Contact allergy and allergic contact dermatitis in children – a review of current data

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Summary

Allergic contact dermatitis (ACD) in children was previously considered to be a rare occurrence. However, the growing number of case reports and cross-sectional studies through the past three decades indicate that ACD is, in fact, a highly relevant diagnosis in children. Furthermore, the frequency of ACD in children seems to be increasing. In 1999, a review of the literature reported prevalence rates of 14.5–70% in selected paediatric populations. The current paper reviews the studies on the prevalence of positive patch test reactions and ACD in the paediatric population during the past decade, and provides an overview of the main findings. We found reported sensitization rates of 26.6–95.6% in selected groups of children. The associated relevance was 51.7–100%. The most common allergens were nickel, cobalt, thimerosal, and fragrance. Tailored patch testing increases the rate of relevant patch test reactions. Children with atopic dermatitis are as frequently sensitized as children with no history of atopic dermatitis, and there are no differences associated with sex. Children and adults can be tested with equal concentrations of patch test allergens. Our findings may support the notion that the prevalence of ACD in children is increasing over time or indicate an increased awareness.

Key words: allergic contact dermatitis; children; patch test; prevalence; selected.

Only 30 years ago, allergic contact dermatitis (ACD) in children was considered to be a very rare occurrence. This assumption was based on the beliefs that children were less exposed to contact allergens and that the immune system in children was less susceptible to contact allergens (1, 2). Through the past three decades, the number of case reports and cross-sectional studies on ACD in children has grown, which has fostered a higher awareness, but also the assumption that the occurrence is increasing (3). The apparent increase is thought to be the result of more frequent exposure to allergens at a younger age, new trends in body piercing, use of cosmetic products, and participation in sports and hobbies, in addition to improved recognition of ACD and increased patch testing of children (4).

ACD acquired in childhood has important repercussions for patients, and may affect decisions regarding future occupation in adulthood (5). The morbidity from ACD depends on the ability to avoid repeated or continued exposure. The patient may experience chronic or recurrent episodes of dermatitis if the source is not correctly identified as early as possible by patch testing (6).

The epidemiology of ACD among asymptomatic children is only sparsely described, as most studies provide estimates of prevalence in selected populations. In 1999, Mortz and Andersen (7) reviewed the existing literature on prevalence rates of ACD among children in selected and unselected populations. In unselected groups of children from the general paediatric population, the authors found a prevalence rate of positive patch test reactions of 13.3–23.3%. Since then, only a few studies on unselected populations have been published. Bruckner et al. (8) patch tested 85 North American children between the

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ages of 6 months and 5 years, and found a sensitization rate of 24.5%. The authors only included 2+ or 3+ reactions in the study, and performed patch test readings 48 hr after removal. Even so, 45% of the positive reactions were observed in children <18 months of age. Mortz et al. (9) found one or more positive patch test reactions in 15.2% of 1146 Danish unselected adolescents aged 12–16 years from the general population. Of the 174 positive patch test reactions, 47.7% were considered to be relevant, suggesting a prevalence of present or past ACD of 7.2%. Nickel and fragrance were the most common allergens.

In selected populations, Mortz and Andersen found prevalence rates of 14.5–70%, with an associated relevance in 56.4–93.3% (7). Since then, the interest in ACD among children has grown, and recent reports suggest that the prevalence of sensitization and ACD has increased (10).

The current paper reviews the studies on the prevalence of positive patch test reactions and ACD in paediatric populations during the past decade. Our aim was to evaluate the prevalence of ACD in selected populations, and provide an overview of the main findings.

Materials and Methods

A review of the literature was performed with Pubmed-Medline and contact dermatitis textbooks. The literature search through Pubmed-Medline was carried out with the MeSH words 'allergic contact dermatitis', 'contact sensitization', 'contact eczema', and 'patch test', with limits on age, language, and date of publication. Only literature describing the prevalence of ACD in the age group 0–18 years, in English, and published in 1999–2010, was included. The last literature search was performed on 1 November 2010.

Results: Prevalence of Positive Patch Test Reactions in Selected Populations

The studies reviewed represent paediatric populations from around the world; however, the majority describe North American and European children. This section provides an overview of the main findings. Table 1 shows the results of the studies reviewed. Table 2 gives an overview of the main findings. With the exception of one study, all studies present the results from dermatology or allergy clinics, and provide sensitization rates among referred children with suspected ACD, recalcitrant atopic dermatitis, or eczema.

