Pediatric allergic contact dermatitis. Part I: Clinical features and common contact allergens in children

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Learning objectives
After completing this learning activity, participants should be able to describe the most common clinical presentation of allergic contact dermatitis in children; identify pediatric patients who are appropriate for patch testing; discuss current trends in allergic contact dermatitis in children; recognize the significant negative impact on the quality of life allergic contact dermatitis has on children; and name and discuss the most common allergens causing allergic contact dermatitis in children.

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Allergic contact dermatitis (ACD), a delayed hypersensitivity skin reaction to environmental allergens, has a prevalence that is similar in children and adults. However, diagnostic testing for ACD in pediatric populations accounts for less than one tenth of all patch tests. The relative infrequency of pediatric patch testing may be attributed to the difficulty in testing in this population, which includes a smaller surface area for patch test placement and maintaining cooperation during patch testing, especially in younger children. Diagnosis can be difficult in children because the appearance of ACD can mimic other common pediatric skin conditions, particularly atopic dermatitis and irritant contact dermatitis. Comprehensive history taking, guided by patient presentation, age group, and location of dermatitis, helps build clinical suspicion. Such clinical suspicion is one of the major reasons behind patch testing, with additional indications being recalcitrant dermatitis and dermatitis with atypical distribution. US pediatric data have shown the top allergens to be metals, fragrances, topical antibiotics, preservatives, and emollients. These trends are important to recognize to guide management and accurate diagnosis, because ACD tends to persist if the allergen is not identified and can affect patients' quality of life. (J Am Acad Dermatol 2021;84:235-44.)

Key words: ACD; allergens; allergic contact dermatitis; childhood dermatitis; pediatric ACD; pediatric contact dermatitis.

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EPIDEMIOLOGIC TRENDS
Key points
- Allergic contact dermatitis affects children at similar rates to adults, but childhood cases are likely underdiagnosed
- Children of all ages may develop allergic contact dermatitis, with increased prevalence with age

Allergic contact dermatitis (ACD) is a biphasic, type IV hypersensitivity reaction of the skin. In the first phase (sensitization phase), initial exposure to 1 of many environmental haptens (allergens) results in allergen processing in regional lymph nodes and subsequent formation of antigen-specific T cells.[1] In the second phase (elicitation phase), re-exposure to the allergen results in sensitized T cells migrating to the epidermis and triggering an inflammatory response seen in acute ACD including erythema, vesiculation, pruritus, and edema.[2] Although it was once believed to be rare for young children to develop ACD because of immature immune systems and lack of allergen exposures, data over the past several decades have shown a prevalence comparable to that in adults.[3] Infants as young as 1 week have been reported to develop ACD,[4] and more than 20% of asymptomatic healthy children are sensitized to common allergens such as nickel.[5,6]

Despite increased awareness of pediatric ACD, less than 10% of patch tests (the current diagnostic standard) are performed on children,[3,7] although children comprise more than 22% of the US population.[8,9] In the hopes of eliminating this diagnostic discrepancy, the goal of part 1 of this continuing medical education series is to describe current epidemiologic and clinical characteristics of childhood ACD, pediatric-relevant allergens, and indications for patch testing. Part 2 discusses childhood patch-testing approaches, providing both diagnostic and management strategies.

Prevalence
The estimated prevalence of pediatric ACD is 16.5%,[10] currently affecting 4.4 million children in the United States.[11] Although the prevalence of pediatric ACD is increasing,[12] cases remain underreported. Only 1% to 10% of patch tests are performed on children,[3,7,13,14] even though the frequency of positive patch test reactions does not differ significantly from that of adults.[10,15]

Demographics
Although ACD can occur in infancy,[4,6] the majority of pediatric cases are diagnosed in older children. Reports suggest more than 75% of diagnosed children are older than 10 years,[16] but this may reflect age referral bias because other studies report no difference in prevalence of ACD and age.[15]

