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Allergic contact dermatitis in children and proposal for an Australian Paediatric Baseline Series

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Title: Allergic Contact Dermatitis in Children and Proposal for an Australian Paediatric Baseline Series

Running Title: Paediatric Allergic Contact Dermatitis

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Article type : Original Research

Title: Allergic Contact Dermatitis in Children and Proposal for an Australian Paediatric Baseline Series

Abstract:

Background: Allergic contact dermatitis (ACD) is an increasingly common diagnosis in children. The objectives of this study were to review our experience with ACD in children in tertiary settings, to ascertain the spectrum of allergens in this population, and to subsequently propose the first Australian Paediatric Baseline Series for patch testing.

Methods: We conducted a retrospective analysis of patch test data from 1993-2017 from two tertiary referral patch-testing centres in Melbourne, Victoria.

Results: A total of 511 children were patch tested during the study period. Of these, 58.3% (298/511) of children tested had a positive patch test, and 65.1% (194/298, or 38.0% of the total) had a relevant positive patch test. The most common relevant patch test reactions were to fragrance mix, methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) and methylisothiazolinone (MI), *Myroxylon pereriae*, nickel sulphate, and colophonium.

Conclusion: Allergic contact dermatitis is not uncommon in children and patch testing should be considered in children with suspected ACD or with recalcitrant atopic dermatitis.

Based on our experience over 25 years, we propose the first Australian Paediatric Baseline Series.

Key words: allergic contact dermatitis, patch testing, paediatric, children, allergens

Main Text:

Introduction:

Allergic contact dermatitis (ACD) is an immune-mediated condition, with a primary sensitisation phase followed by secondary elicitation by haptens, leading to activation of T lymphocytes. Patch testing is the gold standard for the diagnosis of ACD. Patch testing appears to be performed infrequently in children, and consequently ACD is likely underdiagnosed (1, 2). This is unfortunate, because ACD can have a significant impact on a child's quality of life, and early, correct, identification of allergens and subsequent avoidance can lead to substantial improvement in symptoms, preventing progression to a chronic disease state (3).

Historically the prevalence and significance of ACD in children has been underestimated. It was previously believed that ACD was uncommon in children, who were thought to have immature immune systems and limited exposure to allergens (4, 5). Now ACD is increasingly recognised in paediatric populations (6). The rate of positive patch tests in children has been increasing, with a 2011 meta-analysis finding higher positive rates in studies published after 1995 (7). Studies of paediatric populations have found positive patch test reaction rates of 54% – 65%, and sensitisation has been considered to be relevant in 61% – 91% of those tested (2, 8, 9). Reported rates of relevant reactions are in fact higher than in adult patch testing, which would fit with the fact that proportionately fewer children are being tested, perhaps only when there is a very high suspicion of ACD (10).

The objective of our study was to estimate the prevalence of ACD in children attending two tertiary patch-testing clinics, which provided most of the patch testing services in Victoria in this time period, and to determine which allergens were the most common and relevant in this population. This information would be used to propose the first Australian Paediatric Baseline Series.

Materials/Methods:

Patients:

Results of patch testing were retrospectively reviewed from 3 sources at 2 locations**.**

(i) Contact Dermatitis Clinic at Monash Medical Centre from January 1, 1993 to December 31, 2017

(ii) Occupational Dermatology Clinic from January 1, 1993 to December 31, 2017 at Monash Medical Centre and then at the Skin and Cancer Foundation

(iii) Contact Dermatitis Clinics at the Skin and Cancer Foundation Inc from January 1, 2002 to December 31, 2017.

Patients were referred to these specialist tertiary clinics for further assessment of suspected contact dermatitis. Children were defined as 17 years old and under.

There were many apprentice hairdressers aged 17 or under attending the Occupational Dermatology Clinics, so we examined our data with hairdressing apprentices included and excluded.

Ethics:

As this was deemed to be a low risk retrospective analysis of our database, the study was reviewed in-house by the Skin and Cancer Foundation Inc. Quality Assurance Committee.

