

Allergic Contact Dermatitis in Children: Review of the Past Decade

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Abstract Allergic contact dermatitis (ACD) is a type IV delayed hypersensitivity reaction. During the last decade, there has been a heightened awareness of this disease in the pediatric population. The gold standard for diagnosis is patch testing. The prevalence of positive patch tests in referred children with suspected ACD ranges from 27 to 95.6 %. The most common allergens in children in North America are nickel, neomycin, cobalt, fragrance, *Myroxylon pereirae*, gold, formaldehyde, lanolin/wool alcohols, thimerosal, and potassium dichromate. The relationship between ACD and atopic dermatitis (AD) is complicated with conflicting reports of prevalence in the literature; however, in a patient with dermatitis not responding to traditional therapies, or with new areas of involvement, ACD should be considered as part of the work-up.

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

Introduction

Contact dermatitis is a category of diseases whose common denominator is an external inciting factor, in contrast to the endogenous dermatoses, e.g., atopic dermatitis and psoriasis.

Included in this group are: irritant contact dermatitis (ICD); contact urticaria (CU); protein contact dermatitis (PCD); and allergic contact dermatitis (ACD) [1].

The most common form of all the contact dermatoses is ICD. It does not require prior sensitization, but rather is caused by direct damage to keratinocytes by an irritating substance (e.g., an alkaline or acidic chemical). This leads to a localized release of proinflammatory cytokines and the subsequent development of an eczematous dermatitis [2]. Importantly, besides avoidance of the causative agent (which in acute cases can usually be identified by the subject), therapy targeted at barrier repair is paramount and can include the use of ceramides, pseudoceramides, and filaggrin degradation products [3].

While beyond the scope of this article, it is important to mention the Type I immediate hypersensitivity reactions seen in the skin, as they have important clinical consequences. CU specifies the appearance of pruritic wheals, as the unique symptom after contact with the triggering substance [4]. In this type of reaction, the subject will experience degranulation of mast cells in the dermis as well as a perivascular leukocyte infiltrate which triggers the release of histamine and other inflammatory mediators, that, in turn, cause local vasodilation, itch, and swelling in the skin (i.e. wheal and flare formation) [2]. There are two subcategories of CU, namely non-immunologic contact urticaria (NICU) and immunologic contact urticaria (ICU). NICU involves the release of vasogenic mediators without the involvement of immunologic processes; it is typically less severe than ICU and occurs 45–60 min after contact [4, 5]. ICU requires a prior sensitization phase and occurs 15–20 min after contact, and in contrast to NICU, ICU can spread beyond the localized contact point [5]. Additionally, this category includes PCD, which is thought to be caused by a combination of type I and type IV reactions [4]. Clinically, rather than the urticarial response, the skin lesions are characterized by chronic or recurrent eczematous dermatitis upon exposure to specific proteins (e.g., as meat,

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fish, vegetable, and latex) [4, 6]. Across the board, the first line treatment in this category of diseases is avoidance of the eliciting trigger. In addition, treatments that inhibit the release and effect of mast cell mediators and possibly other inflammatory mediators can ameliorate or suppress symptoms. Specifically, anti-histamines can be considered for urticaria and topical corticosteroids and/or calcineurin inhibitors can be used for dermatitis [4].

ACD is a type IV (delayed) hypersensitivity reaction, a complex type of reaction, which requires a prior sensitization, and elicitation. The sensitization phase is characterized by an exogenous allergen entering the epidermis through an impaired skin barrier. These allergens then bind with self-proteins to create complete antigens that are taken up and expressed by dendritic cells on the cell surface of major histocompatibility complexes (MHC) [7–10]. The elicitation phase occurs upon repeated exposure to the allergen at which time a clinical dermatitic response occurs. The repeated exposure can occur trans-epidermally or systemically through ingestion, inhalation, or intravenous entry [11]. As opposed to ICD, which clinically consists of well-demarcated, erythematous, and sometimes follicular papules and plaques localized to the area of contact, ACD usually expands beyond the contact area. In addition, there can be transfer of the allergen from one body area to another or activation of dermatitis at distant sites via ‘recall reactions’, which are flares at sites of prior allergen exposure [1]. In contrast to ACD, a pearl in the diagnosis of ICD is that the dermatitis will spare ‘protected’ areas. For example, in diaper dermatitis, the folds are spared, as the skin–skin contact prevents urease and fecal enzymes from touching and breaking down the skin in these areas, further underscoring the role of barrier integrity, maintenance, and repair in the treatment of ICD.

In the last decade (especially in the United States), there have been an increasing number of children patch tested which has led to more confirmed cases of ACD. This increased ability to recognize the diagnosis, find clinically relevant allergens, and, with avoidance regimens, improve the lives of these children and families has heightened the awareness of this highly relevant disease by pediatric clinical practitioners.

