

Contact dermatitis: etiologies of the allergic and irritant type

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Abstract

The term *contact dermatitis* describes an inflammatory process of the skin that occurs in response to contact with exogenous substances and involves pruritic and erythematous patches. Approximately 80% of all contact dermatitis is primary irritant contact dermatitis (ICD), whereas allergic contact dermatitis (ACD) makes up only 20% of contact dermatitis cases, the estimated prevalence of contact dermatitis in the United States being 1.4%. Among patch-tested patients, nickel has been identified as the most common allergen. Cobalt is the second most common metal allergen and is found in various dental alloys, paints, and coloring components of porcelain and glass. The average prevalence of dermatitis due to p-phenylenediamine (PPD) was found to be 4.3% in Asia, 4.0% in Europe, and 6.2% in North America. Rubber gloves are a major cause of occupational ACD in healthcare workers. Occupations involving frequent handwashing, between 20 and 40 times per day, have shown an increased incidence in cumulative ICD. The prevalence of occupational hand dermatitis was 69.7% in workers that reported a handwashing frequency exceeding 35 times per shift. The use of alcohol-based sanitizers is much more prevalent among today's healthcare workers than frequent handwashing. Both allergic and ICD are worldwide problems.

Keywords: contact dermatitis, epidemiology, pathogenesis, treatment

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Introduction

The term *contact dermatitis* describes an inflammatory process of the skin that occurs in response to contact with exogenous substances and involves pruritic and erythematous patches. Contact dermatitis can occur in any region of the body; however, the face, hands, and neck are most commonly involved (1). The clinical manifestations of contact dermatitis depend on the exogenous substance, which is classified as either an allergen or an irritant, and the duration of exposure. Allergic contact dermatitis (ACD) and irritant contact dermatitis (ICD), the two subtypes of contact dermatitis, are classified according to the causative agent. ACD is a delayed Type IV hypersensitivity reaction to exogenous contact antigens that the person has previously been sensitized to, whereas ICD is a nonspecific inflammatory response to direct chemical damage to the skin (Fig. 1) (2). The two subtypes of contact dermatitis are often present simultaneously (Fig. 2) (3).



Figure 1 | Allergic contact dermatitis (38).

Epidemiology

Approximately 80% of all contact dermatitis is ICD, whereas ACD makes up only 20% of contact dermatitis cases. According to the National Health and Nutrition Examination Survey (NHANES), the estimated prevalence of contact dermatitis in the United States is 1.4%. A similar prevalence rate of 1.2% was found specifically for ACD in a Dutch study (4). The incidence of occupational contact dermatitis can vary from nine to 49 cases per 100,000 workers per year (5).

Correlations have been observed between the prevalence of contact dermatitis and both age and sex. The implications of age on the prevalence of contact dermatitis involve the differential exposure to allergens and irritants experienced by children versus adults. Common causes of ACD in children include, but are not

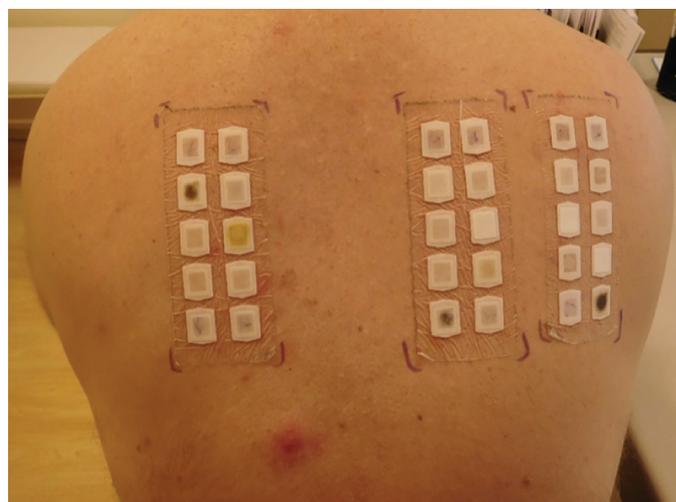


Figure 2 | Patch testing with 30 standard haptens.

limited to, footwear, due to rubber allergy; metal objects, due to nickel content in earrings and various household items; plants, specifically poison ivy; and various medications, which may also cause ACD in adults. Diaper dermatitis is a well-observed form of ICD in children and is thought to be due to colorants and dyes in disposable diapers. Adults and elderly persons mainly experience ACD as a result of topical medications (5). Occupational risk factors are frequently cited as a cause of both ACD and ICD in adults. Occupations that particularly involve frequent handwashing and repeated exposure of the skin to water showed an increased incidence of contact dermatitis. The prevalence of occupational hand dermatitis was 69.7% in workers that reported a handwashing frequency exceeding 35 times per shift (6). High-risk populations include sanitation workers, healthcare providers, food industry workers, and hairdressers (7).

