical creams and hair products. It is a well-recognized cause of nonimmunological CoU. Cases in the literature describe localized CoU without systemic symptoms.

CoU to sorbic acid was described by Rietschel in a 22-year-old student who developed hives on her face when she shampooed her hair. Open testing and closed patch testing viewed at 2 hours revealed sorbic acid as a cause for the CoU.[100] Perez et al. report a case of localized CoU to sorbic acid that developed with the first use of an ointment for varicose veins.[101]

CoU to both sorbic and benzoic acid, occurring in the perioral region, was observed in 18 of 20 kindergarten children after exposure to a mayonnaise salad dressing. The salad dressing was tested in healthy adult controls, in which nine of 12 reported stinging and four of 10 reacted positively to a closed 20-minute patch test. Closed 20-minute patch testing was performed to the ingredients of the dressing, with sorbic acid and benzoic acid proving to be the culprits. Varying concentrations (0.1% up to 10%) were tested in healthy controls, with an increase

in the number of wheal-and-flare reactions with higher concentrations. Local antihistamine was tested to see whether it reduced the reaction, and provided partial blockade.[13] The reactions to sorbic acid and benzoic acid were determined to be nonimmunological in nature given the number of individuals affected, a dose-related response, lack of systemic symptoms, and the number of positive reactions occurring in controls.

Soschin et al. conducted a study to investigate the erythema and edema caused by sorbic acid at different concentrations on different sites of the body and whether corticosteroid creams or systemic corticosteroids, oral antihistamines, oral nonsteroidal anti-inflammatories, intradermal lignocaine, and topical capsaicin reduced these effects. A dose-related response to sorbic acid was evident at all body sites, and there were significantly more strong reactions to 0.1% sorbic acid on the face than other parts of the body. Oral prednisolone and antihistamines had little to no effect on reactions. Aspirin, however, significantly reduced the degree of erythema, intradermal lignocaine diminished the edema, capsaicin reduced the flare, and topical 1% hydrocortisone cream reduced both erythema and edema. The authors concluded the reactions to sorbic acid do not seem to involve mast cell degranulation, but prostaglandins are possible mediators for the erythema caused by sorbic acid, given the significant reduction with aspirin, a nonsteroidal anti-inflammatory drug.[102] Morrow et al. confirmed the reduction of erythema to sorbic acid by aspirin and implicated prostaglandin D2.[103]

Sulfadiazine

Oral sulfadiazine has been documented to cause anaphylaxis and generalized urticaria.[104,105] This is believed to be caused by an IgE-mediated mechanism as a result of a sensitizing event occurring [104] and a positive passive transfer test.[105] There are, however, no documented reports of CoU to silver sulfadiazine, which is used as an antiseptic in some topical medicaments.

Triclosan

Triclosan is a preservative used in health care and consumer products, including soaps, deodorants, mouthwashes, toothpastes, cosmetics, and topical medicaments. Ozkaya et al. described a case of suspected immune mediated CoU to triclosan. A 44-year-old female reported experiencing an immediate localized urticarial response after contact with numerous topical products. The use of a toothpaste had also resulted in swelling of her lips, tongue, and breathing difficulties. She also experienced lip swelling after kissing her husband who had used the same product and wheals involving her face after kissing friends on the cheek who had used certain topical products on their faces. The suspected products all contained triclosan 0.2%–0.5%. A severe localized urticarial reaction occurred with open testing to 2% triclosan within 15 minutes. No tests were performed to confirm an immunological mechanism; however, the authors suspected this to be the case because of a positive urticarial response to triclosan within 15 minutes, a history of angioedema to the triclosan-containing toothpaste, and because no immediate reactions were seen in five control subjects who were open tested to 2% triclosan.[106]

Conclusion

CUS to preservatives and disinfectants is rare, though does occur. It is important to consider CUS to preservatives and disinfectants in patients describing immediate symptoms after exposure to these chemicals. In these cases, it is certainly worthwhile proceeding with both open testing and prick testing of patients and controls.

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29

Seminal Plasma Hypersensitivity and Immediate Contact Skin Reactions to Bodily Fluids

Jonathan A. Bernstein

Introduction

Seminal plasma hypersensitivity (SPH) was first reported by a Dutch gynecologist, J.L.H. Specken, in 1958.[1] Since that time, numerous well-documented cases and case series of women experiencing systemic and/or localized SPH have been reported in the literature.[2–4] SPH is increasingly being recognized as a cause of anaphylaxis and/or intermittent episodic vulvovaginitis. SPH is defined as a spectrum of clinical symptoms manifesting as either systemic and/or localized reactions after exposure to specific protein components in seminal plasma.[5] Women with systemic SPH present with symptoms of diffuse urticaria, facial, tongue, lip and throat angioedema with or without stridor, wheezing with severe dyspnea, pelvic and vulvovaginal pain, nausea, vomiting, diarrhea, general malaise, and in the most extreme circumstance, life-threatening hypotension, loss of consciousness, and complete circulatory failure.[5] These reactions typically occur postcoitally within 30 minutes after exposure to seminal plasma proteins (SPP) and resolve over a 24-hour period, although urticaria, vaginal pain, and malaise may persist for several days to weeks. To date, there have been no deaths reported from anaphylaxis secondary to SPH.[5]

Women with systemic SPH frequently may experience localized symptoms as well.[6] Women with localized SPH present with immediate postcoital vulvovaginal burning, pain, and swelling rarely associated with vesicles.[5,7] The severity of pain has been described as excruciating like "a thousand needles being injected into the vagina." Localized symptoms may persist for hours, days, or weeks.[1,2] The "gold standard" required for making a diagnosis of either localized or systemic SPH is complete prevention of symptoms with use of a condom.[5,7] Interestingly, women with SPH rarely experience symptoms when they come in contact with SPP orally or by direct skin contact.[3]

Needless to say, the presence of systemic and/or localized SPH results in significant interpersonal strain on relationships because of the inability of couples to have spontaneous, unimpeded sexual intercourse.[8] Furthermore, these reactions may hinder or delay couples from starting a family because of the inability to have unprotected intercourse.[8]

