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THERAPY IN PRACTICE

The Role and Diagnosis of Allergic Contact Dermatitis in Patients with Atopic Dermatitis

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Abstract Patients with atopic dermatitis (AD) have increased penetration of allergens, immune dysregulation (including shared cytokine pathways), and frequent use of emollients and topical medications, all of which may predispose toward developing allergic contact dermatitis (ACD). Recent systematic reviews have suggested that ACD is a significant clinical problem in both children and adults with AD. While this remains controversial, ACD remains an important comorbidity and potential exacerbant of AD in clinical practice. Common relevant allergens, include lanolin, neomycin, formaldehyde, sesquiterpene lactone mix, compositae mix, and fragrances that are commonly found in AD patients' personal care products. We herein review the clinical scenarios where patch testing is indicated in AD. In addition, we review the contraindications, preferred patch-testing series, pitfalls, and challenges determining the relevance of positive patch-test reactions in AD patients.

Key Points

Patients with atopic dermatitis (AD) appear to have an increased risk of developing allergic contact dermatitis.

Patch testing should be considered in adolescent- or adult-onset AD, worsening or more generalized dermatitis, localized or atypical lesional distribution, refractory disease, prior to systemic immunosuppressive treatment, or when AD worsens with topical therapy.

Patch testing in AD should use an expanded patch-test series and the results interpreted with caution.

1 Introduction

1.1 Atopic Dermatitis (AD)

Atopic dermatitis (AD) and allergic contact dermatitis (ACD) are both common and burdensome inflammatory skin disorders. AD is a chronic disease that is caused by a combination of genetic predisposition, skin-barrier disruption, immune factors, and environmental exposures. AD affects up to 15–20% of children and 1–10% of adults worldwide, including 13% of US children and 7.2% of US adults [1–4]. AD is a heterogeneous disorder associated with a constellation of signs and symptoms, including pruritus, skin pain [5], mental health symptoms, xerosis, oozing/weeping in acute lesions, lichenification and

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prurigo nodules in chronic lesions. AD also has a chronic relapsing or persistent course, with an age-related distribution of cutaneous lesions, with facial dermatitis affecting infants, extensor dermatitis in toddlers, flexural lesions in older children and adults, and more facial and hand dermatitis in adults [6].

Given the varied presentation of AD, it is often challenging to diagnose with certainty, particularly in adults. AD is diagnosed clinically based on its signs and symptoms. There are no currently accepted tissue or blood biomarkers to diagnose AD. The original diagnostic criteria for AD are those of Hanifin and Rajka [7], published in 1980 and developed via clinical experience and expert consensus; however, various modifications of these criteria, as well as other diagnostic criteria, were subsequently developed [8–12].

1.2 Allergic Contact Dermatitis (ACD)

ACD is caused by a delayed-type hypersensitivity response to contact allergens. The incidence of ACD is not clearly defined but is thought to be rising [13]. A recent study found that all forms of contact dermatitis (CD), including irritant CD (ICD) and ACD, had a claims-based prevalence of 4.17% within the US [14]. The most recent estimated annual medical costs in the US in 2013 for AD and CD were $314,000,000 and $1,529,000,000, respectively [14]. ACD is the second most common type of CD after ICD, and may present with similar signs and symptoms as AD. The most common symptoms are pruritus, along with burning and stinging. ACD commonly presents acutely with erythematous, indurated papules and plaques, vesiculation, edema, and bullae formation in severe cases, while chronic ACD can present with scaling, lichenification, and fissuring. Furthermore, ACD typically presents with a well-defined, exposure-dependent distribution, commonly involving the hands, face, or eyelids; however, irregular or diffuse distributions can occur due to secondary allergen transfer or systemic allergen sensitization. ACD is diagnosed via a combination of clinical signs and symptoms and patch testing, the gold standard for ACD diagnosis, where non-irritating concentrations of allergens are used to determine the presence of an allergic reaction in vivo [15].

