

The Role of Contact Allergy in Atopic Dermatitis

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KEYWORDS

• Allergic contact dermatitis • Atopic dermatitis • Patch testing

BACKGROUND AND PATHOGENESIS

Atopic dermatitis (AD) causes a significant economic and quality-of-life burden among the 15.2 million Americans who have this disease, according to estimates from the Society of Investigative Dermatology and American Academy of Dermatology study. Almost five times that number (72.4 million) suffer from contact dermatitis (CD).¹ A previously held belief was that patients with AD were less likely to have allergic contact dermatitis (ACD) than the general population because of the presence of decreased lymphocyte-mediated hypersensitivity.

AD was traditionally considered mostly an IgE-mediated disease (extrinsic AD) in which T cells with the skin-homing receptor cutaneous lymphocyte-associated antigen (CLA) produce Th2 cytokines after encountering allergens in lymph nodes.^{2,3} These cytokines promote growth of eosinophils and switch to IgE immunoglobulin production with concomitant reduction in cell-mediated immunity.² However these CLA+ T cells also produce low levels of interferon (IFN)- γ (a Th1 cytokine) that inhibit Th2 function and chronic AD skin lesions have increased numbers of interleukin (IL)-5, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-12, and IFN- γ -expressing cells.⁴

Clinically, patients with AD display an increased rate of viral (herpes simplex, human papillomavirus, molluscum contagiosum) and chronic dermatophyte infections but less susceptibility to poison ivy and cutaneous anergy to allergens.⁵⁻⁷ However, the

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epidermal skin barrier dysfunction in patients with AD facilitates introduction of foreign antigens. Filaggrin functions to aggregate keratin filaments, leading to formation of the stratum corneum layer, and its defect has been linked to *Ichthyosis vulgaris* and AD.⁸ This impaired barrier function may represent a mechanism for sensitization to topical agents, allergens, and microbes in atopsics by facilitating the penetration of contact allergens and irritants into the epidermis.^{2,9} Two filaggrin mutations were screened in a European cross-sectional population that underwent patch testing (PT) with a standard panel of 25 allergens.⁹ Results suggest that the filaggrin loss of function mutations represent a risk factor for contact sensitization to nickel, especially in combination with a history of adverse reactions to jewelry.⁹ No association with sensitization to other common allergens was seen.

IL-31 is a cytokine produced mainly by activated CD4+ T cells through a heterodimeric receptor to activate Jak/STAT, PI3K/AKT, and MAPK pathways; in mice models, it produces a pruritic dermatitis closely resembling AD.¹⁰⁻¹² Recent studies using polymerase chain reaction (PCR) have shown IL-31 in skin biopsies of patients with AD,¹³ implying that this cytokine contributes to the development of inflammation and pruritus. Neis and colleagues¹² analyzed RNA from skin biopsy specimens from patients with AD, ACD, and psoriasis and from healthy controls. They found statistically significant increased levels of IL-31 mRNA in patients with AD; these levels were also increased in 24 of 56 patients with ACD but in none of those with psoriasis (n = 60).¹²

Similarities and differences are seen in CD and AD. Irritant contact dermatitis (ICD) results from contact with agents that abrade, irritate, or traumatize the skin, such as detergents, solvents, alcohol, lotions, and extreme wetness, dryness, or temperature. This perturbation of the skin barrier may lead to disorganization of the lipid bilayers in the epidermis¹⁴ and increase of cytokine production (IL-1 α and - β , tumor necrosis factor [TNF]- α , and GM-CSF) in the epidermis,¹⁵ which can lead to direct tissue damage and increase in transepidermal water loss. ICD is nonimmunologic and does not require prior sensitization. The inflammatory response is dose- and time-dependent.

ACD is recognized as the prototypic type IV cutaneous cell-mediated hypersensitivity reaction. The environmental allergens are haptens that bind to carrier proteins to form complete antigens before they can cause sensitization. The hapten in the epidermis activates keratinocytes to release inflammatory cytokines and chemokines (TNF- α , GM-CSF, IL-1 β , IL-10, and macrophage inflammatory protein [MIP]-2), which activate Langerhans cells, other dendritic cells, and endothelial cells. In the afferent limb, the Langerhans cells then process the antigen while migrating to regional lymph nodes, where they present it to naive T cells and cause the activation of CD4+ and CD8+ hapten-specific T cells.¹⁶

On subsequent exposure of the skin to the allergen, the sensitized T cells that home in to the hapten-provoked skin site release their inflammatory mediators that contribute to epidermal spongiosis (eczema). Spongiosis is the hallmark of the epidermis in eczema, whether caused by CD or AD. It is characterized by the widening of intercellular spaces, and intercellular edema that may progress to the formation of intraepidermal vesicles.