Constituents of Human Seminal Plasma

The average human ejaculate volume is approximately 3 mL but can range between 2and 6 mL. Although the ejaculate comprises spermatozoa and seminal plasma, the volume of spermatozoa represents less than 1% of the total ejaculate.[5,7] Seminal plasma is formed from the secretions of the epididymis, vas deferens, seminal vesicles, prostate, Cowper's (bulbourethral) gland, and gland of Littre.[5,7] The male ejaculate is formed from secretions primarily from the seminal vesicles (1.5–2 mL), prostate (0.5 mL), and Cowper gland and gland of Littre (0.1–0.2 mL).[9] Seminal plasma contains high concentrations of potassium, zinc, citric acid, fructose, phosphoryl choline, spermine, free amino acids, prostaglandins, prostate-specific antigens (PSAs), and enzymes (e.g., phosphatase, diamine oxidase, glucuronidase, lactic dehydrogenase, amylase, lysozyme, plasminogen activators, pepsinogen), which are all important for supporting a healthy environment for spermatozoa.[5,7] Zinc

binds to several different proteins, including PSA, and, when absent, affects sperm chromatin stability, leading to decreased fertility.[5,7] Zinc also serves as a prostate antibacterial factor because of its broad antibactericidal activity.[5,7] Prostaglandins, primarily derived from seminal vesicles, have strong stimulatory and inhibitory effects on smooth muscle important for controlling erection, ejaculation, sperm motility, and transport. Prostaglandin E2 (PGE2) can modify dendritic cell function by affecting their differentiation, maturation, and migration but also increases dendritic cell capacity to produce higher levels of proinflammatory cytokines/chemokines, express higher levels of major histocompatibility complex class II molecules and Toll-like receptors, as well as activation of the nuclear factor kβ signaling pathway. All of these functions are important for regulating tissue inflammation.[7,9]

The three major PSAs secreted by the prostate into seminal plasma include PSA (seminin or γ-seminoprotein), prostatic acid phosphatase, and prostate-specific protein (PSP-94, β-microseminoprotein, or β-inhibin).[5,7] PSA, a serine kallikrein protease with chymotrypsin- and trypsin-like activity, may be important in initial clotting and subsequent lysis of clotted ejaculates and is an important marker for monitoring prostate cancer.[9] It also activates peripheral blood mononuclear cells, resulting in secretion of interferon γ by natural killer cells. [5,7] Semenogelin, a seminal vesicle secretory protein, serves as a substrate for PSA. Although the mechanisms of semenogelin's action and its targets are still unknown, its improper degradation decreases fertility by reducing sperm motility.[5,7] Experimental evidence indicates that PSA rapidly cleaves semenogelin, leading to semen liquefaction and initiation of sperm motility.[5,7]

Human seminal plasma contains measurable levels of immunoglobulin G (IgG) (7–22 mg/dL) and IgA (0–6 mg/dL). The source of these antibodies is unclear, but they can also be measured in prostatic secretions.[5,7] Expressed prostatic fluid also contains the C3 component of complement (1.82 mg/dL) that is increased 10-fold in patients with prostatic adenocarcinoma. The function of these proteins in SPH is unknown.[5,7]

Prevalence of SPH

The prevalence and incidence of SPH disorders are still not fully known but it is believed that this condition is more common than recognized. The first large cases series was reported by Presti et al., who performed an extensive world literature search on SPH and summarized the characteristics of 32 cases published between 1958 and 1989.[10] Women were between 20 and 30 years of age and had localized vaginal pain associated with systemic symptoms of urticaria and pruritus.[10] Interestingly, 13 of the 32 women experienced symptoms the first time they had intercourse.[10] This information was important in establishing preliminary demographic characteristics of women presenting with SPH.

A subsequent questionnaire study of women with suspected SPH revealed 88 of 1073 respondents (8%) had symptoms consistent with probable SPH.[11] Extrapolation of this figure to the US population suggests approximately 20 to 40,000 women could have this condition. In this population, the onset of SPH was between 20 and 30 years of age.[11] Localized SPH reactions were more commonly reported and were often associated with systemic symptoms.[11] Neither atopy nor promiscuity was a risk factor for SPH.[11] Interestingly, similar to what was reported by Presti et al., the onset of symptoms occurred after first intercourse in approximately 30% to 40% of cases.[11] Symptoms began within seconds to minutes after seminal fluid contact and could last several hours.[11] In all cases, donning condoms before coitus prevented symptoms.[11]

More recently, a questionnaire survey designed to distinguish women with probable SPH was made available via the Internet.[6] Systemic symptoms included generalized pruritus, urticaria, angioedema, wheezing, chest tightness, shortness of breath, dizziness, and loss of consciousness, whereas localized symptoms included vaginal burning, pain, swelling, erythema, or blister formation.[6] Respondents with localized or systemic symptoms, and whose symptoms were prevented with the use of a condom, were included in the analysis. Of the 135 respondents included in the analysis, 79 were characterized as systemic, with the remaining 86 characterized as localized, reactors. Differences between systemic and localized SPH respondents are summarized in Table 29.1.[6] Systemic reactors were significantly older (29.2 years) than localized reactors (26.4 years) at the time of survey. Duration of SPH symptoms at the time of the survey was significantly longer in systemic compared with localized reactors (58 months vs. 40.8 months).[6] No significant difference was observed between systemic (24.2 years) and localized (22.5) reactors in age of onset. Symptoms after first intercourse were reported in

