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Patch test in Brazilian children with a clinical diagnosis of atopic dermatitis: a cross-sectional study using an extended patch test battery

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Abstract
Introduction: Atopic dermatitis (AD) is a chronic and relapsing inflammatory skin disease mainly affecting children. Similarly, Allergic contact dermatitis (ACD) is an inflammatory skin disease, but unlike AD it results from direct exposure to an external agent. Theoretically, the impaired skin barrier facilitates the penetration of potential allergens. Therefore, AD patients are at risk for an associated ACD, exacerbating their skin condition. Because eczema is similar, performing a patch test (PT) for the differential diagnosis is essential.
Methods: In this cross-sectional transversal study, we performed a PT with 30 sensitizers in 26 children with AD, selected according to established criteria for suspected ACD, and treated at an AD center of a pediatric university hospital in Rio de Janeiro. Clinical presentation, patient profile, main sensitizers, and frequency of ACD caused by therapeutic skincare products were evaluated.
Results: In all, 23 (88.5%) patients reacted to at least one allergen, 21 (80.7%) had a relevant positive patch test, and 15 (57.7%) were polysensitized. The main positive sensitizers were nickel (38.5%), blue disperse (30.8%), fragrance mix (30.8%), and neomycin (23.1%). Nineteen (73%) patients reacted to substances present in therapeutic or skincare products.
Conclusion: Our data underscore the importance of performing a PT in AD children whose eczema has atypical distribution. The expressive percentage of positive tests, especially of allergens in skincare products, indicates the constant need to review the proposed treatments. Therefore, we recommend a specific and expanded PT battery for pediatric AD patients, including a negative control, to increase sensitivity for diagnosing ACD.

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Introduction

Atopic Dermatitis (AD) is a chronic and relapsing inflammatory skin disease that mainly affects children. AD is present in localized and disseminated forms. It is characterized by pruritus, chronic or recurrent lesions, and variable distribution and morphology. The classic lesion is eczema—an acute, subacute, or chronic skin inflammation.[1] Allergic Contact Dermatitis (ACD) is another inflammatory skin condition triggered by a change in patient's immune system induced by a sensitizing substance called contact allergen.[2] Previously, ACD was rarely observed in children because it was not well understood. However, as ACD tests were conducted, sensitized children were observed more frequently.

Patients with AD may have an underlying ACD. It is difficult to distinguish between AD and ACD as both can coexist as eczematous dermatitis. Some authors debate whether patients with AD have an increased risk for ACD, compared to patients not presenting AD. In case of some patients, performing a patch test (PT) is important for differential diagnosis and optimization of therapeutic management.[3]

The study aimed to describe the frequency of positive PT results, identify the main sensitizers, correlate test positivity with clinical relevance, and report the frequency of ACD triggered by therapeutic skincare products.

Table 1 Clinical criteria for performing patch testing in patients with atopic dermatitis.

Inclusion criteria
1. Patients whose dermatitis has atypical distribution or is suggestive of contact dermatitis with a predominant presentation on the head and neck, hands or feet, eyelids, and cheilitis/perioral.
2. Patients with therapy-resistant hand eczema.
3. Onset of AD in adolescents with no previous history of eczema in childhood or improbable previous history.
4. Severe or diffused dermatitis before starting systemic immunosuppressive therapy.
Exclusion criteria
1. Controlled AD or no recent changes in the distribution of dermatitis or its severity.
2. Current or very recent use of high doses of systemic corticosteroids, UV light therapy, or excessive exposure to solar radiation in the last 2–3 weeks.
3. AD exacerbated at the patch test application site.
4. Patient using systemic immunosuppressive drugs.
5. Confirmed or suspected pregnancy.

Adapted from the 2016 consensus of the American Contact Dermatitis Society.[6]

Materials and Methods

A cross-sectional descriptive observational study was carried out between April 2021 and October 2021. Patients with AD, aged 3–17 years, and suspected of ACD were followed up in a specialized service of a pediatric university hospital.

Pediatric patients with a clinical diagnosis of AD were included according to the Hanifin and Rajka Criteria.[4] At the time of first consultation, a routine physical examination of patients was carried out to analyze areas of the skin suspected of having AD. Then, severity of AD was assessed by the "Severity Scoring of Atopic Dermatitis" (SCORAD) index and classified as mild (<25 points), moderate (25–50 points), or severe (>50 points).[5] The following numerical and nominal variables were collected: gender, race (self-declared), age of patients, age at the onset of AD, allergic comorbidities, PT indication criteria, and body parts affected with suspected AD.