Prior to 2008, there had been a paucity of studies in children in the United States, especially when compared to the dearth of information available from Europe. In 1931, H.W. Straus demonstrated that infants could develop delayed type hypersensitivity (DTH) to poison ivy, and thus it was established that the immune system could be primed to respond early in life [12]. In 1985, Weston and colleagues in Denver, Colorado, evaluated 314 healthy children for contact allergy using the American Academy of Dermatology Patch Test Kit, 1984 to 1985 (Hermal Pharmaceutical Laboratories; Oak Hill, NY) and found a sensitization rate of 20 % [13]. Later, these findings were replicated in 2000, when Bruckner

et al. evaluated the Thin-Layer Rapid Use Epicutaneous Patch Test (T.R.U.E.)TM (Smart Practice; Phoenix, AZ, USA) in healthy children with a detected contact sensitization rate of 24.5 % [14]. These studies demonstrated that patch testing in healthy North American children was safe, and confirmed Straus’ 1931 observation.

The year 2008 marked the appearance of the first two multi-center North American studies describing patch testing in pediatric patients afflicted with ACD [15, 16]. These landmark papers further corroborated the efficacy of patch testing in children and found that allergen sensitivity rates were not different in children when compared to that of adults in the US; however, frequency of relevant allergen reactions differed between the two populations. Another striking difference was the frequency of the concomitant diagnosis of atopic dermatitis which was seen 34.0 % of children with a relevant positive patch test (RPPT) reaction compared to only 11.2 % in adults [16]. This article reviews the increasing body of knowledge on ACD in children, which has emerged over the last decade, further solidifying the importance of including this diagnosis in the work-up of children with chronic eczema.

Review of the Literature

The last decade has been a fruitful time in the field of pediatric ACD both in the US and in other parts of the world. There has been an increasing availability of literature evaluating the prevalence of ACD in children, the frequency of positive patch test reactions (PPT) in children and the clinical relevance of these reactions [15–17]. Patch testing has been found to be safe and effective in pediatric patients [18]. Although the incidence of ACD in patients with atopic dermatitis (AD) remains unknown, newer insights into this relationship have led to the recommendation that patch testing be considered in patients with AD who are refractory to standard therapies [19]. Furthermore, methods and results have been analyzed to compare similarities and differences between pediatric ACD and adult ACD, finding a similar rate of contact sensitization, though with differing allergen frequencies [16]. A selection of these articles with their key findings is highlighted in (Tables 1 and 2) and discussed in the text below [15–42].

Clinical Relevance of Contact Sensitization

The gold standard for the diagnosis of ACD is patch testing; however, not all positive patch test (PPT) reactions are clinically relevant to a patient’s dermatitis. A PPT reaction that is not found to be clinically relevant is termed ‘contact allergy’ rather than ‘allergic contact dermatitis’ [36]. The prevalence range of PPT reactions in children with suspected ACD is 27–95.6 % [15–23, 27, 29, 32], while the relevancy of these PPT