50.6% and 38.4% in systemic and localized reactors, respectively. Systemic respondents (65.8%) reported more frequently a family history of atopy than localized respondents (50%) ($p < 0.04$).[6] Of note, 78.5% of systemic reactors and 69.8% of localized reactors experienced symptoms exclusively with their current sexual partner.[6] There were no significant differences between respondent groups reporting recent pregnancy, gynecological surgery, or other gynecological problems or differences between systemic and localized reactions with respect to environmental, food, or drug allergies.[6] Prior allergen skin prick testing was reported in 30.4% and 27.9% of systemic and localized reactors, respectively.[6] Of those reporting prior allergy testing, systemic reactors were more likely to report dog sensitization compared with localized reactors (11.4% vs. 2.3%).[6] Chronic candidiasis was commonly reported by both systemic and localized reactors (43% vs. 41.2%), but no significant difference in the number of vulvovaginal candidiasis infections was evident when the two groups were compared.[6] Among the 79 women classified as systemic reactors, generalized itching was very prevalent (93.7%), whereas urticaria was only reported in 19 of 79 (24.1%) of these women. Respiratory symptoms were prevalent, with 15.2% reporting chest tightness and shortness of breath, 6.3% reporting cough, and 7.6% reporting wheeze. Dizziness and faintness was reported by 19% and 13.9% of women with systemic reactions, respectively.[6] More ominous symptoms such as complete vascular collapse and unconsciousness were reported in 2.5% and 1.3% of these women, respectively.[6] Severe vaginal burning was the most common localized reaction reported by both groups but was significantly more prevalent among localized reactors.[6]

TABLE 29.1

Systemic and Localized SPH Demographic Characteristics [6]

	Systemic (N = 79)	**Localized (N = 86)**	**P Value**
Mean Age, years	29.2 (SD = 7.9)	26.4 (SD = 6.5)	0.01
Mean Age at Onset, years	24.2 (SD = 6.6)	22.5 (SD = 5.5)	0.08
Duration of symptoms, months	58 (SD = 59.6)	40.8 (SD = 41.1)	0.03
Exclusively with your current sexual partner	62 (78.5%)	60 (69.8%)	0.20
Mean number of partners you have experienced problem	2.79 (SD = 1.1)	2.46 (SD = 1.1)	0.36
Problem experienced with first intercourse	40 (50.6%)	33 (38.4%)	0.11
Mean number of months after first intercourse that problem occurred	47.7 (SD = 54.3)	30.7 (SD = 41.7)	0.11
Before the first reaction, did you have:	8 (10.1%)	4 (4.7%)	0.18
Recent pregnancy	3 (3.8%)	4 (4.7%)	0.79
Recent gynecologic operation	14 (17.7%)	7 (8.1%)	0.07
Other gynecologic problem			
Mean time in minutes after intercourse that reactions occur	94.1 (SD = 378.7)	188.3 (SD = 927.2)	0.41
Mean time in minutes reactions last	2947.2 (SD = 3810.2)	2106.5 (SD = 5723.2)	0.28
Report environmental allergy	46 (58.2%)	36 (41.8%)	0.06
Prior allergy prick test	24 (30.4%)	24 (27.9%)	0.73
Reports dog sensitization	9 (11.4%)	2 (2.3%)	0.02
Number reporting food allergy	30 (38%)	22 (25.9%)	0.10
Number reporting drug allergy	35 (44.3%)	26 (31%)	0.08
Family history of allergy	52 (65.8%)	42 (50%)	0.04
Family history of HSP	3 (3.8%)	5 (6%)	0.51
Prior treatment for HSP	9 (11.4%)	6 (7.1%)	0.34
Number reporting chronic vaginal candidiasis	34 (43%)	35 (41.2%)	0.81
Mean number of *Candida* infections per year	4.86 (SD = 3.97)	4.06 (SD = 3.0)	0.34

Note: SD, standard deviation.

Differential Diagnosis of SPH

The diagnosis of SPH requires the exclusion of other underlying disorders that may have similar presenting symptoms. The differential diagnosis of SPH is summarized in Table 29.2.[12]

Involvement of the female genital tract during systemic allergic reactions was first described in 1922 by Cooke, who reported two patients who experienced hives, asthma, and uterine bleeding after a systemic reaction to an allergy injection.[12] Subsequently, there were other instances of women who experienced uterine and pelvic pain during systemic reactions to immunotherapy. Rosenzweig et al. used the passive transfer assay (the "Prausnitz-Kuestner" [P-K] reaction) to demonstrate that pollen extracts applied to the vaginas of nonatopic volunteers previously injected with serum from atopic patients caused itching, pain, and swelling one to two hours after application. Other investigators demonstrated that the vaginal discharge of atopic girls and women during peak pollen seasons was rich in eosinophils.[13] These observations supported the diagnosis of "seasonal allergic vulvovaginitis."[13] These women may experience temporary relief of their localized vulvovaginal symptoms with topical corticosteroid creams or systemic antihistamines. Long-lasting symptomatic improvement in women with seasonal allergic vulvovaginitis has also been achieved using allergen-specific immunotherapy. One study reported significant improvement in 13 of 16 women with seasonal allergic vulvovaginitis after 3 years of allergen-specific immunotherapy.[13]

Foreman and Catterall were the first investigators to suggest that women expressing recurrent vulvovaginal *Candida* infections may have developed localized hypersensitivity reactions to *Candida albicans*.[14] Kudelko empirically treated 70 women diagnosed with recurrent *Candida* vulvovaginitis by *C. albicans* immunotherapy.[15] Women were treated primarily based on a history of recurrent or chronic vaginal yeast infections and confirmatory immediate scratch or intracutaneous skin test reactivity to *C. albicans*. However, not all treated women exhibited positive skin test reactivity to *C. albicans*.[15] In this uncontrolled, nonblinded clinical trial, more than 90% of these women responded to *C. albicans* immunotherapy with good to excellent results.[15] Rosedale et al. treated 10 women experiencing recurrent *C. albicans* vaginitis with *C. albicans* immunotherapy.[14] Eight of the 10 women significantly improved after treatment. The average interval between recurrent infections increased from 5.1 to 15.7 months after 18 months of therapy in these women.[14] Rigg et al. treated 18 women with recurrent allergic *Candida* vulvovaginitis by *C. albicans* immunotherapy.[16] They reported that 16 women responded to treatment, with a decrease in the mean number of episodes of vaginitis from 17.2 to 4.3 per year.[16] However, these investigators emphasized the importance of performing a placebo controlled, double-blinded study using a standardized *C. albicans* extract in a homogenous population of women with this disorder before *C. albicans* immunotherapy could be recommended as a standard treatment for recurrent allergic *Candida* vulvovaginitis.[16]