Patch Testing:

Prior to 2012, children were tested to an extended European baseline series (11). From 2012, the Australian Baseline Series (ABS) was tested (10), although not all children were

tested to the whole ABS, because of limited body surface area. Additional allergens were tested based on history of exposures and the use of the patients' own products. Readings were performed on days 2 and 4 according to the International Contact Dermatitis Research Group guidelines. Relevance was based on a positive patch test reaction to an allergen with a reaction of 1 + or greater, a compatible clinical history of contact dermatitis and exposure to the allergen.

Statistical Analysis:

We performed the Chi square test to compare the percentage of female versus male subjects, atopic versus not atopic subjects, occupational versus non-occupational cases, and differences in the site of the rash (hands, legs, face), between children and adults.

We also performed the Chi square test to compare the percentage of female versus male subjects with relevant positive patch test reactions to the ten most common relevant allergens listed in table 3. We considered differences to be statistically significant at $p < 0.05$.

Results:

A total of 9658 patients were patch tested in the period January 1, 1993 to December 31, 2017. Of these, 511 (5.3%) were children, 61.1% (312/511) were female and 38.9% (199/511) were male. The median age of children patch tested was 14, with an interquartile range of 5. 35% (175/511) of children tested were initially assessed to be atopic, based on a personal history of asthma, eczema or hay fever.

Table 1 compares this data to adults tested in the same period. There was no significant difference in the percentage of female patients ($p = 0.153$) nor atopy ($p = 0.292$) between children and adults. Not surprisingly, there were significantly more occupational cases in adults (24.5%) compared with children (8.2%), $p < 0.0001$. With regards to the distribution, there was significantly more hand dermatitis in adults (38.3%) compared with children (24.5%) ($p < 0.0001$), and significantly more leg dermatitis in children (10.2%) compared with adults (7.6%) ($p = 0.037$).

Where possible, patients were assigned multiple diagnoses listing the contributing factors to their skin condition. Following patch testing, almost 50% (255/511) of children had a primary, secondary, or other diagnosis of endogenous eczema (atopic dermatitis) (AD). The most common primary diagnosis in children was AD (41.5%, 212/511), followed by ACD (36.2%, 185/511), irritant contact dermatitis (ICD) (8.2%, 42/511), contact urticaria (1.8%, 9/511) and latex allergy (0.2%, 1/511). ACD was a secondary diagnosis in 11.9% (61/511) of children. Overall, ACD accounted for 38.7% (258/668) of total diagnoses in this population, while 169/511 children had multiple diagnoses.

In comparison, ACD was the most common primary diagnosis among adults patch tested during the study period, followed by AD and ICD.

Overall sensitisation rates were 58.3% (298/511), and 65.1% (194/298) of these children or 38.0% of the total (194/511) were found to have one or more relevant reactions.

Table 2 reports the most common reactions in the cohort including the 26 hairdressing apprentices, and also includes the percentage of relevant reactions. Fragrance mix, nickel sulphate, *Myroxylon pereriae*, colophonium and cobalt were the most common allergens in this population, while the allergens with the most number of relevant reactions were fragrance mix, methylchloroisothiazolinine/methylisothiazolinone (MCI/MI) and methylisothiazolinone (MI) combined, *Myroxylon pereriae,* nickel sulphate and colophonium. In addition, hairdressing allergens also figured highly in terms of the numbers of relevant reactions and included p-phenylenediamine (PPD), ammonium persulphate, toluene diamine sulphate, p-aminophenol and glyceryl monothioglycolate.

Table 3 reports the relevant reactions noted in males versus females (excluding hairdressers). Relevant positive patch test reactions to nickel sulphate were more common in females compared with males ($p = 0.013$). There were no statistically significant differences in relevant reactions observed between the sexes for the other nine most common relevant allergens listed.

Relevant reactions are further assessed in age groups (Table 4). Very few children were tested in the 0 to 5 age group with the majority tested aged between 11 to 17. Fragrance mix and colophonium were the most common allergens in the 6-10 age group with *Myroxylon pereriae*, fragrance mix and nickel sulphate the most common in the 11-17 age group, excluding the apprentice hairdressers.