When ACD is suspected, patch testing is the diagnostic gold standard procedure (12). Recommendations for patch testing children have been controversial. Previously, several authors have suggested that children should be tested with lower concentrations of allergens, in order to avoid the risk of irritant reactions and false-positive results (13, 14). Most recently, Jacob et al. (15) argued that the methodology for patch testing children should be re-evaluated, referring to several possible pitfalls, including the above-mentioned risk of irritant reactions as opposed to true allergic reactions. Furthermore, there is a risk of losing patch test material because of movement (16), and some authors have highlighted the difficulties of patch testing children, owing to the smaller test area (17, 18).

Roul et al. (18) suggested the use of a shortened version of the European baseline series when testing children aged <5 years. The authors patch tested 337 French children aged 1–15 years with suspected ACD, and found a sensitization rate of 67.1%. Children under the age of 5 years were tested with a shortened series of 17 allergens, and the remaining children were tested with 34 allergens from the European baseline series and additional series, depending on the history.

Jacob et al. (19) advocated the use of customized test series. In 2008, the authors published a US-based retrospective study of 65 children aged 1–18 years. The children were tested with individually customized allergen series based on exposure history and physical presentation of the eczema. Information on the number and types of allergens was not available. Of the 65 children, 83.1% had at least one positive patch test reaction, and 92.6% had at least one positive patch test reaction that was considered to be of 'definite' or 'probable' current relevance, giving a prevalence of ACD in the study population of 76.9%.

Hogeling et al. (4) suggested that the high sensitization rate of 70% in their study could be attributable to the fact that their test series included 65 allergens. The authors patch tested 100 children and adolescents with the North American baseline series and additional allergens if indicated by the history. The authors pointed out that the children in the study population were older (the youngest was 4 years old), and noted that this could be a possible source of bias. A similar high sensitization rate of 65.7% was reported by Zug et al. (20), who also used 65 allergens, as opposed to Onder and Adisen (21), who used only 24 allergens and found a sensitization rate of 32.8% among 360 Turkish children. The associated relevance was 93.2%.

The highest rate of sensitization was reported by Jacob et al. (22) in 2010. The authors found a sensitization rate of 95.6% among 45 children aged 0–16 years who were evaluated for ACD at the University of Miami Pediatric Contact Dermatitis Clinic. The children were tested with their paediatric baseline screen series of 40 allergens

Table 1. Results of diagnostic patch tests by geographical location in selected groups of children and adolescents with suspected allergic contact dermatitis

Author	Year of publication	Country	Study period	Children (n)	Age (years)	Sensitization rate (%)[a]	Relevance (%)[b]	Top three allergens
Roul et al.	1999	France	1995–1997	337	1–15	67.1	Not given	Nickel, fragrance, wool alcohol
Wöhrl et al.	2003	Austria	1997–2000	79	1–10	62.0	Not given	Nickel, ethylmercury, thimerosal
Duarte et al.	2003	Brazil	1996–2001	102	10–19	55.9	100.0	Nickel, tosylamide/formaldehyde resin, thimerosal
Heine et al.	2004	Germany	1995–2002	285	6–12	52.6	Not given	Thimerosal, benzoyl peroxide, phenylmercuric acetate
				2175	13–18	49.7	Not given	Nickel, thimerosal, benzoyl peroxide
Lewis et al.	2004	UK	1993–2003	191	<16	41.0	51.7	Nickel, fragrance mix, thiuram
Clayton et al.	2005	UK	1995–2004	500	0–16	26.6	61.0[c]	Nickel, fragrance mix, cobalt
Vozmediano et al.	2005	Spain	1990–2000	96	<15	54.2	57.7	Fragrance mix, thimerosal, nickel
Seidenari et al.	2005	Italy	1988–1994	1094	<12	52.1	70.0	Neomycin, nickel, lanolin alcohols/thimerosal
Goon and Goh	2006	Singapore	1986–2003	2340	<21	45.4	Not given	Nickel, thimerosal, colophonium
Beattie et al.	2006	UK	1999–2002	114	3–15	53.5	100.0	Nickel, cobalt, rubber chemicals
Zug et al.	2008	USA	2001–2004	391	0–18	65.7	77.8	Nickel, cobalt, thimerosal
Onder and Adisen	2008	Turkey	1993–2005	360	2–16	32.8	93.2	Nickel, cobalt, *p*-phenylenediamine
Hogeling et al.	2008	Canada	1996–2006	100	4–18	70.0	55.8[c]	Nickel, cobalt, fragrance mix
Jacob et al.	2008	USA	2001–2006	65	1–18	83.1	92.6	Nickel, thimerosal, *Myroxylon pereirae*
de Waard-van der Spek	2009	The Netherlands	2003–2008	79	1–18	50.6	84.7[c]	Nickel, own shoes, potassium dichromate
Czarnobilska et al.	2009	Poland	2007	96	7	43.8	Not given	Nickel, thimerosal, cobalt
				133	16	52.6	Not given	Nickel, thimerosal, cobalt
Hammonds et al.	2009	USA	2000–2006	136	3–18	61.0	89.0[c]	Nickel, cobalt, gold
Sarma et al.	2010	India	2005–2008	70	5–15	80.0	60.7	Paraben, potassium dichromate, fragrance mix
Milingou et al.	2010	Greece	1980–1993	232	<16	47.8	Not given	Nickel, cobalt, potassium dichromate
			1994–2007	255	<16	60.0	Not given	Nickel, thimerosal, cobalt
Jacob et al.	2010	USA	2004–2006	45	0–16	95.6	100.0	Nickel, cocamidopropyl betaine, *Myroxylon pereirae*