Recurrent allergic *Candida* vaginitis has been postulated to occur as a consequence of either transient inhibition of cell-mediated immunity or mast cell–mediated mediator release, or both.[9,17] Women with this disorder have been demonstrated to have reduced in vitro lymphocyte proliferation in response to *C. albicans*.[9] This has been postulated to be a result of a macrophage-driven increased production of PGE2 that directly

TABLE 29.2

Differential Diagnosis of SPH [12]

1. Seasonal allergic vulvovaginitis
2. Recurrent allergic *Candida* vulvovaginitis
3. Seminal plasma fluid transfer of a drug or drug metabolite to a drug-sensitive female
4. Seminal plasma transfer of food allergens to a food-allergic female
5. Infection
   a. Chronic yeast infections
   b. Sexually transmitted diseases (i.e., *Herpes simplex virus, Cytomegalovirus, Gonorrhea, Syphilis, Trichomonas)*
6. Contact dermatitis secondary to condoms or diaphragms or their constituents, such as lubricants, gels or spermatocides
7. Structural problems (i.e., small vaginal introitus)
8. Physically induced symptoms (exercise or vibratory angioedema)
9. Reactions secondary to vaginal exposure to chemicals, soaps, scented, and/or tinted toilet tissues and sanitary napkins

inhibits interleukin-2 production and subsequent T-cell proliferation.[9,17] Vaginal washings from some of these women contain elevated PGE2 levels, supporting a role for PGE2-induced inhibition of cell-mediated immunity and subsequent occurrence resulting in development of localized vaginal allergic responses to *Candida*.[9,17] Previously it had been demonstrated that PGE2 levels are also increased in the vaginal washings of females who experience direct vaginal allergic reactions in response to sensitizing agents such as pollens, chemicals in soaps and detergents, sanitary napkins, or contraceptive spermicides.[17] Vaginal washings analyzed for specific IgE antibodies by radioallergosorbent test (RAST) in such cases during episodes of vaginitis revealed anti-*Candida* IgE, anti-rye grass IgE, and anti-SPP IgE in 19%, 4%, and 25%, respectively.[17] Increased levels of specific IgE antibodies to *Candida* were found more frequently in vaginal washings from women with recurrent *Candida* vulvovaginitis than in their peripheral blood.[17]

Seminal plasma transfer of food allergens and drugs and/or their metabolites have been documented to cause localized and systemic reactions in susceptible atopic females. For example, a woman with a known penicillin drug allergy experienced diffuse urticaria within 30 minutes after sexual intercourse.[18] After further discussion, it was revealed that her sexual partner had been taking dicloxacillin for a skin infection.[18] Further reactions were prevented with the use of a condom until he completed the course of antibiotics.[18] Another illustration of transfer allergy concerned a woman with documented contact dermatitis to the periwinkle plant, from which the vinca alkaloid chemotherapeutic agent, vinblastine, is derived.[19] She experienced severe vaginitis if she had sexual intercourse with her husband three to four days after he received vinblastine for treatment of his Hodgkin's disease.[19] This reaction was completely prevented with the use of a condom.[19] Finally, a woman with documented allergy to walnuts was reported to experience diffuse urticaria and a sensation of throat swelling within minutes after sexual intercourse. Further history revealed her boyfriend had eaten walnuts shortly before sexual intercourse.[2] These case reports indicate the potential for allergic reactions to occur in response to allergens being transferred to susceptible atopic females by seminal plasma. In some cases, the semen has been found to contain high levels of IgE. Presumably, specific IgE in semen could bind to IgE receptors on mast cells or basophils in the female reproductive tract. If the corresponding allergen is also present in the semen, an immediate hypersensitivity reaction could ensue.

Other agents that may potentially elicit localized or systemic symptoms that could simulate SPH include latex condoms or diaphragms, constituents of condoms, and other barrier contraceptive methods such as spermatocidal gels and lubricants, sanitary napkins, and scented or colored toilet paper.[9] Localized or systemic physical urticaria and/or angioedema can be elicited by the exercise or vibration associated with sexual intercourse. All women with a diagnosis of SPH should be excluded for common sexually transmitted diseases caused by *Herpes simplex, Cytomegalovirus, Neisseria gonorrhea, Papilloma virus, Treponema pallidum,* and *Trichomonas vaginalis* because these infections may present with similar symptomatology. Finally, the size of a woman's vaginal vault must be assessed to exclude trauma associated with sexual intercourse from a small introitus.

Other Clinical Conditions Manifesting as SPH

In 1991, Gulf War veterans reported burning of their semen after ejaculation, which in some cases caused localized vaginal burning, pain, and swelling in their female sexual partner.[20] This condition, called burning semen syndrome (BSS), resembled localized SPH reported in the civilian population.[20] Questionnaire surveys distributed to 188 male Gulf War veterans suspected of having BSS from 41 states, Puerto Rico, Canada, and the United Kingdom revealed that 7% of respondents had preexisting symptoms before the Gulf War and less than 50% of their sexual partners experienced resolution of symptoms with a condom, excluding localized SPH.[20] Interestingly, several male veterans had positive skin test results to their SPPs.[20] Dividing respondents into "healthy" and "unhealthy" groups based on absence or presence of multiple physical symptoms revealed a significant correlation between posttraumatic stress disorder and the unhealthy group.[20] Five Gulf War couples from the "healthy" group who met criteria for systemic or localized SPH were treated with seminal plasma protein desensitization.[20] Three couples had complete response to treatment, one had partial improvement, and one had no response.[20] In general, BSS evaluation was hindered by poor case definition of the underlying problem, multiple concomitant somatic and psychological symptoms hindering a focused evaluation, and logistical difficulties in evaluating geographically dispersed individuals during the study.[20] Although the pathogenesis

of BSS was not identified, it is plausible that external environmental insults disrupted innate immune responses in the male seminal fluid, which subsequently interfered with protective vaginal immune responses in the female genital tract, leading to a TH2 hypersensitivity immune response.[20]