Importantly, due to the large symptom burden, including the sequelae of itch, pain, sleep, and mental health disturbance, AD and ACD both have a significant negative impact on quality of life (QOL) [16–20]. While these two cutaneous eruptions may appear similar and often co-exist [21], the etiologies, distributions, and therapeutic options often differ. This makes differentiating the two diseases critical to the successful treatment of the dermatitis. The goal of this article is to review ACD in AD patients, i.e. when to suspect ACD and how best to test for ACD in patients with AD.

2 Mechanisms

2.1 AD

The pathogenesis of AD is multifactorial, with both epidermal barrier and immunologic defects. A subset of AD patients have filaggrin (*FLG*) gene null mutations that are inherited in an autosomal semi-dominant fashion. Barrier disruption may occur secondary to exogenous insults, even in those without germline *FLG* mutations, possibly through direct insult to the skin-barrier and/or epigenetic alterations [22, 23]. Such factors include fragrances, pruritogens, stress, climate, and pollution, among others. Thymic stromal lymphopoietin (TSLP) and other cytokines are released by damaged keratinocytes from the disrupted skin barrier and contribute to skin inflammation, and may also be involved in gene-environment interactions in AD [23]. Due to impaired barrier function, there is an increased risk of transcutaneous allergen penetrance [24] and potentially antigen sensitization and presentation.

The AD inflammatory signature is primarily of the T-helper (Th) cell 2 type in both the acute and chronic phases, with a contribution from Th1 in the chronic phase [25–27]. Th2 cells produce interleukin (IL)-4, -5, -13, and -31, all of which have downstream effects in AD. Notably, IL-4 and IL-13 promote skin barrier disruption. Thus, epidermal inflammation may precede and be sufficient to cause skin-barrier disruption, even in those without preceding barrier defects. Some studies have shown upregulation of IL-17 and IL-22 (secreted by Th17 and Th22 cells, respectively) in the acute phase of AD. These cytokines may induce epidermal hyperplasia and/or alter terminal differentiation proteins. Th2 cytokines also impair antimicrobial peptide (AMP) responses to pathogens, which, in conjunction with barrier disruption, allows for increased pathogen penetration [28–35].

Recent studies have also shown a potential role for Th9 and Th17 pathways in AD. The mechanism by which IL-9, secreted by Th9 cells, contributes to AD pathogenesis is not fully known; however, IL-9 promotes mast cell activity, eosinophils, and innate immune cells [36]. IL-9 levels have been shown to be increased in both pediatric and adult AD patients and correlate with AD severity [31, 37, 38]. IL-9 also enhances the secretion of IL-13, a key cytokine in AD pathogenesis. Importantly, a significant association between IL-9 and IL-9 receptor gene polymorphisms with AD was found in a Korean population [39]. Th17 levels have also been found to correlate with AD severity [32], and may be related to host defense and skin remodeling

[40, 41]. Th17 cytokines may play a greater role in intrinsic AD, i.e. AD without comorbid atopy or atopic disease [35].

2.2 ACD

ACD is a classic type IV hypersensitivity reaction requiring two phases: sensitization and elicitation. In the sensitization phase, an allergen is captured by antigen-presenting cells (APCs), which migrate to the draining lymphoid tissue. Subsequent activation of naive T cells occurs, leading to differentiation of memory T cells specific for that allergen. In the elicitation phase, re-exposure to the allergen or a cross-reacting allergen results in activation of memory T cells. T cytotoxic (Tc) 1 cells are activated and lead to the hallmark inflammation and adaptive immune response resulting in dermatitis [42]. The primary ACD inflammatory signature is a Tc1 or Th1 response. However, Th2, Th17, and Th22 responses appear to play a role in ACD, sometimes depending on the allergen [43–45]. For example, nickel was found to be a potent inducer of the innate immune Th1, Th17, and Th22 pathways, while fragrance and rubber promoted Th2 activity with less Th1 and Th17 involvement [46].