[a]Sensitization rate = share of children with at least one positive patch test reaction.
[b]Relevance = no. of children with relevant patch test reactions/no. of children with at least one positive patch test reaction.
[c]No. of relevant patch test reactions/no. of positive patch test reactions.

Table 2. Methodology and results of diagnostic patch tests in selected groups of children and adolescents with suspected allergic contact dermatitis

Author	Year of publication	Country	Children (n)	Age (years)	Sex distribution (F/M)	Share of children with AD (%)	Reason for referral	Test series	Allergens (n)	Reading day	Sensitization rate[a] (%)
Roul et al.	1999	France	337	1–15	—	76.0	—	European baseline series + additional allergens[b]	≤34	2 + 3	67.1
								Children <5 years: limited series	17	2 + 3	—
Wöhrl et al.	2003	Austria	79	1–10	40/39	—	Eczema	Locally revised standard series	34	3	62.0
Duarte et al.	2003	Brazil	102	10–19	93/9	48.0	Suspicion of ACD[c]	Standard battery of patch tests + additional allergens[b]	30+	2 + 4	55.9
Heine et al.	2004	Germany	285	6–18	153/132	37.5	Suspicion of ACD	Standard series + additional allergens[b]	—	3	52.6
			2175	13–18	1559/616	36.0	—	—	—	—	49.7
Lewis et al.	2004	UK	191	<16	—	—	—	European baseline series	—	—	41.0
Clayton et al.	2005	UK	500	0–16	310/190	—	—	British Contact Dermatitis Society baseline series + additional allergens[b]	37+	2 + 4	26.6
Vozmediano et al.	2005	Spain	96	<15	64/32	28.1	Suspicion of ACD	Baseline battery of the Spanish Contact Dermatitis Research Group + additional allergens[b]	—	2 + 3	54.2
Seidenari et al.	2005	Italy	1094	0.58–12	585/509	36.9	Suspicion of ACD	Paediatric series	30	3	52.1
								Children >10 years: +16 allergens	46	3	
Goon and Goh	2006	Singapore	2340	<21	—	38.0	—	Baseline series + additional allergens[b]	35	2–3	45.4
Beattie et al.	2006	UK	114	3–15	66/48	24.5[c,d]	Uncontrollable AD or suspicion of ACD	European baseline series	—	2	53.5
								British Contact Dermatitis Society baseline series	37	—	—
Zug et al.	2008	USA	391	0–18	253/137	—	—	North American Contact Dermatitis baseline series	65	2–3	65.7
Onder and Adisen	2008	Turkey	360	2–16	—	—	Suspicion of ACD	European baseline series + additional allergens[b]	24+	2–3	32.8
Hogeling et al.	2008	Canada	100	4–18	62/38	—	Suspicion of ACD	North American Contact Dermatitis baseline series + additional allergens[b]	65	2.4 + 5	70.0
Jacob et al.	2008	USA	65	1–18	35/30	—	Recalcitrant AD or localized dermatitis	Individually customized allergen series[d]	—	2 + 4[e]	83.1

Table 2. *Continued*

Author	Year of publication	Country	Children (n)	Age (years)	Sex distribution (F/M)	Share of children with AD (%)	Reason for referral	Test series	Allergens (n)	Reading day	Sensitization rate[a] (%)
de Waard and Oranje	2009	Netherlands	79	1–18	48/31	24.0	Suspected ACD or uncontrollable AD	True test	29	2 + 4	50.4
Czarbolinska et al.	2009	Poland	96	7	54/42	—	Self-reported eczema	10 common allergens	10	2 + 3	43.8
			133	16	88/45	—	—	—	—	—	52.6
Hammonds et al.	2009	USA	136	3–18	89/47	—	—	Different series based on clinical presentation	25–185	2–3 + 4–7	61.0
Sarma et al.	2010	India	70	5–15	89/47	18.6	Suspicion of ACD	Indian baseline series + additional allergens[b]	27	2.4 + 7	80.0
Milingou et al.	2010	Greece	232	<16	145/87	31.5	Suspicion of ACD	A modified European baseline series + additional allergens[b]	—	2 + 4	47.8
			255	<16	162/93	48.0			—		60.0
Jacob et al.	2010	USA	45	0.83–16	24/21	76.7	Referred to 'rule out ACD'	Paediatric baseline Screen Series + additional allergens[b]	40+	2 + 3	95.6