In 2002, men experiencing severe fatigue, low-grade fevers, nasal congestion, burning eyes, concentration difficulties, irritability, and flulike symptoms occurring after ejaculation were described.[21] This condition was termed postorgasmic illness syndrome (POIS).[22] Criteria for establishing a diagnosis of POIS based on demographic characterization of 45 men with this condition include the following: 1) a flulike state, extreme fatigue or exhaustion, muscle weakness, mood disturbances/irritability, memory/concentration difficulties, incoherent speech, nasal congestion, rhinorrhea, and itching eyes; 2) immediate or slightly delayed onset of symptoms after ejaculation; 3) occurrence in more than 90% of ejaculation events; 4) duration for two to seven days; and 5) spontaneous resolution.[22] Reactions are speculated to be the result of an autoallergic reaction to the male's own semen involving IgE and cell-mediated immune responses.[22] Successful desensitization of two men using their own semen was reported.[23] However, the risk of the male subjects developing spermatozoa autoantibodies using this approach has not been adequately addressed. Further investigation of POIS is warranted because it appears to be affecting growing numbers of men.

Histopathology

On gross examination, the external genitalia of women with localized SPH appear excoriated and erythematous usually without the presence of vesicles. Vaginal biopsies of two women with localized SPH revealed mild to moderate lymphocytic infiltration in the submucosa with generalized dilatation of the blood vessels. On occasion, extravasation of polymorphonuclear cells into the interstitium was observed. There was significant edema in the connective tissue associated with the inflammatory infiltrate. There was no evidence of increased eosinophils or mast cells. The biopsies were consistent with nonspecific inflammation and inconsistent with a typical allergic IgE-mediated reaction. Further studies investigating the histopathologic features of localized and/or systemic SPH reactions are lacking.

Immunosuppressive Properties of Human Seminal Plasma

Early scientific interest in seminal plasma centered about the question of immunological tolerance to spermatozoa. Tung et al. found a high incidence of antisperm antibodies present at an early age (1–10 years) in both males and females.[24] They speculated that the presence of antisperm antibodies in children was the result of immune responses to exogenous antigens such as microorganisms that cross-react with human sperm.[24] Investigators have identified immunosuppressive factors that may be important in regulating the production of these antisperm antibodies and for distinguishing self and nonself proteins. Lord et al. demonstrated that SPP had a suppressive effect on cellular immunity using the mixed lymphocyte reaction and mitogen induced lymphocyte blast transformation assays.[25] They determined that SPP contained one or more factors capable of suppressing cell-mediated humoral immune responses. The molecular weight of one of these SPP suppressive factors was greater than 200,000 Daltons, which is similar in size to inhibitory proteins found in bovine seminal plasma.[25] This seminal plasma immunosuppressive factor has been speculated to be important for suppressing local immune responses to spermatozoa in the female reproductive tract.[25]

Marcus et al. performed a series of experiments to investigate the correlation between infertility and antisperm antibodies.[26–30] They found that spermatozoal proteins either inhibit or stimulate in vitro normal lymphocyte DNA synthesis depending on the dose. In addition, they suppressed mitogen-induced lymphocytic responses in a dose-dependent fashion.[27] Pretreatment of spermatozoa with the glycoprotein specific enzymes, neuraminidase and α-methyl-D-mannoside, abrogated these suppressive effects.[27] Several fractionated SPPs were also found to exhibit potent immunosuppressive properties.[26] They found that Sephadex G-100 fractions 1 and 4 inhibited spontaneous blast transformation, whereas fractions 1 and 3 inhibited mitogen-induced blastogenesis.[26] These findings indicated that suppression of lymphocyte proliferation could occur from either spermatozoan or seminal plasma constituents.[26] Both SPP and spermatozoa were also shown to inhibit T-cell

associated E-Rosette formation.[29] The inhibitory effect of seminal plasma persisted after repetitive, freeze-thaw cycling but disappeared when these fractions were heated to 100°C.[29] Finally, these investigations demonstrated that inhibition of lymphocyte cultures persisted after a 24-hour incubation period with SPP. Addition of fresh T-lymphocytes but not B-lymphocytes restored the mitogenic activity of lymphocyte cultures previously exposed to SPP.[29] Their findings indicated that SPP was important in regulating T-lymphocyte responses and could suppress lymphocyte responses directed against spermatozoa.[31]

Seminal plasma has also been demonstrated to be a potent inhibitor of complement. A seminal plasma factor, called complement cytolysis inhibitor, has been isolated and is capable of suppressing the cytolytic potential of the terminal components, C5b to 7. The presence of a complement cytolysis inhibitor in SPP suggests that it may protect spermatozoa and vaginal epithelial tissues from complement attack.[32]

Wasson et al. demonstrated the presence of immunosuppressive factors in seminal plasma obtained from the spouse of a woman with SPH.[33] A series of experiments were performed to investigate the effect of seminal plasma immunosuppressive factors on peripheral blood mononuclear cell (PBMC) proliferation.[33] They studied target PBMCs of a nonatopic female donor that had a brisk proliferative response to the mitogen, phytohemagglutinin (PHA) but not to SPP.[33] When these PBMCs were preincubated with SPP and subsequently stimulated with PHA, proliferation to PHA was significantly suppressed. Similar results were found when her PBMCs were stimulated by SPP from the husband of an SPP-hypersensitive female or a normal male.[33] These findings confirmed previous experiments about the immunosuppressive properties of SPP on cell-mediated immune responses.

The major allergen in SPH has been demonstrated to be PSA.[34–36] However, investigators have identified allergenic activity in response to other SPPs and therefore most likely more than one SPP is involved in this disorder.[5,12]

It has been speculated that a common protein cross-reacting with PSA may explain the high incidence of cases occurring after first time sexual intercourse. Recently, a prostatic kallikrein protein isolated from dog urine and epithelial extract was reported to be >80% structurally homologous to human PSA.[37,38] Investigators have postulated that women who experienced SPH after first-time intercourse could have become sensitized to prostatic kallikrein through previous exposure to dogs.[37,38] However, this hypothesis has yet to be proven and our unpublished observations have not found any correlations between dog ownership, exposure, or sensitization and localized or systemic SPH.

