

Patch Testing in Children From 2005 to 2012: Results From the North American Contact Dermatitis Group

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Background: Allergic contact dermatitis is common in children. Epicutaneous patch testing is an important tool for identifying responsible allergens.

Objective: The objective of this study was to provide the patch test results from children (aged ≤ 18 years) examined by the North American Contact Dermatitis Group from 2005 to 2012.

Methods: This is a retrospective analysis of children patch-tested with the North American Contact Dermatitis Group 65- or 70-allergen series. Frequencies and counts were compared with previously published data (2001–2004) using χ^2 statistics.

Conclusions: A total of 883 children were tested during the study period. A percentage of 62.3% had ≥ 1 positive patch test and 56.7% had ≥ 1 relevant positive patch test. Frequencies of positive patch test and relevant positive patch test reaction were highest with nickel sulfate (28.1/25.6), cobalt chloride (12.3/9.1), neomycin sulfate (7.1/6.6), balsam of Peru (5.7/5.5), and lanolin alcohol 50% petrolatum vehicle (5.5/5.1). The ≥ 1 positive patch test and ≥ 1 relevant positive patch test in the children did not differ significantly from adults (≥ 19 years) or from previously tested children (2001–2004). The percentage of clinically relevant positive patch tests for 27 allergens differed significantly between the children and adults. A total of 23.6% of children had a relevant positive reaction to at least 1 supplemental allergen. Differences in positive patch test and relevant positive patch test frequencies between children and adults as well as test periods confirm the importance of reporting periodic updates of patch testing in children to enhance clinicians' vigilance to clinically important allergens.

Epicutaneous patch testing is an excellent tool for diagnosing allergic contact dermatitis (ACD) and identifying relevant allergens.¹ Patterns of positive reactions with patch testing vary

with time, geographic location, and age (Table 1).^{7,11} Through analysis and understanding of trends over time and changes in the frequency of positive patch tests, the clinician can be better prepared to test more potentially relevant allergens and counsel patients, including children and their parents, regarding allergen avoidance.

This study provides an updated list and analysis of the frequency of positive reactions in patch-tested children from 2005 to 2012 by the North American Contact Dermatitis Group (NACDG). Comparisons were made with other studies within and outside of North America and with a previous NACDG study on children patch-tested from 2001 to 2004.² We also calculated the hypothetical sensitivity of the 3 panels of the Thin-Layer Rapid Use Epicutaneous (T.R.U.E.) TEST (SmartPractice, Phoenix, Ariz).

METHODS

Patients and Patch Test Procedures

Deidentified patch test results from patients aged 18 years or younger who were referred on suspicion of having ACD and

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TABLE 1. Summary of the Current Study and Other Select Studies on Patch Testing in Children

Source; Location	Study Period, y	No. Children in Study	Age range, y	≥1PPT%/≥1RPPT%	Common Allergens* (%PPT/%RPPT)
Current study; 13 centers distributed across North America	2005–2012	883	0–18	62.3/57.7	Nickel sulfate (28.1/25.6) Cobalt chloride (12.3/9.1) Neomycin sulfate (7.1/6.6) Balsam of Peru (5.7/5.5) Lanolin alcohol 50% pet (5.5/5.1) Fragrance mix (5.2/4.9) Bacitracin (5.2/4.6) Carmine (3.8/2.1) <i>p</i> -Phenylenediamine (3.3/2.9) Quaternium-15 (3.2/2.9) Nickel sulfate (28.3/26.0) Cobalt chloride (17.8/12.4) Thimerosal (15.4/2.1) Neomycin sulfate (8.0/4.4) Gold sodium thiosulfate (7.8/3.6) Fragrance mix (5.1/4.1) Balsam of Peru (3.9/2.3) Quaternium 15 (3.6/3.6) Lanolin alcohol 30% pet (3.6/2.8) Potassium dichromate (3.6/2.1)
Previous study; Zug et al ² ; 13 centers distributed across North America	2001–2004	391	0–18	62.3/56.7	Nickel sulfate (31/NR) Wool alcohols (18/NR) PTBPF (15/NR) Balsam of Peru (12/NR) Cobalt (11/NR) Formaldehyde (10/NR) Fragrance mix 1 (10/NR) Colophonium (9/NR) Potassium dichromate (8/NR) Neomycin sulfate (8/NR) Tixocortol pivalate (7/NR) Nickel (22.2/19.3) Cobalt (16.9/14.7) Gold (11.8/10.1) Thimerosal (16.9/11.9) Benzalkonium chloride (7.1/7.1) Fragrance mix (6.3/6.3) Neomycin (6.3/6.3) Potassium dichromate (6.2/5.5) Nickel sulfate (26.8/15.3) Potassium dichromate (9.0/2.5) Cocamidopropyl betaine (7.2/5.6) Cobalt chloride (6.2/3.4) Neomycin sulfate (5.0/1.5) MCI/MI (4.4/1.9) Disperse blue 124 (3.1/1.2) Disperse red 1 (2.8/1.2) Disperse yellow 3 (1.9/0.3) Balsam of Peru (1.2/0.3)
Herro et al ³ ; California	2008–2009	101	6–18	78/NR	
Hammonds et al ⁴ ; Jacksonville FL, Phoenix AZ and Rochester MN	2000–2006	136	3–18	61/54	
Belloni Fortina et al ⁵ ; Italy	2002–2008	321	≤3	62.3/NR	

(Continued on next page)

TABLE 1. (Continued)