Discussion:

In our retrospective analysis of patch testing performed in children aged 17 or less at two tertiary referral patch testing centres in Melbourne between 1993 and 2017, we found a sensitisation rate of 58.3%, with 65.1% of these reactions being relevant, meaning that 38.0% of those patch tested had a relevant reaction to their presenting skin condition. These rates are similar to those of other large studies of paediatric patch testing (2, 8, 9). The most common relevant allergens found in our study, once apprentice hairdressers were excluded, were fragrance mix, MCI/MI together with MI, *Myroxylon pereriae*, nickel sulphate and colophonium.

The higher rates of relevant positive patch tests in females to nickel is consistent with the literature, and likely attributable to the increased use of jewellery in females (8). Nickel has been a commonly identified allergen in many studies of ACD in children (8, 12, 13). Nickel may be found not only in jewellery, but also in children's toys, metal components of children's clothing, and some mobile phones and electronic equipment. Nickel allergy has been shown in multiple studies to be more common in people with piercings (14). Nickel allergy is associated with wearing jewellery and earrings, and so is not surprisingly more common in females. Some studies have attributed an increased incidence of ACD in females to nickel allergies alone (2, 12, 13).

Fragrance mix allergy is increasing in children, possibly because of its increased use in cosmetics and the fact that children are using a wider range of cosmetics earlier in life (12). *Myroxylon pereirae*, which is also a fragrance allergen, is found in cosmetics, skincare products and flavourings in foods, such as tomato sauce and pizza sauce (1, 15).

MCI/MI and MI are preservatives which have been extensively used in cosmetics, wet wipes, liquid soaps, shampoos and other skincare products. Rates of contact allergy have increased

significantly in recent years. At our tertiary patch test centre in Melbourne, 2787 patients were tested with MI over 7 years from 2011 – 2017, and 14.5% had positive patch test results, with 77% deemed to be relevant reactions. The percentage of positive reactions to MI peaked at 20.3% in 2015, and remained high at 11.4% in 2017 (16). It is important to test for both MCI/MI and MI. Testing for only MCI/MI can mean up to 40% of patients with MI contact allergy are missed (12). It is not surprising that the MI epidemic has also affected the paediatric population (17), considering that common sources of MI include baby wipes (18) and the emerging childhood hobby, "slime" (19). Contact allergy to MCI/MI has been detected in up to 11% of children referred for patch testing (20).

Colophonium allergy is most often associated with adhesive dressings (2). Although colophonium sensitisation can be a marker of fragrance allergy, it may also relate to exposure to leather shoes, lipstick, and playing musical instruments (2).

This is the first study to investigate paediatric patch testing results in Australia. There have been similar large studies in the US and Europe, with notable differences in relevant allergens when compared with our study. Patterns of positive and relevant patch testing results have been shown to vary with geographic location, hence the importance of constructing a series from local data (9). For example, the most common sensitisers in a German population of children in 2004 were thimerosal, benzoyl peroxide, phenylmercuric acetate, gentamicin sulphate, nickel sulphate, ammoniated mercury, cobalt chloride, fragrance mix, bufexamac, compositae mix, propylene glycol and oil of turpentine: many of these are uncommon in our population (21). Similarly, the topical antibacterials neomycin and bacitracin are common relevant allergens in the US, where they are readily available over the counter and often marketed towards children (8). In our study neomycin was detected as an allergen in only 4 out of 487 children tested (0.8%) and was deemed to be relevant in only 1 case.

We have proposed the first Australian Paediatric Baseline Series predominantly based on the most common and relevant allergens found in this study, together with input from our team of experienced patch testers (Table 5). It is of course important to combine patch testing with careful history taking which may elicit any unusual exposures, as well as test the patients' own products. One of the first decisions to be addressed is the size of the series. The decreased surface area available for testing in children means that testers must be

judicious in their allergen selection, and use a focused, exposure-targeted baseline series (22). Our group previously decided to include 60 allergens in the Australian Baseline Series for patch testing in adults (10).

