Allergic Contact Dermatitis

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KEYWORDS

• Contact dermatitis • Allergic contact dermatitis • Irritant contact dermatitis
• Systemic contact dermatitis • Eczema • Nickel allergy

KEY POINTS

- Allergic contact dermatitis is a common skin disorder affecting millions of Americans.
- Common allergens are seemingly ubiquitous and are found in daily products, at work, and even in foods.
- Allergic contact dermatitis can present as an acute, subacute, or chronic dermatitis.
- Diagnosis of allergic contact dermatitis is based on a thorough history, physical examination, and patch testing.
- Once the allergen is identified, the mainstay of treatment is avoidance.

INTRODUCTION

Contact dermatitis is a common inflammatory skin disorder affecting millions of Americans and is the chief complaint for thousands of clinic visits to the internist every year. The disorder is characterized by pruritus, erythema, vesicles and scaling of the skin. Contact dermatitis can be further divided into allergic contact dermatitis (ACD) and irritant contact dermatitis (ICD), with ICD being more common (~80% of contact dermatitis)[1] ACD is a type IV-mediated hypersensitivity to a specific allergen, resulting in an inflammatory response with exposure. ICD is a nonimmunologically driven, inflammatory reaction to an irritating substance. These 2 types of dermatitis are often indistinguishable clinically.

PATHOPHYSIOLOGY

ACD is a type IV delayed-type hypersensitivity reaction resulting from the activation of allergen-specific T cells. The first phase is sensitization, when a person is first exposed to an allergen. The allergen is a hapten, which is defined as a low-molecular-weight antigen that, when bound to a larger carrier, can elicit an immune response. Initially, the hapten is engulfed by Langerhans cells or dermal dendritic cells. The hapten–peptide

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complexes migrate to regional lymph nodes of the skin, where they prime hapten-specific T cells (Th1, Th2, Th17, and T regulatory cells) that proliferate and circulate in the blood. The naïve T cells that specifically recognize allergen–major histocompatibility complex molecule complexes expand and create effector and memory T cells. The next phase is elicitation, where reexposure to the allergen results in recognition by the now-sensitized, hapten-specific T cells, causing an inflammatory cascade of cytokines and cellular infiltrates producing the clinical symptoms of ACD.[2]

EPIDEMIOLOGY

ACD is common, with some studies demonstrating prevalence rates as high as 20% of the general population.[3] Certain groups are at higher risk of developing ACD, which seems to be a result of both genetic tendencies and environmental exposures. Not all people exposed to a particular allergen become sensitized. Individuals sensitized to 1 allergen are more susceptible to sensitization with another.[4] Family members have been shown to have an increased rate of developing ACD, suggesting a genetic predisposition; however, a confounding factor is the shared environment.[4] Studies further evaluating genetic contributions to ACD are vast and ongoing. Patients with a history of atopic dermatitis have higher susceptibility in developing ICD, which is likely related to disruptions in the skin barrier and a greater inflammatory response.[2]

Contact dermatitis, both allergic and irritant, accounts for the vast majority of occupational skin disorders in the Western world.[5] Hairdressers, health care workers, food handlers, building and construction workers, and metal workers have high rates of developing ACD based on their close and repeated contact with common allergens.[6] ACD can have a significant negative impact on workplace productivity and expenses.[7] Many workers with significant disease require prolonged absences from work, need to alter practices at work, or may even change to another line of work based on the severity of their disease.[8]

Women seem to be at higher risk of developing ACD. This difference is thought to be a result of exposures as opposed to inherent to sex; for example, women have higher rates of nickel allergy potentially owing to the increased frequency of wearing jewelry.[9]

DIFFERENTIAL DIAGNOSIS

It can be difficult to distinguish ACD from other forms of dermatitis. A wide range of disorders, from common entities such as ICD, atopic dermatitis, seborrheic dermatitis, psoriasis and tinea, to the less common, mycosis fungoides, are all part of the differential diagnosis.[1] Importantly, these various disorders may coexist in the same patient.[1] History, patch testing, and other forms of testing (ie, biopsy, potassium hydroxide scraping) may help to clarify the diagnosis.