Girls are at higher risk for ACD[16-19] because of behavioral and exposure differences between the sexes. It has been found that female patients are more likely to react to nickel,[20] which may be explained by an increased tendency for ear piercings.[21] This trend may also reflect testing patterns, because up to 91% of adolescents patch tested are female.[18] Notably, some research suggests that in younger children (<10 years), boys are more likely to have relevant positive patch tests (RPPTs),[16] whereas other studies have found no difference in sensitization between boys and girls.[22]

Current pediatric patch testing data show that White children are more likely to be diagnosed with ACD compared to children of other races.[7,18] There are no known geographic prevalence differences among North America, Europe, and Asia.[10]

CLINICAL PRESENTATION
Key points
- The clinical presentation, along with exposure history, can help guide need for patch testing in children
- Understanding the indications for pediatric patch testing (suggestive clinical history, dermatitis with atypical distribution, recalcitrant dermatitis) may help overcome undertesting
- Atopic dermatitis can co-occur and complicate the diagnosis of allergic contact dermatitis

Symptoms and morphology
ACD is difficult to diagnose in children because it may present with similar signs and symptoms as atopic dermatitis (AD). Recognizing the distinguishing features of ACD, such as the distribution of dermatitis and the clinical course, can prompt evaluation. Acute ACD presents as pruritic, eczematous papules and plaques with erythema, edema, vesicles or bullae, and serous crust.[23] Chronic ACD presents with lichenification, fissuring, and hyperpigmentation (Fig 1).

The body area where allergen contact occurs usually coincides with dermatitis distribution. Distributions that should raise clinical suspicion of ACD in children include the head and neck,[12,17,23] hands,[13,17] and legs.[17,23] The feet and lips are more commonly affected in children compared to adults.[13] Special attention should be paid to diapered areas in young children, because ACD affects this area more often than AD.[24] It is important to note that ACD can affect any area of the body, and atypical morphologies such as purpuric and pustular reactions have been reported.[25]

Abbreviations used:

ACD: allergic contact dermatitis
ACDS: Allergic Contact Dermatitis Society
AD: atopic dermatitis
BoP: balsam of Peru
CAPB: cocamidopropyl betaine
FM: fragrance mix
IBOA: isobornyl acrylate
ICD: irritant contact dermatitis
MCI: methylchloroisothiazolinone
MI: methylisothiazolinone
PG: propylene glycol
PPT: positive patch test
RPPT: relevant positive patch test
Th: T helper

Exposure history

Patients may not be able to recall an inciting exposure during the visit because there are thousands of potential exposures in daily life. Understanding environmental allergen sources helps guide thorough and targeted interview questions (Table I).

Children can develop ACD at any age. Specific predisposing factors, other than exposure, are not yet known. Therefore, all children should be asked about the use of personal care products such as shampoos, soaps, lotions, detergents, and topical medications. Clothing, shoes, sports, hobbies, after-school activities, and jewelry are similarly pertinent. Additionally, systemic contact dermatitis can occur through oral ingestion of contact allergens in food, such as carmine in red velvet cupcakes,[26] nickel in oatmeal and cocoa,[27-29] and balsam of Peru (BoP) in ketchup.[30,31]

Targeted history can also be guided by affected body area, age group, and lifestyle. Questions about diapers, baby powder, creams, and toilet training are applicable for infants and toddlers.[24,25,32,33] In school-aged children, toys and crafts are known exposure sources, such as slime, which has resulted in pediatric hand ACD.[34-39] In adolescents, hair dye,[40,41] perfume,[42] nail polish,[43] and henna tattoos[44,45] may be exposure sources. Questioning about after-school activities is essential, because several cases of ACD have been reported from sporting equipment[46-48] and occupational exposures,[49] especially in older children.

Because exposures could be from the home, school, work, pets, or homes of peers and caregivers, a complete understanding of the child's daily life is an important element of patient history.[50] Information gathered can aid management decisions, such as the choice to patch test, include patient products in a patch test, or empirically avoid suspected allergens (discussed in part 2).