EPIDEMIOLOGY

Numerous studies in the early 1990s advocated the need for PT in patients with AD, reporting a frequency of 40% of ACD in patients with AD (**Table 1**). A prospective study performed in 137 atopic children in France showed a contact sensitization of

43% among children tested.¹⁷ The most common allergens were metals (nickel, 19.3%), fragrance and lanolin (4.4%), Balsam of Peru (2.6%), and neomycin and emollients (2.6%). The children were negative to corticosteroids as screened by budesonide and tixocortol pivalate and children older than 5 years had a greater risk of developing contact allergy.¹⁷

A recent study in Poland performed in atopic school children and teenagers with eczema similarly found that 49.4% of 229 children tested had a positive PT.¹⁸ These children (96 of whom were age 7 years and 133 were 16 years) underwent PT with a 10-allergen panel of the most frequent contact sensitizers in Europe. The most common positive results were to nickel sulfate (30.2%), thimerosal (10.4%), cobalt chloride (8.3%), and fragrance mix I (7.3%). Among the 16-year-olds, contact allergy to nickel was four times higher in girls with pierced ears than in those without. The diagnosis of ACD was confirmed to be relevant in 36.5% of the 7-year-olds and 26.3% of the 16-year-olds.¹⁸

In a smaller series of 30 children with AD in India with mild to moderate eczema, PT results for a standard panel of 31 antigens were positive in a smaller proportion of patients with AD.¹⁹ Seven patients (23%) had a positive PT reaction to a total of eight allergens, the most common being neomycin and gentamycin, and those who had positive reactions had a longer duration of AD.

A prospective study from Tunisia in children and adults (63 children, 26 adults) with AD according to Hanifin and Rajka²⁰ criteria evaluated PT using the European Standard series, and supplemented with special series and personal products when necessary. Results showed PT to be positive in 42.7% and clinically relevant in 38.2% of overall subjects; and to be positive in 50% of adults and 39.7% of children, with nickel being the most common allergen.²¹ Severity of AD was evaluated using the SCORAD (Scoring Atopic Dermatitis) index, which showed that positive PT reactions were more frequently seen in patients with severe AD (60.9%) than in those with moderate and mild AD (37.5% and 30%, respectively). These results correlated with the duration or course of AD. The authors speculated that numerous and prolonged topical treatments increase the risk of CD, in contrast to previous reports of reduced sensitization in patients with severe dermatitis.²² This study found that risk of a positive PT reaction was significantly ($P = .017$) correlated with duration of AD.²¹

Mailhol and colleagues²³ examined 641 pediatric patients with AD for positive response to PT using antiseptics, emollients, and corticosteroids. All patients were tested to bufexamac, chlorhexidine, hexamidine, sodium fusidate, budesonide, tixocortol pivalate, and personal emollient. Among the children, 40 (6.2%) had 45 positive PT reactions. The allergens were emollients (47.5%), chlorhexidine (42.5%), hexamidine (7.5%), tixocortol pivalate (2.5%), and bufexamac (2.5%). Similar to results reported by Giordano-Labadie and colleagues,¹⁷ 3% were positive to their current emollient. Assessment of age, sex, age of onset of AD, presence of asthma, SCORAD score, and skin prick testing in these patients showed that the following risk factors were associated with sensitization to topical treatment products in AD: (1) significantly younger age (2.8 years vs 4.8 years; $P < .001$), with onset of AD before 6 months of age (75% vs 53.1%, odds ratio [OR], 2.6); (2) more severe AD with higher SCORAD (29 vs 21; $P = .006$); and (3) IgE sensitization (OR, 2.5; 95% CI, 1.1–5.9). Neither sex nor history of asthma was associated with risk of sensitization to topical AD treatment. This study shows that although the prevalence of CD to treatments for AD is low, it is not negligible, and ACD in AD should be suspected, especially to antiseptics and emollients, when treatment fails to control the AD.

In a retrospective review of 110 children in the United Kingdom, certain subsets of patients with AD yielded higher positive PT results: patients with eyelid dermatitis

