

Invited Commentary: Recommendation for a North American Pediatric Patch Test Series

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Abstract Given the increased recognition of pediatric allergic contact dermatitis and lack of patch testing consensus in children, we present a minimum *basic* 20-allergen North American pediatric series, for screening children ages 6–12 with suspected contact allergy.

Keywords Pediatric · Children · Patch test · Allergic contact dermatitis · Atopic dermatitis · Allergen · Recommendation

Introduction

Allergic contact dermatitis (ACD) is being more frequently recognized as a highly relevant diagnosis in children [1–3]. Patch testing should be considered in every pediatric case of chronic, recurrent, or therapy-resistant dermatitis, as it has been shown to be both safe and effective in children [4–6]. The approach to patch testing children should be guided by history and conducted systematically using standardized protocols [7].

While product review for repeated chemicals can prove invaluable, it can be cumbersome and challenging; thus, we

recommend an initial *basic* screening panel of 20 contact allergens, which we suggest as a minimal standard series in children ages 6–12 years, similar to those utilized in Europe [8]. The American Contact Dermatitis Society (ACDS) Core Allergen Series contains 80 individual allergens and mixes, many of which have low relevance in pediatrics and therefore may not be appropriate to include for every child with dermatitis (e.g., ethyl cyanoacrylate, epoxy resin, and glyceryl thioglycolate) [9].

Methods

A literature search was performed utilizing the PubMed database to identify North America-based articles on patch testing children ages 0–18, with the aim to create a *basic* 20-allergen North American pediatric standard series (henceforth referred to as *the series*). The prevalence and relevance of the most common allergens listed in these articles were then examined and reviewed in conjunction with case reports and the case databases of the authors for final inclusion into *the series*.

The series was then cross-referenced against available data from the three larger-scale (>100 patients) North American pediatric studies to measure the percentage of positive patch tests (PPTs) that would have been detected utilizing *the series* alone, henceforth referred to as detection rates [4, 10, 11]. In the Weston et al study, 314 well patients had been patch tested with 20 allergens using the American Academy of Dermatology (AAD) Patch Test Kit (Hermal Pharmaceutical Laboratories; Oak Hill, NY) [10]. The North American Contact Dermatitis Group (NACDG) performed a retrospective review of 391 pediatric patients who were patch tested between the years of 2001 and 2004 with the NACDG standard series (consisting of 65 allergens from 2001 to 2002 and 71 allergens from 2003 to 2004) [11]. These patients were also tested with supplemental allergens as needed. Of note, allergens were

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excluded when necessary for individual considerations (e.g., previous known positive reaction to an allergen). And, Jacob et al. evaluated the safety and efficacy of T.R.U.E. Test™ (Smart Practice; Phoenix, AZ) panels 1.1, 2.1, and 3.1 (total of 28 allergens) in 102 children and adolescents in the Pediatric Research Equity Act (PREA-1) trial [4].

Finally, to further highlight the prevalence of these allergens, the terms “contact dermatitis AND children AND [specific allergen or (specific allergen OR synonym)]” were entered [e.g., “contact dermatitis AND children AND (colophonium OR colophony)”] in the PubMed search field and the total number of literary citations for each allergen through 12 March 2014 was recorded.

Results

The allergens included in *the series* for children ages 6–12 years were selected based on their high prevalence and relevancy data as evidenced and recorded in North American publications and in the clinical experience of the authors (see Table 1) [4, 10–39]. Also included in Table 1 are the results of the PubMed query showing total literary citations for each

allergen with nickel, the most prevalent allergen in pediatric patch-tested populations, having the most citations (289), and cocamidopropyl betaine (CAPB), an increasingly recognized allergen, having the least (5). There were additional allergens identified that demonstrated high clinical relevance, which may need to be tested if there is a suggestive exposure history, examples of which are listed in Table 2 [4, 11, 14, 15, 18, 25–27, 40].

In comparing *the series* to the allergens reported in the three larger North American pediatric studies, it was noted that ten of the allergens (50 %) tested by Weston et al. were included in *the series*. Weston et al. detected 118 PPT reactions, of which 81 % (95) would have been detected by *the series* [10]. The PREA-1 study utilized the T.R.U.E. Test™ (Smart Practice; Phoenix, AZ) that contained 14 (70 %) of the allergens included in *the series*. A total of 195 PPTs were identified. Use of *the series* alone would have detected 139 (71 %) of these reactions and 152 (78 %) of PPTs in the 6–12 age group [4]. The PREA-1 trial specifically reported the frequency and 95 % confidence intervals for PPTs by age category. The NACDG tested with a more extensive panel including 19 of 20 (95 %) of *the series* allergens. This group detected 426 clinically relevant positive patch test reactions,