Fig 1. Chronic allergic contact dermatitis to methyliso-thiazolinone in hand soap.

Comorbid AD

ACD is traditionally thought to be primarily mediated by T helper (Th) type 1 cells and cytotoxic T cells, whereas AD is mediated by Th2 cells.[51,52] Because of this polarization, it was initially thought that patients with AD are less likely to develop ACD because of Th2 skewing in AD. However, recent literature has indicated that both ACD and AD have shared immune pathways, including Th1, Th2, and/or Th17.[53-55]

In fact, more than one third of children diagnosed with ACD have concurrent AD.[15,56-58] Not only can AD mask underlying ACD, but the conditions can also mimic each other by involving similar areas such as the hands, lips, eyelids, and flexural locations.[15] Furthermore, topical treatments used for AD like emollients and corticosteroids[59-62] may contain allergens that can lead to sensitization; 38% of corticosteroid formulations were shown to contain common allergens.[62] Children with ACD and AD exhibit unique sensitization profiles compared to those with ACD alone, with increased reactions to substances found in topicals advertised for eczema such as cocamidopropyl betaine (CAPB), wool alcohol (lanolin), tixocortol-21-pivalate, and parthenolide.[57] Continued use of topical medicaments containing allergens may perpetuate dermatitis. Up to three quarters of those with treatment-resistant AD were discovered to have coexisting contact allergy in 1 report.[63] Hence, worsening or treatment-refractory AD should heighten suspicion for ACD.[64]

Table I. Targeted history by age group

Age group	High-yield history questions
Infants and toddlers	What type of diapers, wipes, and powders are used?
	Has the child recently begun toilet training?
	Who else cares for the child (eg, day care, grandparents, babysitters)?
	Does the child, parent, or caregiver wear jewelry or perfume?
School-aged children	What toys or crafts does the child play with?
	What sports does the child play at home and at school?
	Does the child play with slime or other putty?
	What after-school activities does the child participate in?
	Is the rash better during the school year or while on vacation?
	Does he or she play an instrument?
Adolescents	Are any other cosmetic products (hair dye, nail polish, makeup) used?
	What sporting and recreational activities are performed?
	Does her or she have any after school jobs?
	Does he or she do any chores requiring cleaning or household products?

Children with AD have impaired skin barrier function (eg, filaggrin mutation), which may lead to higher risk of allergen sensitization[65-67] However, a pediatric-specific review showed only a small difference in contact sensitization (56% AD vs 55% non-AD),[68] and many recent reports show similar overall rates of ACD in children with and without AD.[19,22,57] Further studies are needed to fully understand this complex relationship.

Differential diagnosis

Irritant contact dermatitis (ICD) is a nonimmunologic reaction due to direct keratinocytic damage that can mimic ACD.[69] Some of the usual affected areas of ACD overlap with areas that may be affected by ICD, such as the face, hands, or shins.[70] Examples of ICD include perioral dermatitis (from saliva), diaper dermatitis (from urine, feces, residual cleaning products on toilet seats, and friction), and hand dermatitis (from sanitizers, harsh soaps, and excessive washing).[71] ICD may be more common in children with AD because of impaired barrier function.[72]

Other differential diagnoses should also be considered depending on medical history and clinical examination. These include bacterial and fungal infections, scabies, psoriasis, dyshidrotic eczema, seborrheic dermatitis, juvenile plantar dermatoses, and dermatomyositis.

Indications for patch testing

Information gathered from the history and physical can guide patch testing. In 2015, the European Academy of Allergy and Clinical Immunology Task Force on ACD in children outlined consensus recommendations for patch testing.[73] Table II[76] summarizes indications for pediatric patch testing.