Table 1
Literature review

Author	Criteria for AD	Allergens Patch Tested	Results	Relevance
Giordano-Labadie et al ¹⁷	Hanifin and Rajka 70 M:67 F Mean age: 4.5 y 42.7% mild 47% moderate 10.3% severe	European standard Series, tixocortol pivalate, budesonide, and emollient	43%, positive PT (49/114 tests) Metals, 19.3% Fragrance, 4.4% Lanolin, 4.4% Neomycin, 2.6% Emollient, 2.6%	All positive, relevant; avoidance led to SS improvement
Czarnobilska et al ¹⁸	Patients screened for eczema based on questionnaire 96 children, aged 7 years 133 children aged 16 years	10 common contact allergens	49.4%, positive PT (Allergen, 7-year-old/ 16-year-old) Nickel, 30.2%/23.3% Thimerosal, 10.4%/27.8% Cobalt chloride, 8.3%/10.5%	36.5% of 7- year-olds; 26.3% of 16 year olds
Sharma et al ¹⁹	Hanifin and Rajka 22M:8F Age, 7–50 years AD: mild to moderate	Indian standard battery	23%, positive PT Neomycin, 3/7 Gentamycin, 2/7	Relevance of positive PT was not discussed
Belhadjali et al ²¹	Hanifin and Rajka 63 children (mean age, 69 months) 26 adults (mean age, 34 years)	European standard Series, special series, and personal products	42.7%, positive PT Nickel, 24.7% Chrome, 7.9% Cobalt chloride, 7.9% Parabens, 4.5% More PT positive in severe AD	38.2%

Mailhol et al ²³	UK Working Party 641 children Median age, 3.4 years 48%M:52%F 43%, moderate to severe AD	Chlorhexidine, hexamidine, budesonide, tixocortol pivalate, bufexamac, sodium fusidate, and emollient	6%, positive PT Emollients, 47.5% Chlorhexidine, 42.5% Hexamidine, 7.5% Tixocortol pivalate, 2.5%	Past relevance for most allergens
Beattie et al ²⁴	114 children 48M:66F Median age, 11.5 years Retrospective	66 to European series 48 to British Contact Dermatitis Group Series	54%, positive PT Nickel, 20% Rubber, 10% Fragrance, 7.2%	Current, past or possibly relevant in 54%
Mortz et al ²⁵	Hanifin and Rajka 1146 children 526M:620F	TRUE test panels 1 and 2	15.2% positive PT F>M positive results that were SS Nickel, 8.6% Fragrance mix, 1.8% F>M positive for nickel	Past or present in 47.7%
Ingordo et al ²⁶	280 consecutive adult patients with eczema Hanifin and Rajka AD group, 113M:2F Mean age, 21.3 y Non-AD, 78M:9F Mean age, 24.8 y	GIRDCA standard series	44.3% in AD group 51.7% in non-AD group Nickel was most positive antigen in both groups	Definite ACD in AD group, 29.6% Definite ACD in non-AD group, 35.6%

Abbreviations: AD, atopic dermatitis; F, female; GIRDCA, Gruppo Italiano Ricerca Dermatiti da Contatto e Ambientali; M, male; Neo, neomycin; PT, patch testing; SS, statistically significant; TRUE, thin layer rapid use epicutaneous test.

(86%), hand dermatitis (71%), and vulval dermatitis (100%).²⁴ However, patients who had been referred for worsening of their AD had the lowest rate of relevant positive reactions (22%), along with children with foot or facial dermatitis. Again, nickel was the most common allergen (22%), followed by rubber, fragrance, cobalt, and lanolin. None of the 47 children who underwent PT to corticosteroids had a positive response.

A cohort study conducted in adolescents in Denmark sought to determine prevalence of AD, asthma, allergic rhinitis, and hand and CD among 1501 eighth-grade students using questionnaire, interview, examination, and PT.²⁵ The lifetime prevalence of AD was 21.3%, 6.9% for allergic asthma, 15.7% for allergic rhinitis, and 9.2% for hand eczema. Significantly more girls had positive PT reactions to nickel,²⁵ but no other differences based on sex were noted for the 20 of 24 allergens that yielded positive PT results. In this study, 37% of patients with ACD had a history of AD.

In a group of mostly young men recruited to the Italian army, 280 consecutive adult patients with eczema underwent PT²⁶ with a standard series, with clinical relevance determined for all positive responses. These patients were divided into an atopic group and nonatopic group based on whether Hanifin and Rajka²⁰ criteria were fulfilled. PT showed no differences in sensitization, asserting at least the same incidence of ACD between atopic and nonatopic patients, with nickel, cobalt, and potassium dichromate as the most common allergens.²⁶

COMMON AREAS OF INVOLVEMENT IN CD AND AD

Eyelids

Among patients with AD, 25% may have chronic eyelid dermatitis. However, dermatitis of the eyelid is most often caused by ACD (55%–63.5%). ICD accounts for 15% of eyelid dermatitis, AD accounts for less than 10%, and approximately 4% is attributed to seborrheic dermatitis.²⁷ Data collected by the North American Contact Dermatitis Group (NACDG) showed that in 193 (72%) of 268 patients with only eyelid dermatitis, gold was the most common allergen with a positive patch test. Fragrances, preservatives, nickel, thiuram, cocamidopropyl betaine and amidoamine (shampoos), and tosylamide formaldehyde resins (nail polish) were other allergens to consider in the evaluation of eyelid dermatitis.²⁸ In patients with mixed facial and eyelid dermatitis, nickel, Kathon, and fragrance were the most frequently positive on PT (**Fig. 1**).^{29,30}

Lips

Lesions in the perioral region could be from lip licking, ACD, or AD. Among patients diagnosed by the NACDG with allergic cheilitis, 37% had at least 1 of the atopic triad.³¹ Perioral dermatitis presents as small erythematous papules, vesicles, or tiny pustules and is most common in young women, but also occurs in prepubertal children of either sex. The causes are unknown, although topical glucocorticoid use seems to be a precipitating or exacerbating factor in some patients. Other proposed causative factors include contact allergy (eg, fluorinated toothpastes), occlusive moisturizers, and inhaled or systemic glucocorticoids.