Source; Location	Study Period, y	No. Children in Study	Age range, y	≥1PPT%/≥1RPPT%	Common Allergens* (%PPT/%RPPT)
Schena et al ⁶ ; Italy	2004–2011	349	≤15	69.3/49.0	Nickel sulfate (17/NR) Potassium dichromate (8/NR) Cobalt chloride (7/NR) Kathon CG (4/NR) Neomycin sulfate (4/NR) Thimerosal (2/NR) MBT mix (2/NR)
Milingou et al ⁷ ; Greece	1994–2007	255	≤15	60/NR	Nickel sulfate (21.6/NR) Thimerosal (18/NR) Cobalt chloride (12.9/NR) Potassium dichromate (9.4/NR) Fragrance mix (4.7/NR)
de Waard-van der Spek and Oranje ⁸ ; Switzerland	2003–2008	79	1–18	51/NR	Nickel sulfate (21.5/10.1) Potassium dichromate (6.3/6.3) PTBPFR (3.8/3.8) Formaldehyde (3.8/3.8) Thimerosal (3.8/0)
Toledo et al ⁹ ; Spain	2005–2009	111	0–15	46.8†/NR	Nickel sulfate (14.4/11.7) MCI/MI (11.7/10.8) Fragrance mix I (9.9/9.9) Balsam of Peru (5.4/5.4) Cobalt chloride (5.4/2.7) Thimerosal (3.6/0)
Sarma and Ghosh ¹⁰ ; India	2005–2008	70	5–15	80/49	Potassium dichromate (2.7/2.7) Parabens (42.9/15.7) Potassium dichromate (27.1/15.7) Fragrance mix (25.7/11.4) Cobalt chloride (22.9/4.3) <i>p</i> -Phenylenediamine (15.7/8.6) Neomycin sulfate (12.9/1.4) Nickel sulfate (10.0/4.3) Colophony (10.0/7.1) Gentamicin sulfate (10.0/1.4)

*Excludes supplemental allergens.

†PPT rate for children with hand eczema.

DMAPA, dimethylaminopropylamine; MCI/MI, methylchloroisothiazolinone/methylisothiazolinone; MDBGN, methylidibromo glutaronitrile; n, total number of patch tests performed; NR, not reported; PTBPFR, *p*-tert-butylphenol formaldehyde resin.

underwent patch testing between January 1, 2005 and December 31, 2012, by members of the NACDG were retrieved from a central database. This study qualified for an exempt from review from the Committee for the Protection of Human Subjects at Dartmouth-Hitchcock (CPHS no. 24202). During this test period, the NACDG underwent four 2-year cycles of patch testing (2005–2006, 2007–2008, 2009–2010, and 2011–2012) and 4 slightly modified allergen screening series were used for testing. A total of 87 different allergens, of varying chemical composition, delivery vehicles, or concentrations, were tested from 2005 to 2012. The patch testing was performed using a standard series of 65 (2005–2008; Chemotechnique Diagnostics AB, Malmö, Sweden) or 70 (2009–2012;

allergEAZE by SmartPractice, Calgary, Alberta, Canada) allergens individually housed in Finn Chambers (SmartPractice, Phoenix, AZ) and applied to the patients' upper back in the standard fashion. At the clinician's discretion and depending on the clinical situation, a patient may have been patch-tested with additional supplemental allergens. Details on the number of supplemental allergens tested, if any, are not part of the data set. One or more allergens may have been omitted from testing in an individual patient if the patient had a known history of strongly reacting to that allergen. The patch tests were removed and then evaluated at 48 hours, and second, delayed final reading and interpretation were performed between days 3 and 7 after placement.

Patch Test Interpretation

Patch testing results were interpreted according to previously described methods.¹² Briefly, reactivity to an allergen was recorded as a negative reaction, an irritant patch test reaction, or a positive patch test reaction (PPT). Clinical relevance was considered for each positive reaction to an allergen. Current relevance was defined as definite (a positive patch test and/or provocative use test of an article belonging to the patient known to contain the allergen, such as clothing or skin care product), probable (the allergen was present in a known contactant of the patient), and possible (the patient was exposed to circumstances in which skin contact with materials known to contain the putative allergen was likely to have occurred). Past relevance was defined as having a skin reaction at the point of contact to the allergen in the past but unrelated to the current dermatitis. Relevance could also be coded as unknown. In this study, as in the previous 2001–2004 study,² a positive patch test that was of current (definite, probable, or possible) or past relevance was designated as a relevant PPT (RPPT). The percentage of patients with 1 or more PPTs ($\geq 1\text{PPT}\%$) was calculated as the sum of all patients in a particular group with at least 1 PPT divided by the total number of patients in that group. Similarly, the percentage of patients with 1 or more relevant positive patch tests ($\geq 1\text{RPPT}\%$) was calculated as the sum of all patients in a particular group with 1 or more RPPT divided by the total number of patients in that group. The percentage of positive reactions for each allergen (PPT%) was calculated as the sum of patients that had a positive reaction with that allergen divided by the sum of patients who were patch-tested with that allergen. The percentage of clinically relevant positive patch tests (RPPT%) for each allergen was calculated using a similar approach. To evaluate the performance of the screening series, supplemental allergens were excluded in the calculations of $\geq 1\text{PPT}\%$, $\geq 1\text{RPPT}\%$, PPT%, and RPPT%. We also stratified children into 2 age groups: younger children aged 0 to 5 years and older children aged 6 to 18 years.

To explore the relationship between atopic dermatitis and epicutaneous patch test results, clinicians recorded whether a patient had a history of atopic eczema (hereafter referred to as eczema), allergic rhinitis, and/or asthma. A history of eczema was defined as having a childhood history of flexural eczema or other classic clinical features of atopic dermatitis. The presence of an atopic marker was made on the basis of the individual clinician's judgment.

After patch testing was completed, up to 3 final diagnoses were recorded on the basis of the clinician's assessment. This assessment took into account the patient's history, skin examinations, and patch test results.

T.R.U.E. TEST Comparisons

As of September 2013, the T.R.U.E. TEST panels 1.2, 2.2, and 3.2 were commercially available in the United States and contained 35 allergens or allergen mixtures and 1 negative control.¹³ To study the hypothetical sensitivity of the T.R.U.E. TEST, we used

a previously described method by Saripalli et al¹⁴: a NACDG allergen was deemed present on the T.R.U.E. TEST panel if it was listed as an individual allergen or as part of a mixture, regardless of the delivery vehicle or concentration. To calculate hypothetical PPT%, we included all positive reactions to allergens that are also present on the T.R.U.E. TEST and reported percentages of patients who would have had all their positive reactions detected using only the T.R.U.E. TEST panels 1.2, 2.2, and 3.2. A similar approach was used to calculate the hypothetical RPPT yields, using both current and past relevant positive reactions.

Comparisons With the Previous Study

Data of patch-tested children ($n = 388$) from the previous study period, 2001 to 2004,² were used for comparison. On the whole, the patch testing and data analysis methodologies did not differ between the current and past studies. One exception is that the previous study period considered only currently relevant positive reactions when calculating hypothetical RPPT yields with the T.R.U.E. TEST.

