

Common Allergens and Considerations When Performing Pediatric Patch Testing



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KEYWORDS

• Allergic contact dermatitis • Patch testing • Pediatric • Common allergens • Sensitization

KEY POINTS

- Pediatric allergic contact dermatitis (Ped-ACD) is an increasingly recognized highly prevalent skin disease, thought to be related to exposure to sensitizers at a young age or on an impaired skin barrier.
- Diagnosis of Ped-ACD can be challenging in the setting of other common pediatric skin diseases such as atopic dermatitis and irritant contact dermatitis.
- Knowledge of top pediatric allergens such as nickel, fragrance mix, cobalt, balsam of Peru, neomycin methylisothiazolinone, and formaldehyde releasing preservatives can aid in accurate diagnostic evaluation of pediatric patients with ACD.
- Specificity in allergen selection can lead to fewer false-positive (irritant reaction) results and increased probability of determining a true positive patch test reaction and a clinically relevant allergen.

INTRODUCTION

Pediatric allergic contact dermatitis [Ped-ACD] is an increasingly recognized highly prevalent skin disease that has a significant impact on the quality of life of patients and their families. Many patients presenting for patch testing have had chronic dermatitis for months to years, managed as other common pediatric skin diseases such as atopic dermatitis (AD) and irritant contact dermatitis (CD). Accurate and appropriate patch testing is critical in the diagnosis of Ped-ACD and requires knowledge of the most common allergens in the pediatric population, consideration of concurrent diseases that can complicate the clinical picture, and modification of techniques to lessen exposure

to irritants and sensitizers while obtaining true positive results. This article reviews the most common pediatric allergens and discusses considerations when performing pediatric patch testing.

PEDIATRIC ALLERGIC CONTACT DERMATITIS

Allergic contact dermatitis (ACD) is a type IV delayed hypersensitivity reaction requiring primary sensitization and secondary elicitation response. It is the fifth most common skin disease and is estimated to affect approximately 13 million people in the United States, with 4.4 million of those being pediatric patients.¹ In pediatric patients, increased exposure to sensitizers at a young age or to an impaired barrier (eg, AD) may be a contributing

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factor in the increasing diagnosis rate of pediatric ACD.² Historically, Ped-ACD was thought to be uncommon because of limited allergen exposure and an immature immune system. Repeated studies, however, have demonstrated contact sensitivity (reactivity on patch testing) in patients as young as 6 months of age.^{3,4} Furthermore, repeated clinical trends demonstrate pediatric patients are sensitized to clinically relevant allergens because of exposures to medicaments, personal hygiene products, body piercings, sports-related gear, and certain hobbies.²

Data from the Pediatric Contact Dermatitis Registry (PCDR) showed an allergen sensitization rate of 13% to 25% in currently asymptomatic children,⁵ supporting the prior evidence of significant sensitization in children. Furthermore, this study found that 65% of the tested pediatric patients had a positive patch result, with 48% of those being clinically relevant positive patch tests.⁵ Along this same line, the North American Contact Dermatitis Group (NACDG) data from 2014 reported that 62.3% of patch-tested children had positive patch test results, and 56.7% of symptomatic children had a clinically relevant positive patch test result.^{5,6} It is important to note that both studies demonstrated a significant sensitization rate in patients with AD. The NACDG reported that 48.3% of the pediatric patients with clinically relevant patch tests also carried the diagnosis of AD.⁵ Notably, in concordance, Goldenberg and colleagues³ reported that children with positive patch tests were 3 times as likely to have coexisting AD. This provides supporting evidence that the impaired epidermal barrier allows increased allergen penetration and subsequent sensitization and that patients with AD are at an increased risk for ACD.³

COMMON PEDIATRIC ALLERGENS
Top Allergens and Comparisons Between Pediatric and Adult Populations