The inclusion and exclusion criteria of patients with AD to test for PT were based on the requirements established by the American Society of Contact Dermatitis, 2016 (Table 1).[6,7]

Substances used for PT were selected according to the main sensitizers reported in the literature, found explicitly in patients with AD,[8] and compatible with the extracts in national manufacturers. The PT used in the research contained 30 substances (Table 2). The first 20 substances selected were reported in the Brazilian pediatric battery (PB), which was adapted by a Brazilian manufacturer (IPI ASAC BRASIL) from the PB recommended by the European Academy of Allergology and Clinical Immunology (EACCI).[2] Tixocortol pivalate (group A corticosteroids) was replaced by hydrocortisone (group A), and bufexamac (an anti-inflammatory agent) was withdrawn as it was not found in Brazil. Substances 21–27 were included because they were mentioned as part of the top allergens in a recently conducted American study from the Pediatric Contact Dermatitis Registry.[9] Substances 28 and 29 were included because a large retrospective Italian study reported both as the 10 most prevalent sensitizers.[10] The last substance—petrolatum/vaseline—was added as a negative control, as it was the primary vehicle for allergens tested in this study.

The PT was scheduled and performed in three stages. Camera, Alergo Chamber (Neoflex®, Brazil), with sensitizers was applied on patient's back, where the first reading occurred after 48 h and the second reading after 96 h. Application and readings were performed by the same allergist following EAACI recommendations. According to a Brazilian group of studies on contact dermatitis, the results followed the PT classification. The semi-quantitative results revealed levels of sensitization ranging from 1+ to 3+++.[11] Results with at least 1+ in the second reading were considered positive.

The information was added to a database using Excel 12.0 (Office 2013) and processed using the Statistical Package for Social Sciences (SPSS) version 20.0 for Windows. Descriptive, frequency, and dispersion statistical tools were used. Fisher's Exact Test was used to analyze correlations, with a significance level of 5%.

This study was approved by the Ethics Committee of the IPPMG/UFRJ (CAAE: 40612520.3.0000.5264). All patients signed a written informed consent form.

Results

In all, 34 patients consented to participate in the study. Of these, 8 patients were excluded: 2 with very severe

Table 2 Allergens used in the patch test applied in the present study.

	Name of the substance	Concentrationn (%) mg/mL	Vehicle	Patch test battery
1.	Hydrocortisone acetate	25	Petrolatum	Brazilian pediatric battery
2.	Lanolin alcohols	30	Petrolatum	
3.	Blue disperse	1	Petrolatum	
4.	Potassium bichromate	0.5	Petrolatum	
5.	Budesonide	0.1	Petrolatum	
6.	P-tertiary butylphenol	1	Petrolatum	
7.	Colophony	20	Petrolatum	
8.	Compositae mix	1.9	Petrolatum	
9.	Fragrance mix II	14	Petrolatum	
10.	Mercaptobenzothiazole	2	Petrolatum	
11.	Lyral	5	Petrolatum	
12.	Mercapto mix	1	Petrolatum	
13.	Methylchloroisothiazolinone/methylisothiazolinone	1	Water	
14.	Methyldibromo glutaronitrile	1	Petrolatum	
15.	Neomycin	20	Petrolatum	
16.	Paraphenylenediamine	0.5	Petrolatum	
17.	Perfume mix I	7	Petrolatum	
18.	Sesquiterpene lactone mix	0.1	Petrolatum	
19.	Nickel sulfate	5	Petrolatum	
20.	Thiuram mix	1	Petrolatum	
21.	*Myroxylonpereirae*	25	Petrolatum	Latin American battery
22.	Formaldehyde	1	Water	
23.	Cocamidopropyl betaine	1	Petrolatum	
24.	Propylene glycol	10	Petrolatum	Padron battery
25.	Bronopol	0.5	Petrolatum	Cosmetics battery
26.	Quaternium 15	1	Petrolatum	Latin American battery
27.	Cobalt chloride	1	Petrolatum	
28.	Thimerosal	0.1	Petrolatum	
29.	Carba mix	3	Petrolatum	
30.	Negative control (petrolatum)	-	Petrolatum	-

eczema, hindering the test application; 4 patients did not have time for test; 1 patient did not perform the second reading; and 1 patient tested positive for negative control (petrolatum).

