

Does Sensitization to Contact Allergens Begin in Infancy?

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ABSTRACT. *Objective.* Because previous studies have found allergic contact sensitization common in children by 5 years of age, our aim was to determine the prevalence of positive epicutaneous test results in children <5 years of age and to determine whether sensitization to contact allergens was as common in infancy.

Methods. We recruited 95 asymptomatic children 6 months to 5 years of age from well-child visits at Denver area pediatric practices for epicutaneous patch testing using the T.R.U.E. Test system. Allergens were placed on the skin for 48 hours, and at a later follow-up visit, positive reactions were evaluated.

Results. A total of 85 patients completed the study. Of these, 20 (24.5%) had 1 or more positive reactions to the tested allergens. Positive reactors ranged from 6 to 65.5 months of age, with an average of 30.4 months of age. Of the children, 16 reacted to 1 allergen, and 4 reacted to 2. Eleven positive reactions were observed to nickel, followed by 8 to thimerosal. Other positive reactions were to neomycin, cobalt, and kathon CG.

Conclusions. Children as young as 6 months of age may be sensitized to contact allergens. Within this pediatric population, the prevalence of sensitization is 24.5%. Sensitization to contact allergens may occur in infants. *Pediatrics* 2000;105(1). URL: <http://www.pediatrics.org/cgi/content/full/105/1/e3>; *allergic contact dermatitis, allergic contact sensitization, epicutaneous testing, infants, young children.*

ABBREVIATIONS. ACD, allergic contact dermatitis; PTBFR, p-tert butylphenol formaldehyde resin.

Allergic contact dermatitis (ACD) is an inflammatory reaction of the skin that follows percutaneous absorption of antigen from the skin surface and recruitment of previously sensitized, antigen-specific T lymphocytes into the skin. Contact allergens are usually low molecular weight substances that are able to penetrate the stratum corneum of the skin. These antigens are processed by epidermal, Langerhans' cells that migrate to regional lymph nodes. In the lymph node, the antigen is presented to T lymphocytes that undergo proliferation and clonal expansion. These T cells then enter the vasculature and circulate throughout the body. With subsequent exposure to the antigen, sensitized T lymphocytes release inflammatory mediators, pro-

ducing a localized dermatitis that may last 3 to 4 weeks if untreated. Depending on the strength of the allergen, 1 or many exposures are needed for this process to occur. Sensitization is long-lived, believed to be 30 years to a lifetime.¹⁻⁴

Although sensitivity to contact allergens occurs in ~10% of the adult population,⁵ the exact incidence and prevalence of sensitization in children is not known.⁶ Historically, it was believed that ACD was rare in children, owing to a presumed paucity of exposure to contact allergens and to a less susceptible immune system.⁷ There have been recent series, however, demonstrating a higher level of ACD in children than previously expected. Epicutaneous patch testing in symptomatic children with dermatitis has revealed positive reactions in 15% to 52% of subjects.⁸⁻¹⁹ Additionally, 2 previous studies have examined contact sensitization in asymptomatic, healthy children: Weston et al²⁰ found a sensitization rate of 20% and Barros et al²¹ found a rate of 13%.

All these studies have included a wide range of children, up to 18 years of age, with none exclusively addressing infants or young children. Aside from a few case reports describing ACD in children as young as 1 week of age,^{22,23} there is little in the literature regarding contact sensitization in the youngest children. Because the study of Weston and colleagues²⁰ demonstrated that contact sensitization occurs by the age of 5, our goal was to determine the prevalence of positive epicutaneous test results in children <5 years of age and to determine whether sensitization to contact allergens was as common at a very young age.

METHODS

Children between the ages of 6 months and 5 years who presented for routine well-child care at Denver area pediatric practices were recruited to participate in the study. Parents were given information about the study, and informed consent was obtained. General information regarding the age, sex, past medical history, and parental concerns about the child's skin also was obtained. Patients were not enrolled if they had an active dermatitis on their back, or if they had an infectious disease with fever, because the development of an exanthem could interfere with the interpretation of results.