Clinical Investigation of SPH

Most of the current information about SPH originates from case reports and limited clinical investigation of these cases. Halpern et al. extensively studied a case of a 29-year-old female with human SPH.[39] The woman experienced severe allergic reactions immediately after sexual intercourse. These episodes occurred after her first exposure to seminal plasma and had become progressively worse with each episode of sexual intercourse.[39] Her symptoms consisted of diffuse urticaria, swelling of her lips, eye lids, tongue, and pharynx resulting in difficult breathing, severe shortness of breath with chest congestion, pelvic pain, uterine contractions, general malaise, and loss of consciousness.[39] The culmination of these symptoms occurred within 15 to 30 minutes after SPP exposure and resolved over 24 hours. The authors employed several in vitro and in vivo immunologic assays to characterize the responsible SPPs and the underlying mechanism(s) responsible for this reaction, including zone electrophoresis, immunoelectrophoresis, ionic exchange column chromatography, P-K reactions in humans, passive cutaneous anaphylaxis in guinea pigs and primates, passive hemagglutination tests, agglutinating antibody assays, and complement fixation tests.[39] The patient demonstrated skin test sensitivity to whole seminal plasma obtained from her husband and from normal human donors. Skin test reactivity was negative to spermatozoa. Skin testing was also negative using serum obtained from her husband and semen obtained from rabbit, guinea pig, horse, bull, bovine submaxillary mucin, and bovine testicular hyaluronidase.[39] Therefore, they demonstrated that the responsible allergen(s) were species-specific and originated from the seminal fluid and not spermatozoa. An attempt by these investigators to desensitize this individual using whole seminal plasma was unsuccessful.[39]

Levine et al. reported a case of a 29-year-old atopic female who experienced diffuse hives, swelling, nasal congestion, and sneezing one hour after intercourse.[40] These symptoms progressively worsened with each episode of intercourse. Recurrence of symptoms was completely prevented with a condom during sexual intercourse.[40] SPH was confirmed by skin testing using her sexual partner's whole seminal plasma. Significant histamine release in response to seven different SPP samples was demonstrated using leukocytes isolated from the patient's whole blood. Fractionation of whole seminal plasma obtained from donor vasectomized males revealed that 90% of the allergenic activity was present in fraction 4, which corresponded to proteins with a molecular weight of 20,000–30,000 Daltons, which also elicited the strongest positive skin test reaction in the patient at a dilution as low as 1:100,000.[40]

Chang et al. reported a series of SPH cases occurring in one family that he referred to as "familial allergic seminal vulvovaginitis".[41] These women all experienced severe discomfort after their first contact to seminal fluid during sexual intercourse. Most of their symptoms were localized consisting of stinging, burning, and pain during or immediately after ejaculation.[41] Skin testing with SPP was positive at a concentration of 1:1000, which was a weaker skin test response compared with those reactions elicited in women with systemic SPH.[41]

Voorhorst reported a case of a young woman who experienced postcoital vaginal itching before the birth of her second child.[42] Her reactions progressively became worse, leading to diffuse urticaria with dyspnea and stridor associated with nausea, diarrhea, and shock on two occasions. She exhibited a very strong positive skin test reaction to her husband's seminal plasma confirmed by RAST testing.[42] To identify the origin of the allergenic protein in seminal plasma, she was skin tested for extracts made from different male organs obtained from the urogenital tract of a healthy male who had recently died in a motor vehicle accident. Proteins from the prostate yielded the strongest skin test reactions compared with the extracts derived from the seminal vesicle, bladder, epididymis, or testes. From these results, it was concluded that the most probable origin of relevant allergenic SPPs was the prostate gland.[42] Freeman reported a case of a woman who was allergic to her husband's seminal plasma and sweat.[43] The patient had a six-year history of severe itching and flushing of the face and upper extremities 10 minutes after unprotected sexual intercourse with her husband.[43] Skin testing to her husband's sweat and seminal plasma yielded significant positive skin test reactions. Positive skin test reactions were also elicited in response to pooled donor seminal plasma and sweat obtained from her two sons. Interestingly, she had no reaction to her own sweat during exercise. No further investigation was performed to determine whether SP and sweat share common allergens that could elicit this reaction.[43]

Bernstein et al. studied two women with systemic SPH and two women with localized SPH.[44] Both women with systemic SPH had positive direct skin tests and significant leukocyte histamine release responses to their sexual partner's seminal plasma. One woman also demonstrated cutaneous reactivity to her spouse's spermatozoal extract. Immediate hypersensitivity to spermatozoa in these women was supported by a positive P-K reaction and leukocyte histamine release.[44] A positive P-K reaction, RAST, and specific RAST inhibition in addition to neutralization of passive transfer antibodies by SPP were demonstrated in one of these women. The women with localized SPH reactions did not develop humoral antibodies in response to seminal plasma, although one patient had significant titers of IgM and IgG sperm-agglutinating antibodies to seminal plasma.[44] This woman also demonstrated lymphocyte blast transformation and a migration inhibitory factor response to seminal plasma.[44] All four women and their husbands had histocompatibility leukocyte antigen typing that revealed a marked degree of shared histocompatibility locus antigens between two of the women and their respective spouses.[44] This investigation confirmed that IgE-mediated immune responses were involved in systemic SPH and provided preliminary evidence that cell-mediated responses might be involved in localized SPH reactions.[44]

Our group has demonstrated that women with systemic SPH elicit significant specific IgE antibodies to PSA and other SPPs (semenogelin and acid phosphatase); these specific IgE responses were found to be selective to these proteins by enzyme-linked immunosorbent assay inhibition. We also demonstrated postdesensitization by rush desensitization using relevant SPPs resulted in a shift from a Th2 to a Th1 cytokine profile which correlated with clinical improvement indicating induction of tolerance.[45] These same immune responses, however, were not observed for women with localized SPH undergoing similar treatment even though they clinically improved. This suggests that a non–IgE-mediated mechanism is responsible for the induction of tolerance in women with localized SPH. Further investigation is ongoing to better understand the underlying mechanism(s) for localized SPH.

