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# Contact dermatitis: some important topics

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## KEY WORDS

Contact dermatitis; patch test; allergy irritancy

## Summary

Allergic contact dermatitis (ACD) is a type IV delayed hypersensitivity reaction. The gold standard for diagnosis is patch testing. The prevalence of positive patch tests in referred patients with suspected ACD ranges from 27 to 95.6 %. The relationship between ACD and atopic dermatitis (AD) is complicated with conflicting reports of prevalence in the literature; however, in a patient with dermatitis not responding to traditional therapies, or with new areas of involvement, ACD should be considered as part of the work-up.

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Contact dermatitis is a category of diseases whose common denominator is an external inciting factor, in contrast to the endogenous dermatoses, e.g., atopic dermatitis and psoriasis. Included in this group are: irritant contact dermatitis (ICD); contact urticaria (CU); protein contact dermatitis (PCD); and allergic contact dermatitis (ACD) (1). The most common form of all the contact dermatoses is ICD. It does not require prior sensitization, but rather is caused by direct damage to keratinocytes by an irritating substance (e.g., an alkaline or acidic chemical). This leads to a localized release of proinflammatory cytokines and the subsequent development of an eczematous dermatitis (2). Importantly, besides avoidance of the causative agent (which in acute cases can usually be identified by the subject), therapy targeted at barrier repair is paramount and can include the use of ceramides, pseudoceramides, and filaggrin degradation products (3). While beyond the scope of this article, it is important to mention the Type I immediate hyper-

sensitivity reactions seen in the skin, as they have important clinical consequences. CU specifies the appearance of pruritic wheals, as the unique symptom after contact with the triggering substance (4). In this type of reaction, the subject will experience degranulation of mast cells in the dermis as well as a perivascular leukocyte infiltrate which triggers the release of histamine and other inflammatory mediators, that, in turn, cause local vasodilation, itch, and swelling in the skin (i.e. wheal and flare formation) (2). There are two subcategories of CU, namely non-immunologic contact urticaria (NICU) and immunologic contact urticaria (ICU). NICU involves the release of vasogenic mediators without the involvement of immunologic processes; it is typically less severe than ICU and occurs 45-60 min after contact (4,5). ICU requires a prior sensitization phase and occurs 15-20 min after contact, and in contrast to NICU, ICU can spread beyond the localized contact point (5). Additionally, this category includes PCD, which is thought to be caused

by a combination of type I and type IV reactions (4). Clinically, rather than the urticarial response, the skin lesions are characterized by chronic or recurrent eczematous dermatitis upon exposure to specific proteins (e.g., as meat, fish, vegetable, and latex) (4,6). Across the board, the first line treatment in this category of diseases is avoidance of the eliciting trigger. In addition, treatments that inhibit the release and effect of mast cell mediators and possibly other inflammatory mediators can ameliorate or suppress symptoms. Specifically, anti-histamines can be considered for urticaria and topical corticosteroids and/or calcineurin inhibitors can be used for dermatitis (4). ACD is a type IV (delayed) hypersensitivity reaction, a complex type of reaction, which requires a prior sensitization, and elicitation. The sensitization phase is characterized by an exogenous allergen entering the epidermis through an impaired skin barrier. These allergens then bind with self-proteins to create complete antigens that are taken up and expressed by dendritic cells on the cell surface of major histocompatibility complexes (MHC) (7-10). The elicitation phase occurs upon repeated exposure to the allergen at which time a clinical dermatitic response occurs. The repeated exposure can occur trans-epidermally or systemically through ingestion, inhalation, or intravenous entry (11). As opposed to ICD, which clinically consists of well-demarcated, erythematous, and sometimes follicular papules and plaques localized to the area of contact, ACD usually expands beyond the contact area. In addition, there can be transfer of the allergen from one body area to another or activation of dermatitis at distant sites via 'recall reactions', which are flares at sites of prior allergen exposure (1). In contrast to ACD, a pearl in the diagnosis of ICD is that the dermatitis will spare 'protected' areas. For example, in diaper dermatitis, the folds are spared, as the skin-skin contact prevents urease and fecal enzymes from touching and breaking down the skin in these areas, further underscoring the role of barrier integrity, maintenance, and repair in the treatment of ICD.

### Clinical Relevance of Contact Sensitization

The gold standard for the diagnosis of ACD is patch testing; however, not all positive patch test (PPT) reactions are clinically relevant to a patient's dermatitis. A PPT reaction that is not found to be clinically relevant is termed 'contact allergy' rather than 'allergic contact dermatitis' (12). The prevalence range of PPT reactions with suspected ACD is 27 - 95.6% (13-17), while the relevancy of these PPT is much less frequent.

### Patch Testing

The first indication for patch testing is uncontrollable or worsening chronic dermatitis of greater than 2 months duration. The second is a failure to improve following standard treatment

protocols (18/26). Given the surface area for patch testing, once there is a high index of suspicion for ACD, a detailed exposure history guides the testing for relevant allergens. This is performed either by selecting potential allergens based on history of exposures or by screening with standardized series of allergens and potentially the patient's own personal care products.