Table 1 Emerging Ppediatric Aallergic Ccontact Ddermatitis Ddata

Data studies				
Author/Date	Country	Patient #	Patient Ppopulation/Series Ttested	Findings
Lewis, et al. 2004 [20]	Wales	191	Children <16 yoyears/European Standard Series	• PPT rate 41 % • 51.7 % were clinically relevant • Most common allergens: nickel, fragrance, thiuram, cobalt, PPD, tixocortol pivalate and BOP • Sources of exposure often different from adults (mostly sports, hobbies)
Heine, et al. 2004 [21]	Germany	2,460	Children 6–18yo years/standard series plus other allergens depending on individual indications	• PPT rate 52.6 % in children 6-12 and 49.7 % in adolescents 13-18 years of age • Most common allergens: thimerosal, benzoyl peroxide, phenylmercuric acetate, gentamicin, nickel, ammoniated mercury, cobalt, fragrance, bufexamine, compositae, PPD
Clayton, et al. 2006 [22]	England	500	Children 0–16yo years/British Contact Dermatitis Society standard series, plus additional series when indicated	• PTT rate 27 %, 61 % relevant • Most common allergens: nickel, fragrance, cobalt, mercapto mix, BOP, PPD, colophony, wool alcohols, thimerosal, potassium dichromate
Goon, et al. 2006 [23]	Singapore	2,340	Children <21/Standard Series of the National Skin Center, Singapore and additional series when indicated	• PPT rate 45.4 % • Low percentage of clinical relevance to nickel at yoyearsunger age • 83.5 % reactions to thimerosal not relevant • 61.4 % reactions to colophony were relevant
Beattie, et al. 2007 [24]	Scotland	114	Children 3–15y oyears/European Standard Series or British Contact Dermatitis Group Standard Series	• 54 % PPT, 54 % clinically relevant • Most common allergens: nickel, rubber chemicals, mercapto mix, mercaptobenzothiazole, carba mix, thiuram, fragrance, cobalt, wool alcohol, BOP
Onder, et al. 2008 [25]	Turkey	360	Children 2–16 yoyears/European Standard Series, supplemental series and personal products if indicated	• PPT rate 32, RPPT 30.5 • Most common allergens: nickel, cobalt, PPD, neomycin, formaldehyde, fragrance, MCI, mercapto mix, quaternium-15, benzocaine
Hogeling, et al. 2008 [17]	Canada	100	Children 4–18 yoyears/NACDG standard series, supplementary series if indicated and own products if available	• 70 % PPT, 55.8 % clinically relevant • No gender or age differences • Most common allergens: nickel, cobalt, fragrance, colophony, formaldehyde, lanolin, quaternium-15, and PPD • Nickel co-reacted with cobalt (68 %) and palladium (100 %) • Children with AD were as likely as those w/o AD to have positive reaction
Jacob, et al. 2008 [15]	USA	65	Children 1–18yo years /custom tailored patch testing < 8 yo years & and NACDG + supplemental	• 77 % had at least one PPT thought to be of possible or definite relevance • Most common allergens: nickel, thimerosal, BOP, CAPB, neomycin, carbamates, cinamic aldehyde, cobalt, disperse blue 106, and formaldehyde. • Thimerosal most prevalent allergen with least clinical relevance (secondary to vaccine exposure) • Corticosteroids also found to be relevant allergens
Zug, et al. 2008 [16]	USA	391	Children 0–18yo years [9,670 adults (19 and older)/NACDG series with supplemental series as needed	• No significant difference in frequency of RPPT reaction in children compared to adults • Most frequent allergens: nickel, cobalt chloride, thimerosal, neomycin, gold and fragrance • Frequency of irritant reactions similar to that in adults • Children with AD just as likely as those with out to have RPPT
Jacob, et al. 2008 [26]	USA	3	Children 10 months to 3 years of age / Custom patch tests	• Review of protocol for pediatric patch testing • Proposed series of pediatric allergens recommended by University of Miami • 3 children with severe recalcitrant dermatitis, 2 AD and 1 hand and foot dermatitis, found to have ACD

Table 1 (continued)

Data studies					
Author/Date	Country	Patient #	Patient Ppopulation/Series Ttested	Findings	
de Waard-van der Spek, et al. 2009 [27]	Netherlands	79	Children 1–18 yoyears/T.R.U.E. TM test panels 1 and 2 plus tixocortol-pivalate, budesonide and 3 emollients	- to allergens in the medicaments used to treat the dermatitis • 1 child developed PPT reactions while on therapeutic levels of cyclosporine • 51 % PPT, almost all reactions were relevant • 59 % of patients had refractory AD • Most common allergens: nickel, potassium dichromate, p-tert-butylphenol formaldehyde resin, formaldehyde, 2 of the emollients, p-aminoazobenzene, thimerosal	
Mailhol, et al. 2009 [28]	France	641	Children under 16 yoyears with history of AD/series of 7 allergens and current emollient used by the child	• 6 % PPT • Most common allergens: current emollient, chlorhexidine, hexamidine, tixocortol pivalate, bufexamac	
Hammonds, et al. 2009 [29]	USA	136	Children 3–18 yoyears/custom tailored patch testing	• 61 % had at least 1 PPT • Females tested positive 65 % of the time, males only 53 % • No significant differences between age groups	
Fortina, et al. 2010 [30]	Italy	321	Children < 3 yoyears, pediatric standard series of 30 allergens	• 62.3 % developed at least one positive reaction • Most frequent reactions to nickel, potassium dichromate, CAPB, cobalt, neomycin, MCI/MI • Prevalence of contact sensitization similar in children with and without AD	
Jacob, et al. 2010 [19]	USA	45	Children 6 months to 18 years of age, custom tailored patch testing	• 95.6 % had at least one positive patch test reaction, with 76.7 % of them having a personal history of atopic dermatitis • 76.7 % of children with AD had allergy to CAPB • Idiopathic and systemic reactions can also occur • Children with AD may be more likely to have allergy to disperse dyes	
Kuljanac, et al. 2011 [31]	Croatia	412	Children ≤18 yoyears [440 adults (19 and older)]/standard series of allergens manufactured in Croatia	• Top allergens differed between children and adults • Most common allergens in children: nickel, thimerosal, cobalt, fragrance, white mercury, formaldehyde	
Jacob, et al. 2011 [18]	USA	102	Children 6–18 yoyears/T.R.U.E. TM test	• 76.2 % PPT • Most common allergens: nickel, p-tert-butylphenol formaldehyde resin, wool alcohols, fragrance and cobalt • T.R.U.E.TM test is safe and efficacious in pediatric population	
Schena, et al. 2012 [32]	Italy	349	Children 0–15 yoyears/standard series of allergens of the SIDAPA	• 69.3 % PPT, 69.8 % RPPT • YoYearsunger children had higher rates of sensitization • Most common allergens: nickel, cobalt, MCI/MI, potassium dichromate, fragrance and neomycin • Children with AD had more widespread dermatitis than those without • Children with AD 55.3 % PPT (50 % relevant), children without AD 76.9 % PPT (77.5 % relevant) • Sensitizers were similar in children with and without AD	
Silny, et al. 2013 [33]	Poland	155	Children 1–20 yoyears, 104 with AD, 15 with seborrheic dermatitis, and 36 healthy controls	• Highest proportion of PPT in yoyearsungest age subpopulation of children with AD and more contact allergy found in yoyearsungest subgroup of healthy children may suggests non-specific results secondary to immaturity of the epidermal barrier • Concentrations of contact allergens in current pediatric series seem too high and should be verified	