IL-9 expression has also been found to be elevated in skin from positive patch-test reactions in ACD patients, including reactions to metals, drugs, and polymers; IL-9 also increased in nickel-allergic patients after nickel stimulation [47–49]. Th17 cell expansion occurs upon allergen contact in individuals with ACD [50]. IL-17 secretion increases local inflammation via induction of proinflammatory cytokines, chemokines, and adhesion molecules [51–54]. The potential role of Th17 in ACD was also demonstrated by a recent experimental study showing that ACD reactions were decreased in the absence of IL-17 [55].

3 ACD in Patients with AD

3.1 Plausibility

Many factors are thought to affect prevalence of ACD in patients with AD. The historical perspective is that the Th2-skewed inflammatory response of AD results in less contact sensitivity [56]. For example, some studies showed an increased elicitation threshold in patients with AD compared with controls [56–59]. Other studies demonstrated several reasons for AD patients to have a similar or even increased risk of ACD compared with those without AD. Patients with AD have skin-barrier disruption, with an approximately twofold increase in skin absorption of irritants and contact allergens [60–62]. Irritants lead to further breakdown of the skin barrier, increased penetration of contact allergens, and, eventually, increased risk of contact sensitization [63, 64]. It has also been demonstrated that cutaneous responses and elicitation thresholds in ACD patients were considerably influenced by combined allergen and irritant exposure [65–67]. Additionally, the treatment of AD requires chronic topical application of emollients and anti-inflammatories, and many of these topical products have been found to be contact sensitizers [68, 69]. More recently, potential shared immune pathways were demonstrated for subsets of AD and ACD, including Th1, Th2, Th9, and/or Th17, as reviewed above. An emerging idea is the role of bacterial colonization in AD and how, by stimulating an inflammatory environment, it may lead to enhanced contact sensitization [63, 70–72].

3.2 Evidence

A recent systematic review was performed assessing contact allergy in children with AD. The review assessed 31 studies and found that ACD was significantly greater in children without AD versus those with AD (46.6 and 41.7% sensitized to at least one allergen, respectively; $I^2 = 61.7\%$, $p < 0.001$); however, the authors noted significant variability of sensitization rates, study designs, and criteria that limit conclusions being drawn. The results of the available studies were conflicting with respect to whether AD patients have higher rates of ACD than the rest of the population. Nevertheless, ACD was found to be a common clinical problem in AD, with approximately one-third of children with AD who were patch tested having at least one contact allergy [73].

Another systematic review and meta-analysis, including 74 studies evaluating the prevalence of contact sensitization (defined as a positive patch-test reaction to any allergen) in various patient populations found that AD patients had an increased prevalence of contact sensitization compared with the general population [74]; however, there was an inverse association when patients with AD were compared with a patch-test referral population. The authors postulated that this latter relationship could be because AD patients in a referral population have more severe and recalcitrant disease, which has been shown to have a higher elicitation threshold for contact sensitization [56–58]. Furthermore, severe AD patients are often referred for patch testing to rule out contact sensitization, even without clear clinical suspicion prior to initiating systemic AD therapy [74].

3.3 Relevant Allergens

Results from various studies assessing the relationship of ACD in AD patients have led to the identification of common allergens (Table 1), including nickel, cobalt,

Table 1 Common contact allergens identified in patients with atopic dermatitis

Bacitracin
Carba mix
Chromium
Cinnamic aldehyde
Cobalt
Cocamidopropyl betaine
Colophonium
Compositae mix
Disperse blue dye 106
Epoxy resin
Formaldehyde
Fragrance markers (e.g. fragrance mix I, fragrance mix II, *Myroxylon pereirae*, and hydroxyisohexyl-3-cyclohexene carboxaldehyde)
Isothiazolinones (e.g. methylisothiazolinone and methylchloroisothiazolinone)
Lanolin
Mercaptobenzothiazole and mercaptans
Myroxylon pereirae
Neomycin
Nickel
Para-tertiary butylphenol (PTBP) formaldehyde resin
Paraphenylenediamine
Potassium dichromate
Quaternium-15
Rubber or rubber mixes
Sesquiterpene lactone mix
Topical antiseptics (e.g. chlorhexidine, hexamidine)

potassium dichromate, chromium, lanolin, neomycin, formaldehyde, sesquiterpene lactone mix, compositae mix, and fragrance markers (e.g. fragrance mix I, fragrance mix II, *Myroxylon pereirae*, and hydroxyisohexyl-3-cyclohexene carboxaldehyde) [69, 73–86].