We used the T.R.U.E. Test system for epicutaneous testing in this study. T.R.U.E. Test (Glaxo Wellcome, Research Triangle Park, NC) is a prepackaged, commercially available kit, containing 24 allergens (see Table 1 for allergens tested). Each antigen is impregnated in a .81 cm² polyester patch affixed to surgical tape. There are 2 rows of 6 equally spaced patches per strip of tape. These patches were placed on the child's upper back, outlined with ink to enable the reader to determine the location of the patches, and then reinforced with another layer of paper tape. Parents were given instructions to leave the patches in place for 48 hours and not to bathe the back during that time. The patches were removed at 48 hours by the parent at home, and the child returned to clinic

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TABLE 1. Allergens Tested

Allergen	Source
Nickel sulfate	Jewelry, fasteners
Wool alcohols (lanolin)	Emollients, soaps
Neomycin sulfate	Topical antibiotic
Potassium dichromate	Leather
Caine mix	Topical anesthetic
Fragrance mix	Fragrance
Colophony	Adhesive, sealant
Epoxy resin	Adhesive
Quinoline mix	Germicide
Balsam of Peru	Fragrance
Ethylenediamine dihydrochloride	Preservative
Cobalt dichloride	Metal-plated objects
p-tert butylphenol formaldehyde resin	Glues
Paraben mix	Topical medications, preservative
Carba mix	Rubber products
Black rubber mix	Rubber products
Cl+ Me-isothiazolinone (kathon CG)	Preservative
Quaternium-15	Preservative
Mercaptobenzothiazole	Rubber products
p-Phenylenediamine	Dye
Formaldehyde	Preservative
Mercapto mix	Rubber products
Thimerosal	Preservative
Thiuram mix	Rubber products

4 or 5 days (96 to 120 hours) after initial application of the patches to read the reactions. Reactions were scored according to the North American Contact Dermatitis Group scale: 0 = no skin change, 1+ = macular nonconfluent erythema or rim pattern, 2+ = confluent redness, and 3+ = redness plus blistering, each within the .81 cm² area. Reactions of 2+ and 3+ were considered significant, whereas 1+ reactions were likely irritant reactions and were not included in the final analysis of results.

RESULTS

A total of 95 subjects ranging from 6 to 67.5 months in age were enrolled in the study. The average age was 31.4 months. There were 54 males (57%) and 41 females (43%). Of the patients, 13 (14%) reported a history of eczema or atopic dermatitis, and 5 (5%) reported a family history of ACD. A single patient had a history of rash over the earlobes that occurred after wearing costume jewelry a few years before and had not since recurred.

Of the subjects, 85 successfully completed the study. The remaining 10 were either lost to follow-up or failed to keep the patches on for 48 hours. At least 1 positive reaction was observed in 20 subjects (24.5%). These children ranged from 6 to 67 months of age, with a mean of 30.4 months of age. Of the children, 9 (45%) were <18 months of age, and 11 (55%) were older, 10 (50%) were male, and 10 (50%) were female. Table 2 demonstrates the age, sex, and allergens causing positive reactions in these subjects. Of note, the 1 patient with a history of earlobe dermatitis was sensitized to nickel (patient 19) but had discontinued earring use.

Of the subjects, 16 had 1 positive reaction, and 4 had 2 positive reactions. No subjects had 3 or more positive reactions. There were 11 reactions to nickel and 8 reactions to thimerosal, making these substances our most prevalent allergens. Positive reactions also were observed to kathon CG, neomycin, cobalt and p-tert bu-

TABLE 2. Subjects With Positive Reactions

Patient Number	Age (Months)	Sex	Allergen(s)
1	6	M	Nickel, thimerosal
2	6.5	M	Nickel
3	9	F	Nickel
4	9	F	Nickel
5	9	F	Cobalt
6	10	F	Kathon CG
7	12.5	M	Nickel, kathon CG
8	16	M	Nickel
9	16.5	M	Nickel
10	21	M	Thimerosal
11	25.5	M	Thimerosal
12	32	M	Thimerosal
13	42	M	Nickel
14	44.5	F	Nickel
15	47.5	F	p-tert butylphenol formaldehyde resin
16	51.5	F	Nickel, thimerosal
17	58.5	F	Thimerosal
18	59	M	Thimerosal
19	65.5	F	Nickel, thimerosal
20	67	F	Neomycin

tylphenol formaldehyde resin (PTBFR). All allergens causing positive reactions and the prevalence of those reactions are shown in Table 3.