ACD- allergic contact dermatitis, *AD*- atopic dermatitis, *BOP*- balsam of Peru, *CAPB*- cocamidopropylbetaine, *MCI*- methylchloroisothiazolinone, *MI*- methylisothiazolinone, *NACDG*- North American Contact Dermatitis Group, *PPD*-paraphenylenediamine, *PPT*- positive patch test, *RPPT*- relevant positive patch test, *SIDAPA*- Societa Italiana di Dermatologia Allergologica Professionale e Ambientale, *T.R.U.E.TM*- Thin-Layer Rapid Use Epicutaneous

Table 2 Reviews of Pediatric Allergic Contact Dermatitis Literature in the US and Internationally

Literature Reviews			
Author/Date		Patient Population	Findings
Militello, et al. 2006 [10]	USA	Review of literature on pediatric ACD	• Rate of ACD in children is increasing, prevalence increases with age • Most common allergens: nickel, topical antibiotics, preservative chemicals, fragrances and rubber accelerators • Females have higher rate of ACD on face (nickel, fragrance, preservatives) • Males can have higher rates of ACD to athletic equipment (potassium dichromate, carba mix)
Worm, et al. 2007 [34]	Germany	Recommendations for patch testing in pediatric ACD	• Children under 6 should not be tested unless high degree of suspicion • For children 6–12, patches should be left on for 24 hours with reads at 48 hours and 72 hours • Children over 12 can be tested similar to adults • Series of 12 recommended allergens from DKG with additional allergens added only if history of suggestive clinical picture
Jacob, et al. 2008 [35]	USA	Review of pitfalls in pediatric patch testing	• Pediatric exposures different from adults, not all relevant pediatric allergens picked up on adult screening tools (CAPB, disperse blue, corticosteroid) • Patch testing techniques should be modified for children, they may have lower irritancy thresholds • Counseling and avoidance instructions need to be tailored to fit both child and family's needs
Matiz, et al. 2009 [36]	USA	Review of international studies on pediatric ACD	• Contact allergy is not synonymous with ACD • Top 5 global allergens: nickel, cobalt, antibiotics, fragrances, rubber chemicals • In the US, contact dermatitis has an estimated \$1.6 billion burden of cost • ROAT can help to determine clinical relevance
Jacob, et al. 2009 [37]	USA	Review of environmental exposures in pediatric ACD	• There is a shortage of patch test providers in the US • At a minimum, action should be taken to reduce children's contact with chemicals known to be high-level sensitizers • Overseas stricter level of control for cosmetics • Top sensitizers banned or regulated overseas: nickel, PPD, formaldehyde • Internationally produced products sold in the US are not screened or regulated for potentially harmful chemicals, specifically those made in China
Nelson, et al. 2010 [38]	USA	Review of patch testing and utility of T.R.U.E. TM test	• Since advent of T.R.U.E.TM test, there has been an increase in the performance of patch testing, mostly due to increase in convenience • A great majority of members of ACDS do not use T.R.U.E.TM test as it has a relatively low number of allergens • Only 25–30 % of ACD completely diagnosed with T.R.U.E.TM test • T.R.U.E.TM test now with 35 allergens, this will likely increase diagnostic utility
Pigatto, et al. 2010 [39]	Italy	Review of contact dermatitis in children	• Most common affected areas are legs, feet, hands and face • 'natural' products can also cause ACD, such as tea tree oil • Strict legislation for cosmetics in Italy; however, 'natural' products are not regulated • AD patients more likely to be sensitized during periods of disease quiescence
Sharma, et al. 2010 [40]	India	Review of contact dermatitis in children	• Factors such as age, sex, atopy, social and cultural practices, habit of parents and caregivers and geographic changes can affect ACD presentations • Patch testing should be considered in any child with dermatitis that is difficult to control
Jacob, et al. 2011 [41]	USA	Review of treatment of AD	• Discussion of diagnosis, pathogenesis and clinical manifestations of AD • AD may predispose to ACD given loss-of-function mutation in FLG and cathelecidin LL-37 deficiency • Previously thought patients with AD had depressed Th1 immune system and less likely to develop ACD • Newer literature states individuals with moderate to severe chronic AD express Th1 and have a high prevalence of ACD
Fonacier, et al. 2012 [42]	USA	Review of top allergens in pediatric ACD, diagnosis and treatment	• First line of treatment is allergen avoidance • Supportive measures can include cool compresses, emollients, Burrow's solution, calamine and/or oatmeal baths • Can create barriers to prevent contact with allergens