Analytical Methods

Patch test results were collected in a centralized database and entered in Microsoft Access (Microsoft Corp, Redmond, WA), and statistical analyses were performed with IBM Statistical Package for the Social Sciences Statistics 21 (IBM Corp, Armonk, NY). Statistical significance was determined using the Student *t* test (with the Levene test for equality of variances), χ^2 test, and Fisher exact test (for 2×2 contingency tables with cell[s] having an expected value ≤ 5). The tests were 2-tailed, and *P* values less than 0.05 were considered significant.

RESULTS

Patient Demographics

A total of 18,128 patients underwent epicutaneous patch testing by members of the NACDG from 2005 to 2012 and satisfied our inclusion criteria. Of these, 883 (4.9%) tested patients were children aged 18 years or younger; demographics, such as age, sex, and race, are detailed in Table 2. The anatomic distributions of the dermatitis in the patch-tested children and adults are given in Table 3; "scattered generalized" was the most common distribution in the children (32.5%), whereas the hands were the most affected in the adults (26.7%).

Patch Test Results and Clinical Relevance

A mean (SD) of 67.1 (4.3) allergens was tested per child, with a mode of 70 (range, 17–70), excluding supplemental allergens. In the children, $\geq 1\text{PPT}\%$ was 62.3% (550/883) and $\geq 1\text{RPPT}\%$ was 56.7% (501/883). Young children had $\geq 1\text{PPT}\%$ of 73.2% (30/41) and $\geq 1\text{RPPT}\%$ of 63.4% (26/41). Allergens that yielded the most positive reactions (PPT%) and relevant positive reactions

TABLE 2. Demographics of the Study Population

Characteristic	Value
Age groups, y	n (% of total); mean age, y (SD, median)
0–5	41 (4.6%); 3.9 (1.3, 4)
6–18	842 (95.4%); 13.8 (3.2, 14)
0–18	883 (100%); 13.3 (3.8, 14)
Sex	n (% of total); mean age, y (SD, median)
Male	326 (36.9%); 12.6 (3.8, 13)
Female	557 (63.1%); 13.8 (3.7, 15)
Race	n (% of total)
White	725 (82.1)
Black	60 (6.8)
Asiatic	50 (5.7)
Hispanic	16 (1.8)
Others	32 (3.6)

(RPPT%) in the children are listed in Table 4. Also shown in this table are 7 allergens that did not yield a single RPPT in the children. The most common sources for the top 10 allergens by RPPT% are listed in Table 5.

Effects of Age, Race, and Sex on Patch Testing

The mean (SD) age of the children with ≥ 1 RPPT (13.4 [3.9] years) did not differ significantly from those without (13.3 [3.7] years; $P = 0.98$).

No significant association between race and ≥ 1 RPPT% was observed ($P = 0.38$), although the numbers of nonwhite children are small.

The ≥ 1 PPT% in female children was 64.5% (359/557) and was not significantly different from 58.6% (191/326) in male children ($P = 0.08$). The ≥ 1 RPPT% for the female children, however, was significantly greater than that for the male children (60.0% [334/557] vs 51.2% [167/326]; $P = 0.01$).

Comparison With Adults

In the adults, the ≥ 1 PPT% was 64.0% (11029/17245) and ≥ 1 RPPT% was 57.8% (9976/17245); these frequencies were not statistically significantly different from the children (overall $P \geq 0.31$) or from younger children (overall $P \geq 0.22$). The RPPT% for 27 allergens was significantly different between the children and adults ($P < 0.05$), as illustrated in Table 4. Of these, 8 allergens had $P < 0.001$: the children were more likely than adults to have a relevant positive patch test to nickel sulfate, cobalt chloride, and *Compositae* mix as well as less likely to formaldehyde, balsam of Peru, fragrance mix 8% petrolatum vehicle (pet), methylidibromoglutaronitrile/phenoxyethanol, and quaternium-15.

Comparison With Previous Study

The children tested from 2001 to 2004 had ≥ 1 PPT% of 63.9% (248/388) and ≥ 1 RPPT% of 51.3% (199/388), both of which were not significantly different from the current study (overall $P \geq 0.07$). Similarly, young children tested from 2001 to 2004 had ≥ 1 PPT% of 66.7% (10/15) and ≥ 1 RPPT% of 40.0% (6/15), which were not significantly different from the current study (overall $P \geq 0.12$).

Compared with the 2001–2004 study, the children of the current study saw significant RPPT% decrease with colophony (1.2% vs 2.8%; $P = 0.045$) and diazolidinyl urea 1% aqueous vehicle (aq) (0.2% vs 2.1%; $P = 0.015$) as well as increase with balsam of Peru (5.5% vs 2.1%; $P = 0.007$) and *Compositae* mix (2.3% vs 0.5%, $P = 0.03$).

Atopy

Compared with the adults, the children were more likely to have allergic rhinitis, atopic eczema, asthma, or any of these atopic markers ($P < 0.001$) (Table 6). Compared with the 2001–2004 study, the children in the current study had an increase in frequency of all atopic markers; all except asthma ($P = 0.26$) were statistically significant. The ≥ 1 RPPT% in the children without any atopic marker was not significantly different from those with only allergic rhinitis, atopic eczema, or asthma (ie, having 1 but not the other 2 atopic markers) (Table 7). This was also true between those with any atopic marker and those without. In the children with only eczema, the RPPT% for fragrance mix 8% pet was 1.1%, compared with 4.7% ($P = 0.03$) in those without an atopic marker. In contrast, the RPPT% for amidoamine in the children with only eczema was 1.7%, compared with 0.0% ($P = 0.047$) in the children without an atopic marker.

Final Diagnosis

The percentage of the children with ACD as 1 of the 3 final diagnoses was 57.2% (505/883) and 41.4% (366/883) for atopic dermatitis. The percentage of the children tested from 2001 to 2004

TABLE 3. Anatomic Distribution of the Dermatitis in Children and Adults

Anatomic Presentation	% of Children (n = 883)*	% of Adults (n = 17245)*
Scattered generalized	32.5	23.6
Face	19.7	21.2
Arm	17.1	15.3
Leg	15.6	10.9
Trunk	15.1	12.4
Foot	12.9	6.6
Hand	12.5	26.7
Neck	7.8	9.1
Eyelids	6.8	10.8
Lips	5.8	4.3
Scalp	3.5	5.4
Most exposed areas	2.3	1.5
Ears	1.8	1.6
Anal/genital	1.4	2.7
Only under clothing	0.9	0.8
Eyes	0.6	0.8
Erythroderma	0.0	0.1
Nose	0.0	0.1
Other	2.0	3.1

*Up to 3 sites were recorded per patient, so the total percentage of children and adults could be greater than 100%.