ACD, allergic contact dermatitis; AD, atopic dermatitis.
[a]Beattie et al. (11) Sensitization rate = share of children with at least one positive patch test reaction.
[b]Additional allergens if indicated by history: supplementary series and/or own products.
[c]One hundred and ten children had available case notes, 27 of these had atopic dermatitis.
[d]Except for two children, all children over 8 years of age were tested with the North American Contact Dermatitis Group baseline series + additional allergens and patients' own products.
[e]Children ≤5 years were additionally read on day 3.

supplemented with additional allergens if indicated. The patch tests were evaluated by dermatologists, and all reactions were considered to be relevant.

Unfortunately, not all studies considered the relevance of positive patch test results, and they provide us with a rate of sensitization rather than a rate of ACD. Even the studies that did consider relevance had different criteria for this assessment. Some designated 'current' and 'probable' as actual relevance (19), others grouped 'current', 'questionable' or 'past' relevance as relevant reactions (23), and yet others included only relevant reactions in their analysis (11). The studies that reported the highest rates of relevant positive patch test reactions either customized their patch test series according to the history of the child (22), supplemented the baseline series with historically relevant allergens, or used high numbers of allergens.

Hammonds et al. (23) reviewed the Mayo Rochester, Jacksonville and Arizona patch test database. During a 7-year period, 136 children aged 3–18 years were patch tested. The authors used tailored series based on clinical presentation with up to 185 different allergens. The mean number of allergens was 92. Of the 136 children, 61.0% had at least one positive patch test reaction. Positive reactions were considered to be of current, questionable or past relevance in 89% of cases.

De Waard-van der Spek and Oranje (24) patch tested 79 Dutch children. All patients were suspected of having ACD by history, localization, or deteriorating atopic dermatitis, and were tested with the TRUE™ test (panels 1 and 2) supplemented with other allergens if indicated by the history. Of all patients, 50.6% had at least one positive patch test reaction, and 84.7% of these were considered to be relevant.

Duarte et al. (25) found all positive patch test reactions to be relevant, even though the authors used a baseline series of patch tests (composed of 30 allergens; FDA Allergenic, Rio de Janeiro, Brazil). The sensitization rate among 102 Brazilian children and adolescents was 55.9%; however, the children in this study were relatively old, the youngest child being 10 years old.

Beattie et al. (11) included only reactions that were of current, past or possible relevance in their study, and relevance was therefore reported to be 100%. One hundred and fourteen children were referred for patch testing because of uncontrollable atopic dermatitis, localized dermatitis, or a history of reacting to a specific allergen. They were tested with the European baseline series or the British Contact Dermatitis Group baseline series, and 53.5% had one or more positive patch test reactions.

Clayton et al. (5) reported the lowest sensitization rate, at 26.6%. In this study, 500 children aged 0–16 years with suspected ACD were tested with the British Contact Dermatitis Society baseline series and additional series, if indicated by the history. Of all positive reactions, 61.0% were considered to be relevant.

Age and Contact Sensitization

It is generally agreed that sensitivity to contact allergens increases with age, through childhood and adolescence, because of increased environmental exposure to contact allergens. However, Roul et al. (18) and Seidenari et al. (26) both found the highest sensitization rate in children between the ages of 0 and 3 years. The latter patch tested 1094 Italian children aged 7 months to 12 years at the Department of Dermatology in Modena. All children were tested with a paediatric series of 30 allergens, and children over the age of 10 years were further patch tested with 16 additional allergens. There was an overall sensitization rate of 52.1%, and of these, 70% were considered to be relevant. The sensitization rate among children under the age of 3 years was 63.4%, and this was significantly higher than in the older age groups (4–8 years and 9–12 years).

Similarly, Wöhrl et al. (27) observed the highest incidence of patch test reactivity in children up to 10 years of age, with a steady decrease thereafter. The authors patch tested a total of 2776 Austrian patients aged 2–92 years, suspected of having ACD, and found an incidence of patch test reactivity of 62.0% among 79 children aged 1–10 years.