In pediatric patch testing, it is important to consider exposures that are common in the pediatric population that may differ from common allergens seen in the adult population. The most common allergen in both populations is nickel.³ To determine the most common allergens in children, a retrospective analysis of pediatric patch test results was performed from 2015 to 2016 for the PCDR.⁵ The top 10 most common allergens from the analysis are nickel sulfate, fragrance mix I, cobalt, balsam of Peru, neomycin, propylene glycol, cocamidopropyl betaine, bacitracin, formaldehyde, and gold. Additional data sets have shown high prevalence and clinical relevance to methylisothiazolinone, paraphenylenediamine, cobalt chloride, and quaternium-15.^{3,6} The most frequently encountered allergens in both pediatric and adult populations are compared in **Table 1**.^{7,8}

Worldwide, the most common positive and clinically relevant allergens were nickel sulfate and cobalt chloride.⁶ Common exposures related to these top allergens are piercings, orthodontic braces, coin rolling, school chairs, and ballet dance bars.⁹ In Europe, prevalence of nickel allergy is 8% to 10% of the pediatric population, higher in patients with known dermatitis (5%–30%).¹⁰ Countries such as Denmark, Sweden, Germany, and England have adopted regulations for nickel exposure because of the high prevalence. The European Union Nickel Directive regulates the amount of nickel content allowed to be released from products that may come into direct and prolonged contact with the skin.¹⁰ In 2014, the European Chemicals Agency further specified that prolonged

Table 1 Most prevalent allergens with clinical relevance in pediatric and adult populations		
	Pediatric	Adult
1	Nickel sulfate and cobalt chloride	Nickel sulfate
2	Fragrance mix I	Methylisothiazolinone
3	Balsam of Peru	Fragrance mix I
4	Neomycin sulfate	Formaldehyde 2%
5	Bacitracin	Methylchloroisothiazolinone/methylisothiazolinone
6	Wool (wax) alcohols	Balsam of Peru
7	Formaldehyde 1%	Neomycin
8	Methylisothiazolinone	Bacitracin
9	Bronopol	Formaldehyde 1%
10	Propylene glycol	Paraphenylenediamine

Comparison of the top 10 pediatric allergens from the P.E.A.S. (Pre-emptive Avoidance Strategy) analysis of PCDR & NACDG data,⁷ and the top 10 adult allergens (2015–2016) from the NACDG data.⁸

contact was defined as “more than 10 minutes on three or more occasions within 2 weeks, or 30 minutes on one or more occasions within two weeks.”¹¹ It was later proven that short and repeated contact with the skin, especially in irritated sites/sites with prior dermatitis, can elicit ACD.¹¹

After initiation of the regulations in Denmark, there was noted to be a significant decrease in the prevalence in nickel allergy, especially in young females.¹² Despite this decrease, however, approximately 10% of young women were found to be nickel allergic. Further studies showed a positive association between filaggrin null mutation status and nickel allergy; however, environmental nickel exposure was felt to be the leading cause of persistent allergy.¹² It is important to recognize the impact of concomitant AD in the sensitization of pediatric populations, as chronic exposure to weak allergens may result in sensitization. Conversely, because strong sensitizers such as MI are considered dependent upon a Th1-mediated response, patients with AD are considered to be less prone to sensitization because of an increased Th2/Th1 ratio.⁴

Common Allergens and Where to Find Them

Metals

Worldwide data demonstrate that nickel and cobalt are the top 2 pediatric allergens encountered in clinical practice. Several examples of common exposures have been discussed previously including piercing-associated jewelry allergy, orthodontics, school chairs, and equipment associated with hobbies (eg, ballet bars and sports equipment). Other common exposures include toys with metal components, instruments, electronics such as cell phones or video games, and metal fasteners in clothing.¹³

Topical antibiotics

Both neomycin and bacitracin are commonly used over the counter in the United States, often together, for minor injuries. Societal support for self-administration of topical antibiotics in the United States has led to children being sensitized at a young age, leading to these allergens landing in the top 10. Interestingly, neomycin has remained in the top pediatric allergens for over 3 decades.¹³