Hands

The prevalence of hand eczema is two- to tenfold higher in patients with AD than in those without, and 16% have nail dystrophy. The increasing prevalence of hand involvement with advancing age is probably from repeated wetting and occupational insults, along with coexisting irritant dermatitis. Certain morphologic features can help distinguish the different contributing factors to hand eczema. Involvement of the dorsal hand and finger combined with volar wrist suggest AD as contributing etiologic



Fig. 1. Contact dermatitis of the eyelid and face in a patient with atopic dermatitis.

factor.³² ICD commonly presents as a localized dermatitis without vesicles in webs of fingers; it extends onto the dorsal and ventral surfaces in an “apron” pattern, and includes the dorsum of the hands and palms, and the ball of the thumb. On the other hand, ACD often has vesicles, and favors the fingertips, nail folds, and dorsum of the hands, and, less commonly, involves the palms. ICD often precedes ACD; therefore, some pattern changes should prompt PT, such as increasing dermatitis from web spaces to fingertips or from palms to dorsal surfaces.³³

Flexural Areas of Neck

Flexural areas of the neck are a common site of AD and CD. Common causes of CD in this area are irritant reactions to permanent waves (“perms”), hair dyes, shampoos, and conditioners, perfumes, nail polish, or nickel from necklaces or zippers.

Dermatitis with Scattered Generalized Distribution

Dermatitis with a generalized distribution is a difficult diagnostic challenge because it lacks the characteristic distribution that suggests a diagnosis of ACD. Generalized dermatitis also occurs in AD. The frequency of positive and relevant PT is unknown. Zug and colleagues³⁴ reported that approximately 15% of patients with positive PT results had scattered generalized dermatitis only, and approximately half (49%) had a positive PT reaction deemed at least possibly relevant to their dermatitis. The prevalence of scattered generalized dermatitis was higher in patients with a history of AD. However, 8% to 10% of patients with scattered generalized dermatitis remain in the unclassified eczema category. The two most common allergens identified were nickel and balsam of Peru. Other relevant positive PT reactions in this patient population include those to preservatives (formaldehyde, quaternium 15, methyldibromoglutaronitrile/phenoxyethanol, diazolidinyl urea, 2-bromo-2-nitropropane-1, 3-diol imidazolidinyl urea, and dimethyl-dimethyl

hydantoin) and propylene glycol. Dyes such as Disperse Blue 106 in synthetic fibers in children's garments have also been implicated.³⁵

SPECIFIC CONTACT ALLERGENS IN PATIENTS WITH AD

Topical Antibiotics/Antiseptics

Antibiotic topical preparations and antiseptics are often used as adjuncts in the treatment of AD. Jappe and colleagues³⁶ compared the frequency of sensitization to antibiotics and antiseptics in patients with both active AD and a history of AD versus those without active or previous history of AD. The allergens included were neomycin sulfate, gentamycin sulfate, erythromycin, fusidic acid, polymyxin B, oxytetracycline, nitrofurazone, framycetin, bacitracin, chloramphenicol, benzalkonium chloride, benzyl alcohol, triclosan, chlorhexidine, benzoate, formaldehyde, benzoyl peroxide, chloracetamide, and sulfacetamide. Results controlled for both age and sex did not find a higher risk among patients with AD than among those without. The investigators concluded that patients with AD had no increased risk of developing contact sensitization. A large number of patients with or without AD are sensitized to neomycin; atopy, old age, stasis dermatitis, and leg ulcers are significant risk factors for ACD to neomycin.

Triclosan is a biocide with antibacterial and antifungal activity through its disruption of cellular membranes used in dental, medical, cosmetic, and household products.³⁷ It has also been used in the management of AD and CD. PT to triclosan- and triclosan-containing creams was performed in addition to a standard series in 275 patients, of whom 55 had AD and 122 had ACD.³⁷ None of the 55 patients with AD had a positive PT reaction to triclosan, and only 6 (2.1%) of all patients tested positive for triclosan- or triclosan-containing products, reiterating a low incidence of contact sensitization especially in the atopic population. In a double-blind, prospective, randomized, controlled study, allergy to alcohol-based hand rubs was tested in patients with and without AD using an occlusive PT.³⁸ Tolerance to all five rubs was good among both populations, with no significant differences noted.