Others found no difference in sensitization rates between different age groups (4, 19, 23, 28, 29). Hammonds et al. (23), however, noted a trend for a higher rate among boys aged 3–10 years, which decreased with age, but suggested that this finding could be attributable to the small numbers in the specific age groups (8 patients were male, and 6 of these had positive patch test reactions). Goon and Goh (30) found a sensitization rate of 45.4% among 2340 Singaporean children and young adults aged <21 years, and noted a peak incidence of 48% among the 375 children between 11–15 years.

Heine et al. (31) reported the results of a large multicentre study on 2460 German children and adolescents, and found comparable frequencies of positive patch test reactions in different age groups. Patch testing was performed for diagnostic purposes, and almost all patients were tested with the standard series, and in many cases with supplementary allergens, depending on individual indication. The sensitization rate was 50.0% (52.6% among children and 49.7% among adolescents).

In 2010, Milingou et al. (32) compared the results of patch tests in Greek children with suspected ACD between

two different periods of time. All children were tested with a modified European baseline series plus additional series if indicated. During the first period (1980–1993), 232 children were tested, and a sensitization rate of 47.8% was found. During the second period (1994–2007), 255 children were tested, and the sensitization rate was 60.0%. In the second period, the sensitization rate increased in all age groups, as compared with the first period, with the exception of the youngest age group (0–5 years), where the authors noted a decrease in boys and a stable girl/boy ratio. Overall, however, the findings support a true increase in ACD among Greek children.

A Polish study by Czarnobilska et al. (33) differed from the other studies reviewed. This study was part of an allergy-screening programme, and the reason for patch testing was self-reported symptoms of eczema. The authors patch tested 229 children in two selected age groups. One group consisted of 96 children aged 7 years; the other group consisted of 133 children aged 16 years. The children were patch tested with 10 allergens, which, according to an analysis of 23 European epidemiological studies, were found to be the most common sensitizers in the paediatric population. In the younger age group, there was a sensitization rate of 43.8%; in the older age group, this was 52.6%. A diagnosis of ACD was confirmed in 36.5% of 7-year-olds and 26.3% of 16-year-olds.

Common Allergens and Their Relevance

Allergen exposure varies throughout the world, and is determined by different factors, such as climate, cultural habits, and legislation (34). Bonitsis et al. (10) recently reviewed 49 studies in order to determine the proportion of positive reactions to allergens tested in children, and to identify the allergens that caused positive reactions in at least 1% of the paediatric population. The top five allergens tested by at least two studies included nickel sulfate, ammonium persulfate, gold sodium thiosulfate, thimerosal, and toluene-2,5-diamine.

The studies reviewed in the present paper represent paediatric populations from different parts of the world. Most studies have found nickel to be the most common allergen causing sensitization (4, 5, 11, 18–24, 27, 30–33, 35), which is in agreement with our knowledge of the epidemiology of ACD in paediatric and adult populations (10, 16). Nickel sensitization has several sources: jewellery, belt buckles, metal fasteners, spectacle frames, and, in particular, ear piercings (7). More girls than boys are sensitized, and the general opinion is that this is because girls are more likely to have their ears pierced at a young age than boys (16).

Duarte et al. (25) reported a high rate of nickel sensitization. Thirty-three of 57 children (57.9%) reacted to nickel, and all reactions were relevant. However, as mentioned earlier, these children were 10–19 years old. In the study by Vozmediano and Hita (29), 15 children of 52 (28.8%) reacted to nickel, and 13 of these reactions were relevant. In this study, the children were aged 0–15 years. None of the positive reactions to nickel was observed in the 0–5-year-olds, three were observed among the 6–10-year-olds, and 12 were observed among the 11–15-year-olds; all of these were observed in girls. Czarnobilska et al. (33), however, found no significant difference in the frequency of nickel allergy between 7-year-old and 16-year-old schoolgirls.

Hogeling et al. (4) found little difference in the frequency of nickel sensitization between girls and boys, and Czarnobilska et al. (33) noted an even higher frequency of nickel contact allergy among 7-year-old boys. However, the majority of studies found a tendency for girls to have a higher number of positive reactions to nickel than boys, which is in accordance with previous data (7, 17). The authors agree that the most important cause of nickel sensitization is exposure to metal in clothing and jewellery, for instance through ear piercing (5, 24). Seidenari et al. (26) did, however, find more nickel-sensitized girls than boys under the age of 4 years, and did not find ear piercing to be a risk factor in this age group, being performed in only 17% of the cases.