Table 2 (continued)

Literature Reviews		
Author/Date	Patient Population	Findings
		• For topical corticosteroids ointments recommended, less sensitizing preservatives compared to creams and lotions • Topical calcineurin inhibitors can be effective • Oral immunomodulators such as cyclosporine, methotrexate, azathioprine, mycophenolate mofetil and UV phototherapy can be considered in patients with recurrent disease

ACD- allergic contact dermatitis, *AD*- atopic dermatitis, *CAPB*- cocamidopropylbetaine, *DKG*- German Contact Dermatitis Group, *FLG*- filaggrin, *PPD*- paraphenylenediamine, *ROAT*- repeat open application test, *T.R.U.E.*™™™- Thin-Layer Rapid Use Epicutaneous

ranged from 30.5 to 92.6 % [15-17, 19, 20, 22, 25, 32]. Children in younger age groups and females have been found to have higher rates of PPT reactions, when compared to older children and males [29, 32, 33].

Clinical relevance is designated ‘definite, probable, possible, past, and unlikely’ based on the practitioner being able to identify an exposure source for the allergen to which the subject has demonstrated a PPT reaction (sensitization). Once the exposure source is identified, if the subject withdraws that source and the dermatitis recurs with reintroduction, then the allergen and source are ‘definitely’ relevant. If the allergen is identified and there is avoidance of the suspected source and clinical improvement (but no reintroduction of that allergen and proven associated flare), then the practitioner designates the relevance as ‘probable’ and so forth [15]. Exposure sources are investigated by history taking and encouraging patients to evaluate their environment, once they are made aware of the chemicals to which they are allergic (Fig. 1).

One specific example of an allergen that has a frequently PPT reaction that is rarely clinically relevant is thimerosal. Sensitization to thimerosal, historically, is most associated with routine vaccination [1, 15]. The sensitization is lifelong and thus the patient continues to react on patch testing, even years later, though there may indeed not be any current

exposure source to the chemical. That being said, thimerosal can be found in ophthalmic solutions and some eye makeup [1]. Therefore, if a patient presents with eyelid dermatitis and is exposed to eye-products containing thimerosal, there may be current clinical relevance. Notably, sensitization to thimerosal is not a contra-indication to vaccination and the only vaccine recommended for children under 6 years of age that still contains thimerosal is the inactivated influenza vaccine and even this is only in the multi-dose units; the single dose units do not contain thimerosal [43].

Although geographic location of dermatitis can aid in the determination of clinical relevance of PPT reactions, it is important to keep in mind that a correlation is not always seen between the presenting pattern of dermatitis and the PPT reaction [22]. An example of this is connubial dermatitis; a product does not have to be applied directly to a child, rather, a child can be sensitized through contact with a product that is on a parent [44]. ACD can also manifest as either an idiopathic or systemic reaction [45]. Idiopathic or ‘Id’ reactions are nonspecific dermatitis responses to allergens in sites that lack direct contact with the allergen. There are a variety of manifestations of systemic ACD reactions, which include generalized dermatitis, localized ‘recall-reactions’ (flares at sites of prior allergen exposure), and/or oral lichenoid reactions following ingestion of the offending allergen [19, 46, 47].



Fig. 1 **a** Dermatitis on earlobe in a nickel-allergic patient. **b** Periaxillary bands caused by allergy to fabric dyes with the likely culprit being a blue athletic uniform. **c** Diffuse dermatitis secondary to

fragrance allergy. Fragrance found in both patients over-the-counter and prescription products

Allergen Frequencies

The top 10 most commonly positive allergens in the pediatric population in North America (and their prevalence ranges) are as follows: nickel (17.5–29.7 %), neomycin (6–16.3 %), cobalt (8.8–17.8 %), fragrance (5.1–12.9 %), *Myroxylon pereirae* [aka balsam of Peru (BOP)] (3.9–18.6 %), gold (6–10 %), formaldehyde (3.3–11.6 %), lanolin/wool alcohols (3.6–15.8 %), thimerosal (4–15.8 %) and potassium dichromate (3.6–8.9 %) [15–18, 29]. Eight of these allergens, namely, nickel, cobalt, BOP, neomycin, fragrance, potassium dichromate, and formaldehyde are also in the top 10 allergens seen in adults [48, 49]. The two allergens that differ between the two groups are thimerosal, which has been previously discussed, and lanolin/wool alcohols which can be found in healing ointments, after-shave, baby and bath oil, hand sanitizers, and creams [1].