DIAGNOSIS

A thorough history is central to making the diagnosis of ACD. It is important to elucidate when the lesions developed, how they have evolved over time, and any suspected agents. Suspicious agents may be difficult to identify, because the reaction to the allergen is not always immediate. This delay in reaction, which can be up to 72 hours, can make identifying exposures difficult for both the patient and health care providers. The location and distribution of the lesions can aid in the diagnosis. Often it is difficult to identify any suspect agents at all, especially when the dermatitis has been longstanding. Thorough questioning of occupation, hobbies, and any changes in personal products or clothing is helpful.[10] When asking about work,

questions should include the type of work performed, potential allergens or irritants the patient is in contact with, duration of exposure, and any improving or aggravating factors. In particular, skin improvement during vacation or sick leave can be an important clue.[11] Previous treatments, both prescription and over the counter, and the response to such treatment are important. If previous treatment resulted in worsening of the lesions, suspect a contact dermatitis to those agents.[12] A history of atopy, especially atopic dermatitis, may be a contributing factor in the development of ACD. A family history of psoriasis or other skin diseases is also important, because these entities may be confused for ACD.[4]

ACD may present as acute, subacute, or chronic dermatitis. Acute ACD is most often characterized by erythematous papules and vesicles. Severe cases may present with bullae. Chronic ACD tends to present as erythematous and pruritic lesions that may display the stigmata of more long-standing inflammation, such as lichenification, scaling, and fissuring. With disruption of the epidermal barrier, as can been seen in chronic ACD, superinfection can result. Subacute ACD is more difficult to characterize and can display a mixture of features.

Distribution is helpful in the diagnosis of ACD. Certain distributions, such as on the eyelid, lateral face, central face, neck, or hands, should trigger the consideration of ACD to cosmetics and personal products. **Table 1** lists the top 10 primary sites of ACD. The most common sites are the hands, a scattered or generalized pattern, and the face.[13]

Hands

The hands are the most common primary body site involved in contact dermatitis.[13] The majority of hand dermatitis is due to ICD. Classically, lesions of irritant hand dermatitis involve the palms, dorsal hand, and distal dorsal digits, but may also involve the interdigital web spaces where irritants get caught. In contrast, ACD of the hand usually presents as well-demarcated plaques and vesicles involving the dorsal hands, fingers, and wrists. Common allergens include preservatives, fragrances, metals, rubber, and topical antibiotics.[14]

Vesicular hand dermatitis can be a manifestation of systemic contact dermatitis (SCD), such as after the ingestion of nickel-containing foods by patients sensitized

Table 1
Body sites of dermatitis as the primary involvement

Dermatitis Site	N (%)
Hand	1230 (22.0)
Scattered generalized	995 (17.8)
Face	946 (16.9)
Eyelids	535 (9.6)
Trunk	307 (5.5)
Lips	274 (4.9)
Arm	230 (4.1)
Scalp	225 (4.0)
Leg	207 (3.7)
Foot	120 (2.1)
Total n	5591

Adapted from DeKoven JG, Warshaw EM, Zug KA, et al. North American Contact Dermatitis Group Patch Test Results: 2015-2016. Dermatitis 2018:29(6):297-309; with permission.

to nickel. Other causes of hand dermatitis are atopic dermatitis (more common in adults)[15] as well as dyshidrotic hand eczema, which presents as intensely pruritic, deep-seated vesicles appearing in clusters on the palms (most commonly on the thenar eminence), dorsal hands, and sides of the fingers. The feet can also be affected by dyshidrotic eczema in the same distribution.

Face

The following are general patterns of facial contact dermatitis.

1. Central face
   - Dermatitis involving the central face (cheeks, nose, chin, and forehead) may be due to ACD to gold (released from gold jewelry and contaminating titanium-containing foundation), make-up, moisturizers, wrinkle creams, and topical medications.
2. Lateral face
   - Dermatitis involving the lateral face (preauricular areas, postauricular area, jaw lines, and/or lateral neck) is most commonly due to shampoo and/or conditioner dripping down over these areas (**Fig. 1**).
3. Full face
   - Full facial dermatitis may be due to make-up foundation, facial cleansers, moisturizers, or airborne contactants.
4. Unilateral predominance
   - Unilateral facial dermatitis may be due to an ectopic transfer from the hands of contact allergens in nail products, fragrances, and topical medication. Connubial or consort contact dermatitis to products used by the partner or parent may also be transferred predominantly to 1 side of the face.[16]

Eyelids

The eyelids are one of the most sensitive areas of skin, and thus are susceptible to irritants and allergens. ACD of the lids and periorbital area is primarily caused by cosmetics applied to the hair, face, or fingernails, and include shampoo, conditioner, facial cleansers, make-up remover, mascara, nail polish, acrylic nails, make-up