Fragrances

Fragrances are used to evoke or remove the sense of smell. Commonly used fragrances are fragrance mixes (I and II) and balsam of Peru, both of which are present in the top 10 pediatric and adult allergens. Balsam of Peru is an organic tree sap and as such contains a large number of volatile substances; several cross-react with other substituents found in foods (eg, cinnamic alcohol and tomatoes). Certain

spices such as cinnamon, vanilla, cloves, and anise, in addition to foods such as citrus fruits, soft drinks, and ketchup can lead to a systemic CD in persons sensitized to balsam of Peru.¹³ Another example of a food-related fragrance is cinnamic aldehyde, which is present in cinnamon-flavored products/foods and can lead to a perioral or systemic dermatitis.¹³ Common cross-reactive allergens with fragrances include propolis (derived from bee hives and present in lip balms and moisturizers) and colophony (derived from pine tree sap and present in adhesives, paper products, and shoes), which may be compounded together in products.¹³

Preservatives

Formaldehyde and its releasers are commonly used preservatives with antimicrobial properties. They are present in a significant number of cosmetic and personal care products. In the pediatric population, commonly used products with formaldehyde releasers include wet wipes, shampoos, and body washes.¹³ Quaternium-15, a formaldehyde releaser, is a top 10 pediatric allergen.

Common nonformaldehyde preservatives include MCI and MI, which are becoming increasingly more common in the pediatric population with their presence in wet wipes, shampoos/washes, sunscreen, and homemade slime.¹³ Other nonformaldehyde preservatives include parabens (that have low allergenic potential) and iodopropynyl butylcarbamate.

Surfactants

Surfactants (detergents) are widely encountered components of personal care products such as soaps and shampoos. Cocamidopropyl betaine [CAPB] is encountered frequently in the pediatric population, with its presence in no tear washes and shampoos.^{9,13} It is so common an allergen found in patients with AD that some authors have stated that “Patients with AD should avoid the use of skin-care products containing the surfactant CAPB.”¹⁴

CONSIDERATIONS WHEN PERFORMING PEDIATRIC PATCH TESTING

When performing patch testing in the pediatric population, it is necessary to have a basic knowledge of the most commonly encountered allergens. There are several other considerations (eg, concurrent skin diseases) that can complicate the clinical picture and potential technique modifications to lessen exposure to irritants and sensitizers while obtaining true positive results.

Clinical Presentation

Pediatric ACD may present as a localized dermatitis, nonspecific pruritus, and scattered, generalized

dermatitis. Shorter-duration dermatitis or new-onset dermatitis has a higher association with ACD in children.⁵ Data from the PCDR showed that dermatitis of the ears was 10 times more likely to be associated with ACD to nickel than all other anatomic sites. Dermatitis of the face has also been frequently associated with ACD in relation to goggles/other equipment, fragranced products, and metals (such as cellular phones).¹⁵ In pediatric patients with systemic CD, it is important to consider propylene glycol (present in oral suspension medications and processed foods) and balsam of Peru (a fragrance marker that cross-reacts with a significant number of base chemicals in natural foods); common triggers in children are chocolate or ketchup. Consideration should also be given to allergen exposure through caregiver contact (eg, mother's perfume or recently dyed hair).¹⁵ It is beneficial for caregivers to bring objects and topical products used daily for evaluation and possible testing when considering patch placement.

In addition to predilection for specific sites, there appear to be differences in both gender and ethnic groups. ACD is more common in females, which is thought to be related to increased rates of sensitization through jewelry (nickel) and cosmetic products (fragrance).^{5,16} Hispanic and Asian children are 2 times more likely than other ethnic groups to be diagnosed with ACD, which is attributed to different cultural practices and tendencies,⁵ but also may be because of potential delays in evaluative care.