Reactions to seminal plasma have also manifested as fixed cutaneous eruptions. For example, a woman experienced a pruritic, erythematous, macular rash that blistered and progressed to a purpuric, hyperpigmented, macular lesion in the same regions of her body after exposure to seminal plasma.[46] These reactions involved the vulva, vagina, and isolated regions of one finger, ear, hip, and breast and were not associated with other systemic symptoms.[46] Skin testing using SPP obtained from her husband and a vasectomized male donor were negative. Direct immunofluorescence performed on a skin biopsy from the right breast was also unremarkable. The rash was completely prevented with the use of a condom.[46] Interestingly, the reaction was also prevented by 500 mg of the nonsteroidal anti-inflammatory agent, mefenamic acid, if taken before intercourse.[46] Systemic antihistamines were less effective in providing symptomatic relief. These investigators postulated that mefenamic acid was effective in relieving symptoms by inhibition of prostaglandin synthesis because these mediators had been shown to induce redness, swelling, and pain symptoms characteristic of fixed drug eruptions.[46]

Treatment of SPH

Several different approaches have been attempted for the treatment of women with SPH. Prophylactic use of antihistamines before sexual intercourse has been reported to control localized and systemic symptoms and result in successful pregnancy.[47] As mentioned, nonsteroidal anti-inflammatory agents have been used in an attempt to block prostaglandin production and therefore reduce associated pain in localized SPH.[5] Reports of successful treatment of a woman with localized SPH have also been reported using an 8% topical cromolyn sodium solution.[48] However, none of these therapeutic approaches have been uniformly successful in the long-term treatment of women with either localized or systemic SPH.

The most effective treatment approach for women with IgE-mediated SPH has been immunotherapy using the female's sexual partner's whole seminal plasma or SPP fractions. The most common approaches have been to perform either an intravaginal graded challenge using whole seminal plasma or to perform rush immunotherapy using specific SPP fractions isolated from their partner's whole seminal plasma by column chromatography.[49–54] For rush immunotherapy, those specific protein fractions which elicited a significant wheal-and-flare skin test reaction in the sensitized female are used for immunotherapy.[50–52,54] The patient's sexual partner is used as a negative control for skin testing.[50–52,54] The rationale for using the fractionated SPPs is based on the earlier studies demonstrating that the largest molecular weight proteins found in fraction 1 has immunosuppressive properties and therefore is purposely excluded from the proteins used for immunotherapy.[26] This method has been successful in achieving long-lasting tolerance to SPP allergens in women with systemic SPH, but it is very time consuming to prepare the fractionated proteins and the entire procedure is costly ($4000–$6000).[50–52,54]

Women with localized SPH have also responded to systemic immunotherapy using relevant fractionated SPPs. Bernstein et al. was the first to report successful treatment of three women with localized SPH by rapid immunotherapy using their spouse's fractionated SPPs.[51] One patient demonstrated evidence of desensitization as she manifested a significant change in her skin test threshold response to fraction 3 postimmunotherapy.[51] Subsequently, two of these patients conceived and delivered healthy babies.[51] After rapid immunotherapy, women must maintain their tolerance to SPPs by having frequent and regular sexual intercourse with their partner two to three times a week. This has not always been possible because some patients or their spouses may have job-related traveling responsibilities and may not always be able to maintain this schedule. This problem has been averted by freezing pools of fresh semen ejaculates that the patient can instill in her vagina while her spouse is away on business.

Over the years, several cases have been reported where women with both systemic and localized SPH have been successfully treated with whole unfractionated seminal fluid using an intravaginal graded challenge procedure.[49,53] Successful treatment using this approach contradicts previous concerns about the immunosuppressive properties of the large-molecular-weight proteins contained in fraction 1. Given the success of this approach, rapid immunotherapy protocols in which fractionation of whole seminal fluid to isolate relevant SPPs that elicit a specific IgE immune response in the affected female should be reserved for those cases not responsive to intravaginal graded challenge with whole seminal plasma. Figure 29.1 illustrates a treatment algorithm for women presenting with suspected systemic and/or localized SPH.[12]