Recently, the European Academy of Allergy and Clinical Immunology (EAACI) position paper proposed a patch test series in children of just 9 allergens (nickel sulphate, thiuram mix, colophonium, mercaptobenzothiazole, fragrance mixes 1 and 2, mercapto mix, MCI/MI and sesquiterpenelactone mix) with an additional series of 12 allergens to be used according to history and exposure (23).

We have given some consideration to the proposal of a patch test series for infants. However, we have decided against this, given that our results from testing this age group arose from only 20 cases and some of these allergens related to very specific exposures, including bufexamac, toluene sulfonamide resin and benzophenone 3. When assessing very small children who have limited space for testing, consideration needs to be given to their actual exposures and the tests selected accordingly.

Based on our results and our expert input, we decided on a panel of 30 allergens. It was also decided to construct the Australian Paediatric Baseline Series to be relevant to the average non-working child, which meant that the common hairdressing allergens found in our population which included hairdressing apprentices, were not included. While PPD may be found in temporary 'black henna' tattoos, our usual practice is not to patch test these children, preferably making a clinical diagnosis, so this was not included in the proposed series.

Other allergens which recorded relatively high numbers in our study and yet were not included in the series were Dermatophagoides mix, nutmeg and hydroabietyl alcohol. Despite some historical popularity and relevant reactions documented here, testing to Dermatophagoides mix has largely been discredited over time (24, 25). Nutmeg is known to irritate and had a low rate of relevant reactions. Hydroabietyl alcohol is a proxy for colophonium allergy (26).

On the other hand, emerging fragrance allergens included in the proposed series include hydroperoxide of linalool and hydroperoxide of limonene (27).

Given that almost half the patch-tested children in our study ultimately had a diagnosis of AD, as either a primary, secondary or other diagnosis, it was decided to include a number of topical corticosteroids in the proposed series. Although topical steroid allergy is rare (28), allergic contact dermatitis to topical treatments in AD is not (29).

A prospective study of 641 children with AD assessed the frequency of sensitisation to 7 common topical treatments, and found emollients to be among the most common allergens, testing positive in 3%, along with antiseptics, in particular chlorhexidine (29). Positive patch tests to topical steroids were rare in this study, however this could be partly because only two topical corticosteroids, tixocortal pivalate and budesonide, were included in the testing. Other studies have noted an association between AD and corticosteroid contact allergy (30, 31). Another study reported a contact sensitisation rate of 30% in children with AD, with a relevant allergen in 17% of children, while 8% of children with AD had a contact allergy to an ingredient of a skincare product (32). Contact allergy to topical treatments is not uncommon and should be suspected in children with AD not responding to topical treatment. Patch testing should of course be considered when ACD is suspected, including cases of predominantly hand or foot dermatitis (33), or dermatitis affecting the diaper area in younger children (34). Studies have shown that ACD is frequently missed in patients with AD (33).

While there were relatively few cases of sunscreen allergy detected in our patients, concern about sunscreen reactions is a common reason for referral of children for patch testing, so several sunscreens have been included in the proposed series. Finally, we included propolis, based on our finding of some relevant reactions to its inclusion in skincare products.

The limitations of our study include its retrospective design and the long duration of the study period dating back to 1993. While this has allowed for a large sample size, it has also meant that allergens which may have been more relevant in the 1990s and early 2000s, and possibly not as relevant in 2019, have also been included in the data. However, the Australian Paediatric Baseline Series was comprised not only from this data, but also from the opinion of experienced patch testers. Furthermore, it will undergo continued surveillance and periodic revision on a triennial basis, as does the ABS.

Patch testing may be problematic and quite inconvenient in children, because of their increased tendency to activity. They may also be fearful of patch testing, especially if they have recently experienced prick testing (22). Strategies that some patch testing centres have used to encourage compliance include demonstrating the test on the child's parent, careful reinforcement of patches with medical tape, distraction tools, and rewards systems (22, 34).

Patch testing enables accurate allergen identification. It has the potential to improve the quality of life in children, prevent prolonged exposure to allergens and progression to chronic disease. Our data show that ACD is a relevant diagnosis in children in over a third of cases assessed, although the majority of patients had a primary diagnosis of AD. We found fragrance mix, MI/MCI and MI, *Myroxylon pereriae*, nickel sulphate and colophonium to be the most relevant allergens. Children with suspected ACD should of course be patch tested, but we also recommend patch testing in children with persistent or treatment refractory AD. Based on our extensive data, we propose the first Australian Paediatric Baseline Series to guide patch testing in children.