Similar to age, the influence of sex on the acquisition of contact dermatitis primarily involves distinct exposure patterns of men and women to various allergens and irritants. Women have greater contact with jewelry compared to men and coincidentally experience increased incidence of nickel sensitivity reactions (5). The majority of ACD reactions occur after exposure to fragrances, preservatives, and hair dye; this may also explain the increased incidence of ACD in women (8). Contact dermatitis occurs twice as frequently in women as in men; this correlation between sex and incidence is thought to be due to increased exposure of women to exogenous substances that induce contact dermatitis as opposed to an inherent biological factor (5, 9). No racial predilection of ACD or ICD has been detected. A similar incidence of each was found in Caucasians and African Americans (7).

Etiology

Allergic contact dermatitis

ACD is a Type IV, T-cell-mediated, delayed-type hypersensitivity reaction; it occurs subsequent to sensitization to a particular hapten (8). The inflammatory response of ACD is divided into a sensitization phase and an elicitation phase. The sensitization phase, which typically takes 10 to 14 days, begins upon initial contact with the hapten as it first encounters and infiltrates the epidermal skin barrier (8). Thus, the integrity of the epidermal barrier is heavily implicated in the onset of ACD reactions; barrier disruption could result in increased permeability of irritants or allergens, including but not limited to environmental contaminants and microbial organisms. The elicitation phase occurs upon subsequent exposure to the same hapten; antigen-specific T-cells are activated and recruited to the site of exposure (10). This re-exposure of the skin to the hapten, or allergen, is central to the development of ACD. Typically, the severity of the ACD reaction increases with subsequent re-exposures, whereas the onset of these symptoms becomes quicker (8).

Metals: In 2018, Rastogi et al. found that 38.9% of evaluated patients were diagnosed with contact dermatitis; among these patients, the most common allergens were nickel, mercury, and palladium (11). Among patch-tested patients, nickel has been identified as the most common allergen. Nickel allergy is more prevalent in women, perhaps due to increased exposure to jewelry in those under age 18 (12). Because children frequently encounter nickel in everyday objects, they experience sensitization quite early and thus are at an increased risk for nickel-induced ACD upon re-exposure. Cell phones contain metals and are a po-

tential source of exposure for both young children and adults (Fig. 3) (13). After nickel, cobalt is the second most common metal allergen. It is found in various dental alloys, paints, and coloring components of porcelain and glass. Following cobalt, chromium ranks as the third most prevalent metal inducing ACD. Previously, chromium-induced ACD was more widespread in men working with cement; however, this chromium-containing cement is no longer used. The resultant decreased incidence of occupation-related chromium allergy has caused it to become more common in women. Certain tanned leather clothing articles also contain chromium and are a cause of ACD (14). Palladium, mercury, gold, titanium, silver, tin, and zinc have also been shown to cause ACD. A high prevalence of contact hypersensitivity to metals and preservatives was recently documented in Chinese patients with atopic dermatitis (15).



Figure 3 | Contact dermatitis from cobalt after using a cell phone.

Rubber: Rubber gloves are a major cause of occupational ACD in healthcare workers (16). Specifically, the presence of the chemicals 1,3-diphenylguanidine (DPG) and cetylpyridinium chloride in these gloves was shown to cause ACD among surgical personnel (Fig. 4).



Figure 4 | Contact dermatitis to thiuram in gloves.

Hair dye and temporary tattoos: The chemical p-phenylenediamine (PPD) is frequently used in permanent hair-coloring agents and is also found in henna tattoos (17). PPD is used more frequently in darker hair dyes and serves to increase the duration of henna tattoos as well as quicken the drying time (17). According to Thyssen et al. (18), the average prevalence of dermatitis due to PPD was 4.3% in Asia, 4.0% in Europe, and 6.2% in North

America.

Preservatives: Chemical preservatives are often added to cosmetics, moisturizers, and topical medications and are a major cause of ACD. Methylchloroisothiazolinone (MCI) and methylisothiazolinone (MI) are preservatives commonly employed in industrial products (19). In 2005, the use of MI was permitted in cosmetic products and, since then, a trend of increasing sensitization has been observed. The prevalence of ACD due to MI is 1.5%. Its increased use in industrial, cosmetic, and household products suggests that an epidemic of MI-induced ACD is on the horizon (Fig. 5) (19, 20).



Figure 5 | Allergic contact dermatitis after anti-perspirant use (38).

Fragrances: Linalool is a common organic compound that is found in fragrances. It is not allergenic in pure form, but when oxidized it is a common cause of ACD (21). The face and the eyelids in particular are the prototypical presentation site of cosmetic contact dermatitis, with common sources including shampoo, conditioner, facial cleansers, makeup remover, mascara, nail polish, acrylic nails, makeup sponges, eyelash curlers, and allergens transferred from the hands (22).