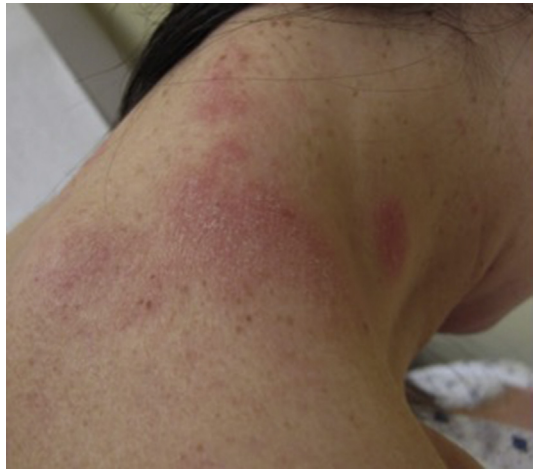

Fig. 1. ACD of the neck owing to fragrance in shampoo.

sponges, eyelash curlers, and allergens transferred from the hands. Marked edema of the eyelids is often a feature of poison ivy or hair dye dermatitis. Airborne pollen, dust and all types of volatile agents may affect the eyelids, and manifest as a type 4 cell-mediated hypersensitivity reaction. This entity should be distinguished from a type 1 IgE-mediated allergic conjunctivitis.

Other common allergens associated with eyelid dermatitis include gold, fragrances, formaldehyde-related preservatives, methylisothiazolinone (MI; a preservative in both industrial and consumer products), and cocamidopropyl betaine (a surfactant in shampoos and soaps).[17] Shellac and pigments in mascara can also cause ACD of the eyelids.[18–20] Shampoos and conditioners are probably the most common causes of isolated ACD of the eyelids.[21] Other hair products such as dyes, bleaching agents, setting lotions, sprays, gels, and mousses are more likely to involve the scalp or forehead in addition to the eyelid. Facial cleansers may cause dermatitis of the eyelid and the face. Ectopic dermatitis from nail polish and acrylic nail dermatitis more commonly affects some combination of the eyelids, face, and neck rather than an isolated eyelid dermatitis.[16] Eyelid dermatitis may also be due to seborrheic dermatitis, atopic dermatitis, or ICD.[22]

OTHER MANIFESTATIONS OF ALLERGIC CONTACT DERMATITIS

Occupational Allergic Contact Dermatitis

The hand is commonly involved in occupational contact dermatitis. The following is a list of some of the more common allergens responsible for ACD in the occupational setting: rubber accelerators, carbamates and thiurams (**Fig. 2**) are used in rubber processing (vulcanization) to speed up the reaction. They are found in the elastic that is commonly used in undergarments, socks, waistbands, surgical bonnets, wrists of surgical gowns, hair ornaments, shoe covers, and shoes. In the workplace, they can also be found in both latex and latex-free gloves.

Epoxy resin exposure can be found in the maritime industry, the electronics industry, dentistry, flooring industry, and industries working with epoxy glues. Epoxy resin is a frequent occupational allergen.[23]

Formaldehyde is a common occupational allergen used in many fields, such as in anatomic pathology laboratories (where it is used to preserve the bodies), farming, furniture making, wood manufacturing, laboratory work, pest control, and construction. Formaldehyde resins are also used in permanent press clothing to prevent wrinkling; therefore, launderers and workers in the textile industries may develop sensitization.[24] Formaldehyde releasers are preservatives that may release molecules of formaldehyde over time and are commonly found in cleansers, detergents, and

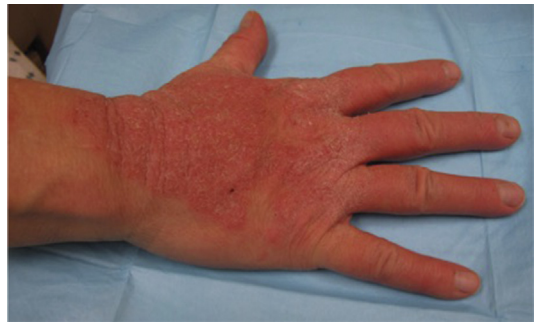

Fig. 2. ACD of the hands owing to rubber accelerator in gloves.

protective creams. People who do not handle these materials in their work may still be affected and can present with a diffuse dermatitis secondary to wearing clothing treated with formaldehyde or its resin.

Nickel is the most common contact allergen in North America[13] and is found in many workplaces, including those involving machines, office supplies, tools, electronics, uniforms, jewelry, keys, and coins.