TABLE 4. Results of 883 Children Patch-Tested by the NACDG From 2005 to 2012 with Data From Adults for Comparison

Allergens*	Age Groups, y											
	Younger Children (0–5)			Older Children (6–18)			Children (0–18)			Adults (>18)		
	PPT%	RPPT%	n	PPT%	RPPT%	n	PPT%	RPPT%	n	PPT%	RPPT%	n
Nickel sulfate 2.5% pet†	34.1	29.3	41	27.9	25.5	833	28.1	25.6‡	874	17.7	15.3	17159
Cobalt chloride 1% pet†	14.6	12.2	41	12.2	8.9	838	12.3	9.1‡	879	7.3	5.1	17205
Neomycin sulfate 20% pet†	12.2	12.2	41	6.8	6.3	837	7.1	6.6	878	9.6	8.3	17200
<i>Myroxylon pereirae</i> (balsam of Peru) 25% pet†	7.3	7.3	41	5.6	5.4	839	5.7	5.5‡§	880	9.8	9.0	17234
Lanolin alcohol 50% pet†	0.0	0.0	13	5.8	5.4	223	5.5	5.1	236	4.6	4.3	3932
Fragrance mix 8% pet†	4.9	4.9	41	5.2	4.9	841	5.2	4.9‡	882	10.6	9.9	17215
Bacitracin 20% pet†	9.8	9.8	41	5.0	4.4	841	5.2	4.6‡	882	8.4	7.0	17214
Carmine 2.5% pet #	7.7	0.0	13	3.6	2.3	222	3.8	2.1	235	3.1	2.0	3929
<i>p</i> -Phenylenediamine 1% pet†	2.4	2.4	41	3.4	2.9	833	3.3	2.9‡	874	5.6	4.6	17185
Quaternium-15 2% pet†	2.4	0.0	41	3.2	3.1	842	3.2	2.9‡	883	8.1	7.6	17223
Propolis 10% pet	5.4	5.4	37	2.9	1.5	661	3.0	1.7	698	3.1	2.1	12877
Formaldehyde 1% aq†	0.0	0.0	41	3.1	3.1	841	2.9	2.9‡	882	7.5	7.0	17230
Carba mix 3% pet†	0.0	0.0	41	3.0	2.9	837	2.8	2.7	878	4.5	4.0	17231
MCI/MI 100 ppm aq†	0.0	0.0	41	2.9	2.9	841	2.7	2.7	882	3.5	3.3	17203
Decyl glucoside 5% pet	5.0	0.0	20	2.6	2.4	422	2.7	2.3	442	1.5	1.2	8071
<i>Compositae</i> mix 6% pet†	2.4	2.4	41	2.6	2.3	836	2.6	2.3‡§	877	1.5	1.0	17214
2-Bromo-2-nitropropane-1,3-diol 0.5% pet†	4.9	2.4	41	2.4	1.8	838	2.5	1.8	879	2.3	1.7	17216
Potassium dichromate 0.25% pet†	7.3	0.0	41	2.0	1.7	839	2.3	1.6	880	3.3	2.1	17233
Propylene glycol 30% aq	0.0	0.0	41	2.4	2.3	841	2.3	2.2	882	2.7	2.5	17218
Fragrance mix II 14% pet	2.7	2.7	37	2.1	1.8	662	2.1	1.9‡	699	4.5	4.4	12888
Black rubber mix 0.6% pet†	0.0	0.0	41	2.0	1.3	837	1.9	1.3‡	878	1.0	0.7	17233
Thiuram mix 1% pet†	2.4	2.4	41	1.8	1.7	838	1.8	1.7‡	879	3.4	3.1	17226
Colophony 20% pet†	0.0	0.0	41	1.8	1.3	840	1.7	1.2‡†	881	2.5	2.0	17234
Lanolin alcohol 30% pet†**	0.0	0.0	28	1.8	1.6	619	1.7	1.5	647	2.2	2.0	13299
(±)- α -Tocopherol 100%	4.9	2.4	41	1.4	1.4	837	1.6	1.5‡	878	0.8	0.8	17217
MDBGN/phenoxxyethanol 2% pet†	2.4	0.0	41	1.5	1.5	839	1.6	1.5‡	880	4.9	4.1	17216
Tixocortol-21-pivalate 1% pet†	4.9	2.4	41	1.3	1.2	841	1.5	1.2‡	882	2.5	2.4	17216
Disperse blue 106 1% pet†#**	14.3	4.8	21	0.7	0.2	412	1.4	0.5	433	1.5	1.1	9136
<i>p</i> -tert-Butylphenol formaldehyde resin 1% pet†	0.0	0.0	40	1.4	1.1	836	1.4	1.0	876	1.3	0.9	17234
Iodopropynyl butylcarbamate 0.5% pet	2.4	0.0	41	1.3	1.3	836	1.4	1.3‡	877	3.6	3.2	17215
Mixed dialkyl thioureas 1% pet	0.0	0.0	41	1.4	1.2	836	1.4	1.1	877	0.9	0.7	17212
Cinnamic aldehyde 1% pet†	4.9	4.9	41	1.2	1.2	838	1.4	1.4‡	879	3.0	2.7	17213
Cocamidopropyl betaine 1% aq	4.9	4.9	41	1.2	1.0	839	1.4	1.1	880	1.4	1.4	17218
Majantol 5% pet	0.0	0.0	20	1.4	0.9	422	1.4	0.9	442	1.3	1.1	8073
Oleamidopropyl dimethylamine 0.1% aq	0.0	0.0	20	1.4	0.7	423	1.4	0.7	443	2.1	1.8	8068
Ylang-ylang oil 2% pet	0.0	0.0	41	1.3	1.3	835	1.3	1.3	876	1.3	1.0	17215
Sesquiterpene lactone mix 0.1% pet	7.3	4.9	41	0.8	0.7	835	1.1	0.9	876	0.6	0.5	17210
Diazolidinyl urea 1% pet†	0.0	0.0	41	1.2	1.2	841	1.1	1.1‡	882	2.9	2.7	17219
DMDM Hydantoin 1% pet	0.0	0.0	41	1.2	1.0	841	1.1	0.9‡	882	2.1	2.0	17219
DMAPA 1.0% aq	0.0	0.0	20	1.2	1.2	423	1.1	1.1	443	1.8	1.7	8079
Budesonide 0.01% pet† #**	0.0	0.0	4	1.1	1.1	175	1.1	1.1	179	1.5	1.3	4327
Budesonide 0.1% pet†	0.0	0.0	41	1.1	1.0	841	1.0	0.9	882	1.0	0.9	17220
Benzocaine 5% pet†	0.0	0.0	41	1.0	0.4	840	0.9	0.3‡	881	1.6	1.1	17233
Paraben mix 12% pet†	0.0	0.0	41	1.0	1.0	841	0.9	0.9	882	1.2	1.1	17218
<i>Lavandula angustifolia</i> (lavender oil) 2% pet	5.0	0.0	20	0.7	0.7	422	0.9	0.7	442	0.3	0.3	8070
Disperse blue mix (124/106) 1% pet†	5.0	5.0	20	0.7	0.5	423	0.9	0.7	443	1.0	0.8	8065
Hydrocortisone-17-butyrate 1% alc† #**	0.0	0.0	14	0.9	0.9	232	0.8	0.8	246	0.5	0.4	4684
Bisphenol F epoxy resin 0.25% pet #**	0.0	0.0	15	0.9	0.9	235	0.8	0.8	250	1.5	0.9	4784