Clinical profile of patients with AD

The demographic characteristics of 26 patients tested for ACD with a prevalence of positive PT were females (73%), self-declared as mulatto (57%), school-age group (57%), and with a SCORAD > 25 (61%). The statistical test did not show significant association between these variables (see Table S1 in Supplementary File). The mean age for all patients was 8.8 ± 3.5 years. Test positivity correlated with onset and duration of AD manifestations had no statistical significance. Regarding the presence of other allergic conditions, 15 (57.7%) patients reported having allergic rhinitis (AR), 10 (38.5%) had asthma, and 9 (34.6%) patients had food allergy, with no statistical significance concerning test positivity.

Regarding the reasons (Table 1) for indicating PT, the majority of patients (23; 88.5%) met the criterion associated with a higher frequency of positive tests (P = 0.027).[1]

PT positivity and clinical relevance

Of the 26 patients who underwent PT, 23 (88.5%) had a positive PT for at least one sensitizer, and three (11.5%) patients had a negative PT. Given the positive PT results, its clinical relevance was analyzed through a detailed survey of the components of the products contacted by patients. Twenty-one (80.8%) patients had a known exposure to one or more substances; there was no exposure in case of five (19.2%) patients or it was infeasible to determine the exposure. Statistical test showed a clinical correlation between the positive test and the recognized exposure to one or more tested substances (P = 0.004).

Polysensitization

Patients with more than two positive substances on PT were considered polysensitized. In all, 15 (57.7%) patients were sensitive to more than two substances, and eight (30.7%) patients demonstrated a mono- or double-sensitization. We assessed whether there was a difference between polysensitized and mono/double-sensitized groups concerning gender, AD severity, age group, and disease duration; however, no statistically significant correlation was determined.

Sensitizers

Seven main substances that tested positive in the study were nickel (9), blue disperse (8), fragrance mix II (7), neomycin (6), cobalt chloride (5), potassium bichromate (5), and thimerosal (5). Six of the first 20 substances that tested positive were not part of the PB, which typically included 20 substances only (Table 3).

Of the 30 PT substances, 20 were discovered in the products potentially used in the treatment of AD. They are found in topical antibiotics and antimicrobials, topical corticosteroids, vehicles and preservatives in ointments and creams, surfactants and emollients in topical preparations, fragrances and perfumes often found in moisturizers and soaps, chemicals from cosmetics, hygiene products, medicines, lubricants, and antimicrobial preservatives (Table 3). Of the 26 patients who underwent PT, 19 (73%) tested positive for one or more substances detected in skincare products. Four (15.4%) patients tested positive for non-therapeutic products, and three had a negative test.

Table 3 Result of the patch test, and the main characteristics of the substances in skincare of patients with atopic dermatitis.