Systemic Contact Dermatitis

ACD begins with sensitization through the skin. Systemic exposure to allergens (including transepidermal routes, intravenous or intramuscular routes, inhalation, and ingestion) that results in a cutaneous eruption is known as SCD.[25] SCD can manifest as a systemic exacerbation, reactivation of a previous dermatitis, vesicular hand eczema, or a flare-up reaction of the previous site of a positive patch test.[26] Studies have shown that, after clinical resolution of ACD, T cells may remain in the affected area.[27] Upon reexposure to the allergen via an alternative pathway, a rash can develop at a previous site of dermatitis or patch test.[26] The presentation of SCD is variable. The reactivation of a previously affected site can occur days after the exposure, making it difficult to identify and associate that exposure as the cause of the flare. In addition to an exacerbation of prior skin site reactions, SCD can present with dyshidrotic eczema on the hands, a generalized maculopapular or vesicular rash, erythema multiforme, and an entity known as the Baboon syndrome.[26] Baboon syndrome is characterized by a bright, erythematous eruption on the buttocks, and has been described more commonly with metals, balsam of Peru (BOP), and medications.[25] Several metals have been described to cause SCD, including nickel, mercury, cobalt, copper, chromium, gold, and zinc.[25] Numerous studies have shown oral ingestion of nickel in food resulting in worsening of dermatitis in nickel-allergic patients.[27–29]

Systemic contact allergy as it relates to metal implants has become of recent interest. Metals are frequently implanted into the human body, in the form of orthopedic, cardiac, gynecologic, and dental devices. As the metal wears down over time, free ions are released and may deposit around the prosthetic site or into other organs in the body.[29,30] Sensitization to metals increased by 6.5% after arthroplasty.[31] In patients with hip arthroplasty, sensitization to nickel, cobalt, or chromium was seen in 25% of well-functioning implants (>2× the general population) and 60% in failed or failing prosthesis (6× the general population).[32] A study of patients with total knee arthroplasty showed a metal sensitization rate of 20% in those with no implant, 48.1% in those with stable implant, and 59.6% in unstable implant group.[33]

Intravascular devices and prosthetic joints are typically made of stainless steel, nitinol, or vitallium (a chromium/cobalt alloy), all of which release varying amounts of nickel.[29,31] Joint failures, restenosis of cardiac stents, oral reactions to dental implants, and skin rashes including urticaria have all been attributed to ACD to implanted metals.[34,35] Because of the widespread exposure to metals in daily products and foods, it is often unclear what the role of the implant plays.

PEARLS AND PITFALLS OF PATCH TESTING

Patch testing is the only practical, scientific and objective method to confirm diagnosis of ACD.

Patch Test Allergens

A core or baseline series of patch test antigens includes those used by the North American Contact Dermatitis Group (NACDG), the T.R.U.E. Test panel, and the

Core Allergen Series outlined by the American Contact Dermatitis Society. Most of these allergens are dispersed in white petrolatum as its vehicle. Those that cannot be dispersed in white petrolatum owing to the chemical stability are supplied in aqueous form.

Studies have shown that approximately 23% to 25% of relevant allergens may be missed if supplementary allergens are not used..[13,36,37] Thus, consider using supplemental patch test allergens based on specific patient exposures, personal products, and workplace materials in addition to the core or baseline series of patch test allergens. Relying solely on these series in all patients is likely to lead to an underdiagnosis of ACD. Kits with allergen panels selected for a specific industry such as machinists, cosmetologists, or dental workers, or for specific exposures such as cosmetics, textiles, plastics, and glues, and medications and topical treatments may be obtained from different manufacturers. The American Contact Dermatitis Society recommends a screening panel of about 80 allergens,[38,39] but the current data suggest that even this number may not be sufficient to adequately screen a significant percentage of patients.

There are no head-to-head studies between the NACDG recommended series, the T.R.U.E. Test, or the American Contact Dermatitis Society core antigen panel. Hypothetically, if only the T.R.U.E. allergens were tested, the T.R.U.E. Test would detect 61.6% to 74.0% of reactions found by the NACDG screening series' results from January 1, 2015, to February 28, 2017.[13] Of the top 40 NACDG allergens, the following are not included in the T.R.U.E. Test and could be missed: MI, fragrance mix II, iodopropynyl butylcarbamate, propylene glycol, oleamidopropyl dimethylamine, 2-hydroxyethyl-methacrylate, dimethylaminopropylamine, decyl glucoside, ammoniumpersulfate, benzophenone-4, ethyl acrylate, cocamidopropyl betaine, methyl methacrylate, and amidoamine and propolis (used in homeopathic remedies).[13]