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Tables:

Table 1: Demographics of children compared with adults

	Children	**Adults**	**P value**
Number	511	9147	-
Female	312 (61.1%)	5870 (64.2%)	P = 0.153
Atopy	175 (34.2%)	2928 (32.0%)	P = 0.292
Occupational/ Work-related	42 (8.2%)	2243 (24.5%)	P < 0.0001
Hand dermatitis	125 (24.5%)	3505 (38.3%)	P < 0.0001
Leg dermatitis	52 (10.2%)	699 (7.6%)	P = 0.037
Face dermatitis	108 (21.1%)	2148 (23.5%)	P = 0.222
Median age	14 (IQR* = 5)	42 (IQR* = 25)	

*IQR = Interquartile range

Table 2: Most common reactions including the percentage of relevant reactions (including hairdressing apprentices)

	Allergen	No. Tested	No. Positive	No. Relevant	Relevant/ positive (%)
1	Fragrance mix	499	48	22	45.8
2	Nickel sulphate	505	42	14	33.3
3	*Myroxylon pereriae*	497	33	18	54.5
4	Colophonium	499	28	14	50.0
5	Cobalt chloride	492	26	7	26.9
6	Dermatophagoides mix -	52	21	10	47.6
7	4-Phenylenediamine base (PPD)	491	19	18	94.7
8	Nutmeg	78	17	4	23.5
9	Hydroabietyl alcohol (abitol)	261	16	9	56.3
10	Ammonium persulphate	90	15	14	93.3
11	Methylchloroisothiazolinone/ Methylisothiazolinone (MCI/MI)	501	15	11	73.3
12	Toluene-2,5-diamine sulphate	38	13	13	100.0
13	Propolis	384	13	5	38.5
14	Amerchol L 101	436	12	4	33.3
15	Potassium dichromate	495	12	7	58.3
16	Methylisothiazolinone (MI)	150	11	11	100.0
17	Formaldehyde	501	9	5	55.6
18	4-Aminophenol	37	8	8	100.0
19	Lanolin alcohol	499	8	4	50.0
20	Thiuram mix	499	7	5	71.4
21	Diazolidinylurea (Germall 2)	497	6	5	83.3
22	Mercapto mix	498	6	6	100.0
23	2-Nitro-4-phenylenediamine	37	5	5	100.0

24	3-Aminophenol	37	5	5	100.0
25	Potassium dichromate 0.25%	79	5	5	100.0
26	Black rubber mix	493	5	4	80.0
27	Mercaptobenzothiazole (MBT)	497	5	5	100.0
28	Hydroperoxides of linalool	18	4	4	100.0
29	Glyceryl monothioglycolate	31	4	4	100.0
30	Propylene glycol	319	4	4	100.0
31	Coconut diethanolamide	473	4	4	100.0

Table 3: Most common relevant reactions in females and males (excluding hairdressing apprentices)

Allergen	**Females**				**Males**				**P value**
	No. Tested	**No. Positive**	**No. Relevant**	**Relevant/ tested (%)**	**No. Tested**	**No. Positive**	**No. Relevant**	**Relevant/ tested (%)**	
Fragrance mix 1	305	26	16	5.2	194	22	6	3.1	P = 0.253
Myroxylon pereriae	305	21	13	4.3	192	12	5	2.6	P = 0.337
Nickel sulphate	308	34	13	4.2	197	8	1	0.5	P = 0.013
MI	103	9	9	8.7	47	2	2	4.3	P = 0.329
Colophonium	305	18	9	3	194	10	5	2.6	P = 0.805
Dermaphagoides mix	28	14	8	28.6	24	7	2	8.3	P = 0.065
MCI/MI	307	10	7	2.3	194	5	4	2.1	P = 0.871
Hydroabietyl alcohol (abitol)	181	10	6	3.3	80	6	3	3.8	P = 0.859
Cobalt chloride	301	18	5	1.7	191	8	2	1	P = 0.575
Potassium	302	5	3	1	193	7	4	2.1	P = 0.321

dichromate									

Table 4: Most frequent relevant reactions according to age groups (including hairdressing apprentices)