Name of the allergen (descending order of positivity)	Total patients with a positive test (%)	Main feature in skincare and/or treatment*	Component of the Brazilian pediatric patch test battery
Nickel sulfate	9 (34.6%)		Yes
Blue disperse	8 (30.8%)		Yes
Fragrancemix II (lyral, citral, farnesol, citronellol, hexyl cinnamic aldehyde, and coumarin)	7 (26.9%)	Creams, lotions, and soaps	Yes
Neomycin	6 (23.1%)	Antibiotics	Yes
Cobalt chloride	5 (23.1%)		No
Potassium bichromate	5 (19.2%)		Yes
Thimerosal	5 (19.2%)	Antimicrobial preservative	No
Lanolin alcohols	4 (15.4%)	Emollient for creams, cosmetics, soaps, and shampoos; vehicle for ointments and and creams	Yes
Bronopol	4 (15.4%)	Antimicrobial preservative of medications and cosmetics (creams and hair products)	No
Formaldehyde	4 (15.4%)	Cosmetic preservative	No
Mercaptobenzothiazole	4 (15.4%)		Yes
Methyldibromo glutaronitrile	3 (11.5%)	Cosmetics preservative and hygiene articles	Yes
Myroxylonpereirae	3 (11.5%)	Bactericide, fungicide, and parasiticide, healing creams, fragrances	No
Carba mix	3 (11.5%)		No
Perfume mix I (eugenol, isoeugenol, geraniol, cinnamic aldehyde, cinnamic alcohol, alpha-amylcinnamic alcohol, hydroxycitronellal)	3 (11.5%)	Cosmetics, soaps, antiseptics, lotions, and deodorants	Yes
Lyral	2 (7.7%)	Creams, lotions, and soaps	Yes
Hydrocortisone acetate	2 (7.7%)	Corticosteroid	Yes
P-tertiary Butylphenol	2 (7.7%)		Yes
Cocamidopropyl betaine	2 (7.7%)	Surfactant for soaps and cosmetics	No
Colophony	2 (7.7%)	Resin in topical medications and cosmetics	Yes
Compositae mix	2 (7.7%)	Anti-inflammatory herbal medicine	Yes
Paraphenylenediamine	2 (7,7%)		Yes
Sesquiterpene lactone mix	2 (7.7%)	Phyto cosmetics, ointments, creams, and topical medications	Yes
Quaternium 15	2 (7.7%)	Preservative	No
Propylene glycol	1 (3.8%)	Antibacterial preservative, humectant used in cosmetics, and a vehicle in pharmaceutical products	No
Thiuram mix	1 (3.8%)	Fungicides, repellents, soaps, and shampoos	Yes
Methylchloroisothiazolinone/ methylisothiazolinone	1 (3.8%)	Antimicrobial preservative in creams	Yes
Mercapto mix	1 (3.8%)		Yes
Budesonide	0	Corticosteroid	Yes
Negative control (petrolatum)	0		No

*Based on the booklet of IPI ASAC Brasil.

We discovered a correlation between PT positivity and the substances detected in products used for therapeutic purposes (P = 0.013).

Discussion

In all, 23 (88.5%) patients reacted to at least one allergen, 21 (80.7%) patients had a relevant positive PT, and 15 (57.7%) were polysensitized. The main positive sensitizers were nickel (38.5%), blue disperse (30.8%), fragrance mix (30.8%), and neomycin (23.1%). Nineteen (73%) patients reacted to the substances discovered in therapeutic or skincare products.

Dysfunction in skin barrier in patients with AD suggested that this group had a similar or even higher susceptibility for developing ACD or irritative contact dermatitis (ICD), compared to the general population. The penetration of sensitizers and skin irritants was observed in patients with AD because of the chronic use of emollients, medications, and topical anti-inflammatories for treatment and skincare. Many so-called hypoallergenic cosmetic products, such as fragrances and preservatives, are potential allergens. In addition, ICD further impaired skin barrier and could increase susceptibility to ACD through innate immune system signaling.[6]

The literature, however, is debatable about the subject. On analyzing the primary studies of the past two to three decades, variation was observed concerning sensitization proportions in patients with AD. Variations could have been influenced by the following reasons: differences in PT batteries used; criteria for selection of patients with AD; test application and interpretation techniques; differences in study design leading to selection bias; regional and cultural differences that influenced different habits and consequently sensitization to diverse substances. Therefore, the prevalence of ACD in patients with AD ranges from 37% to 89% because of methodological differences between studies.[10,12-15]

Increased PT sensitivity was observed in studies targeting patients' complaints and patients with a careful diagnosis of AD and atypical eczema or suspected ACD. PT performed by qualified specialists to differentiate between ICD and ACD increased sensitivity and reduced false-positive results. Moreover, retrospective studies to differentiate AD and ACD altered the sensitivity rates of tests because of potential selection bias. Studies, such as the present study, demonstrated higher sensitization rates when selecting patients with AD referred for PT because of suspected ACD based on specific criteria, including expanded testing.

In the present study, PT was expanded for 30 different substances. Seven of the first 20 main sensitizers that tested positive in our study (Table 3) were not found in PB, indicating the need to expand PT battery in AD children.

A retrospective study conducted by Zug et al. of the North American Contact Dermatitis Group evaluated contact allergy in 883 children from 2005 to 2012 and found 5.1% PT positivity to petrolatum vehicle.[16] Other cases of contact allergy to petrolatum were cited in the literature as well.[17,18] However, many studies did not discuss the relevance or did not use a negative control in PT. Since petrolatum is found in several topical products and is a primary vehicle used in PT extracts, we emphasized its inclusion as a negative control because of its potential effects on ACD. We included vaseline/petrolatum as a negative control in our battery, and one of the patients had a positive PT, justifying its removal from the studied sample.