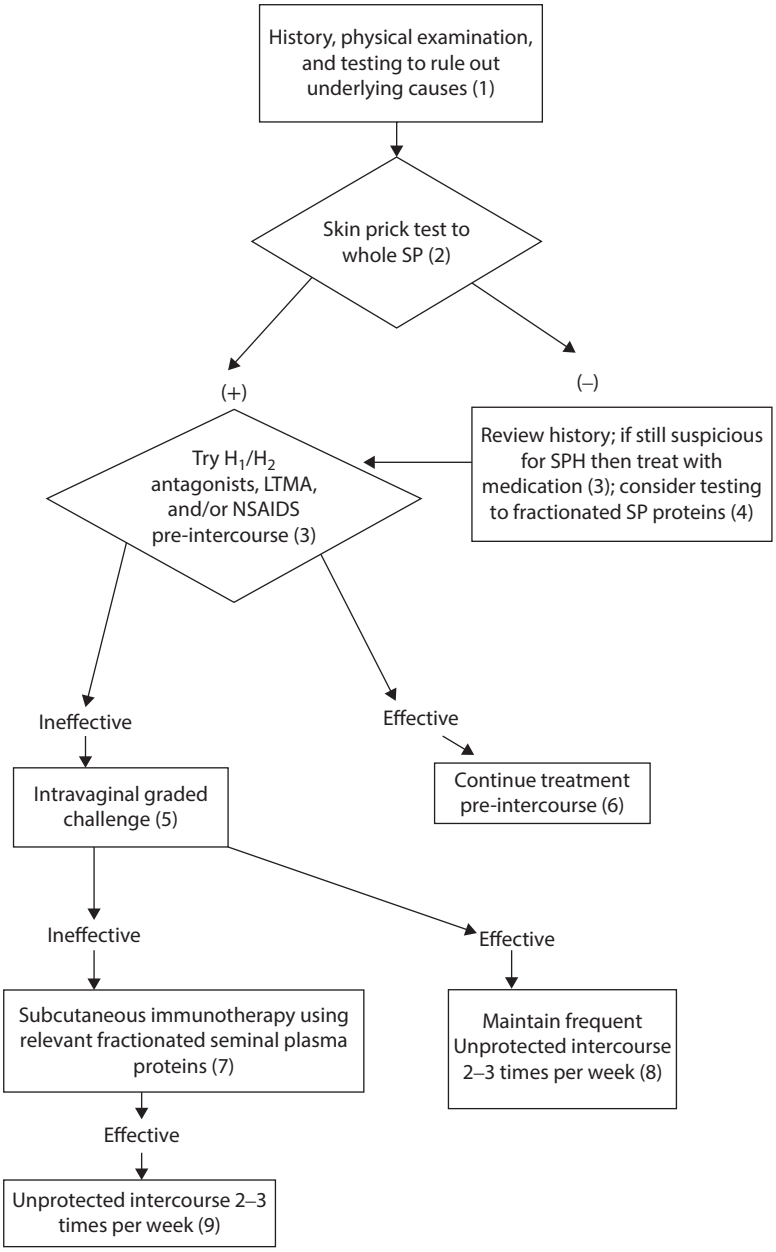

FIGURE 29.1 Human seminal plasma hypersensitivity treatment algorithm. Abbreviations: LTMA, leukotriene-modifying agent; NSAIDs, nonsteroidal anti-inflammatory drugs; SP, seminal plasma; SPH, seminal plasma hypersensitivity. (From Bernstein JA, *Postgrad Med*. 2011;123(1):120–125. With permission.)

Fertility has always been a question for women presenting with SPH. A recent retrospective study assessed the ability of women with localized SPH who had been previously treated with subcutaneous immunotherapy to relevant SPPs to conceive and bear children.[8] Eighteen women who had been treated in Cincinnati, Ohio, for localized SPH were contacted by telephone as part of routine follow-up care. Twelve of the 18 women were available for the interview; the remaining six were lost to follow-up. Eight of the 12 women interviewed were able to

conceive and five had term pregnancies.[8] Of the seven successfully treated subjects, two carried term pregnancies and one was pregnant at the time of the study.[8] Two of the women were able to conceive but had multiple miscarriages. One woman was unable to conceive and one was not interested in conceiving. Of the three women who felt their treatment was unsuccessful, one had a term pregnancy, one was unable to conceive, and one was not interested in conceiving.[8] The subject who was not interested in conceiving experienced marital problems in part because of SPH and their relationship ended in divorce. Among all 12 women, three continued to have mild-moderate intermittent localized symptoms and one felt that her symptoms were unimproved.[8] The results of this long-term follow-up study indicated that women with localized SPH who were treated with subcutaneous immunotherapy to relevant SPPs were able to conceive and have children regardless of whether they deemed treatment was successful or not. Therefore, infertility does not appear to be an inherent complication of localized SPH.[8] Women with localized SPH that have difficulty conceiving and/or having a successful term pregnancy regardless of whether or not they respond to treatment may have a concomitant infertility problem that requires further evaluation by a fertility specialist. In vitro fertilization or washing of spermatozoa followed by artificial insemination has been reported to be successful in similar cases.[55,56]

Conclusions

Systemic and localized SPH probably occur more commonly than previously recognized. Although IgE-mediated immune responses seem to be involved in women with systemic reactions, a specific IgE-mediated reaction in women with localized reactions is appearing increasingly less likely. Thus, there are still many unanswered questions regarding SPH, specifically the localized form. There is still a need to identify female and male risk factors, responsible sensitizing protein(s), and the immunohistopathology of SPH. The current use of intravaginal graded challenge followed by rapid immunotherapy to fractionated SPPs, if ineffective, has been proven to be a practical and effective treatment approach for this disorder. The use of an intravaginal graded challenge treatment approach has made treatment less time-consuming and less expensive and therefore more accessible to all women with this problem. Work is in progress to better understand the natural course of this disorder and to better understand the underlying mechanisms for SPH, particularly in the localized form.

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MEDICINE / DERMATOLOGY

Contact Urticaria Syndrome

In the four decades since contact urticaria syndrome was first described, knowledge about the topic and the number of possible triggers for the syndrome has steadily increased, especially during the increased incidence of contact urticaria syndrome induced by latex in the 1980s.

However, contact urticaria syndrome is often misdiagnosed in part due to a misinterpretation of its clinical manifestation and lack of knowledge of appropriate testing protocols and diagnostic programs. The latter have to be individualized for each patient based on the substance in question, medical history, possible concomitant disease, and clinical symptoms reported after exposure to the suspected culprit.

Contact Urticaria Syndrome discusses the syndrome's definition, history, epidemiology, and occupational relevance. It also provides a detailed discussion of various triggers including proteins, chemical compounds, agricultural chemicals, metals, plants, foods, and other substances. The book is a helpful resource for dermatologists, toxicologists, immunologists, and providers diagnosing and treating patients with contact urticaria syndrome. It summarizes clinical experience that makes it easier for providers to select the appropriate diagnostic tools and therapeutic approaches.

Ana M. Giménez-Arnau, MD, PhD, is a professor of dermatology at the Universitat Pompeu Fabra and Universitat Autònoma de Barcelona. She is also a consultant physician in dermatology and venereology in the Department of Dermatology at the Hospital del Mar, Barcelona. Dr. Giménez-Arnau was president of the 12th ESCD Congress in 2014. Her publications range from the 1995 article on chronic contact aquagenic urticaria to updated 2014 guidelines for the diagnosis and management of urticaria.

Howard I. Maibach, MD, is a professor of dermatology at the University of California, San Francisco. Dr. Maibach's publications range from the groundbreaking 1975 article on contact urticaria syndrome to the more recent books *Dermatotoxicology* (2012) and *Handbook of Cosmetic Science and Technology* (2014).

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