Topical Corticosteroids

Topical corticosteroid contact allergy affects 0.5% to 5.8% of patients.³⁹ Risk factors contributing to the development of delayed hypersensitivity to corticosteroids include chronic inflammatory skin disease (chronic venous leg ulcers [CVLUs], stasis dermatitis, CD), a history of two or more positive PT results, and multiple medicament sensitivities. In one study, 71 children with AD who used corticosteroids for at least 6 months underwent PT using a panel containing tixocortol pivalate 0.1%, budesonide 0.01%, hydrocortisone-17-butyrate 1%, and their own preparations, with readings made at days 2, 4, and 7.⁴⁰ Only one child had a positive reaction to tixocortol pivalate, hydrocortisone-17-butyrate, and Locoidon cream. These data are reassuring in that all corticosteroid groups were screened for, readings were conducted a week out, and personal products were also included.

ACD to topical corticosteroids was also assessed in a group of 140 adult patients with CVLUs (n = 50), AD (n = 30), and CD (n = 30).³⁹ These patients underwent PT using the European standard series, antibiotics, and corticosteroids. Overall positive PT results were seen in 80% of patients with CVLU and CD and 30% of those with AD; 40% of patients with CVLU were positive to corticosteroids versus 3% of those with AD and 20% of those with CD. The positive rate noted among the patients with AD is similar to rates attributed to corticosteroid allergy overall.

PT for corticosteroid allergy should include the groups of simultaneously or cross-reacting corticosteroids,⁴¹ and the vehicle and preservatives in the preparations. Corticosteroids within a group show a sevenfold increase in frequency of positive PT reactions (**Box 1**). Cross-reactivity between groups A and D2 and groups B and D2 also has been reported.⁴² However, 90% of contact allergy to steroids will be detected by screening with tixocortol pivalate, budesonide, and the patient's commercial steroid.^{43,44} A late reading on day 7 is recommended when testing for corticosteroid allergy.⁴⁵

Compositae

Sesquiterpene lactone is an important allergen in the compositae (asteraceae) family of plants that is responsible for ACD.⁴⁶ These plants are valued as medicinal and are used in herbal medicaments and cosmetics.⁴⁶ Compositae sensitization was traditionally believed to be highly prevalent in adults as an occupational disease in florists, farmers, and gardeners,⁴⁷ and in cosmetic dermatitis. However, case reports in the literature have included children with AD.⁴⁸ In one study in which 641 consecutive children and adolescents underwent PT with standard series and compositae mixed in 5% petrolatum, 17 children had positive reactions to this allergen.⁴⁷ Of these patients, 12 had AD, and the compositae allergy was either of current or past relevance. Because of higher prevalence of positive PT reactions to compositae in children with AD compared to those without ($P = .03$), the authors recommended using compositae mix when screening patients with AD experiencing airborne dermatitis.⁴⁷ In summary, contact sensitization to compositae should be suspected in patients with a personal or family history of atopy, and dermatitis exacerbated in summer with plant exposure.⁴⁸

Dyes

New trends in permanent and temporary tattoos have emerged. Henna is used in multiple products, including hair dyes, shampoos, cosmetics, and temporary tattoos. It is obtained from the *Lawsonia alba* or inermis shrub cultivated in North Africa, India, and Sri Lanka,⁴⁹ with lawsone (a naphthoquinone) considered the major allergen. With the addition of dyeing agents such as indigo, p-phenylenediamine (PPD), and/or diaminotoluenes, henna can impart hair colors other than the orange red from its unadulterated version.⁴⁹ An 11-year-old boy with an underlying history of AD and allergic rhinitis developed itch and edema 7 days after applying a temporary black henna tattoo on his right arm. A 4+ reaction to PPD was noted when the patient underwent PT using the European standard series. Although the exact compounds in the preparation used for the tattoo were unknown, the authors postulated that PPD was the allergen of importance because it is often present in henna at high concentrations.⁴⁹ PT using a panel of nine common allergens in a group of hairdressers with and without AD resulted in positive PT reactions in 60% of those with eczematous AD, 53% with asthma or allergic rhinitis, and 58% without AD.⁵⁰

Nail Polish

Tosylamide/formaldehyde resin is a product added to nail polish to ensure good adhesion of polish to the nail bed.⁵¹ It has been found to be clinically relevant in positive PT reactions in patients with eyelid dermatitis.²⁴ A 4-year-old girl with a history of AD was evaluated for new-onset eyelid dermatitis and worsening of flexural AD.⁵¹ Her patch test showed a 1+ reaction to tosylamide/formaldehyde 10% in petroleum. Her history was consistent with the regular application of nail polish by a sibling. Once these products were discontinued the girl showed a significant improvement in symptoms.