Results of PT indicated sensitization, as seen with other *in vivo* tests used in allergy clinics. Therefore, it was important to define the clinical relevance of the products or objects patients were exposed to. All positive results did not constitute contact allergies; careful analysis must be done to discard false positives. Sensitization can indicate potential contact with allergens throughout life and help target skin product choices for preventive therapeutic use.

There is no consensus on the definition of polysensitization, but it is suggested for three or more substances with positive allergic results.[19] In our research, 57% of the patients were polysensitized. A study done by Carlsen et al. concluded that 45% of polysensitized patients and 37% of mono- or double-sensitized patients had atopic eczema.[19,20] Potential risk factors for polysensitization were related to cumulative or simultaneous exposure to allergens, including potency and dose, occlusion, extent and/or duration of exposure, and inflamed or damaged skin.[19,20]

The most frequent sensitizer identified in our work was nickel, which was already reported in adults and children, regardless of whether AD is associated or not.[9,14,21-23] Contact with nickel earrings is probably the leading cause of early sensitization. Nickel ACD occurs when metallic items, corroded by human sweat, saliva, and other body fluids, release free nickel ions that act as haptens, inducing sensitization.[24] Nickel accounts for 6–40% of positive PT in international studies, and its sensitization is more prevalent in children than in adults in North America, compared to Europe, and more in girls, compared to boys.[25,26]

The second most frequent sensitizer was blue disperse, which was similarly prevalent in other recently conducted Brazilian[14] and Italian studies.[10] Sensitization occurs mainly through contact with colored clothes. An Italian study mentioned a rise in textile contact dermatitis caused by blue disperse, particularly in patients with AD.[27]

At third place in list of sensitizers was fragrance mix II, quite widespread in surveys.[22,28-30] From an early age, contact with this substance is frequent through hygiene and skincare products. A large European study demonstrated increased fragrance mix II sensitization and reported no gender difference among children with and without AD.[31]

The fourth sensitizer in our study was neomycin. Children with AD have frequent scratching and wounds because of secondary infections and eczema, and the early use of this topical aminoglycoside could be harmful. It is present with corticosteroids in various formulations and mixtures and is routinely purchased without a prescription. Therefore, it is one of the 10 most common allergens cited in national[14,32] and international studies.[16,25,33]

Following were the allergens in our list of sensitizers: cobalt chloride, potassium bichromate, and thimerosal. Cobalt is a metal associated with nickel, and sensitization happens for both metals, explaining high co-prevalence in our study. Furthermore, it is also present in hair dyes, deodorants, and leather products, explaining the

isolated sensitization to cobalt in 21–40% of our patients.[25] Potassium bichromate is used in textile dyes, shoes, furniture, leather tanning, and detergents. One of the five patients who tested positive for Potassium bichromate had atypical eczema on the feet, as also observed in children with AD by Isaksson et al.[34] However, conflicting evidence was discovered in the literature about the relevance of this substance in children with AD. While Jacob et al. in a study conducted in the United States discovered low prevalence in children with AD, Fortina et al. in Italy observed high prevalence in their patients, probably reflecting regional variation.[10,35] Thimerosal is an antimicrobial preservative in skincare products and multidose vaccine vials.

Our findings showed a high prevalence of sensitizers in skincare products, indicating that these products caused dermatitis, which was either hard to control or resistant to treatment. The clinical correlation of skin products used by patients with AD and the risk of sensitization with ACD progression are cited by other studies, supporting the hypothesis that prolonged use of these products increases the risk of contact sensitization to their ingredients and vehicles.[8,35,36] A study conducted by Hamann et al. demonstrated that most skincare products for children, said to be "hypoallergenic," had at least one contact sensitizer in their formula.[37]

Lanolin alcohol, methyldibromo glutaronitrile, and thimerosal were positive in 11.5–19.2% of our patients and are potentially found in many products used by children with AD on their skin. Lanolin alcohol is an emollient and conditioning agent that facilitates the dispersion of creams and other topical products. Methyldibromo glutaronitrile, thimerosal, formaldehyde, and bronopol are preservatives often found in skincare products. In addition, formaldehyde, a resin used in fabric coloring, is associated with contact allergy due to blue disperse. Formaldehyde is mentioned as a sensitizer in textile contact dermatitis,[38] and, together with the above-mentioned allergens, significantly causes ACD in patients with AD.[39]

Our study's limitations include the absence of a control group and a small sample size. Multicenter studies, including control groups and larger samples, should be conducted to develop a specific PT battery for pediatric patients with AD.