There are additional highly relevant allergens, beyond the ‘top 10’, which occur with significant frequency in the pediatric population and correlate with the unique exposures of childhood and adolescence. For example, methylchloroisothiazolinone/ methylisothiazolinone (MCI/MI) is a chemical preservative found in infant products, such as wet wipes, protective creams and liquid soaps, and shampoos [10]. One component of this mix, MI, was the American Contact Dermatitis Society Contact (ACDS) Allergen of the Year for 2013. The true prevalence of allergy to MI is likely an underestimate as the concentration of the MI in MCI/MI is too low and as a result, 40 % of allergies to MI are missed using this combination patch test alone [50]. Cocamidopropyl betaine (CAPB) is another relevant allergen that is a non-ionic surfactant used in a significant number of child-intended cleansing products (e.g., No More Tears™ formulations) [15]. Disperse dyes can be found in diaper material and colored garments such as school and athletic uniforms [10]. The disperse dyes are present in a variety of synthetic fibers. A clue to diagnosis of ACD to clothing is the presence of dermatitis in areas of high friction such as the peri-axillary bands (but sparing the vault), and the anterior thighs [38] (see figure). Carbamates and thiuram are compounds used in rubber production that can be found in gloves, garments, shoes, and toys. Additionally, a highly relevant source of exposure to rubber compounds and neoprene components (diakyl thioureas and p-tert-butyl formaldehyde resin) is sporting equipment, which includes shin guards, protective pads, and wetsuits [1, 10].

Allergic Contact Dermatitis and Atopic Dermatitis

The relationship between ACD and atopic dermatitis (AD) is complex, confounded further by conflicting reports in the literature. AD is an inflammatory skin condition in which there are defects in the epidermal barrier. Studies postulate that the barrier defects inherent to AD may enhance allergen

penetration and subsequent sensitization [26, 51], specifically, loss-of-function mutation in the filaggrin (FLG) gene and decreased antimicrobial peptides (AMPs) such as cathelicidin LL-37 [9, 10, 52–55].

Prior literature has described patients with AD, especially severe AD, as having a depressed Th1 immune system and therefore being less likely to become sensitized to allergens and develop ACD [56, 57]. An alternative possibility has been hypothesized that this population may actually have a decreased detection rate of ACD, because of the Th2 axis flare inhibition seen in this disease and especially in persons with severe AD [58]. It has been postulated that sensitization is more likely to occur in periods of disease quiescence rather than exacerbation as a result of the shift towards a Th1-mediated reaction [39]. More recent literature suggests that moderate to severe atopic individuals with chronic disease begin to express Th1-cytokines, and thus the development of ACD may be enhanced [16, 59–61].

Fontina et al. in 2011 and Hogeling et al. in 2006 showed similar rates of ACD in patients regardless of AD designation, showing frequencies of PPT reactions in patients with AD of 63–74 % and without AD of 61.3–67 % [17, 30]. In a study by Zug et al. in 2008, of the children with PPT reactions, 19.95 % reported a history of AD; however, 34 % had AD listed as one of their final diagnoses [16]. Finally, in 2010, Jacob et al. evaluated 69 children with suspected ACD, and 95.6 % had at least one PPT reaction, while of these, 76.7 % had a history of AD [19].

Patients with AD are chronically exposed to an array of sensitizers in skin care preparations intended to improve their condition. Many of the common allergens seen in AD are similar to those seen in the general population, such as fragrances and lanolin; however, there are certain topical agents that are especially relevant in atopic patients, including topical antibiotics and topical corticosteroids [9, 19, 26, 41]. The antibiotics neomycin and bacitracin are widely available in the United States as over-the-counter preparations for minor cuts and abrasions. Both are significant causes of sensitization and ACD, and, notably, reports of anaphylactic reactions induced by bacitracin have also been reported in patients who often first demonstrated CU reactions to topical use [9, 62, 63]. The mainstay of treatment for AD is topical corticosteroids. Allergic reactions to topical steroids can be caused by a component of the vehicle (e.g., preservative, fragrance, emulsifier); however, prolonged corticosteroid use increases the risk of becoming sensitized to the corticosteroid component itself [41]. In cases of true corticosteroid allergy, not only must the medication in question be avoided but other corticosteroids in the same class must also be avoided. For example, a patient who is allergic to triamcinolone, a group B steroid, must also avoid desonide, fluocinonide, and budesonide.