Box 1**Structural groups of corticosteroids^a**

Class A (hydrocortisone and tixocortol pivalate: have C17 or C21 short-chain ester)

Hydrocortisone

Hydrocortisone acetate

Tixocortol

Prednisone

Prednisolone

Prednisolone acetate

Cloprednol

Cortisone

Cortisone acetate

Fludrocortisone

Methylprednisolone acetate

Class B (acetonides: have C16 C17 cis-ketal or -diol additions)

Triamcinolone acetonide

Budesonide

Desonide

Fluocinonide

Fluocinolone acetonide

Amcinonide

Halcinonide

Class C (nonesterified betamethasone: have 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

Betamethasone-valerate

Betamethasone-dipropionate

Aclometasone dipropionate

Fluocortolone caproate

Fluocortolone-pivalate

Mometasone furoate

Class D2 (labile esters without C16 methyl or B ring halogen substitution)

Hydrocortisone 17-butyrate

Hydrocortisone-17-valerate

Hydrocortisone-17-aceponate

Hydrocortisone-17-buteprate

Methylprednisolone aceponate

^a Cross-reactivity is based on two immune recognition sites: C 6/9 and C16/17 substitutions.

Latex

ACD to latex allergens is traditionally believed to be secondary to rubber chemicals (thiuram mix, mercapto mix) used in the manufacturing process.⁵² Children suspected of having rubber ACD underwent PT using standardized rubber chemicals (thiuram, carba, and mercapto mix) in addition to a limited pediatric panel and natural rubber latex (NRL) allergen.⁵² Of these children, 32 had positive reactions to both NRL preparation and personal rubber items but negative reactions to rubber chemicals. Of clinical significance, 30 of 32 patients had AD, with 2/3rds classified as mild to moderate AD and 1/3rd classified as severe AD according to SCORAD.⁵² These patients with AD were also found to have other sensitizing contact allergens, positive prick tests to foods non-cross-reactive with NRL proteins, and inhalant allergen sensitization. Of these 32 children, 27 who had positive results to NRL who were retested 1 year later were still positive to this antigen.⁵²

Makela and colleagues⁵³ evaluated ACD in patients with AD based on location of the dermatitis, dividing 801 patients with AD into 5 groups: hand dermatitis, facial dermatitis, hand and face dermatitis (HFD), dermatitis other than hands or face (OD), and patients without dermatitis (ND) but history of allergic rhinitis, allergic conjunctivitis, or asthma.⁵³ These patients underwent PT to 24 common contact allergens in the International Contact Dermatitis Research Group standard series. Nickel was the most common allergen in all groups, and fragrance mix and Balsam of Peru were especially common in the hand dermatitis group. After 16 years, these patients were sent a questionnaire inquiring about location and symptoms of dermatitis over the previous 2 weeks.⁵³ Responses showed that the number of patients in the hand dermatitis and OD groups decreased, those in the ND and HFD groups increased, and no change occurred in face dermatitis group.

PT for patients with AD is recommended for accurate identification of allergens that may be exacerbating the disease, particularly for topicals being used by the patient if they experience disease persistence or flaring despite appropriate therapy.⁵⁴ With positive PT results that are relevant, avoidance can be implemented and exacerbations may be curtailed.⁵⁴

SUMMARY

CD is at least as common in patients with AD as in the general population, if not more. Thus, patients with AD should be considered for PT. Although conflicting data exist, the severity of the AD may impact the results obtained through PT. Younger patients with AD may yield more positive results on PT. Hand eczema and compositae allergy are more common in patients with AD. Reassuringly, PT is positive for antiseptic topicals and corticosteroids in only a small subset of patients. When personal products are patch tested, emollients should be included in the series.

REFERENCES

1. Bickers DR, Lim HW, Margolis D, et al. The burden of skin diseases: 2004 a joint project of the American Academy of Dermatology and the Society for Investigative Dermatology. *J Am Acad Dermatol* 2006;55:490–500.
2. Wolf R, Orion E, Matz H, et al. Still elusive relationship between atopic dermatitis and allergic contact dermatitis. *Acta Dermatovenerol Croat* 2003;11(4):247–50.
3. Leung DY, Boguniewicz M, Howell MD, et al. New insights into atopic dermatitis. *J Clin Invest* 2004;113(5):651–7.