Lastly, age should be taken into consideration when evaluating a pediatric patient for ACD. Children under 5 years of age commonly become sensitized to personal hygiene products and are more likely to react to *compositae* mix than older children,⁵ while children from age 6 to 18 years are most likely to be sensitized to allergens contained in their environment such as disperse blue and gold.⁵ Furthermore, in evaluating CD in children it is important to consider allergens associated with sports equipment, musical instruments, school affects, and electronic devices when gathering pertinent history in the clinical encounter. Consideration of differences in exposures can guide allergen selection and determination of clinical relevance in the setting of a positive patch test. In a recent review, a set of guidelines was given to aid clinicians in determining the appropriate time to perform patch testing (**Box 1**).¹

Concurrent Skin Disease

Evaluation in the setting of multifactorial pediatric dermatitis may be challenging, as many common skin diseases appear similar in presentation and may have concurrent expression. Examples

Box 1

Clinical scenarios in which clinicians should consider patch testing

Consider patch testing if:

- A patient's dermatitis increases in severity, changes distribution, does not improve with standard therapy, or quickly recurs after discontinuation of therapy
- A patient has a unique distribution of dermatitis
- A patient in the workforce has recalcitrant hand dermatitis (teens)
- A patient has adolescent-onset AD without prior history of childhood AD
- A patient has severe, widespread dermatitis that could require immunosuppressive medications, or has been repeatedly treated with systemic steroids

From Borok J, Matiz C, Goldenberg A, et al. Contact dermatitis in atopic dermatitis children-past, present, and future. Clin Rev Allergy Immunol 2019;56(1):86-98; with permission.

include AD, irritant CD, seborrheic dermatitis, and nummular dermatitis.

In a recent review of PCDR data, it was determined that 49% of patients with positive patch testing had a history of AD and 30% had a concurrent known diagnosis.^{5,17} These patients typically presented for patch testing at a younger age and were more likely to present with a generalized dermatitis.¹ Concurrent AD confounds the clinical picture and has the potential to alter rates and the prevalence of contact sensitizers, increasing the risk of developing ACD. Patients with AD have decreased barrier function, leading to altered absorption of chemicals across the barrier and increased sensitization to certain allergens. Common allergens in this population include cocamidopropyl betaine, wool alcohol, lanolin, tixocortol pivalate, and parthenolide (a component of *compositae*). Many of these products are used daily in AD patients in topical medications and skin care products.^{1,17}

When evaluating patients with concurrent skin disease such as AD, it is important to obtain a thorough history and physical examination. Suspicion for ACD is increased when there is development of a new-onset dermatitis in a patient with chronic dermatitis, or increased body surface area.⁵ In addition, recalcitrant dermatitis despite adherence to treatment recommendations should prompt further investigation for ACD.³ Untreated ACD can lead to chronic pruritus, sleep disturbances for the child and the family, secondary infections, economic burden, social stigma, and absence

from work or school.^{2,3} These factors have a profound impact on the quality of lives of both patients and their families.

Diagnostic Modifications

After considering the possibility of differences in clinical presentation and concurrent skin diseases, it is important to ensure accurate, quality patch testing. When considering patch testing in a pediatric patient, necessary factors are determination of body surface area available for testing, specification in allergen selection, potential reduction in allergy concentration, or exposure time modifications to the patch testing procedure.

In children, the body surface area available for patch placement is significantly smaller in size than that of adults. Because of this, there are limitations in the overall number of patches that can be placed. There is no standardized guideline on the correct number of allergens/patches to be placed when comprehensively evaluating a pediatric patient, as all reasonably suspected allergens deserve evaluation. That said, it is critical that the allergens be appropriately placed without risk for self-removal. In a 2- to 4-year-old patient, the average number of allergens that can be placed per average surface area on the

back is 40 to 45,⁴ while the back of a 6- to 8-year-old patient may easily accommodate 60 to 80 allergens. Because of these space limitations, it is important to use the history and physical examination in the guidance and selection of the most suspected allergens for patch testing, as these would likely cover the greatest clinical relevance (and potential for remission with guided avoidance) in the patient. Specificity in allergen selection is also important for reducing false positives, or irritant reactions.⁵

Determining which allergens to test can be challenging for clinicians. In 2017, the thin-layer rapid-use epicutaneous patch (T.R.U.E. TEST, Smart-Practice, Phoenix, Arizona) test was approved by the US Food and Drug Administration (FDA) for patch testing in children aged 6 to 18 years. This test contains 35 commonly encountered allergen components (and 1 negative control) and may serve as a basic screening tool; however, highly relevant allergens are not included in the kit (eg, cocamidopropyl betaine), while others have a high false-negative rate (eg, methylisothiazolinone).⁹ In 1 study, 39% of pediatric patients had relevant positive patch tests to allergens that were not included in the T.R.U.E. TEST.¹⁸ In an effort to expand on this test and provide a