A high index of clinical suspicion is the main indication for patch testing. More than 90% of patch test referrals from dermatologists are considered appropriate,[78] and several studies have found that more than half of patch tests in children with clinically suspected ACD have positive results.[14,16,74,79] Unusual distributions of AD (eg, the face, eyelids, hands, feet, or anogenital area),[24,74,75] as well as severe, worsening, or recalcitrant dermatitis, should further heighten clinical suspicion. Persistent dermatitis, such as AD, that worsens or fails to improve despite standard therapy may also suggest ACD, indicating that patch testing may be necessary.[17] Late-onset AD, such as in adolescence or adulthood, without a prior childhood history of AD, may also suggest ACD.[77]

TOP ALLERGENS IN CHILDREN
Key points
- Allergens such as metals, fragrances, surfactants, topical antibiotics, and preservatives make up the majority of high-yield pediatric allergens
- Emerging allergens that are not contained in traditional patch tests should also be considered and tested based on history and physical examination

A thorough understanding of common allergens and sources in children is useful in daily practice (Table III). Nickel, fragrance mix (FM) I, BoP, propylene glycol, CAPB, bacitracin, neomycin, cobalt, formaldehyde (and its releasers), methylisothiazolinone (MI), and lanolin are top relevant allergens in the United States.[58]

Children and adults react to different allergens at varying frequencies. The North American Contact Dermatitis Group patch test results of 883 children

Table II. Summary of patch test indications in children

Indication	Example
Clinical suspicion	Elements of history such as allergies, hobbies, recreational activities, occupation, topicals, personal care products, and patient or family history of eczema or atopy[73]
	Physical examination findings of acute ACD include pruritic, erythematous papules, vesicles, or bullae
	Subacute and chronic ACD can present with lichenification, fissures, and scales
Dermatitis with atypical distribution	Face, eyelids, hands, feet, and anogenital area[74,75]
Recalcitrant dermatitis	Dermatitis that worsens or fails to improve despite standard therapy (>2 months)[64,76]
Late-onset atopic dermatitis	Adolescent- or adult-onset atopic dermatitis without prior history of eczema in childhood[77]
Severe dermatitis	Consider patch testing before initiating systemic therapy[11,77]

ACD, Allergic contact dermatitis.

Table III. The most common US relevant pediatric allergens by category

Category	Potential allergens	Sources	US RPPT, %[57]
Metals	Nickel	Jewelry, food, toys, clothing, electronics	13
	Cobalt	Metal-plated products, crayons, deodorant	4
Topical antibiotics	Neomycin	Topical antibiotics	4.4
	Bacitracin		4.6
Fragrances	*Myroxylon pereirae* (balsam of Peru)	Cosmetic and personal care products, perfume, cleaning products	6.5
	Fragrance mix I		9.4
	Fragrance mix II		3.4
Preservatives	Formaldehyde	Cosmetic and personal care products, toys, glue, slime, household cleaning products	4.4
	Quarternium-15		2.6
	MI		3.6
	MCI/MI		3.1
Emollients and surfactants	Amerchol-L101 (lanolin)	Moisturizer, lip balm, cosmetics, packaged foods, cleaning products	3.5
	Propylene glycol		5
	Cocamidopropyl betaine		4.6

MCI, Methylchloroisothiazolinone; *MI*, methylisothiazolinone; *RPPT*, relevant positive patch test.

(<18 years) showed that RPPT frequencies for 27 allergens were significantly different between children and adults.[3] Relevant pediatric reactions were more likely due to nickel, cobalt, and Compositae mix and were less likely with FM I, BoP, methyldibromoglutaronitrile, formaldehyde, and quaternium-15 than in adults.