Ages 0-5					**Ages 6-10**					**Ages 11-17**				
Allergen	**No. Tested**	**No. Positive**	**No. Relevant**	**Relevant/ tested (%)**	**Allergen**	**No. Tested**	**No. Positive**	**No. Relevant**	**Relevant/ tested (%)**	**Allergen**	**No. Tested**	**No. Positive**	**No. Relevant**	**Relevant/ tested (%)**
Bufexamac	4	1	1	25.0	Fragrance mix 1	72	14	6	8.3	PPD	406	18	18	4.4
Fragrance mix II	5	1	1	20.0	Colophonium	74	6	5	6.8	*Myroxylon pereriae*	410	30	16	3.9
MI	5	1	1	20.0	MCI/ MI	75	5	3	4.0	Fragrance mix I	410	33	15	3.7
Benzophen-one 3	10	1	1	10.0	MI	12	3	3	25.0	Ammonium persulphate	87	15	14	16.1
Cocamido-propyl betaine	12	1	1	8.3	Lemon grass oil	3	2	2	66.7	Nickel sulphate	414	36	13	3.1
Toluene-sulfon-amide resin	13	1	1	7.7	Grevillia flower	5	3	2	40.0	Toluene – 2,5 – diamine sulpha	37	13	13	35.1

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Amerchol L 101	14	1	1	7.1	Dermaphag-oides mix	6	3	2	33.3	Colophonium	409	22	9	2.2
Nickel sulphate	16	2	1	6.3	Potassium dichromate 0.25%	13	2	2	15.4	p-Aminophenol	37	8	8	21.6
Fragrance mix I	17	1	1	5.9	Hydroabietyl alcohol (abitol)	25	4	2	8.0	Dermapha-goides mix	44	18	8	18.2
MCI/MI	18	1	1	5.6	Potassium dichromate 0.5%	70	3	2	2.9	MI	124	7	7	5.6
Germall II	19	1	1	5.3	Black rubber mix	72	2	2	2.8	Hydroabietyl alcohol (abitol)	231	12	7	3.0
					Myroxylon pereriae	72	3	2	2.8	MCI/MI	408	9	7	1.7
					Mercapto mix	73		2	2.7	Cobalt chloride	409	20	6	1.5
										2-Nitro	36	5	5	13.9

										– 4-pheny lenedi amine				
										Potass ium dichro mate 0.5%	410	9	5	1.2
										Thiura m mix	411	7	5	1.2
										Forma lde-hyde	412	9	5	1.2

Table 5 – Proposed Australian Paediatric Baseline Series

	Allergen
1	Nickel sulphate
2	*Myroxylon pereriae*
3	Colophonium
4	Diazolidinylurea (Germall 2)
5	Mercaptobenzothiazole (MBT)
6	Formaldehyde
7	Potassium dichromate
8	Lanolin alcohol (wool alcohol)
9	Hydroperoxides of linalool
10	Cobalt chloride

11	Paraben mix
12	Thiuram mix
13	Mercapto mix
14	Fragrance mix I
15	Methylchloroisothiazolinone/methylisothiazolinone
16	Fragrance mix II
17	Tixocortol-21-pivalate
18	Budesonide
19	Propylene glycol
20	Methylprednisolone aceponate
21	Hydroperoxides of limonene
22	Benzophenone 3 (2-hydroxy-4-methoxy-benzophenone)
23	Benzophenone 4 (2-hydroxy-4-methoxy-benzophenon-5-sulfonic acid)
24	Amerchol L 101
25	Betamethasone -17, 21 dipropionate (Diprosone ointment)
26	2-Ethylhexyl-4-methoxycinnamate (Octinoxate)(Parsol MCX, Escalol 557)
27	Betamethasone-17-valerate
28	Triamcinolone acetonide
29	Methylisothiazolinone
30	Propolis