Most studies have found that the frequency of patch test reactions to nickel increases with age; others, however, have reported the opposite pattern. Zug et al. (20) found relevant reactions to nickel among 0–5-year-old children, but stated that, even though sensitization can and does occur early in life, this does not necessarily mean that it is the cause of clinical disease.

Wöhrl et al. (27) found nickel to be responsible for 32.4% of the positive patch test reactions in children aged 1–10 years. Among 21–30-year-olds and in patients aged >70 years, nickel was responsible for 28.4% and 11.2% of positive test reactions, respectively. The authors suggested that their findings may indicate very high susceptibility to sensitization by common contact sensitizers early in life, which, according to the authors, seems to be particularly obvious in the study of nickel hypersensitivity. Wöhrl et al. did not include information on clinical relevance in their paper, and pointed out that this is 'somehow limiting'.

Heine et al. (31) studied two different age groups. In the older age group (13–18 years), nickel was the most common sensitizer. In the younger age group (6–12 years), this was thimerosal, followed by benzoyl peroxide. The authors did not find any of the reactions to the latter to be relevant. They highlighted the fact that the irritant capacity of benzoyl peroxide should

be kept in mind, and stated that the reactions were most likely to be false positives. In this study, *Myroxylon pereirae*, fragrance and lanolin were common allergens in an adult control group, but were rarely positive in children and adolescents. According to the authors, this indicates differences in the contact allergen profile between different age groups. Zug et al. (20) compared the results of patch testing children and adults, and found that children were more likely to have positive reactions to nickel, cobalt, and thimerosal, whereas adults were more likely to have positive reactions to neomycin, fragrance mix, and *M. pereirae*. The authors suggested that this difference in patch test reactivity to different allergens between different age groups reflects the differences in age at exposure, and the frequency, type and length of exposure required to induce sensitization.

In four studies, fragrances were the second most common allergens (5, 18, 30, 35). In the study by Clayton et al. (5), fragrance was responsible for 11% of the positive reactions, and almost all of these were relevant (87.5%). The authors attributed the fragrance allergy in children to the increased production of perfumed products made specifically for children. They also suggested that it may be attributable to girls being more likely to wear perfumed cosmetics and hair products, and that young children may play with cosmetics. In the study by Roul et al. (18), 9.5% of positive reactions were to fragrance. The authors stated that clinical relevance 'was found in most cases', and explained this by the use of cosmetics or other topical products containing fragrances.

Several studies found thimerosal to be one of the most common allergens causing patch test reactivity (11, 19, 20, 25, 26, 29, 31–33). It is used as an antiseptic, disinfectant and preservative agent in contact lens solutions, eye drops, and vaccines (16), and is generally thought to have low clinical relevance (20, 22). Thimerosal was relevant in eight of 18 positive reactions in the study by Vozmediano and Hita (29). In the study by Goon and Goh (30), 15% had a positive reaction to thimerosal. However, these reactions were not relevant in 83.5% of cases. Similarly, in the study by Zug et al. (20), patch tests with thimerosal gave positive results in 15.4% of cases, and the authors found little to no current or past relevance of this allergen in their study population. Even though Hammonds et al. (23) found that 7% of thimerosal tests gave positive results and a high relevance of 70%, the authors agreed with the general assumption that this allergen has little true relevance to the patients' dermatitis.

One study differs from the rest in terms of the most common allergens. In the study by Sarma and Ghosh (28), 70 children were tested with the Indian baseline series of 27 allergens. The patch tests were read on days 2, 4, and 7. According to the authors, an effort was made to distinguish allergic reactions from irritant reactions, in order to ensure that only true allergic reactions were included. However, doubtful results showing persistent reactions of the same or an increased grade on day 2 or 7 were considered to be allergic and counted. Paraben mix (43%), potassium dichromate (27%) and fragrance (26%) were the top three allergens. Thirty-six per cent of reactions to paraben mix were relevant. The authors suggested that this finding could be explained by the fact that the concentration of parabens used in Indian goods may be higher than the usual levels. The top three allergens reported by Jacob et al. (22) in 2010 are also noteworthy. In this study, the authors found that cocamidopropyl betaine caused ACD as frequently as nickel (23.3%). However, strong indications exist that cocamidopropyl betaine is an irritant that often causes false-positive reactions (36).

Another common allergen was cobalt (4, 5, 11, 20, 21, 23, 28, 32, 33). In the study by Hogeling et al. (4), 68% of patients with cobalt allergy also had a positive patch test reaction to nickel. The authors therefore regarded this as co-sensitization caused by a primary nickel allergy. Patch test reactivity to cobalt is often found associated with sensitization to nickel, and this is thought to be attributable to the metals being commonly associated with one another. The significance of an isolated positive cobalt patch test reaction is often difficult to determine, and cobalt allergy is therefore usually synonymous with metal or nickel allergy (7, 12, 16).