Table 2
Pediatric baseline series

Nickel sulfate	Carba mix
Quaternium-15	Imidazolidinyl urea
Neomycin	Lanolin
Balsam of Peru	Compositae mix
Fragrance mix I	Cinnamic aldehyde
MCI/MI	Paraben mix
Bacitracin	Thiuram mix
Propylene glycol	Bronopol
MI	Sesquiterpene lactones
Fragrance mix II	Colophony
Cocamidopropyl betaine	p-tert-Butylphenol-formaldehyde resin
Cobalt chloride	Clobetasol-17-propionate
Formaldehyde	Decyl glucoside
Propolis	Iodopropynyl butylcarbamate
Tixocortol-21-pivalate	Benzophenone-3
Hydrocortisone-17-butyrate	Amidoamine
Diazolidinyl urea	Tea tree oil
DMDM hydantoin	Carmine
Budesonide	Dimethylaminopropylamine

Abbreviations: MCI, methylchloroisothiazolinone; MI, methylisothiazolinone.

Components of proposed pediatric baseline series that captures the most common allergens encountered in pediatric patch testing.

Data from Yu J, Atwater A, Brod B, et al. Pediatric baseline patch test series: pediatric contact dermatitis workgroup. *Dermatitis* 2018;29(4):206–12.

pediatric baseline series, Yu and colleagues¹³ conducted surveys and workgroups with patch testing professionals to determine the most commonly encountered pediatric allergens that would be of greatest benefit to include in a pediatric baseline patch testing series. The workgroup suggested 38 allergens be considered for inclusion in a basic pediatric screening series (**Table 2**).

Because of an increased body surface area to volume ratio in young children, there is the potential for increased relative absorption of topical preparations. It is important, especially in children younger than 8 years (age at which most children reach 75% of their adult body surface area to volume ratio⁵), to either consider modifying concentrations of allergens or time interval for exposure during patch testing.³ Specific allergens in which modifications were recommended by Fisher include nickel, formaldehyde, and rubber additives.¹⁹ Evidence from the last decade from the German Contact Dermatitis Research Group²⁰ and several United States-based groups have adopted the measure of decreased exposure to 24 hours (with reads at 48 and 72–120 hours) for children younger than 8 years of age, and the resulting true positive patch test results have been comparable.^{4,20} On the other hand, for children older than 12 years of age, a typical adult patch testing procedure can be employed (removal at 48 hours, with reads at 96 and 120 hours).

A psychosocial tool that has been used to help young children cope with the patch test experience (sitting through an extensive consultation and diagnostic patch test evaluation), is video distraction assist. Using techniques to distract pediatric patients through play or developing a rewards system improves the patch placement and evaluation experience by reducing stress.^{4,15} Counseling parents on techniques to reinforce the importance of keeping patches in place is crucial. Because of the significant increase in the detection rates of clinically relevant allergens, consideration of using repeat open application testing (R.O.A.T.) with the patient's personal hygiene products should be considered in conjunction with conventional patch testing.⁴

SUMMARY

With the increasing prevalence of Ped-ACD, it is becoming even more crucial to consider this diagnosis in pediatric patients with chronic, generalized, or recalcitrant dermatitis. Rapid evaluation will lead to decreased time to resolution and increased quality of life for patients and their families. Remaining up to date on the most common pediatric allergens in conjunction with clinical decision-making based on a thorough history and physical examination will

lead to selective patch testing. Selective patch testing allows increased probability of determining the causative allergen and decreased risk of false-positive results. As these techniques are employed, pediatric ACD will be diagnosed earlier and more accurately.

DISCLOSURE

A. Sindle and K. Martin have nothing to disclose. S.E. Jacob is the CEO of Dermatitis Academy, a webucation company dedicated to CD education.

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