It has recently been demonstrated that commonly used personal care products, including those self-identified as hypoallergenic, contain potent contact allergens [68, 87]. Furthermore, AD patients with frequent emollient use were found to have increased urinary levels of such allergens, particularly parabens and phthalate metabolites, indicating that such allergens do have cutaneous penetrance [88]. Topical treatment with emollients in AD has been shown to be associated with cutaneous sensitization [69]. A retrospective Dutch study of pediatric patients found that children with AD had significantly increased reactivity to lanolin and fragrances [83]. Furthermore, a retrospective analysis of 26,479 patients patch tested with the North American Contact Dermatitis Group (NACDG) screening series found that patients with positive reactions to lanolin were more likely to have a history of AD [89].

4 Clinical Assessment for Contact Dermatitis in Patients with AD

4.1 When to Consider Patch Testing in a Patient with AD

Guidelines for when to perform patch testing in AD patients are based largely on consensus expert opinion [90]. Recommendations for when to consider patch testing include adolescent- or adult-onset AD as ACD can occasionally present with a flexural distribution and can mimic AD. Pediatric and adult AD patients with worsening or more generalized dermatitis should also be patch tested as there may be an allergenic trigger of their underlying AD.

Patch testing is also indicated in both children and adults when there is a lesional distribution that is atypical for AD, or one that is localized and suggestive of CD (e.g. eyelids, head and neck, hand and foot, perioral, or periorbital). This is a particularly important consideration in adults with AD, for whom previous studies have demonstrated higher rates of lesions affecting the head and neck, or hands and feet (even in the absence of CD) [91].

Patch testing should be considered in both children and adults if the dermatitis is recalcitrant to topical therapy, and prior to initiation of systemic immunosuppressive therapy. Identification and avoidance of a relevant positive allergen on patch testing may decrease the severity of the underlying AD and abrogate the need for systemic therapy.

Patch testing should be considered in children and adults when the AD worsens with therapy or rebounds quickly upon cessation of therapy. This may signal that the patient has developed ACD to the active ingredients or excipients in their topical therapy, e.g. corticosteroids or propylene glycol.

In addition, previous studies have shown high rates of ACD in patients with nummular eczema. Nummular lesions have been shown to occur with greater frequency in school-age children with AD [92] and adult-onset AD [91]; however, widespread nummular lesions may be a sign of ACD in an AD patient [93, 94].

4.2 When is Patch Testing Not Routinely Recommended in AD

Situations in which patch testing is less likely to be helpful include stable and well-controlled AD, AD flare, and/or active dermatitis involving the back and other potential sites of application for the patch tests, current or recent use of systemic immunosuppressive medications, recent exposure to ultraviolet therapy or excessive solar radiation, and use of a limited patch-testing series that do not incorporate the full spectrum of allergens previously shown to be relevant in AD [90].

A commonly encountered clinical situation is a patient with active, often severe, dermatitis on the back and other potential sites of application for the patch tests. This scenario should delay and may even prevent patch testing. Patch testing on actively inflamed skin may lead to both false positive and false negative reactions. The patient may also experience immense discomfort secondary to pruritus and pain from the adhesives used, increased heat and sweat, and exposure to potentially irritating reagents being tested. In addition, the term 'angry back syndrome' has been used to describe when patients develop positive reactions to most or all allergens tested.

Efforts should be made to first treat and resolve the active dermatitis on the back and other potential sites of application for the patch tests. Ideally, this should be done using topical therapy, e.g. corticosteroids and calcineurin inhibitors. If successful, the patient should discontinue application of topical therapy to the back for 1–2 weeks and then undergo patch testing. Systemic therapy or phototherapy may be required if the patient has an inadequate response to topical therapy or immediately experiences a flare of their dermatitis; however, such therapies may decrease the sensitivity of the patch-testing process.