Standard patch testing series have been suggested by both the Contact Dermatitis Group (19) and by centers in the US (18). Notably, a 24-h application period can be efficacious in patients with atopic dermatitis as it can reduce the irritation reactions that may be seen in these subgroups (20,21). In addition to standard comprehensive patch testing, the commercially available Thin-Layer Rapid Use Epicutaneous Patch Test (T.R.U.E.<sup>TM</sup>, Smart Practice; Phoenix) has received FDA-indication for use in adults. The T.R.U.E.<sup>TM</sup> Test consists of three panels of allergens/mixes and one negative control as uniform dried gel coatings on polyester sheeting. Hypoallergenic adhesive surgical tape secures these patches to the skin. Per the prescribing instructions, it is recommended that the patches be applied for 48 h with reads at 72 and 96 h (22). Since that time, the TRUE test was expanded to include 35 allergens and the negative control. Of note, PREA-2 is currently under way to determine the safety and efficacy of these additional 7. Patch test readings are based on recommendations from the International Contact Dermatitis Research Group (ICDGR) (23). A doubtful reaction by definition consists of faint macular erythema. A weak positive (1+) reaction is non-vesicular with erythema, mild infiltration, and potentially discrete papules. A strong positive reaction (2+) is vesicular with erythema, moderate infiltration and papules. Finally, an extreme positive reaction (3+) denotes a coalescing papular-vesicular plaque with deep erythema and significant infiltration, which may become bullous or ulcerative and often expands beyond the margin of the patch well. Notably, irritant reactions may present as pustules or patchy follicular erythema with no infiltration and are not indicative of a true allergy (23). The irritant reactions often appear within the first 48 h of patch testing and improve by 96 h, as opposed to contact allergy reactions, which typically worsen between 48 and 96 h.

If possible, patients should refrain from taking oral corticosteroids during the patch test. In adults, a dose of 20 mg in a 75-kg male is known to significantly suppress patch test reactions (24). In addition, topical corticosteroids should not be applied to the testing area for the 3-7 days prior to patch testing, as this can result in false negative reactions (25). Flare up reactions of the patient's dermatitis may be elicited during patch testing. For this reason, all prior dermatitis sites (excluding the test site) should continue to be treated with topical corticosteroids or immune modulators throughout the duration of the patch test (26). Patients can take oral antihistamines for symptomatic management of the pruritus, and this will not alter the results

of the patch testing. Although systemic immunosuppression is not optimal during patch testing, some patients' dermatitis is so wide-spread that these agents may be warranted, and the minimal suppressive dose may need to be determined to suppress the dermatitis and yet still allow for the patch test to function (25).

## Discussion and Conclusions

ACD is a common condition in the general population which has been previously under-recognized, as it is often difficult to distinguish clinically from other eczematous skin eruptions such as AD and chronic irritant reactions (10). The negative impact of ACD extends to include a decrease in quality of life secondary to pruritus, loss of sleep, and feelings of inferiority among peer groups, in addition to a significant economic burden. Rates of contact sensitization are higher than historic literature had predicted, which may be secondary to an increase in allergen exposure associated with new trends (e.g., body piercings, the use of cosmetic products, and participation in sports and hobbies) (17,20), or improved recognition of ACD with patch testing being more frequently performed in the population. In the studies reviewed, the rate of PPT reactions ranged from 27 to 95.6% while the relevancy of the PPT ranged from 30.5 to 92.6%. These data may not be applicable to the population at large, given that these studies were done at major referral centers on selected patients.

The goal of patch testing is to optimize true PPT and reduce false PPT

This is most effectively done with comprehensive patch testing; however, comprehensive patch testing can be time/labor intensive and requires the practitioner to have access to a wide range of allergens. Since the advent of the T.R.U.E.<sup>TM</sup> test, the number of practitioners providing patch testing in their clinics has greatly increased due to the increased convenience afforded by this commercially available tool (27). That being said, not all relevant allergens are included in the T.R.U.E.<sup>TM</sup> test, such as the relevant allergens CAPB and dialkyl-thioureas.

When planning for patch testing, it is important for both the clinician and the patient to have realistic expectations. When a relevant allergen is identified, an avoidance regimen is prescribed. In patients with extensive chronic dermatitis, 8-12 weeks of avoidance may be needed before a true assessment of clinical improvement can be made. Even with the most compliant patients, avoidance regimens may be difficult to follow, especially with ubiquitous allergens with a multitude of potential exposure sources or when the product manufacturing ingredients (e.g., shin guards) are not available. Products that are marketed as 'natural' can also cause ACD. It is well known that some 'unscented' products contain a masking fragrance, thus are not 'fragrance-free'. 'Fragrance-free' products can contain essential oils that can also lead to contact sensitization (27).

Resources such as the ACDS Contact Allergen Management Program (CAMP), available at <http://www.contactderm.org>, and the Contact Allergen Replacement Database (CARD), available at <https://card.preventice.com>, can be helpful in providing a list of products that patients are allowed to use, in addition to giving them allergen information sheets. It is also important to note that 'allergen avoidance' may require adaptive measures to prevent contact of the allergen with the patients' skin. For example, if a patient is allergic to a component of a shin guard, the shin guard can be lined with canvas as an adjunct to the patient wearing a protective sock underneath, to prevent direct skin contact. In addition, patients can be given instructions on the repeat open application test (ROAT) or 'use test' for testing new products prior to full body application. This test consists of applying a product, twice a day for 1 week, to a designated area on the upper inner arm while monitoring for an eczematous skin reaction.

One population in particular can especially benefit from patch testing: the AD patients. Although the exact prevalence of ACD in patients with AD remains unclear, it is known that ACD can be misdiagnosed as AD and/or the concurrent presence or development of ACD can lead to AD flares. As a result, in those patients with moderate-severe dermatitis, correct use of patch testing can allow for cessation of systemic immunosuppressant therapies, a decrease in the need for topical corticosteroid therapy, and ultimately a drastic improvement in their quality of life.

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