Discussion

This review summarizes the main findings from published studies on the prevalence of patch test reactivity and ACD in selected paediatric populations during the period 1999–2010. The authors reported positive patch tests in 26.6–95.6% of the cases and an associated relevance in 51.7–100% of those with positive patch test reactions (Tables 1 and 2).

The studies presented differ in several parameters, which makes comparisons difficult and complicates the drawing of strong conclusions. The selected patient populations varied in size from 65 to 2460 patients, and the studied age groups varied from infants to young adults up to the age of 21 years. Furthermore, the results are difficult to compare, owing to variations in demographic, clinical and technical factors, such as age, sex, inclusion criteria, selection of patch test series, and patch test methodology. However, when comparing studies from different parts of the world, there are no distinct differences

in sensitization rates, and the most common allergens do not differ significantly (Tables 1 and 2).

The studies reviewed all used the same concentrations of allergens as used in adults, but the selection and number of allergens differed. Overall, the majority of studies presented high numbers of negative patch test results, suggesting that children tolerate the same allergen concentration as adults, and the authors generally agreed that modification of allergen concentrations for patch testing children is unnecessary (18, 20, 26).

The North American studies present rather high sensitization rates (65.7–95.6%), but they all used test series with a high number of allergens (4, 19, 20, 22, 23). The highest rates of relevant reactions were reported by authors who customized the patch test series according to the history of the child or supplemented the standard series with relevant allergens.

Other technical differences include the inclusion criteria and the evaluation of patch tests. Most studies described children who were referred for patch testing because of suspected ACD (4, 21, 25, 26, 28, 29, 31, 32), others described children who were referred because of recalcitrant atopic dermatitis (11, 19, 24), and yet others provided no information on reasons for referral (5, 20, 23, 35). The differences in referral criteria could undoubtedly be a source of bias. Furthermore, in the presented studies, dermatologists or paediatricians, who have different backgrounds and training, carried out readings. This could also potentially bias the results, as the differentiation between allergic and irritant reactions requires substantial dermatological training and education (34). Furthermore, some studies evaluated patch test results on days 2 and 3 only, which implies a risk of missing late positive reactions (37).

Generally, the belief is that sensitivity to contact allergens increases with age through childhood and adolescence, because of increased environmental exposure to contact allergens. However, both previous and recent studies have reported high sensitization rates in younger children (1, 8, 18, 26, 27, 38). Although some authors from the present review found no difference in sensitization rates between different age groups (4, 19, 23, 28, 31), the majority of studies reviewed agreed that the frequency of positive patch test reactions increases with age (5, 24, 28, 29, 32), and it seems reasonable to question the reliability of patch test results in infants and very young children; the high rates of reactivity could be explained by the occurrence of non-specific or irritant reactions.

The majority of studies found higher sensitization rates among girls (5, 21, 25–27, 29, 32); however, all studies had different girl/boy ratios, and most of them had a preponderance of girls. Table 3 shows the studies that provided exact information on sex distribution. Despite the fact that more girls were tested, the likelihood of having a positive patch test reaction did not differ between the sexes.

The question of whether children suffering from atopic dermatitis are more prone to ACD than non-atopic individuals has been controversial. Active skin disease, such as atopic dermatitis or even irritant contact dermatitis, disturbs the integrity of the epidermal barrier, allowing potential allergens to penetrate (39), and several authors have previously stressed the risk of overlooking ACD in children with atopic dermatitis (40, 41). Accordingly, some authors reported higher sensitization rates in children with atopic dermatitis, although relevance was either low or not considered (5, 28). Previously, it was a fairly common belief that children with atopic dermatitis were less likely to suffer from ACD, and several authors reported a decreased frequency of patch test reactivity among adult atopic individuals (7, 39). Most recent studies, however, found no difference in rates of sensitization or ACD in atopic dermatitis children as compared with non-atopics (18, 20, 24–26, 29, 30, 32). There are several possible reasons for the variation in results between studies. First, the methodologies used differed: study design, criteria for atopic dermatitis, the severity of the disease at the time of the study, age and sex distribution, allergens included, and patch test evaluation. The criteria for the diagnosis of atopic dermatitis differed between studies. Most studies used the Hanifin and Rajka criteria, but, often, the criteria for atopic dermatitis were not revealed. Furthermore, reasons for referral differed. Some studies included children who were referred in order to exclude ACD as the reason for exacerbation of atopic dermatitis (11, 24), whereas other studies included only children with suspected ACD (18, 26, 29). Table 4 shows the results of the studies that compared sensitization rates between children with atopic dermatitis and non-atopic children. Only the studies that provided exact numbers are included. When selected groups of children with suspected ACD are compared, children with atopic dermatitis are as frequently sensitized as children with no history of atopic dermatitis. It is, however, noteworthy that most studies reported sensitization rates of $>50\%$ among atopic children; this could indicate that too few children with atopic dermatitis are patch tested (12).