4. Boguniewicz M, Leung DY. 10. Atopic dermatitis. *J Allergy Clin Immunol* 2006; 117(Suppl 2 Mini-Primer):S475–80.
5. Forsbeck M, Hovmark A, Skog E. Patch testing, tuberculin testing and sensitization with dinitrochlorobenzene and nitrosodimethylanilini of patients with atopic dermatitis. *Acta Derm Venereol* 1976;56(2):135–8.
6. Jones HE, Lewis CW, McMarlin SL. Allergic contact sensitivity in atopic dermatitis. *Arch Dermatol* 1973;107(2):217–22.
7. Palacios J, Fuller EW, Blaylock WK. Immunological capabilities of patients with atopic dermatitis. *J Invest Dermatol* 1966;47(5):484–90.
8. Candi E, Schmidt R, Melino G. The cornified envelope: a model of cell death in the skin. *Nat Rev Mol Cell Biol* 2005;6(4):328–40.
9. Novak N, Baurecht H, Schafer T, et al. Loss-of-function mutations in the filaggrin gene and allergic contact sensitization to nickel. *J Invest Dermatol* 2008;128(6):1430–5.
10. Sonkoly E, Muller A, Lauerma AI, et al. IL-31: a new link between T cells and pruritus in atopic skin inflammation. *J Allergy Clin Immunol* 2006;117(2):411–7.
11. Zhang Q, Putheti P, Zhou Q, et al. Structures and biological functions of IL-31 and IL-31 receptors. *Cytokine Growth Factor Rev* 2008;19(5–6):347–56.
12. Neis MM, Peters B, Dreuw A, et al. Enhanced expression levels of IL-31 correlate with IL-4 and IL-13 in atopic and allergic contact dermatitis. *J Allergy Clin Immunol* 2006;118(4):930–7.
13. Bilsborough J, Leung DY, Maurer M, et al. IL-31 is associated with cutaneous lymphocyte antigen-positive skin homing T cells in patients with atopic dermatitis. *J Allergy Clin Immunol* 2006;117(2):418–25.
14. Fartasch M, Schnetz E, Diepgen TL. Characterization of detergent-induced barrier alterations – effect of barrier cream on irritation. *J Invest Dermatol Symp Proc* 1998;3(2):121–7.
15. Wood LC, Jackson SM, Elias PM, et al. Cutaneous barrier perturbation stimulates cytokine production in the epidermis of mice. *J Clin Invest* 1992;90(2):482–7.
16. Krasteva M, Kehren J, Horand F, et al. Dual role of dendritic cells in the induction and down-regulation of antigen-specific cutaneous inflammation. *J Immunol* 1998;160(3):1181–90.
17. Giordano-Labadie F, Rance F, Pellegrin F, et al. Frequency of contact allergy in children with atopic dermatitis: results of a prospective study of 137 cases. *Contact Dermatitis* 1999;40(4):192–5.
18. Czarnobilska E, Obtulowicz K, Dyga W, et al. Contact hypersensitivity and allergic contact dermatitis among school children and teenagers with eczema. *Contact Dermatitis* 2009;60(5):264–9.
19. Sharma AD. Allergic contact dermatitis in patients with atopic dermatitis: a clinical study. *Indian J Dermatol Venereol Leprol* 2005;71(2):96–8.
20. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol* 1980;92S:44–7.
21. Belhadjali H, Mohamed M, Youssef M, et al. Contact sensitization in atopic dermatitis: results of a prospective study of 89 cases in Tunisia. *Contact Dermatitis* 2008;58(3):188–9.
22. Uehara M, Sawai T. A longitudinal study of contact sensitivity in patients with atopic dermatitis. *Arch Dermatol* 1989;125(3):366–8.
23. Mailhol C, Lauwers-Cances V, Rance F, et al. Prevalence and risk factors for allergic contact dermatitis to topical treatment in atopic dermatitis: a study in 641 children. *Allergy* 2009;64(5):801–6.