Top pediatric allergens vary geographically. Nickel is the most common allergen in the United States, thimerosal is the most common in Spain,[14] and the most common allergen in Asia is gold.[80] Furthermore, the regulation of allergens varies by country (eg, quaternium-15 is banned in Europe but not in the United States), which affects overall sensitization rates.[15,22]

Metals

Nickel is the most frequently detected allergen in children worldwide,[81] responsible for 6% to 40% of positive patch tests (PPTs).[3,14,19,20,82,83] Sensitization is more common in children compared to adults, in North America compared to Europe, and in girls compared to boys.[20] Sources of nickel include piercings,[84] costume jewelry,[85] toys,[86-88] video game consoles,[89] belt buckles,[90] clothing,[91] and food.[28,29] Because of the prevalence of nickel allergy, the European Union implemented a nickel directive in 1994 to regulate the release of nickel in consumer products to less than 0.5 $\mu g/cm^2/week$.[92] Since then, the frequency of nickel allergy has declined in adults and children in Europe.[93]

Cobalt is often compounded with nickel and is thus also found in metal-plated products such as jewelry, belt buckles, and zippers. Although children are often cosensitized to both nickel and cobalt, cobalt sensitization can occur independently 21% to 40% of the time.[57] Aside from metal-plated products, cobalt is used as a blue/green pigment in crayons, paints, and pottery.[94] Other sources include hair dye, vitamins, foods, deodorants,[95] and leather goods.[96]

Topical antibiotics

Neomycin, an aminoglycoside,[97] is one of the most frequently reported allergens in children in the United States and some European countries[98] because of widespread availability, accounting for 3% to 13% of PPT reactions in children.[3,58,98] It is often used as a topical antibiotic for the treatment or prevention of superficial skin infections and is available as an over-the-counter preparation and in several corticosteroid formulations.[62] In patch testing, neomycin often coreacts with bacitracin, another topical antibiotic, because of its simultaneous use in triple antibiotics.[99]

Fragrances

Fragrances are ubiquitous environmental allergens, and although there are potentially thousands of allergenic fragrance chemicals, fragrance markers such as BoP, FM I, and FM II are most frequently used in patch testing.[100] FM I consists of 8 common fragrance allergens. FM II consists of 6 fragrance allergens. BoP is an aromatic tree sap derived from *Myroxylon balsamum* trees in El Salvador with a large mixture of various fragrance allergens.[101,102]

Sources of fragrance include perfume,[103] cosmetics, personal care products, essential oils, and baby-scented products including detergent, shampoo, and wipes.[24,104,105] Fragrances are often used in household products like candles and cleaning supplies.[106] BoP can also be found in some citrus- and tomato-based foods.[31] Children may also be exposed to fragrances used by their care takers, such as perfumes, leading to cases of connubial ACD.[107]

Preservatives

Preservatives are added to personal care products such as shampoos and soaps to prevent microbes from growing. Formaldehyde (and its releasers), MI, and methylchloroisothiazolinone (MCI) are frequent culprits of pediatric ACD.

Formaldehyde is found in cosmetic and personal care products (including baby products), cleaning supplies, adhesives, sporting equipment, and paints.[108] One study showed that more than 25% of those with PPTs to formaldehyde were also sensitized to its releasers such as quaternium-15, dimethyloldimethyl hydantoin, bronopol, diazolidinyl urea, and imidazolidinyl urea.[109] Often, products such as baby wipes may contain formaldehyde releasers even though they may not be listed among the ingredients.[110] Formaldehyde (and releasers) contact allergy is more frequent in the United States compared to Europe, likely reflecting stricter regulation of product concentration and labeling in Europe.[111]

MCI/MI was often used in a 3:1 fixed mixture in personal care products, but because of the perceived allergenicity of MCI, there has been a shift toward using MI alone. Since then, the prevalence of ACD caused by MI is rising and is now more common than ACD caused by MCI/MI.[112] Sources include rinse-off products such as shampoos, conditioners, soaps, nail polish,[113] laundry detergents,[104] and household cleaning products.[114,115] MI is also found in paints and glues, explaining numerous cases of hand dermatitis from homemade slime containing these preservatives.[34]

Emollients and surfactants

Propylene glycol (PG) is used as an emulsifier in moisturizers and personal products. PG has been identified in topical medications such as topical corticosteroids and calcineurin inhibitors.[116] This allergen is also used as a thickening agent in foods and can be found in oral medications like antihistamines; there are rare reports of systemic dermatitis from PG ingestion.[117,118]