(Continued on next page)

TABLE 4. (Continued)

Allergens*	Age Groups, y											
	Younger Children (0–5)			Older Children (6–18)			Children (0–18)			Adults (>18)		
	PPT%	RPPT%	n	PPT%	RPPT%	n	PPT%	RPPT%	n	PPT%	RPPT%	n
Bisphenol A epoxy resin 1% pet†	2.5	0.0	40	0.7	0.7	835	0.8	0.7	875	1.7	1.2	17224
Tea tree oil, oxidized 5% pet	0.0	0.0	40	0.8	0.4	836	0.8	0.3	876	1.2	1.0	17211
Mercaptobenzothiazole 1% pet†	0.0	0.0	40	0.8	0.8	838	0.8	0.8	878	0.8	0.7	17233
Imidazolidinyl urea 2% pet†	0.0	0.0	41	0.8	0.8	841	0.8	0.8‡	882	2.4	2.3	17219
Cocamide diethanolamine 0.5% pet	0.0	0.0	41	0.7	0.7	838	0.7	0.7	879	1.0	1.0	17217
Ethylenediamine dihydrochloride 1% pet†	0.0	0.0	41	0.7	0.4	838	0.7	0.3	879	1.6	1.0	17226
Carvone 5% pet ¶	0.0	0.0	20	0.7	0.7	422	0.7	0.7	442	0.9	0.7	8071
Dithiomorpholine 1% pet¶##	0.0	0.0	4	0.6	0.6	172	0.6	0.6	176	1.9	1.2	4303
Iodopropenyl butylcarbamate 0.1% pet¶##	0.0	0.0	4	0.6	0.6	174	0.6	0.6	178	0.5	0.4	4326
Glutaral 1% pet	2.5	2.5	40	0.4	0.2	828	0.5	0.3	868	1.2	0.6	17167
Benzophenone-3 3% pet##	0.0	0.0	21	0.5	0.5	414	0.5	0.5	435	0.8	0.7	9147
Imidazolidinyl urea 2% aq†##	0.0	0.0	20	0.5	0.5	416	0.5	0.5	436	1.5	1.3	9156
Lidocaine 15% pet	0.0	0.0	41	0.5	0.5	834	0.5	0.5	875	0.9	0.6	17205
Mercapto mix 1% pet†	0.0	0.0	40	0.5	0.5	838	0.5	0.5	878	0.6	0.6	17234
Amidoamine 0.1% aq	2.4	2.4	41	0.4	0.2	837	0.5	0.3‡	878	1.4	1.3	17216
Clobetasol 17-propionate 1% pet	0.0	0.0	41	0.5	0.4	838	0.5	0.3	879	0.5	0.4	17216
Shellac 20% alc ¶	0.0	0.0	20	0.5	0.2	422	0.5	0.2	442	1.7	1.1	8071
Benzophenone-3 10% pet ¶	0.0	0.0	20	0.5	0.5	424	0.5	0.5	444	0.9	0.8	8070
2-Hydroxyethyl methacrylate 2.0% pet	0.0	0.0	36	0.5	0.5	657	0.4	0.4‡	693	2.3	1.9	12876
Ethyl 2-cyanoacrylate 10% pet ¶#	0.0	0.0	13	0.5	0.5	222	0.4	0.4	235	0.3	0.3	3929
(±)-Limonene 2% pet ¶#	0.0	0.0	13	0.5	0.0	222	0.4	0.0	235	0.2	0.2	3929
Dibucaine 2.5% pet†	2.5	0.0	40	0.2	0.2	831	0.3	0.2	871	0.9	0.7	17202
Tosylamide formaldehyde resin 10% pet	2.5	0.0	40	0.2	0.1	835	0.3	0.1‡	875	1.1	0.9	17212
Jasmine absolute 2% pet¶	0.0	0.0	24	0.3	0.3	598	0.3	0.3	622	0.9	0.9	12409
Hydrocortisone-17-butyrate 1% pet†¶	0.0	0.0	24	0.3	0.3	600	0.3	0.3	624	0.6	0.5	12401
DMDM hydantoin 1% aq##	0.0	0.0	20	0.2	0.2	414	0.2	0.2	434	1.3	1.2	9143
Diazolidinyl urea 1% aq†##	0.0	0.0	20	0.2	0.2	414	0.2	0.2‡‡†	434	2.0	1.9	9143
Ethyl acrylate 0.1% pet	0.0	0.0	40	0.2	0.2	832	0.2	0.2	872	1.0	0.8	17207
Methyl methacrylate 2% pet	2.5	0.0	40	0.1	0.1	832	0.2	0.1‡	872	1.0	0.9	17217
Triamcinolone acetonide 1% pet##	0.0	0.0	21	0.2	0.2	417	0.2	0.2	438	0.3	0.3	9144
Benzyl alcohol 1% pet	0.0	0.0	37	0.2	0.2	662	0.1	0.1	699	0.3	0.3	12892
Chloroxylenol (PCMX) 1% pet	0.0	0.0	41	0.1	0.1	836	0.1	0.1	877	0.5	0.4	17218
Desoximetasone 1% pet	0.0	0.0	37	0.0	0.0	661	0.0	0.0	698	0.2	0.2	12879
Dimethylol dihydroxyethyleneurea 4.5% aq**	0.0	0.0	28	0.0	0.0	611	0.0	0.0	639	0.5	0.4	13275
Glyceryl thioglycolate 1% pet**	0.0	0.0	27	0.0	0.0	604	0.0	0.0‡	631	1.4	0.9	13265
<i>Mentha piperita</i> oil (peppermint oil) 2% pet ¶	0.0	0.0	20	0.0	0.0	422	0.0	0.0	442	0.5	0.4	8072
(±)-Limonene 3% pet ¶**	0.0	0.0	7	0.0	0.0	201	0.0	0.0	208	0.1	0.1	4143
Ethyleneurea melamine formaldehyde 5% pet¶##	0.0	0.0	4	0.0	0.0	174	0.0	0.0	178	2.1	1.6	4319
Bisphenol F epoxy resin 1% pet¶##	0.0	0.0	4	0.0	0.0	171	0.0	0.0	175	0.2	0.1	4309