Conclusion

Our data highlighted the importance of carrying out PT in children with AD. A high sensitization rate in this group of children showed that ACD is a prevalent disease in AD, especially dermatitis with atypical distribution or challenging to control.

Nickel, fragrances, blue disperse, and neomycin were the most critical allergens in our sample. A significant proportion of sensitizers used in skincare products are relevant clinically, indicating a constant need to review the proposed topical treatments.

Positive reactions to substances absent in PB indicate an urgent need for expanding PT in children with AD and inclusion of more relevant sensitizers to the PB list. In addition, PTs must include a negative control (petrolatum).

Conflict of interest

The authors declare no potential conflicts of interest regarding this article's research, authorship, and/or publication.

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Author Contributions

Janete Raad Rigolon: conception and design of the study; collection, analysis and interpretation of data; statistical analysis; article writing and critical review of important intellectual content; obtaining, analyzing and interpreting data; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; final approval of the final version of the manuscript. Ekaterini Simões Goudouris: conception and design of the study; collection, analysis and interpretation of data; statistical analysis; critical review of important intellectual content; obtaining, analyzing and interpreting data; effective participation in research guidance; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; final approval of the final version of the manuscript. Simone Saintive Barbosa: conception and design of the study; data collection, or analysis and interpretation of data; article writing and critical review of important intellectual content; obtaining, analyzing and interpreting data; effective participation in research guidance; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; final approval of the final version of the manuscript.

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Supplementary

Table S1 Patch test positivity and its correlation with clinical characteristics, indication criteria, and clinical and therapeutic relevance.

Variables	Category (n)	Negative tests (n = 3)	Positive tests (n = 23)	Fisher's exact test (P value)	Presence of correlation
Gender	Males (5) (19%)	1 (4%)	4 (15%)	0.488	No
	Females (21) (80%)	2 (7%)	19 (73%)		
Age group	Preschool (2–4 years) (2)	0	2	0.415	No
	Scholar (5–11 years) (16)	1	15		
	Adolescents (12–18 years) (8)	2	6		
Self-declared race	White (9)	2	7	0.254	No
	Mulatto (16)	1	15		
	Afro-American (1)	0	1		
Type of allergic comorbidity	Asthma (10)	2	8	0.323	No
	Allergic rhinitis (15)	3	12	0.175	No
	Food allergy (9)	1	8	0.732	No
	Drug allergy (2)	0	2	0.778	No
	Urticaria (2)	0	2	0.778	No
	Insect allergy (3)	0	3	0.681	No
Presence of any allergic comorbidity	Yes (20)	3	17	0.438	No
	No (6)	0	6		
SCORAD	Mild (7)	0	7	0.373	No
	Moderate or severe (19)	3	16		
The onset of atopic dermatitis (AD) symptoms (age)	<1 year (12)	3	9	0.2	No
	1–5 years (13)	0	13		
	>5 years (1)	0	1		
Length of illness (concerning AD)	0–2 years (3)	0	3	0.365	No
	2 years and 1 month–5 years (7)	0	7		
	5years and 1 month–10 years (13)	2	11		
	>10 years (3)	1	2		
Patch test indication criteria	1. Patients whose dermatitis has atypical distribution or is suggestive of contact dermatitis with a predominant presentation on the head and neck, hands or feet, eyelids, and cheilitis/perioral	1	22	0.027*	Yes (item 1)
	2. Patients with therapy-resistant hand eczema	1	0		
	3. Onset of AD in adolescents with no previous history of eczema in childhood or improbable previous history	0	0		
	4. Severe or diffused dermatitis before starting systemic immunosuppressive therapy	1	1		
Did the patient have recognized exposure to one or more tested substances? (Clinical relevance)	Yes (21)	0	21	0.004*	Yes
	No/Not determined (5)	3	2		
Any substance contained in skincare products or used for therapeutic purposes (ointments, moisturizers, and medications of therapeutic relevance)	Yes (19)	0	19	0.013*	Yes
	No (7)	3	4		

SCORAD index: Severity scoring of atopic dermatitis.
*Clinical relevance ($p < 0,05$)