24. Beattie PE, Green C, Lowe G, et al. Which children should we patch test? *Clin Exp Dermatol* 2007;32(1):6–11.
25. Mortz CG, Lauritsen JM, Bindslev-Jensen C, et al. Prevalence of atopic dermatitis, asthma, allergic rhinitis, and hand and contact dermatitis in adolescents. The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis. *Br J Dermatol* 2001;144(3):523–32.
26. Ingordo V, D'Andria G, D'Andria C, et al. Clinical relevance of contact sensitization in atopic dermatitis. *Contact Dermatitis* 2001;45(4):239–40.
27. Ayala F, Fabbrocini G, Bacchilega R, et al. Eyelid dermatitis: an evaluation of 447 patients. *Am J Contact Dermat* 2003;14(2):69–74.
28. Rietschel RL, Warshaw EM, Sasseville D, et al. Common contact allergens associated with eyelid dermatitis: data from the North American Contact Dermatitis Group 2003-2004 study period. *Dermatitis* 2007;18(2):78–81.
29. Guin JD. Eyelid dermatitis: experience in 203 cases. *J Am Acad Dermatol* 2002;47(5):755–65.
30. Valsecchi R, Imberti G, Martino D, et al. Eyelid dermatitis: an evaluation of 150 patients. *Contact Dermatitis* 1992;27(3):143–7.
31. Zug KA, Kornik R, Belsito DV, et al. Patch-testing North American lip dermatitis patients: data from the North American Contact Dermatitis Group, 2001 to 2004. *Dermatitis* 2008;19(4):202–8.
32. Simpson EL, Thompson MM, Hanifin JM. Prevalence and morphology of hand eczema in patients with atopic dermatitis. *Dermatitis* 2006;17(3):123–7.
33. Warshaw E, Lee G, Storrs FJ. Hand dermatitis: a review of clinical features, therapeutic options, and long-term outcomes. *Am J Contact Dermat* 2003;14(3):119–37.
34. Zug KA, Rietschel RL, Warshaw EM, et al. The value of patch testing patients with a scattered generalized distribution of dermatitis: retrospective cross-sectional analyses of North American Contact Dermatitis Group data, 2001 to 2004. *J Am Acad Dermatol* 2008;59(3):426–31.
35. Seidenari S, Giusti F, Pepe P, et al. Contact sensitization in 1094 children undergoing patch testing over a 7-year period. *Pediatr Dermatol* 2005;22(1):1–5.
36. Jappe U, Schnuch A, Uter W. Frequency of sensitization to antimicrobials in patients with atopic eczema compared with nonatopic individuals: analysis of multicentre surveillance data, 1995–1999. *Br J Dermatol* 2003;149(1):87–93.
37. Schena D, Papagrigoraki A, Girolomoni G. Sensitizing potential of triclosan and triclosan-based skin care products in patients with chronic eczema. *Dermatol Ther* 2008;21(Suppl 2):S35–8.
38. Kampf G, Wigger-Alberti W, Wilhelm KP. Do atopics tolerate alcohol-based hand rubs? A prospective, controlled, randomized double-blind clinical trial. *Acta Derm Venereol* 2006;86(2):140–3.
39. Zmudzinska M, Czarnecka-Operacz M, Silny W. Contact allergy to glucocorticosteroids in patients with chronic venous leg ulcers, atopic dermatitis and contact allergy. *Acta Dermatovenerol Croat* 2008;16(2):72–8.
40. Foti C, Bonifazi E, Casulli C, et al. Contact allergy to topical corticosteroids in children with atopic dermatitis. *Contact Dermatitis* 2005;52(3):162–3.
41. Lepoittevin JP, Drieghe J, Dooms-Goossens A. Studies in patients with corticosteroid contact allergy. Understanding cross-reactivity among different steroids. *Arch Dermatol* 1995;131(1):31–7.
42. Wilkinson SM. Corticosteroid cross-reactions: an alternative view. *Contact Dermatitis* 2000;42(2):59–63.
43. Bjarnason B, Flosadottir E, Fischer T. Assessment of budesonide patch tests. *Contact Dermatitis* 1999;41(4):211–7.

44. Boffa MJ, Wilkinson SM, Beck MH. Screening for corticosteroid contact hypersensitivity. *Contact Dermatitis* 1995;33(3):149–51.
45. McFadden J. Contact allergic reactions in patients with atopic eczema. *Acta Derm Venereol Suppl (Stockh)* 2005;(215):28–32.
46. Paulsen E. Contact sensitization from Compositae-containing herbal remedies and cosmetics. *Contact Dermatitis* 2002;47(4):189–98.
47. Belloni Fortina A, Romano I, Peserico A. Contact sensitization to Compositae mix in children. *J Am Acad Dermatol* 2005;53(5):877–80.
48. Paulsen E, Otkjaer A, Andersen KE. Sesquiterpene lactone dermatitis in the young: is atopy a risk factor? *Contact Dermatitis* 2008;59(1):1–6.
49. Corrente S, Moschese V, Chianca M, et al. Temporary henna tattoo is unsafe in atopic children. *Acta Paediatr* 2007;96(3):469–71.
50. Sutthipisal N, McFadden JP, Cronin E. Sensitization in atopic and non-atopic hairdressers with hand eczema. *Contact Dermatitis* 1993;29(4):206–9.
51. Jacob SE, Stechschulte SA. Tosylamide/formaldehyde resin allergy—a consideration in the atopic toddler. *Contact Dermatitis* 2008;58(5):312–3.
52. Guillet G, Guillet MH, Dagregorio G. Allergic contact dermatitis from natural rubber latex in atopic dermatitis and the risk of later Type I allergy. *Contact Dermatitis* 2005;53(1):46–51.
53. Makela L, Lammintausta K, Kalimo K. Contact sensitivity and atopic dermatitis: association with prognosis, a follow-up study in 801 atopic patients. *Contact Dermatitis* 2007;56(2):76–80.
54. Vender RB. The utility of patch testing children with atopic dermatitis. *Skin Therapy Lett* 2002;7(6):4–6.