*Unless marked, each allergen was a component of the NACDG's patch test screening series for each year from 2005 to 2012.

†Allergen that is present on the T.R.U.E. TEST panels 1, 2, 2.2, or 3.3 as an individual allergen or as a component of a mixture.

‡Statistically significantly different ($P < 0.05$) compared with adults.§Statistically significantly greater ($P < 0.05$) than the same age group from 2001 to 2004.²

||Years 2005 to 2006 for which the allergen was absent from the NACDG screening series.

¶Years 2007 to 2008 for which the allergen was absent from the NACDG screening series.

#Years 2009 to 2010 for which the allergen was absent from the NACDG screening series.

**Years 2011 to 2012 for which the allergen was absent from the NACDG screening series.

††Statistically significantly less ($P < 0.05$) than the same age group from 2001 to 2004.²

aq, aqueous vehicle; DMAPA, dimethylaminopropylamine; MCI/MI, methylchloroisothiazolinone/methylisothiazolinone; MDBGN, methylidibromo glutaronitrile; n, number of patch test performed; NACDG, North American Contact Dermatitis Group; PCMX, p-chloro-m-xylene; pet, petrolatum vehicle; PPT, positive patch test; RPPT, relevant positive patch test.

TABLE 5. Sources of the 10 Most Common Allergens That Yielded RPPT in Children

Allergen	Most Common Source (% of total RPPT)
Nickel sulfate 2.5% pet	Jewelry (35.7)
Cobalt chloride 1% pet	Jewelry (38.8)
Neomycin sulfate 20% pet	Antibiotics (75.9)
Balsam of Peru 25% pet	Cosmetics, beauty preparation, skin and health care products (58.4)
Lanolin alcohol 50% pet	Cosmetics, beauty preparation, skin and health care products (75.0)
Fragrance mix 8% pet	Cosmetics, beauty preparation, skin and health care products (76.7)
Bacitracin 20% pet	Antibiotics (95.1)
Formaldehyde 1% aq	Cosmetics, beauty preparation, skin and health care products (36.4)
Quaternium-15 2% pet	Cosmetics, beauty preparation, skin and health care products (69.2)
p-Phenylenediamine 1% pet	Hair dyes (64.0)

aq, aqueous; pet, petrolatum.

with ACD as 1 of 3 final diagnoses was 51.0% (198/388), which is significantly less than that in the current study ($P = 0.04$). In those with ≥ 1 RPPT, 37.3% (187/501) of the children had atopic dermatitis as 1 of the 3 final diagnoses, compared with 12.5% (1246/9976) in the adults ($P < 0.001$). In the children with atopic dermatitis as 1 of the 3 final diagnoses, the ≥ 1 RPPT% was 51.1% (187/366), compared with 60.7% (314/517) in the children without atopic dermatitis as 1 of the 3 final diagnoses ($P = 0.004$).

Supplemental Allergen Reaction Rates

Three hundred and thirty-three (37.7%) children did not have a single PPT to an NACDG screening allergen. Of these, 15.0% (50/333) had a relevant positive reaction to a supplemental allergen; 47.7% (159/333) had atopic dermatitis, 22.8% (76/333) had irritant dermatitis, and 17.1% (57/333) had ACD as 1 of the 3 final diagnoses. Overall, 208 children (23.6%) had an RPPT to a supplemental allergen; for 59 (28.4%) of these children, their only positive *relevant* reaction was to a supplemental allergen. Non-NACDG allergen sources and their frequencies are detailed in Table 8.

TABLE 6. Frequency of Atopic Markers in Children (2005–2012) Compared With Adults (2005–2012) and Children From the Previous Study (2001–2004)

Atopic Marker	Children in the Current Study (2005–2012)	Adults in the Current Study (2005–2012)		Children in Previous Study (2001–2004)	
	Fraction (%) [*]	Fraction (%) [*]	$P^{\dagger}$	Fraction (%)	$P^{\dagger}$
Allergic rhinitis	311/881 (35.3)	5160/17211 (30.0)	0.001	94/388 (24.2)	<0.001
Eczema	454/879 (51.6)	3772/17197 (21.9)	<0.001	156/388 (40.2)	<0.001
Asthma	216/879 (24.6)	2587/17224 (15.0)	<0.001	84/388 (21.6)	0.259
Any atopic marker [‡]	563/883 (63.8)	7397/17245 (42.9)	<0.001	221/388 (57.0)	0.022

^{*}Data of atopic marker were not available for all 833 children (2005–2012) and 17245 adults (2005–2012).

[†] P value generated with χ^2 tests comparing data with patch-tested children of the current study (2005–2012).

[‡]Having 1 or more of the 3 atopic markers.

TABLE 7. Comparing the ≥ 1 RPPT% in Children With Various Atopic Markers

Atopic Marker Status	No. Children	≥ 1 RPPT% (P^*)
Only allergic rhinitis	58	58.6 (0.985)
Only atopic eczema	181	55.2 (0.446)
Only asthma	22	77.3 (0.086)
Any atopic marker [†]	563	55.6 (0.363)
None	320	58.8

^{*} P value generated with χ^2 tests when compared with the group that has no atopic markers (None).

[†]Having 1 or more of the 3 atopic markers.