There is insufficient experimental data to precisely define the extent to which each immunosuppressive medication decreases the sensitivity threshold of patch testing. An expert consensus opinion from the NACDG [95] suggested that the following medications were at high risk for leading to false negative patch-test results: prednisone >10 mg/day and intramuscular triamcinolone (avoid for 4 weeks), topical corticosteroids or calcineurin inhibitors at the patch-test application sites (avoid for 1 week), azathioprine, cyclosporine, mycophenolate mofetil, and systemic tacrolimus. Not enough data were available for the panel to make specific avoidance period recommendations for the non-corticosteroid immunosuppressants, other than to say that their effect on the results of patch testing are dose-dependent. Ultraviolet exposure to the testing site was recommended to be avoided for 1 week prior to testing [95]. The following medications were considered generally acceptable for patients to be taking during patch testing: methotrexate, prednisone <10 mg/day, tumor necrosis factor-α inhibitors, ustekinumab, and antihistamines. Another expert consensus opinion echoed these suggestions but noted the lack of information regarding the effects of immunosuppressive agents on patch-test reactions [96]. There is no consensus regarding the avoidance of newer agents being used in the treatment of AD, including crisaborole, Janus kinase inhibitors, or dupilumab.

In the authors' personal experience, many patients experience false negative reactions to patch testing up to 4 weeks (or longer) after intense ultraviolet radiation, e.g. sunny vacation, cyclosporine at a dose of >2.0 mg/kg/day or methotrexate at a dose of >0.20 mg/kg/week. If patch testing is performed in these scenarios, results should be interpreted with caution. Weak or irritant reactions should be considered as true positives. Negative patch tests should be considered as false negatives and repeat patch testing should be considered upon discontinuation and washout from such treatments.

5 Patch Testing in Patients with AD

5.1 Choosing the Right Patch-Testing Series

Once the decision has been made to perform patch testing, allergen selection is critical for a satisfactory outcome and should be made on an individual patient basis. Factors to be considered during allergen selection include the region or country, occupation, hobbies and recreations, and other exposures. One option is the Thin-Layer Rapid Use Epicutaneous (TRUE) test; however, it should be noted that this test lacks multiple allergens that are commonly relevant and present on expanded patch-testing series, e.g. American Contact Dermatitis Society (ACDS) or NACDG

Table 2 Pitfalls in patch testing in AD patients

Current or recent exposure to systemic immunosuppressive medications (Sect. 4.2), ultraviolet therapy or excessive solar radiation can decrease the sensitivity threshold of patch testing and lead to false negatives. Repeat patch testing should be considered upon treatment discontinuation and washout
Patients with AD have a lower irritancy threshold, which may lead to higher rates of irritant or false positive reactions (most commonly with metals, fragrance, formaldehyde, and lanolin)
Positive reactions in AD patients may display as weaker reactions and be misdiagnosed as an irritant reaction (i.e. negative reaction)
Active or flaring AD may result in false negative reactions due to decreased contact sensitization

AD atopic dermatitis

core series. Examples include cinnamic aldehyde, propylene glycol, dimethylol dimethyl hydantoin, iodopropynyl butylcarbamate, amidoamine, acrylates, tea tree oil, propolis, benzophenone-3, and sesquiterpene lactone mix.

While evidence-based guidelines are lacking as to which allergens should be included for patch testing in AD patients, several recommendations have been made by different authors. In summary, the majority of studies recommend expanded screening for the most commonly encountered allergens in AD patients (e.g. metals such as nickel, potassium dichromate, carba mix, formaldehyde, neomycin sulfate, balsam of Peru, fragrances, and preservatives), allergens that are common components of over-the-counter and prescription topical therapies, and allergens specific to a patient's environment (i.e. patient's personal care products or occupational exposures). For adults in North America, an expanded screening series, such as the ACDS or NACDG core series, appear to reasonable. Screening series may vary regionally based on the most prevalent allergens. More targeted patch testing can be considered in younger children [69, 90, 97–100], but standardized screening series are not well-established. Patch-test reads should be performed at 48 and 72 h, and preferably with a delayed read between 96 and 144 h.