Irritant reactions to tape were observed in 7 children (7.4%). There were also 5 children who removed their patches within 24 hours of placement because of discomfort. The remainder of the subjects reported no problems and seemed to tolerate the patch testing well.

DISCUSSION

A review of the English literature reveals only 2 studies about allergic contact sensitization in asymptomatic children. Barros et al²¹ studied 562 school children from 5 to 14 years of age and found that 13.3% were sensitized to 1 or more contact allergens. Weston et al²⁰ studied 314 children from 6 months to 18 years of age and found a 20.3% prevalence of at least 1 positive reaction. Within that group, 129 children were ≤5 years of age, and 26 (20%) had positive skin test results. Our study examined 85 children from 6 to 67.5 months of age and found a prevalence of 24.5% sensitization.

By targeting patients who presented for well-child care, we were able to obtain a patient population that is likely to reflect that of the Denver area. The low percentage of patients with skin problems in our sample group suggests that our results are not skewed. We were able to limit the number of false-positive reactions in our study in 2 ways. We counted only 2+ or 3+ reactions as significant, lim-

TABLE 3. Most Prevalent Allergens

Allergen	Number of Positive Reactions	Percentage of Total (N = 85)
Nickel	11	12.9
Thimerosal	8	9.4
Kathon CG	2	2.4
Neomycin	1	1.2
Cobalt	1	1.2
p-tert butylphenol	1	1.2

iting the number of irritant reactions that might be considered relevant. Irritant reactions tend to fade quickly, and all our patients followed up at least 48 hours after removal of their patches. By waiting for irritant reactions to clear, and by only including the strongest reactions as positive, we feel that our positive reactions are a more accurate reflection of true sensitization. Our prevalence of 24.5% sensitization is consistent with that previously found by Barros et al²¹ and Weston and colleagues²⁰ and is a general reflection of sensitization in children ≤ 5 years of age.

Our most prevalent allergen was nickel with 12.9% of the population sensitized. Nickel is a strong sensitizer, and it is not surprising that we found this many positive reactions. Although nickel is known to produce irritant reactions in children, we performed late readings when irritant reactions should subside and true allergic reactions persist, and therefore, we believe our nickel reactions represent allergy. Metal components such as snaps and buckles are common parts of infants' and children's clothing. Additionally, youngsters are frequently touched by caretakers wearing jewelry or may even wear jewelry themselves. Numerous studies of children with dermatitis have indicted nickel as a common allergen, often as the most prevalent allergen as well.⁸⁻¹⁹ In the previous study by Weston et al,²⁰ nickel was the second most prevalent allergen with 7.6% sensitized, whereas Barros et al²¹ demonstrated only 5.7% of his population sensitized (7th most prevalent allergen). Although direct comparisons of these numbers would not be valid owing to differences in sample ages and size, it is interesting that our prevalence is greater and that a number of our youngest patients were sensitized to nickel.

Our next most prevalent allergen was thimerosal, a preservative found in vaccines and topical medications such as eye drops. There has been much controversy in the adult literature about the relevance of thimerosal sensitization, but vaccines seem to play a large role in sensitization in children.^{25,26} Osawa et al²⁷ demonstrated that diphtheria-tetanus-pertussis vaccination produces sensitivity to thimerosal in a guinea pig model. The American Academy of Pediatrics recommends that children begin routine vaccinations at 2 months of age, a process that continues until they are ready for school entry.²⁸ In light of the number of vaccinations that children receive these days, it is not surprising that thimerosal is frequently reactive in skin testing. We found that 9.4% of our subjects were sensitized to thimerosal. In contrast, Weston et al²⁰ previously found only 3.5%, and Barros et al²¹ found 14.9%, differences likely attributable to varying exposures and test methods. The majority of our thimerosal reactions occurred in children >18 months of age, possibly suggesting that thimerosal is a weak allergen and that multiple exposures are needed to produce sensitization.