In certain distributions, such as in eyelid, lip, and facial dermatitis, it may be necessary to include the patient's personal products. In general, leave-on products (such as lipstick, blush, moisturizer, and foundation), clothing, and gloves can be tested as is. Rinse-off products (shampoo, conditioners, and antiperspirant) can be irritants and should be diluted.[26] Other nonstandardized allergens, household cleansers, and industrial products should only be tested by physicians with expertise in this type of testing after evaluating the material safety data sheets information. De Groot's Test Concentrations and Vehicles of 4350 Chemicals are available to help determine appropriate testing concentrations, vehicles, and controls.[40]

The standard and/or additional series of patch test allergens are sold by companies working in close connection with the International Contact Dermatitis Research Group and other international and national groups.

ALLERGENS CAUSING ALLERGIC CONTACT DERMATITIS

The most frequently positive allergic reactions in the most recent NACD Series report[13] included 2 metals—nickel sulfate (17.5%) and cobalt (6.2%); 2 antibiotics—neomycin (7.0%) and bacitracin (6.9%); 3 fragrances—fragrance mix I (11.3%), fragrance mix II (5.3%), and myroxylon pereirae (7.0%); 4 preservatives—MI [13.4%], methylchloroisothiazolinone (MCI)/MI (7.3%), formaldehyde 1% (6.4%) and 2% (8.4%); and iodopropynyl butylcarbamate (3.9%), propylene glycol (4.0%), p-phenylenediamine (PPD; 6.4%), lanolin alcohol (4.1%), and carba mix (4.6%; **Table 2**).

Table 2
Selected allergens and common sources of exposure

Allergen	Common Sources of Exposure
Fragrances	
BOP	Cosmetics, fragrances, dental hygiene products, topical medications, food
Fragrance mix I and II	Fragrances, scented household products
Formaldehyde and formaldehyde-releasing preservatives	
Formaldehyde	Fabric finishes, cosmetics
Quaternium-15	Preservative in cosmetics and skin care products
Diazolidinyl urea	Products for personal care, hygiene and hair care, cosmetics, pet shampoos
Imidazolidinyl urea	Products for personal care, hygiene and hair care, cosmetics, liquid soaps, moisturizers
2-Bromo-2-nitropropane-1,3-diol	Topical antibiotic/antifungal creams/ointments, finger paints, kitty litter, detergents, toiletries and cleansers, cleansing lotions, mouthwash, shampoos
DMDM hydantoin	Wipes, personal care/hygiene products, cosmetics, baby care products, polishes
Nonformaldehyde-releasing preservatives	
Parabens	Preservative in topical formulations, cosmetics, personal care products
MCI-MI	Baby products, personal care/hygiene products, cosmetics
Methyldibromoglutaronitrile-phenoxyethanol	Skin care products, sunscreens, baby care, personal hygiene products (moist toilet paper, shampoos, shower gel)
Iodopropynyl butylcarbamate	Baby care, personal care/hygiene products, cosmetics, hair dye, industry, lip products, paints, yard care
Surfactants	
Cocamidopropyl betaine	Hair and bath products, medicated ointments and creams, cosmetics, oral care
Oleamidopropyl dimethylamine	Cosmetics, conditioners, baby lotions, body lotions, deodorants
Decyl glucoside	Cosmetics, baby shampoo, body washes
Dimethylaminopropylamine	Personal care/hygiene products, medicated ointments and creams, cosmetics, hair detanglers
Amidoamine	Personal care/hygiene products, medicated ointments and creams, cosmetics, hair detanglers
Acrylates	
2-Hydroxyethyl-methacrylate	Possible exposure to acrylic compounds include nail polish, artificial finger nails, hair spray, paints, plastics, adhesives
Ethyl acrylate	Cross-link agent in rubber
Methyl methacrylate	Resin used in dentistry, bone cement, adhesive artificial nails
Metals	
Nickel	Buckles, snaps, jewelry, food
Cobalt	Metal plated utensils, keys, fasteners, paints, cobalt based pigments, vitamin B_{12} supplements
Gold sodium thiosulfate	Gold or gold plated jewelry, dental restorations

(*continued on next page*)

Table 2
(*continued*)