Table 1 Pediatric North American standard series for children

	Allergen	Concentration	Evidence ^c	Literary citations ^d
1	Bacitracin	20 % pet.	11–13	9
2	Budesonide	0.1 % pet.	4, 11, 14, 15	16
3	Carba mix	3 % pet.	4, 10, 11, 14–16	12
4	Cobalt chloride	1 % pet.	4, 11, 14, 15, 17–19	98
5	Cocamidopropyl betaine	1 % aq.	11, 14–16	5
6	Colophonium (colophony)	20 % pet.	4, 10, 11, 15, 18	33
7	Compositae mix/dandelion extract	6 % pet./2.5 % pet.	11, 15, 20, 21	25
8	Disperse blue 124/106 ^a	1 % pet./1 % pet.	11, 14–16, 22	9
9	Formaldehyde	1 % aq.	4, 11, 13, 14, 16, 18, 23	81
10	Fragrance mix I	8 % pet.	4, 11, 14–16, 18, 19, 24	87
11	Fragrance mix II (Lyrall)	14 % pet. (5 % pet.)	13, 24	8
12	Lanolin alcohol	50 % pet.	4, 10, 11, 15, 18, 25	20
13	Methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) ^b	(3:1) 0.01 % aq.	4, 10, 11, 15, 17, 26, 27	18
14	<i>Myroxylon pereirae</i> (balsam of Peru)	25 % pet.	4, 11, 14–16, 23, 24, 28	64
15	Neomycin sulfate	20 % pet.	4, 10, 11, 14–19	64
16	Nickel sulfate	2.5 % pet.	4, 10, 11, 14–19, 23, 29–39	289
17	Potassium dichromate	0.25 % pet.	4, 10, 11, 13–15, 19	56
18	Propylene glycol	30 % aq.	11, 14, 15	11
19	Quaternium 15	2 % pet.	4, 10, 11, 13, 15, 18	16
20	Tixocortol-21-pivalate	1 % pet.	4, 11, 14, 15	13

Pet petrolatum, *aq* aqueous

^a Mix these two components in equal amounts

^b MI can be tested alone as well

^c Evidence based on cases reported by North American authors (please see correlating citation for more details)

^d Total number of worldwide literary citations found using search terms “contact dermatitis AND children AND [allergen]”

Table 2 Examples of additional allergens to consider based on history

Allergen	Concentration	Relevant exposure history
Amerchol L-10125 [40]	50 % pet.	Emollients, lotions
Black rubber mix [4]	0.6 % pet.	Tires, playgrounds, toys
Clobetasol 17-propionate [11]	1 % pet.	Topical steroid, chronic dermatitis patients
Mixed dialkyl thioureas [11]	1 % pet.	Rubber-containing footwear, bras, sports gear
Mercaptobenzothiazole [4, 11]	1 % pet.	Rubber cements, gardening hose, rubber in sports equipment/wear, toys
Methylisothiazolinone [26, 27]	0.2 % aq.	Preservative
<i>Para</i> -phenylenediamine [4, 11, 14, 15, 18]	1 % pet.	Hair dye, black henna tattoo
<i>P-tert</i> butyl phenol formaldehyde resin [4, 11, 15]	1 % pet.	Rubber-containing footwear, bras, sports gear
Sorbitan sesquioleate1 [4]	20 % pet.	Emulsifier, emollients, lotions
Thiuram [4, 11]	1 % pet.	Rubber-containing footwear, bras, athletic gear, toys

Pet. petrolatum, *aq.* aqueous

of which 69 % (294) would have been detected screening with *the series* alone [11]. Clinical relevance was not assigned to children in the Weston et al. and PREA-1 study.

Discussion

The allergens listed in *the series* are by no means extensive or comprehensive but rather are offered as a minimum guide to assist practitioners in the *basic* work-up of children ages 6–12 with suspected ACD. For children in this age group, the standard International Contact Dermatitis Research Group (ICDRG) protocol can be performed with a 48-h patch removal and initial reading, in addition to a delayed read between 72 and 96 h [41]. That said, in children 6–12 years of age, patch application for 24 h and readings performed at 48 and 72 h have been suggested [8]. Furthermore, a 24-h application period has also been suggested to be efficacious in younger children and those with atopic dermatitis, as it can reduce the irritation reactions that may be seen in these subgroups [3]. We concur that children under the age of 6 should be patch tested when there is a high index of suspicion and with allergens selected based on exposure and environmental history [7, 8]. Moreover, evidence suggests that children aged 12 years of age and older may be patch tested similarly to adults, with the same screening series [8].

In cross-referencing *the series* against the three larger pediatric patch test data studies, the observed detection rate of PPTs was 81 % for the Weston et al. study, 71 % for the PREA-1 study, and 69 % (of the clinically relevant PPT reactions) for the NACDG study, suggesting that utilization of *the series* could positively impact clinical outcomes [10, 11]. In addition, there was correlation between the number of total published articles regarding each of the 20 allergens in *the series* (PubMed query: included multicenter studies, case series, cases, and clinical pearls) and the reported prevalence and relevance data in the larger studies. This implies that

despite the diversity and heterogeneity of the published studies, there are clinical trends.