Hypothetical Yields With T.R.U.E. TEST

Of the 87 allergens that were tested by the NACDG from 2005 to 2012, a total of 40 were deemed present on the T.R.U.E. TEST panels as either an individual allergen or a component of a mixture. These allergens are identified in Table 4. Of the 550 children with ≥ 1 PPT using the NACDG series, the 3 T.R.U.E. TEST panels would hypothetically have detected all PPTs in 66.5% (366/550), some PPTs in 24.5% (135/550), and no PPTs in 8.9% (49/550) of the children. Similarly, the 3 T.R.U.E. TEST panels would have hypothetically detected all RPPTs in 70.1% (351/501), some RPPTs in 21.8% (109/501), and no RPPTs in 8.2% (41/501) of the 501 children with ≥ 1 RPPT.

DISCUSSION

Positive Patch Tests and Their Relevance

This study identifies several important findings. First, most allergens yielding positive reactions in children were also relevant. With the exception of carmine, the majority (9/10) of the 10 allergens with the highest PPT% were also on the list of 10 allergens with the highest RPPT%. One would expect carmine to have significant clinical relevance because it is a commonly used natural red dye in food, cosmetics, and excipients in medicaments.¹⁵ This may be explained by the small sample size of children tested with carmine owing to its recent introduction to the NACDG test tray for the 2011–2012 cycle or that clinicians frequently have difficulty distinguishing irritant from allergic reactions to carmine. Carmine

TABLE 8. Sources of Supplemental Allergens

Supplemental Allergen Source	% of Children (n = 208)
Cosmetics, beauty preparations, skin and health care products	22.6
Jewelry	11.1
Clothing	8.7
Hair dyes	4.8
Moisturizers, lotions, creams	4.8
Shoes, boots, sandals, slippers	4.8
Recreational and athletic equipment	4.3
Poison ivy, oak, and other <i>Toxicodendron</i> species	3.8
Steroids	2.9
Antiacne medications	2.4
Clothing, wearing apparel, protective equipment, textiles	2.4
Sunscreens	2.4
Antibiotics	1.9
Disinfectants	1.9
Gloves	1.4
Lipsticks	1.4
Makeup	1.4
Medications (topical)	1.4
Antifungals	1.0
Eye-care products	1.0
Food products (fresh or processed)	1.0
Ores and metals, radiating	1.0
Shampoos	1.0
Shrubs (grasses)	1.0
Swimming pool/spa water	1.0
Artificial nails	0.5
Dentistry materials and products	0.5
Deodorants and antiperspirants	0.5
Drugs, medications, alcoholic beverages	0.5
Flowers	0.5
Medications (oral, intramuscular, or subcutaneous)	0.5
Minerals (metallic)	0.5
Musical instruments	0.5
Perfumes and fragrances	0.5
Safety equipment, miscellaneous (eg, masks, respirators)	0.5
Tapes, band-aids, adhesive aids	0.5
Textiles and fabrics	0.5
Watches	0.5
Not elsewhere classified	2.4

was removed from the NACDG screening series for 2013 to 2014 because of a low rate of relevant positive reactions. The overall increase in relevance rate compared with the previous study may be caused by the removal of thimerosal and gold sodium thiosulfate after 2004, both of which were of minimal clinical relevance.²

As in our previous study of patch testing in children, nickel and cobalt yielded the most positive reactions, the majority of which were clinically relevant. Nickel was also the top allergen for 7 of 8 external studies we had summarized (Table 1). We also noticed that RPPT% to nickel was significantly greater in children compared with adults ($P < 0.001$), although this is likely caused by referral bias.

Sex Differences

The ≥ 1 RPPT% in the female children was significantly greater than that for the male children (60.0% vs 51.2%; $P = 0.01$). We also observed that the female children with ≥ 1 RPPT were significantly older than the male children with ≥ 1 RPPT (results not shown). Taken together, these findings likely reflect the more frequent use of jewelry, cosmetics, and skin care products in females, especially adolescents. Other authors have also observed these trends.^{4,6,10}

Age Differences

Compared with the adults, the children had significantly different RPPT% for the 27 allergens. Of these, the children had lower RPPT% for fragrance mix 8% pet, fragrance mix II 14% pet, and balsam of Peru, which may reflect the relatively less frequent use of scented products in children, or perhaps that cumulative exposure or some other factor is a requisite for sensitization.¹⁶ The children also had lower RPPT% for imidazolidinyl urea 2% pet, diazolidinyl urea 1% aq/pet, and formaldehyde, all of which are used as preservatives in topical medicaments and leave-on skin-care products which adults are more likely to use. Greater exposure to products such as dentures and acrylic nails may explain the higher RPPT% for 2-hydroxyethyl methacrylate in adults compared with children (1.9% vs 0.4%).¹⁷ On the whole, however, the ≥ 1 PPT% and ≥ 1 RPPT% were not significantly different between children, younger children, and adults, reaffirming the importance of patch testing in adults and children of all ages.

Comparison With Data From the 2001–2004 Study

The rates of PPTs for individual allergens have been known to change with time, as demonstrated by Milingou et al⁷ in Greece and Seidenari et al¹¹ in Italy. Compared with children patch-tested from 2001 to 2004, the RPPT% significantly decreased for colophony and diazolidinyl urea 1% aq and increased for balsam of Peru and *Compositae* mix, although these P values are large relative to the multiple tests performed (overall $P \geq 0.007$). On the whole, however, the ≥ 1 PPT% and ≥ 1 RPPT% in the children did not differ significantly between the 2 test periods.

Relationship Between Atopic Dermatitis and Positive Patch Tests

The relationship between atopic dermatitis and ACD has been unclear. Conflicting data exist because some authors have reported a higher PPT% in patients with a history of atopic dermatitis,^{3,18} whereas others have reported no significant differences.^{5–7,9,11} It seems, however, that the severity of atopic dermatitis may have some influence on the outcome of patch testing in these individuals.^{3,19,20} For example, Herro et al³ observed that children with an eczema area and severity index of greater than 10 had a higher probability of having more than 3 PPTs. Further exacerbating the problem is the presence of various diagnostic criteria for atopic dermatitis (eg, United Kingdom diagnostic criteria,

Hanifin and Rajka criteria, etc), which makes meaningful comparisons difficult between studies.^{21,22} Unfortunately, our study did little to alleviate this issue because we also did not use a standard criteria to diagnose children with atopic dermatitis. Nonetheless, we observed that children with an atopic marker (ie, allergic rhinitis, asthma, or atopic eczema) did not have a significantly different $\geq 1\text{RPPT}\%$ compared with those without. We did find, however, that the $\geq 1\text{RPPT}\%$ in the children who were given atopic dermatitis as 1 of the 3 final diagnoses was significantly smaller than those without (51.1% vs 60.7%; $P = 0.004$). This could reflect a clinician's tendency to attribute the dermatitis in a child whose patch test was negative to atopic dermatitis. Not surprisingly, children were more likely to have a history of atopic markers and a final diagnosis of atopic dermatitis compared with adults, which is consistent with our current understanding that atopy is more prevalent at a young age.²³ Children are more likely to have signs that are well recognized as atopic dermatitis; those with recalcitrant or difficult-to-manage disease are referred for patch testing to evaluate for possible contact allergens, which aggravate their dermatitis or make it refractory to treatment.