Allergen	Common Sources of Exposure
Chemical additives integral to rubber manufacturing	
Carba mix	Rubber products, shampoo, disinfectants
Mercaptobenzothiazole	Rubber products, nitrile, neoprene, sports equipment
Thiuram	Rubber products, adhesives
Other allergens	
Propolis	Homeopathic remedies, food supplements, cosmetics, gum, medicated ointments/creams
Benzophenone-4	Chemical sunblock
Ammonium persulfate	Hair color allergen added to hydrogen peroxide
p-Phenylenediamine	Permanent or semipermanent hair dyes, cosmetics, printing ink, black henna tattoo
Propylene glycol	Vehicle in topical medications, personal care/hygiene products, auto care, cosmetics, foods, household cleaners, oral care, industry, sunscreens, wipes, yard care
Lanolin (wool alcohols)	Cosmetics, skin care products, personal hygiene items, facial masks, sunscreens, over-the-counter and prescription medications, pet grooming aids

Cosmetics and Personal Products

The term "cosmetic" is used synonymously with "make-up" in the general population. However, cosmetics include personal care products, hair care, nail products, and sunscreens. The number of cosmetic products available on the market today continues to increase together with the rates of adverse cutaneous reactions. The most common responsible cosmetic allergens are fragrances and preservatives.

Fragrances

It is important to keep in mind that many products labeled as unscented, hypoallergenic, or even fragrance free do, in fact, contain masking fragrances and many of the specific fragrance ingredients are considered trade secrets protected by the Fair Packaging and Labeling Act.

Balsam of Peru

BOP (myroxylon pereirae resin) is an aromatic fluid that consists of a mixture of potential contact allergens.[41] It is a complex mixture of many ingredients, including benzoyl cinnamate, benzoyl benzoate, benzoic acid, vanillin, and nerodilol. BOP chemicals can be found in fragrance in personal products such as cosmetics, perfumes, and medicinal products.

Although BOP extract itself is not commonly used in cosmetic products,[42] it is chemically related to many fragrances[43] and allergy to BOP is considered a marker for fragrance allergy.

Patients with contact allergy to BOP may also react to a number of substances that are well-known cross-reactants with BOP such as Balsam of Tolu, benzoin, benzyl acetate, benzyl alcohol, cinnamic alcohol/cinnamic aldehyde, cinnamon oil, clove oil, essential oils of orange peel, eugenol, and propolis.

BOP chemicals are also commonly found in spices, flavoring agents, food and drinks, as well as medications. For some patients allergic to BOP, topical

avoidance of fragrance may not be enough to eliminate their dermatitis. Ingesting BOP-containing foods or beverages can also trigger SCD[44,45] and a diet containing low BOP may help. A BOP elimination diet avoids foods containing BOP constituents such as eugenol, cinnamates, vanillin, and benzoic acid derivatives. These potential allergens are commonly found in citrus fruits, sweets, tomatoes, certain spices, condiments, and some liquors (http://www.foodfacts.com, 2002–2012).

Fragrance mix I consists of 8 components: sorbitan sesquioleate, isoeugenol, eugenol, cinnamic aldehyde, cinnamic alcohol, hydroxycitronellal, geraniol, α-amylcinnamaldehyde, and oakmoss absolute. Fragrance mix II has 6 components: citral, hydroxyisohexyl 3-cyclohexene carboxaldehyde, farnesol, citronellol (0.5%),α-hexyl cinnamic aldehyde, and coumarin.[46] Currently, the 3 most common ingredients used to screen for fragrance allergy are BOP, Fragrance Mix I and Fragrance Mix II. Historically, it is estimated that most patients with fragrance allergy reacted to 1 or more of the 3 ingredients.[26]

Preservatives

Preservatives were identified as the most common cosmetic contact allergens in several recent studies. Preservatives can be further divided into formaldehyde preservatives, formaldehyde-releasers, and nonformaldehyde-releasing preservatives. Formaldehyde-releasing preservatives include quaternium-15, diazolidinyl urea, imidazolidinyl urea, 2-bromo-2-nitropropane-^{1,3}-diol, and DMDM hydantoin. Nonformaldehyde-releasing preservatives include parabens, MCI-MI, methyldibromoglutaronitrile-phenoxyethanol, and iodopropynyl butylcarbamate.

Formaldehyde-sensitized individuals may also be allergic to any of the formaldehyde-releasing preservatives and may experience an exacerbation of ACD with a number of foods, including cod fish, caviar, coffee, shiitake mushrooms, smoked ham, maple syrup, and aspartame.[47] These reactions may manifest as SCD, distinguishable from an IgE-mediated type 1 hypersensitivity reaction to food.