There are allergens that have been included in *the series* (Table 1) and brief supplemental panel (Table 2) that warrant special mention, namely, disperse dyes, propylene glycol, Amerchol L-101, and methylisothiazolinone (MI). Disperse blue dyes 124/106 (1 %/1 %) were selected for *the series* because they are used in polyester-blended textiles, such as children's gym clothes and school uniforms [22]. We acknowledge that there is potential cross-reactivity between *para*-phenylenediamine (PPD) and disperse dyes; however, disperse blue only has a 16 % co-sensitization with PPD, as opposed to 66 % with disperse orange [42]. Since PPD is one of only five allergens recognized by the Consumer Product Safety Commission (formerly designated by the Food and Drug Administration) as “strong sensitizers” and has been noted to cause intense reactions in children and adolescents, it was not included in *the series*. That said, testing may be warranted, if a relevant history is elicited [43, 44].

Propylene glycol 30 % aq. was selected because it has been identified as an important relevant allergen in children, and it is frequently positive in patients with generalized dermatitis [11, 14, 15, 45]. Methylisothiazolinone (MI) is frequently used in personal care products marketed for children, such as wet wipes, moisturizers, and body washes. Recently, there has been an increase in the number of children reported with an allergy to MI. The majority of standard screening panels test methylchloroisothiazolinone (MCI) and MI as an MCI/MI mix (3:1) 0.01 % aq. Studies have shown that the MCI/MI mix can miss approximately 40 % of MI allergies and testing with MI (0.2 % aqueous) may be necessary to improve detection rates [46]. In one study, Amerchol L-101 100 and/or 50 %, which contains 10 % wool wax alcohols (obtained from the hydrolysis of wool fat) in mineral oil, was shown to have a higher frequency of PPT (12.1 %) in sensitized persons than wool wax alcohols [lanolin] 30 % (2.7 %), suggesting inclusion of both may be warranted [40]. These aforementioned allergens are especially

relevant in pediatric patients with atopic dermatitis (AD) and generalized disease as the diffuse use of topical medications and emollients by these patients potentially increases propylene glycol, preservative, and lanolin/Amerchol L-101 exposures.

Additionally, there are allergens that may be frequently positive (prevalent in the pediatric population) for which there may be lower clinical relevance, for example, thimerosal, gold, and benzalkonium chloride [4, 9, 11, 14, 18, 19]. Children are typically sensitized to thimerosal during routine vaccination. Other exposure sources of thimerosal include contact lens solution and ophthalmic and otic preparations [9]. Sensitization to gold has been reported through the cultural practices of piercing and skin adornment [47]. Several studies have also shown a high prevalence rate of sensitization to benzalkonium chloride, which can be found in antiseptic solutions, mouth washes, and medicated towelettes [9, 11, 14, 18]. Again, as the relevancy of these allergens is typically lower, they were excluded from *the series*, but should be tested, if there is a strong index of suspicion.

If the patient's history or clinical presentation warrants further investigation, ideally, expansion of the number of potentially relevant allergens tested would occur (e.g., additional rubber chemicals, *para-tert* butyl formaldehyde resin, dialkyl thioureas, sorbitans, alternative corticosteroid classes, or additional formaldehyde-releasing preservatives) (see Table 2). Inclusion of the patients' products (e.g., personal care products and sports equipment samples) may also be helpful; however, extended patch testing is not always an option. Furthermore, a significant number of children with ACD also carry a diagnosis of AD. And, while atopy patch testing may be of clinical utility in these patients, it has limited availability, variability in protein allergen test substances, lack of reproducibility of reactions, and low reimbursement rates. As a result, this test is not always practical and was deemed beyond the scope of this *basic* screening series [3, 48]. Epicutaneous patch testing is the *gold standard* for the diagnosis of ACD; this acknowledged, *the series* could potentially be used to guide preemptive avoidance in patients who do not have access to patch testing [49].

Conclusions

Ideally, a pediatric screening series should include the allergens with the highest proportion of relevant positive patch test reactions, while excluding those with higher irritation and sensitization risk. We suggest the use of at least this *basic* 20-allergen North American pediatric series, in the routine screening of children ages 6–12 with suspected contact allergy, being cognizant that

reaction rates may vary by referral bias, target population, and region, and that manufacturing and incorporation of allergens in products change over time.

Compliance with Ethics Guidelines

Conflict of Interest Sharon E. Jacob and Elise M. Herro served as investigators on the safety and efficacy of T.R.U.E. Test™ (Smart Practice; Phoenix, AZ) panels 1.1, 2.1, and 3.1 in children and adolescents, Pediatric Research Equity Act (PREA-1) trial. Dr. Jacob has also served as a consultant for Johnson & Johnson. Sharon E. Jacob and Shehla Admani are currently investigators on the PREA-2 trial, and Shehla Admani is a research fellow at UCSD/Rady Children's Hospital funded by a grant from the National Psoriasis Foundation.

Human and Animal Rights and Informed Consent This article does not contain any studies with animal subjects performed by any of the authors. With regard to the authors' research cited in this paper, all procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000 and 2008.

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