All personal care products and topical medications should be inspected for possible allergens. An important limitation is the US FDA's Cosmetic Labeling Guide regulations. Although all ingredients, including those with $<1\%$ concentration, are supposed to be listed on product labels, there are numerous ways around this. 'Incidental ingredients' (ingredients present at an insignificant level and having no technical or functional effect) and/or a 'trade secret ingredient' (an ingredient that offers one's business potential to obtain an advantage over those not using or knowing about it) are exempt from ingredient declaration and the phrase 'and other ingredients' may be used in place [101]. Thus, there may be additional unknown exposures to lower concentrations of allergens. Leave-on products can be patch tested as they are formulated, but may be subject to false negative reactions. However, rinse-off products should be diluted given their high potential for irritancy [96].

5.2 Pitfalls and Determining the Relevance of Positive Patch-Test Reactions in Patients with AD

There are several potential pitfalls to be considered when patch-testing patients with AD (Table 2). As mentioned previously, patients with AD have a lower irritancy threshold, which may lead to higher rates of irritant or false positive reactions, with the most common occurring with metals, fragrance, formaldehyde, and lanolin [63, 98, 102]. Additionally, as mentioned, patch-test reactions should be interpreted with caution in patients receiving specific immunosuppressants. Weak or irritant reactions should be considered as true positives, while negative patch tests should be considered as possible false negatives.

On the other hand, irritant reactions may also be more difficult to distinguish from true positive reactions. That is, some relevant positive reactions in AD patients may display as weaker reactions that would be mistaken as irritant reactions, i.e. a negative patch test. One reason for this is that patients with AD are less likely to exhibit the 'crescendo' pattern of increasing reactivity between patch-test reads seen in true positive reactions [98]. Another reason is that positive reactions may be weaker in patients with AD, especially with increasing severity of disease, as they may be less effective at acquiring sensitization [56, 103]. Delayed reads of >96 h may be somewhat helpful to overcome this [104–106]. Some patients may benefit from an empiric trial of allergen avoidance despite only displaying an irritant or weak positive reaction. In addition, if patch testing was performed but only displayed no or irritant reactions in a patient with a compelling history and/or physical examination for ACD, then false negatives should be contemplated. In such patients, particularly those with uncontrolled dermatitis during patch testing, repeat patch testing should be considered at a later date and may successfully identify relevant positive reactions, despite false negative or weak reactions upon initial patch testing.

Finally, active AD may paradoxically result in false negative reactions on patch testing. The risk of false negatives was found to be higher with increasing severity of AD; this may be true even when the patches are applied to

apparently non-lesional skin and patients are not receiving systemic immunosuppressive medications [90, 96]. One experimental report demonstrated that well-controlled AD (< 10% body surface for at least 1 month) is associated with lower rates of false negative reactions [56]. Taken together, the results of patch testing in AD patients should be interpreted with caution.

6 Conclusions

The risk of ACD appears to be increased in patients with AD, although this association remains controversial. Regardless, ACD is an important comorbidity and potential exacerbant of AD in clinical practice. Mechanisms of ACD developing in AD patients include epidermal barrier dysfunction leading to increased allergen and irritant penetrance, repetitive exposure to allergens secondary to frequent use of topical medications and personal care products, and bacterial colonization in AD promoting inflammation and potentiating contact sensitization.

Patch testing should be considered in adolescent- or adult-onset AD, worsening or more generalized dermatitis, localized or atypical lesional distribution suggestive of CD, refractory AD, prior to systemic immunosuppressive treatment, or when AD worsens with topical therapy. Patch testing in AD should use an expanded patch-test series, although more research is needed to determine the optimal screening series in AD patients.

Compliance with Ethical Standards

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