In the AD patient refractory to standard treatments or with development of dermatitis at a new body site (e.g., eyelids,

hands), a work-up for ACD should be a basic component of the evaluation algorithm [40]. In addition, given the ability of certain allergens to provoke both type I and IV reactions [64], and the high incidence of both in patients with AD, it is recommended that these patients be evaluated by prick test, radioallergosorbent test (RAST), and comprehensive patch testing [19]. Patch testing has been referred to as a “steroid sparing agent” in AD, as proper diagnosis of ACD and implementation of avoidance regimens can lead to not only a decreased need for systemic and topical corticosteroids but also for other systemic immunosuppressant agents [26].

Patch Testing

Although the awareness of ACD in the pediatric population has heightened and the gold standard for diagnosing ACD is patch testing, not all children with suspected ACD will have patch testing accessible to them. The first indication for patch testing is uncontrollable or worsening chronic dermatitis of greater than 2 months duration. The second is a failure to improve following standard treatment protocols [26]. Given the smaller surface area for patch testing in young children, once there is a high index of suspicion for ACD, a detailed exposure history guides the testing for relevant allergens. Although, patch testing in pediatric patients is not Food and Drug Administration (FDA)-indicated, the majority of contact dermatitis experts advocate patch test evaluation for ACD in affected children meeting indication criteria. This is performed either by selecting potential allergens based on history of exposures or by screening with standardized series of allergens and potentially the patient’s own personal care products.

Standard pediatric patch testing series have been suggested by both the German Contact Dermatitis Group (DKG) [34] and by centers in the US [26]. Per recommendations of the DKG and in concurrence with US centers, children under 6 should only be patch tested if there is a high degree of clinical suspicion, under 6 should only be patch tested when there is a high degree of clinical suspicion and with history-indicated allergens [26]. In children 6–12 years of age, the DKG recommends that patches be applied for 24 h and readings performed at 48 and 72 h [34]. That said, patch test referral centers worldwide have demonstrated safety and efficacy utilizing a 48-h patch test application period in children 6–12 years of age [16, 18]. Notably, a 24-h application period can be efficacious in younger children and children with atopic dermatitis (S.E.J., personal observation), as it can reduce the irritation reactions that may be seen in these subgroups [65, 66]. Notably, the DKG does not recommend altering the allergen concentration from that used in adults. Furthermore, they note that children over the age of 12 can be tested in the same manner as adults [34].

It has been proposed that young children have lower irritancy thresholds, lower surface area to volume ratios, and

distinct epidermal barrier properties compared to adults; as a result, the allergen concentrations for patch testing in adults may not always be appropriate for testing in very young children [33, 35]. In 1975, Alexander Fisher recommended halving the concentration of nickel and formaldehyde when testing children under 8 [66]. In addition to nickel and formaldehyde, rubber additives, such as carbamates, may also need to be reduced in concentration in children under 5, especially in those who also have AD [26].

In addition to standard comprehensive patch testing, the commercially available Thin-Layer Rapid Use Epicutaneous Patch Test (T.R.U.E.)TM (Smart Practice; Phoenix) has received FDA-indication for use in adults. The T.R.U.E.TM Test consists of three panels of allergens/mixes and one negative control as uniform dried gel coatings on polyester sheeting. Hypoallergenic adhesive surgical tape secures these patches to the skin. Per the prescribing instructions, it is recommended that the patches be applied for 48 h with reads at 72 and 96 h [67]. In a 2011 Pediatric Research Equity Act (PREA)-1 study by Jacob et al., the T.R.U.E.TM test, which at that time included 28 allergens and 1 negative control, was used in 102 children aged 6–18 years and was found to be efficacious and safe [18]. Since that time, the TRUE test was expanded to include 35 allergens and the negative control. Of note, PREA-2 is currently under way to determine the safety and efficacy of these additional 7 allergens in children aged 6–18.

Patch test readings in pediatric skin are analogous to those in adults and are based on recommendations from the International Contact Dermatitis Research Group (ICDRG) [68]. A doubtful reaction by definition consists of faint macular erythema. A weak positive (1+) reaction is non-vesicular with erythema, mild infiltration, and potentially discrete papules. A strong positive reaction (2+) is vesicular with erythema, moderate infiltration and papules. Finally, an extreme positive reaction (3+) denotes a coalescing papular-vesicular plaque with deep erythema and significant infiltration, which may become bullous or ulcerative and often expands beyond the margin of the patch well. Notably, irritant reactions may present as pustules or patchy follicular erythema with no infiltration and are not indicative of a true allergy [67]. The irritant reactions often appear within the first 48 h of patch testing and improve by 96 h, as opposed to contact allergy reactions, which typically worsen between 48 and 96 h.