Comparison With Other Studies

Geographic location plays a significant role in patterns of PPTs. For example, Herro et al³ and Hammonds et al⁴ studied patch-tested children in the United States and listed allergens such as nickel, cobalt, fragrance mix, and neomycin as top allergens, which are similar to our study. In contrast, 4 of 5 European studies found a greater prevalence of positive reactions to potassium dichromate. We suspect it may be caused by a higher use of genuine leather, which contains chromate as a tanning agent.^{24,25} Sarma and Ghosh¹⁰ reported $\geq 1\text{PPT}\%$ of 80% and $\geq 1\text{RPPT}\%$ of 49% in patch-tested Indian children. The authors suggested that India's rapid urbanization, relaxed regulations, and poor manufacturing adherence to product safety guidelines may be responsible for these high percentages. In addition, they presented the only study in our review that did not have nickel as the top allergen, a position that was surprisingly held by parabens (PPT% of 43%). The authors appreciated the abnormally high PPT% with parabens and hypothesized that Indian goods likely contained higher level of parabens. Of note, concentration and composition of the parabens tested were not reported and other studies of patch-tested adults from India documented lower rates of positive reactions to parabens.^{26,27}

Comparison With the T.R.U.E. TEST

Approximately 67% of the children with $\geq 1\text{PPT}$ would have had all their PPTs detected by the T.R.U.E. TEST. Similarly, 70.1% of the children with $\geq 1\text{RPPT}$ would have had all their RPPTs detected by the T.R.U.E. TEST, an improvement over the 61.5% observed in the children tested from 2001 to 2004, when the T.R.U.E. TEST consisted of only 2 panels.² Thirteen of the 15

allergens with the highest RPPT% when tested with the NACDG series are allergens included in the T.R.U.E. TEST; the exceptions were propylene glycol and decyl glucoside. The 3-panel T.R.U.E. TEST, then, is a good screening tool for children suspected to have an ACD. A clinician who frequently uses the T.R.U.E. TEST will benefit from being aware of the common allergens that yielded relevant positive reactions with the NACDG series but are not a component of the T.R.U.E. TEST (RPPT%), such as decyl glucoside (2.3), propylene glycol (2.2), carmine (2.1), fragrance mix II 14.0% pet (1.9), propolis (1.7), ($\pm$)- α -tocopherol (1.5), ylang-ylang oil (1.3), iodopropynyl butyl carbamate 0.5% pet (1.3), mixed dialkyl thioureas (1.1), and cocamidopropyl betaine (1.1).

Supplemental Allergens

Testing with selected supplemental allergens beyond a standardized screening series is an important component of patch testing in children. As this study has shown, approximately 23.6% of children had a relevant positive reaction to a supplemental allergen; of these, 28.4% would not have had their relevant allergen identified if only the NACDG screening series was used. This emphasizes the importance of history taking to elucidate potential supplemental allergens for patch testing because patients are unlikely to disclose these without prompting. As would be suspected, the important additional supplemental allergens in children are their own toiletries, including cosmetics, beauty preparations, skin and health care products, as well as creams and lotions (27% of the supplemental allergen sources).

Limitations

This study has several limitations. Our patient cohort was not racially diverse because the majority of subjects were white and were referred for suspicion of ACD; hence, there is little generalizability. In addition, analyses and comparisons may contain false positives because of the multiple tests performed at $\alpha = 0.05$ without multiple test corrections. Although multiple test corrections, such as the Bonferroni correction, may have been useful in reducing this error, it also carries the risk of being too strict a criterion, possibly leading to false negatives.²⁸ The data used in this study came from many centers in North America, and interobserver variability is a potential limitation. For example, features of atopic markers and assigning final diagnoses were made by the experienced clinician's judgment.

CONCLUSIONS

This study provides data on one of the largest cohorts of children patch-tested in the recent literature. The most common allergens that yielded positive patch tests, such as nickel and cobalt, were also common in studies from other regions as well (eg, Italy, Greece, India, and different states within the United States). Potassium dichromate was more common in studies from Europe.

The frequencies of clinically relevant positive reactions for the 27 allergens differed significantly between children and adults. In particular, clinically relevant positive patch tests to nickel and cobalt were more common in children. This may reflect an increased exposure in children to jewelry and clothing containing nickel or cobalt. Overall, $\geq 1\text{PPT}\%$ and $\geq 1\text{RPPT}\%$ in children did not differ significantly from adults or with children tested from 2001 to 2004. The T.R.U.E. TEST would have detected 13 of the 15 allergens that yielded the most relevant PPTs with the NACDG series. The next 10 most common relevant allergens not screened for by the T.R.U.E. TEST, as mentioned previously, have RPPT% of 2.3% or less. Regular testing of these allergens may be low yield and best reserved until after testing a child with suspected ACD has yielded no relevant positive reactions to the T.R.U.E. TEST. In addition, it is important to consider patch testing with supplemental allergens (allergens not part of a screening series) because we have found this to be high yield: 23.6% of children had a relevant positive reaction to a supplemental allergen and 6.7% of children had their only relevant positive reaction to a supplemental allergen. Common sources of supplemental allergens in this study include cosmetics, beauty preparations, skin and health care products, jewelry, as well as clothing. Children with atopic dermatitis are equally as likely as those without to have $\geq 1\text{RPPT}$. Our results and sentiment align with those of Czarnobilska et al,²⁹ that patch testing is an important component in the workup of a child with chronic atopic dermatitis. This large study of a patch-tested pediatric population reaffirms that patch testing in appropriately selected children is a worthwhile endeavor to elucidate important relevant allergens.

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