Formaldehyde in both 1% and 2% aqueous solutions are very frequently positive on patch testing. Formaldehyde 2% aqueous solution has been shown to be a worthy screen for formaldehyde with little increase of irritant reaction[48,49]

The International Agency for Research on Cancer, a special agency of the World Health Organization, classified formaldehyde as a human carcinogen in 2004, and in 2011, the US Department of Health and Human Services, named formaldehyde as a known human carcinogen and it has thus been eliminated by many large companies from their products as a preservative.[50]

Methylchloroisothiazolinone/methylisothiazolinone and methylisothiazolinone

MCI and MI in a 3:1 combination (MCI/MI; trade names: Kathon CG, Euxyl K 400) is a widely used preservative in both industrial and consumer products. The rates of contact allergy to MCI/MI increased to levels of up to 8% when it was first introduced as a preservative in 1980.[51,52] This move prompted more strict use concentration recommendations from expert panels in both the European Union and the United States.

MCI is the more potent allergen in the combination MCI/MI. In 2005, MI was approved for use as a preservative in cosmetics and household products and sensitization to MI is increasing. MI can be found in baby products (lotion, oils, powders, and creams), bath products (soaps, detergents, and bubble baths), makeup (eyeliners, eye makeup remover, blushes, and face powders), hair care products (shampoos, conditioners, sprays, straighteners, rinses, and wave sets), hair-coloring products (dyes and colors, tints, and bleaches), nail care products, deodorants,

shaving products (aftershaves and shaving creams), skin care products (cleansers, creams, lotions, and moisturizers), suntan products, and sunscreens, among others.

Patch testing to MCI/MI but not MI alone, could miss MI allergy in 33% to 60% of the cases. This is likely because of the low concentration of MI in the MCI/MI patch test substance (3:1). Testing MI alone at a higher concentration enables the detection of contact allergy more reliably.[53]

Nickel sulfate

Nickel retained its position as the most commonly positive allergen in the screening series, reaching a prevalence of 17.5%.[13] The European Union and institute regulations limit the levels of leachable nickel in items that are likely to have prolonged direct skin contact. In addition to its direct skin contact manifestation, nickel has been reported to cause SCD.

P-Phenylenediamine

The main source of exposure to PPD is hair dye. However, increasing exposure and sensitization have been reported from black henna tattoos.[54] PPD is added to temporary henna tattoos to darken the color and decrease the drying time.[55] Other sources of exposure to PPD include leather, fur, textiles, and industrial rubber products. ACD from PPD can manifest as a range of clinical patterns and can be severe, sometimes mimicking angioedema.

Cross-reactivity with other para-amino compounds such as benzocaine, para-aminobenzoic acid, sulfa drugs, aminoazobenzene, isopropyl-para-phenylenediamine and azo dyes has been reported.[56,57] Patients who test positive to PPD may try the semipermanent hair dye products such as Elumen (Goldwell, Linthicum Heights, MD), which is PPD free or Clairol Basic Instincts-Loving Care (The Proctor & Gamble Company, Cincinnati, OH), a semipermanent hair dye.[58]

Lanolin

Lanolin is a wax made of a mixture of esters, diesters, and hydroxyl esters of high-molecular-weight lanolin alcohols and high-molecular-weight lanolin acids.[59] Lanolin allergy is more common among patients with atopic dermatitis. Sources of exposure to lanolin include personal care products and toiletries, and clothing, as well as industrial sources. Lanolin is found in moisturizers, lipsticks, shampoos, and soaps. Lanolin is also found in ointment bases for topical medicaments such as antibiotics, corticosteroids, and analgesics.[60]

TREATMENT

The most important aspect of ACD treatment is avoidance of the offending allergen. Because many agents are found in everyday products, avoidance can be difficult, even if the allergen has been identified. Patients may find it difficult to read through ingredient lists of products, especially because many of the common contact allergens bear long, similar-looking chemical names. Many allergens cross-react with other allergens, further complicating avoidance. Two databases were developed to help patients identify and avoid products that contain the allergens to which they are sensitized as well as cross-reactive allergens. They are the American Contact Dermatitis Society database called the Contact Allergen Management Program (https://www.contactderm.org/resources/acds-camp) and the Contact Allergen Replacement Database (www.AllergyFreeSkin.com).

Both of these sites maintain a product database that can generate a list of safe products that is created for each patient by entering all positive results from patch

testing. The list includes a wide variety of products, including hygiene products, cosmetics, and topical medications, that do not have the allergen to which the patient had patch tested positive.