If possible, patients should refrain from taking oral corticosteroids during the patch test. In adults, a dose of 20 mg in a 75-kg male is known to significantly suppress patch test reactions [69]. In addition, topical corticosteroids should not be applied to the testing area for the 3–7 days prior to patch testing, as this can result in false negative reactions [70]. Flare up reactions of the patient’s dermatitis may be elicited during patch testing. For this reason, all prior dermatitis sites (excluding the test site) should continue to be treated with topical

corticosteroids or immune modulators throughout the duration of the patch test [71]. Patients can take oral antihistamines for symptomatic management of the pruritus, and this will not alter the results of the patch testing.

Although systemic immunosuppression is not optimal during patch testing, some patients' dermatitis is so widespread that these agents may be warranted, and the minimal suppressive dose may need to be determined to suppress the dermatitis and yet still allow for the patch test to function [26, 70].

Discussion and Conclusions

ACD is a common condition in the pediatric population which has been previously under-recognized, as it is often difficult to distinguish clinically from other eczematous skin eruptions such as AD and chronic irritant reactions [10]. The negative impact of ACD extends to include a decrease in quality of life secondary to pruritus, loss of sleep, and feelings of inferiority among peer groups, in addition to a significant economic burden [26]. Most of the current data on ACD come from adult studies; however, this data cannot always be directly extrapolated to children as the allergen frequencies may differ in both the populations [31]. Rates of contact sensitization in children are higher than historic literature had predicted, which may be secondary to an increase in allergen exposure associated with new trends (e.g., body piercings, the use of cosmetic products, and participation in sports and hobbies) [17, 20], or improved recognition of ACD with patch testing being more frequently performed in this population [17]. In the studies reviewed, the rate of PPT reactions ranged from 27 to 95.6 % while the relevancy of the PPT ranged from 30.5 to 92.6 %. These data may not be applicable to the population at large, given that these studies were done at major referral centers on selected patients.

The goal of patch testing is to optimize true PPT and reduce false PPT, utilizing the limited available surface area on children [35]. This is most effectively done with comprehensive patch testing; however, comprehensive patch testing can be time/labor intensive and requires the practitioner to have access to a wide range of allergens. Since the advent of the T.R.U.E.TM test, the number of practitioners providing patch testing in their clinics has greatly increased due to the increased convenience afforded by this commercially available tool [38]. That being said, not all relevant allergens in the pediatric population are included in the T.R.U.E.TM test, such as the relevant allergens CAPB and diakyl-thioureas. Furthermore, some allergens may not be necessary to test on all children, such as epoxy and paraphenylenediamine.

When planning for patch testing, it is important for both the clinician and the patient/patient's family to have realistic expectations. When a relevant allergen is identified, an

avoidance regimen is prescribed. In patients with extensive chronic dermatitis, 8–12 weeks of avoidance may be needed before a true assessment of clinical improvement can be made [26]. Even with the most compliant patients, avoidance regimens may be difficult to follow, especially with ubiquitous allergens with a multitude of potential exposure sources or when the product manufacturing ingredients (e.g., shin guards) are not available. Products that are marketed as 'natural' can also cause ACD [39]. It is well known that some 'unscented' products contain a masking fragrance, thus are not 'fragrance-free'. 'Fragrance-free' products can contain essential oils that can also lead to contact sensitization [39, 72].

Resources such as the ACDS Contact Allergen Management Program (CAMP), available at <http://www.contactderm.org>, and the Contact Allergen Replacement Database (CARD), available at <https://card.preventice.com>, can be helpful in providing a list of products that patients are allowed to use, in addition to giving them allergen information sheets. It is also important to note that 'allergen avoidance' may require adaptive measures to prevent contact of the allergen with the patients' skin [42]. For example, if a patient is allergic to a component of a shin guard, the shin guard can be lined with canvas as an adjunct to the patient wearing a protective sock underneath, to prevent direct skin contact. In addition, families can be given instructions on the repeat open application test (ROAT) or 'use test' for testing new products prior to full body application. This test consists of applying a product, twice a day for 1 week, to a designated area on the upper inner arm while monitoring for an eczematous skin reaction [36, 73].

One pediatric population in particular that can especially benefit from patch testing is the AD patients [19]. Although the exact prevalence of ACD in patients with AD remains unclear, it is known that ACD can be misdiagnosed as AD and/or the concurrent presence or development of ACD can lead to AD flares [15, 41]. As a result, in those patients with moderate-severe dermatitis, correct use of patch testing can allow for cessation of systemic immunosuppressant therapies, a decrease in the need for topical corticosteroid therapy, and ultimately a drastic improvement in their quality of life [26, 74].

Compliance with Ethics Guidelines

Conflict of Interest Sharon E. Jacob is a board member for the American Contact Dermatitis Society and has served as a consultant for Johnson & Johnson.

Shehla Admani declares that she has no conflict of interest.

Dr. Jacob and Dr. Admani are independent investigators for the PREA-2 study evaluating the safety and efficacy of the 3 panel T.R.U.E.TM test in children.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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