Sensitivity to preservatives other than thimerosal was less common. Only 2.4% of our patients reacted to kathon CG and 1.2% to PTBFR. Because of our small sample size, it is not surprising that there were no reactions to other preservatives. Preservatives are unfortunately a ubiquitous component of topical

preparations and can cause significant problems of contact allergy, even in children. Conti et al²⁹ studied sensitization to preservatives in 811 Italian children with atopic dermatitis or other eczema and found 4.9% reacted to kathon CG, whereas $\sim 1\%$ reacted to other preservatives such as formaldehyde and imidazole urea. Similar to our study, a previous study by Weston et al²⁰ also demonstrated a lower prevalence of sensitivity to preservatives such as formaldehyde (1.5%), Quaternium 15 (1.5%), and PTBFR (.9%). Conversely, Barros et al²¹ found a high amount of sensitization to PTBFR with 13.8% of his subjects reacting.

Metals other than nickel did not play a large role in sensitization. Only 1 patient (1.2%) was sensitized to cobalt, and no positive reactions to potassium dichromate were noted. Sensitivity to all 3 metals can be seen together, but we did not observe this phenomenon. Weston et al²⁰ observed that 7.6% of his population were sensitized to potassium dichromate, which he attributed to exposure to shoe leather. Barros et al²¹ found only 1.1% positive to potassium dichromate but did find 3.4% of subjects reacting to cobalt.

A surprising finding of our study was that only 1 patient (1.2%) reacted to neomycin, a common allergen in the past. Both Weston et al²¹ and Barros et al²⁰ found neomycin to be the most prevalent allergen in their studies: Barros and colleagues found 18.4% positive and Weston and co-workers found 8.1% positive. Neomycin is a topical antibiotic, often used as a first-aid medication for minor cuts and scrapes. It is also a known allergen that has been removed from several popular children's skin preparations, and this fact could account for the decrease in its rate of sensitization.

As previously mentioned, there have been case reports of ACD in infants, but no formal studies addressing infants and ACD as a group. Seidenari et al²³ described 3 cases of ACD in children <1 year of age: 6- and 12-month-old infants allergic to nickel and a 12-month-old child allergic to para-phenylenediamine. Fisher²² described a 7-month-old infant who developed nickel dermatitis to the snaps in his sleepwear and a 1-week-old infant with ACD to the epoxy resin in his vinyl identification band. In a clinical update, Fisher³⁰ also summarized the past work of Strauss, who demonstrated that infants can be sensitized to poison ivy extract, and the work of Uhr, who showed that premature infants also can be sensitized to allergens. These cases illustrate that the immune system of an infant is capable of producing the responses necessary to evoke ACD. From our results, we offer that sensitization within the general pediatric population frequently occurs at a young age. Of our patients with positive reactions, 45% were <18 months of age. Given the variety of clothing, topical medications, and skin care products available today, the skin of infants and young children is exposed to a wide range of allergens, and this level of sensitization is not surprising.

The T.R.U.E. Test system has not been previously used in children <5 years of age. In older children, the sensitivity and specificity of this testing system

are not different from other contact allergy testing systems.

CONCLUSION

In summary, we found that 24.5% of asymptomatic children from 6 months to 5 years of age were sensitized to 1 or more contact allergens. Nickel and thimerosal were the most prevalent allergens. We also found that children as young as 6 months of age can be sensitized to allergens, and that approximately one half of our sensitized children were <18 months of age. Sensitization to contact allergens begins in infancy and continues to be common in older infants and young children.

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