Plant species: Chinese hibiscus (*Hibiscus rosa-sinensis*) is a unique flower that has been shown to cause ACD. A unique case of ACD resulting from exposure to *H. rosa-sinensis* was documented in a Hindu priest that used *H. rosa-sinensis* flowers as part of monthly rituals. The patient presented with recurrent dermatitis and painful cracks in the fingers of his right hand, which was the hand used to perform rituals. *H. rosa-sinensis* has been shown to cause skin irritation, dermatitis, and immediate hypersensitivity reactions. It can be seen in gardeners as well, but overall it is quite rare. The leaves and stems of *H. rosa-sinensis* contain β -sitosterol, stigma, sterol, taraxeryl acetate, and 3-cyclopropane compounds. The flowers of the plant, however, contain cyanidin diglucoside and flavonoids (22).

Acrylates: Acrylates and methacrylates are the most common resin monomers used in cosmetics, production of artificial nails, and dental materials. These monomers cause sensitizations of the skin and contact dermatitis. At various times patients are found with contact allergies to methacrylates and other acrylate monomers. Very often contact dermatitis caused by acrylates can be assigned to occupational dermatitis (Fig. 6) (23). Various wearable devices used in type 1 diabetes mellitus, such as insulin pumps, flash glucose monitoring (FGM), and continuous glucose monitoring (CGM) devices, are increasingly reported to cause ACD. Although epoxy resin was the first reported contact allergen in these

devices, today in newer technologies these are most often acrylates: ethyl cyanoacrylate, cyanoacrylate, and isobornyl acrylate (24).



Figure 6 | Positive patch test reaction to formaldehyde.

Drugs: Various topical drugs can cause ACD, including antibiotics, local anesthetics, corticosteroids, and antifungals. In particular, an allergic reaction to neomycin is commonly noted due to its use as treatment of chronic stasis dermatitis and venous ulcers. Such ACD is less prevalent when neomycin is used as a topical antibiotic for cuts and scrapes in children (25). Systemic drugs are also known to cause ACD. Antihistamines often contain allergens that a person may be sensitized to, and, upon ingestion, can precipitate systemic contact dermatitis. In particular, brompheniramine and doxepin preparations contain allergenic substances, whereas fexofenadine has been shown to be free of them (26).

Irritant contact dermatitis

Unlike ACD, ICD is a non-immunologic inflammatory reaction that does not require previous sensitization and occurs in response to a wide range of irritants, which can be of a physical, chemical, or mechanical nature (8). Multiple factors are considered to be involved in the pathophysiology of ICD, including disruption of the skin barrier, damage to epidermal cells, keratinocyte release of proinflammatory cytokines, and involvement of the innate immune system (27). For ICD to ensue, exposure to a specific irritant must result in disruption of the epidermal barrier, specifically the stratum corneum. The epidermal damage created by this irritant will then facilitate transepidermal water loss due to increased skin permeability (8). Along with increased skin permeability, the irritant-induced insult will cause release of proinflammatory cytokines such as interleukin (IL)-1 α , IL-1 β , IL-6, and tumor necrosis factor (TNF)- α from keratinocytes (28–31). The presence of these cytokines at the site of exposure facilitates further release of proinflammatory cytokines, which act as a signal for the migration of mononuclear and polymorphonuclear cells to the site of irritant exposure (32).

Dry air and temperature variation: An increase in temperature by more than 20 °C increases the cutaneous effect of an irritant (33).

Cumulative ICD: Occupations involving frequent handwashing, between 20 and 40 times per day, have shown an increased incidence in cumulative ICD. The use of alcohol-based sanitizers is prevalent among today's healthcare workers and has been shown to cause less irritation than frequent handwashing. These alcohol-based sanitizers may also be useful in decreasing irritation that could result from handwashing because they aid in eliminating the detergent (34).

Mechanical trauma: Irritation such as sweating and friction from clothing can contribute to the irritancy of contact dermatitis. In a retrospective analysis of eight children 9 to 16 years old that wore protective shin guards during soccer and presented with recurrent dermatitis, it was determined, after evaluating their negative patch test results to over 50 standard allergens and shin guard components, that ICD was the cause of their dermatitis (35).

Alkali: Endogenous factors, such as moisture of the skin, anatomical site, age, sweat, and sebum production, as well as exogenous factors including detergents and cosmetic products, influence the skin's naturally acidic pH. These changes from physiological pH are associated with pathogenesis and onset of

ICD, as well as atopic dermatitis and acne (36).

Conclusions

Both ACD and ICD are worldwide problems. Almost any exogenous substance can precipitate contact dermatitis if the exposure is prolonged or the concentration is high. Confounding factors may be a consideration too, as with phytophotodermatitis, a non-ACD from a photosensitizing chemical followed by exposure to solar or artificial ultraviolet light (37). Although the pathogenesis of ACD and ICD are distinct, the presentations of each subtype of contact dermatitis are highly similar.

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