Lanolin (Amerchol L-101, Dormer Chemotechnique, Toronto, Ontario, Canada) is an oily substance released from sheep's wool that is used as an emollient in topical creams, ointments, and lip balms. Lanolin allergy is particularly relevant in children with AD, with reports that those with AD had 4 times the odds of having an RPPT to lanolin compared to those without, likely secondary to an increased use of emollient products in children with AD.[57]

CAPB, a surfactant derived from coconuts, can be found in products labeled as natural or organic, such as shampoo, conditioner, body wash, toothpaste, and makeup remover. One study found CAPB in 65 of 212 baby products analyzed, making it the most abundant sensitizer in baby products labeled as hypoallergic or safe.[119]

Glucosides are plant-derived surfactants and are considered gentle because of their low irritancy. They are widely used in hypoallergenic and/or natural products. Because of emulsifying, cleansing, and foaming properties, they are used in a variety of rinse-off and leave-on products marketed for children.[120] The North American Contact Dermatitis Group found RPPTs to glucosides (2.3%) to be more common than to CAPB (1.1%) in children.[3]

Emerging pediatric allergens

As new potential allergens are used with increasing frequency in consumer products and novel allergens are identified through various

biochemical investigations, case reports of ACD are published, leading to increased awareness and testing of new emerging allergens. A recent example of the rising prevalence of MI as a relevant pediatric allergen shows the need for constant vigilance and reporting.[121] The American Contact Dermatitis Society (ACDS) names a new "Allergen of the Year" to highlight important and emerging allergens. MI was Allergen of the Year in 2013.[122]

Acetophenone azine is a novel allergen identified in foam shin guards and shoes; its exact role is unknown, although it is thought to be a byproduct of other additives.[123] Although the majority of shin dermatitis is due to ICD from sweating or products used to clean the shin guards, some undiagnosed cases of shin guard dermatitis may be due to acetophenone azine. If shin guards are suspected to be a culprit, a piece of shin guard and acetophenone azine can be patch tested.[124] Acetophenone azine is considered a strong sensitizer, and reactions can be severe, with rapid spreading and dissemination.[125-128] However, acetophenone azine is often missed because it is not included in traditional patch test series, but it should be considered, particularly in foot and shin dermatitis. It has been named the 2021 ACDS Allergen of the Year (Amber Reck Atwater, MD, personal communication).

Recently, there have been increasing reports in children with diabetes of ACD to isobornyl acrylate (IBOA).[128-131] This allergen is often found in the adhesive portion of insulin pumps and glucose sensors.[132] In patients with diabetes referred for patch testing because of suspected ACD to Freestyle Libre (Abbott, Chicago, Illinois), 81% of patients had a PPT to IBOA.[133] IBOA was the ACDS Allergen of the Year in 2020.[134]

Hydroperoxides of linalool and limonene are 2 emerging pediatric fragrance allergens. In 1 study, 17.9% and 13.0% of children were sensitive to hydroperoxides of linalool and limonene, respectively.[135] The hydroperoxides are found in various personal care products, ranging from shampoos to moisturizers. Because they are not included in either FM I or II, they are frequently missed if not specifically patch tested for.

QUALITY OF LIFE
Key point
- Pediatric allergic contact dermatitis has a significant impact on quality of life and emotional well-being

Children with ACD have worsened quality of life measures such as reduced sleep quality, impaired school performance, and problems with friends or relatives.[136] Younger children with ACD were found to have lower occupational and functional quality of life scores compared to older children.[137] Validated ACD-specific questionnaires have shown that the emotional aspect of the disease is most burdensome, a measure that improved months after allergen avoidance.[138,139] The significant impact on the patient, his or her caregivers, and medical professionals undermines the importance of suspicion for and diagnosis of pediatric ACD. Part 2 of this CME will focus on diagnosis through patch testing and management strategies.

Conflicts of interest
None disclosed.

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