Recently, the key role of the protein filaggrin in maintaining an effective skin barrier against the external environment has been shown (42). Lack of expression of filaggrin has been shown to increase the risk of developing allergic sensitization and atopic dermatitis (43, 44), but the association between mutations in the filaggrin gene and ACD in children remains to be thoroughly explored.

Table 3. Sex distribution of selected studies

Author	Children (n)	Female (n)	Male (n)	Female/male ratio[a]	Females with PPT (%)	Males with PPT (%)	Ratio of females/males with PPT[b]
Clayton et al.	500	310	190	1.63	30.0	21.1	1.40
Vozmediano	96	64	32	2	56.3	50.0	1.10
Seidenari et al.	1094	585	509	1.15	51.3	53.0	0.97
de Waard-van der Spek	79	48	31	1.59	45.8	58.1	0.79
Czarnobilska et al.[c]	96	54	42	1.29	31.5	59.5	0.53
Czarnobilska et al.[d]	133	88	45	1.96	58.0	42.2	1.37
Hammonds et al.	136	89	47	1.89	65.2	53.2	0.82
Milingou et al.[e]	232	145	87	1.67	53.1	39.1	1.36
Milingou et al.[f]	255	162	93	1.74	61.1	58.1	1.05
Total[g]	2621	1545	1076	1.44[h]	48.7	46.6	1.05[h]

PPT, at least one positive patch test reaction.
[a]Number of girls/number of boys.
[b]Share of girls with at least one positive patch test reaction/share of boys with at least one positive patch test reaction.
[c]Seven years old.
[d]Sixteen years old.
[e]1980–1993.
[f]1994–2007.
[g]Sum of absolute figures.
[h]Average share.

Table 4. Distribution of children with/without atopic dermatitis in selected studies

Author	Children (n)	With PPT (n)	With AD (n)	With AD + PPT (n)	With AD + PPT (%)	Without AD (n)	Without AD + PPT (n)	Without AD + PPT (%)
Roul et al.	337	226	257	165	64.2	80	61	76.3
Duarte et al.	102	57	49	25	51.0	53	32	60.4
Vozmediano et al.	96	52	27	14	51.9	69	38	55.1
Seidenari et al.	1094	570	404	223	55.2	690	347	50.3
Beattie et al.	114	61	27	10	37.0	83	51	61.4
de Waard-van der Spek	79	40	47	22	46.8	32	18	56.3
Milingou et al.[a]	232	111	73	32	43.8	159	79	49.7
Milingou et al.[b]	255	153	122	67	54.9	133	86	64.7
Total[c]	2309	1270	1006	558	55.5[d]	1299	712	54.8[d]

AD, atopic dermatitis; PPT, at least one positive patch test reaction.
[a]1980–1993.
[b]1994–1007.
[c]Sum of absolute figures.
[d]Average share.

Conclusion

Data from the past decade show us that contact allergy is common in the paediatric population, and should always be considered when children with recalcitrant eczema are encountered.

We reviewed the recent literature and found reported sensitization rates of 26.6–95.6% in selected groups of children with suspected ACD, which is higher than the prevalence found in similar material from 1982 to 1998 (7). The associated relevance was 51.7–100%. Neither sex nor the presence or absence of atopic dermatitis seems to influence the risk of ACD in children. When tailored patch tests with allergens appropriate to the presenting history are used, the rate of positive patch test reactions increases, which should also reduce the risk of false-positive results. The more you look, the more you will find. Patch testing with high numbers of allergens will inevitably produce high sensitization rates, which is why assessment of relevance is of utmost importance. Ideally, children should be patch tested with a selection of allergens having the highest proportion of positive, relevant patch test reactions. From our review of the current data, we find it appropriate to use the European baseline series supplemented with allergens according to the child's history. Patch test readings should be carried out by dermatologists, and standardized methods for the evaluation

of relevance should be used. Children and adults can be tested with equal concentrations of patch test allergens. The allergen exposure pattern differs between age groups, and adolescents may be exposed to occupational allergens. For future investigation in this area, we therefore recommend that different age groups be separated.

The probability of a true increase in the prevalence still remains to be elucidated. A study on a large selected cohort with statistical analysis that accounts for all possible confounders could be valuable.

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