In addition to avoidance, topical treatments can be used to alleviate symptoms. First-line medical treatment begins with topical corticosteroids (TCS). For acute ACD, mid- to high-potency corticosteroids can be used. If the dermatitis is especially severe, for example, with acute rhus dermatitis (poison ivy), systemic corticosteroids can provide quick relief.[26] For adults, 40 mg/d with a taper for a total course of 14 days is suggested.[26] Application of diphenhydramine topical preparations for pruritus should be avoided, because this practice can lead to cutaneous sensitization.[10]

For chronic ACD, systemic corticosteroids should be avoided if possible, because the course of dermatitis may be very long and its use can result in rebound flares. Low-potency TCS are preferred owing to the prolonged nature of use. Barrier creams and emollients can be helpful in treating chronic ACD and may decrease dryness and subsequent pruritus of the affected areas. Emollients should be fragrance free to avoid the risk of further sensitization.[10] Calcineurin inhibitors (tacrolimus, pimecrolimus) have not been approved for use in ACD, but are a reasonable alternative in chronic cases and those that involve delicate areas (face, eyelid, etc).[61] Phototherapy can be considered in the treatment of refractory cases.

Antihistamines have not been shown to be helpful in treating the intense pruritus associated with ACD.[26] They may prove helpful by acting as a sedative, however, to help patients sleep at night. Avoidance of wet work, excessive hand washing, hot water, soap, and sweating is advised.[62] Personal protective equipment is particularly important in cases of occupation-related ACD.[63]

If treatment with TCS does not improve or worsens the dermatitis, one should suspect ACD to the topical medication. Allergy to TCS has been described to affect 0.5%

Box 1
Corticosteroids cross-reactivity

Class A (hydrocortisone and tixocortol pivalate: has C17 or C21 short chain ester)
Hydrocortisone, hydrocortisone acetate, tixocortol, prednisone, prednisolone, prednisolone acetate, cloprednol, cortisone, cortisone acetate, fludrocortisone, methylprednisolone acetate

Class B (acetonides: has C16 C17 cis-ketal or –diol additions)
Triamcinolone acetonide, triamcinolone acetonide alcohol, budesonide, desonide, fluocinonide, fluocinolone acetonide, amcinonide, halcinonide

Class C (nonesterified betamethasone; C16 methyl group)
Betamethasone sodium phosphate, dexamethasone, dexamethasone sodium phosphate, fluocortolone

Class D1 (C16 methyl group and halogenated B ring)
Clobetasone 17-butyrate, clobetasone 17-propionate, bethamethasone valerate, bethamethasone dipropionate,
Aclometasone dipropionate, fluocortone caproate, fluocortone caproate pivalate, mometasone furoate

Class D2 (labile esters without C16 methyl nor B ring halogen substitution)
Hydrocortisone 17-butyrate, hydrocortisone 17-valerate, hydrocortisone 17-aceponate, hydrocortisone 17-buteprate, methylprednisolone aceponate

From Boguniewicz M, Aquino M, Fonacier L. Atopic Dermatitis and Contact Dermatitis. In: Adelman DC, Casale TB, Corren J, editors. Manual of Allergy and Immunology, 5th edition. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012; with permission.

to 5.8% of patients.[64] The anti-inflammatory nature of TCS makes this an especially difficult diagnosis, with a high index of suspicion needed.[12] If suspected, the patient should undergo patch testing to the suspected medication and ingredients that are known to be contact sensitizers.[65] Additionally, there can be cross-reactivity between different corticosteroids based on similar chemical structures.[26] Corticosteroids are divided into groups A, B, C, and D (**Box 1**). Group D is subclassified into D1 (halogenated with C16 substitution) and D2 (labile esters without halogenation or C16 methyl group). Although these groups may predict cross-reactivity, many exceptions occur.[26]

Although corticosteroids are very effective in decreasing symptoms, they should be used with caution, especially when the dermatitis is located on a large portion of the body or regions of delicate skin (such as the intertriginous areas or face). Side effects of overuse can include atrophy of the skin, change in pigmentation, telangiectasia, and rebound dermatitis.

Contact allergy to nickel, as described elsewhere in this article, can present as an SCD. In this situation, a low nickel diet may prove helpful.[66] If the combination of nickel avoidance and a low nickel diet does not bring remission, disulfiram tablets have been reported to be effective.[26] Disulfiram works by binding to nickel and allowing for its excretion in urine and stool.

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