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Contact Dermatitis in Children

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1. Introduction

Allergic contact dermatitis is increasingly being recognized as a disease that affects children in addition to adults. Historically, irritant contact dermatitis such as 'diaper dermatitis' was a frequent diagnosis made in children, while allergic contact dermatitis was not considered a significant disease in this age group. Clinicians may have attributed this to children's lack of exposure to allergens or to the belief that pediatric immunity was not vigorous enough to result in sensitization. Some suspect that the infrequent diagnosis of this condition was due to scarce patch testing in this age group. It is true that contact allergy has not been studied as intensely in children as in adults and data from adult studies may not always reflect results in children. By means of many reports and epidemiological studies in the literature, it has become clear that allergic contact dermatitis is a significant diagnosis to consider in young children, and even infants, with eczematous disease.

This chapter was written as a review of the current literature. Background regarding allergic contact dermatitis will be provided with a discussion of its prevalence in children. The most common allergens that affect children will be reviewed, and important pearls regarding patch testing will be discussed.

2. Epidemiology

Recent studies suggest that allergic contact dermatitis remains more common in adults than in children (Kwangsukstith & Maibach, 1995) affecting approximately 10% of the adult population (Marks, 1997) and accounting for just over 4% of all dermatologic consultations (Mendenhall et al., 1973). Though the condition is increasingly being recognized in the pediatric population, most epidemiologic studies have been completed retrospectively and investigate the occurrence of positive patch tests in symptomatic patients only. Generally, standard series are used. For example, the European Standard Series is commonly utilized in European studies. Yet, some variation in tested allergens exists and studies often evaluate specific pediatric populations, making it difficult to compare studies. The exact rates of incidence and prevalence remain less clear, potentially due to only recent interest in studying this condition in children. Furthermore, only a minority of studies report on the relevance of positive patch test results.

2.1 Prevalence in infants and young children

A common explanation for low rates of allergic contact dermatitis in children was their lack of a robust immune system. Early studies seemed to support this theory. For instance, Straus

found negative patch test results after evaluating 119 infants with poison ivy dermatitis (Straus, 1931). However, in 1960, Uhr and colleagues were able to demonstrate allergic responses to dinitrofluorobenzene in a small series of infants. Of note, premature infants were less likely to have positive reactions compared to infants aged 2-12 months (Uhr et al., 1960). Uhr's study supported that infants could indeed be sensitized, but the younger the infant, the weaker the response. After his work, it would be another twenty years before contact allergy was investigated in children on a broader scale.

The literature now provides numerous studies describing the presence of allergic contact sensitization in very young children. In 1995, Motolese and colleagues reported that up to 60% of symptomatic infants aged 3-24 months elicit positive patch tests (Motolese et al., 1995). Three years later, Manzini and colleagues patch tested a total of 670 children aged 6 months – 12 years old, with suspected disease, and detected positive results in 42% of patients. Furthermore, at least two studies have shown that the highest rate of sensitization occurs in children less than 3 years old (Manzini et al., 1998; Roul et al., 1999). Interestingly, many children (77%) in one such study had concurrent atopic dermatitis, which introduces a much contended issue regarding the relationship between atopic dermatitis and contact dermatitis and whether atopic skin predisposes children to contact allergy (Manzini et al., 1997). In 2003, Wohrl tested 2770 children and adults with suspected disease, finding positive patch tests in 49% of study participants. The highest rate of sensitization was found in children less than 10 years old at a rate of 62% (Wohrl et al., 2003).

There are also many reports that describe the occurrence of allergic contact dermatitis in very young patients, even as young as 1 month of age (Fisher, 1994; Seidenari et al., 1992). This may be related to the fact that infants and children are increasingly exposed to more antigens. This is illustrated by the report of a 5-month-old infant with contact allergy to colophony found in electrocardiogram electrodes used to monitor for sudden infant death syndrome (Oestmann et al., 2007). Or, consider the series of three young children, aged 9 months to 2 years, who developed a diaper dermatitis as a result of disposable diaper dye (Alberta et al., 2005). Such new exposures may, in part, explain the increase in diagnosis of pediatric allergic contact dermatitis.

2.2 Prevalence in symptomatic versus asymptomatic populations

Studies of various sizes attempt to assess the prevalence of pediatric allergic contact dermatitis. However, because of their retrospective nature, most of these studies are limited in that they evaluate symptomatic patients only (Table 1). In the majority of studies, subjects were either suspected of having allergic contact dermatitis or suffered from additional dermatoses including atopic dermatitis and psoriasis. Prevalence in these groups of patients ranges from 14.5% to 83% (Balato et al., 1989; Zug et al., 2008). Though most often, the prevalence is within the range of 40-60%. The most common allergens detected in this setting are nickel, fragrances, cobalt, thimerosal and neomycin. Unfortunately, many of these studies do not indicate the percentage of positive tests that were considered clinically relevant, and this value may be as high as 92% (Rademaker et al., 1989). The responsibility remains with the clinician to determine whether a dermatitis is likely attributable to a contact allergen in the setting of positive test results.

Study	No.	Age	Positive Patch Test	Relevance	Most Frequent Allergens
Brasch & Geier (1997)	416	6-15 yo	40.9%	Not addressed	Nickel sulfate (15.9%) Thimerosal (11.3%) Benzoyl Peroxide (8.9%) Fragrance Mix (8.2%) Cobalt sulfate (7.5%)
Manzini et al. (1998)	670	6mo–12 yo	42%	Not addressed	Thimerosal (23%) Nickel (7.76%) Kathon CG (5.67%) Fragrance Mix (5.52%) Neomycin sulfate (3.58%)
Roul et al. (1999)	337	1-15 yo	66%	Nickel not relevant, Fragrance & Rubber Chemicals relevant	Nickel (23.7%) Fragrance (9.8%) Wool wax alcohols (8.6%) Potassium dichromate (8%) Balsam of peru (4.7%)
Heine et al. (2004)	285 217	6-12 yo 13-18 yo	52.6% 49.7%	Not addressed	Thimerosal (18.2%, 14.3%) Benzoyl Peroxide (16.5%, 8.0%) Phenylmercuric Acetate (13.1%, 7.1%) Gentamicin sulfate (12.5%, 2.9%) Nickel (10.3%, 16.7%)
Seidenari et al. (2005)	1094	7 mo-12 yo	52.1%	Not addressed	Neomycin 20% gel (13.2%) Nickel 5% (10.9%) Wool Alcohols (10.1%) Thimerosal (10.1%) Ammoniated Mercury (8.9%)
Clayton et al. (2006)	500	<16 yo	27%	61%	Nickel (33%) Fragrance Mix (18%) Cobalt (11%) Para-phenylenediamine (8%) Balsam of peru (8%)
Goon et al. (2006)	2340	< 21 yo	45.4%	27 – 83% depending on age and allergen	Nickel (40%) Thimerosal (15%) Colophony (9%) Lanolin (8%) Cobalt (8%)
Zug et al. (2008)	391	0-18 yo	51.2%	Not addressed	Nickel (28.3%) Cobalt Chloride (17.9%) Thimerosal (15.3%) Neomycin (8.0%) Gold Sodium Thiosulfate (7.7%)

| Milingou et al. (2010) | 232 (1980-93) | < 16 yo | 47.8% | Not addressed | Nickel (16.3%) Cobalt Chloride (8.6%) Fragrance Mix (7.3%) Potassium Dichromate (4.3%) Thimerosal (1.7%) |
| | 255 (1994-07) | | 60% | | Nickel (21.56%) Thimerosal (18.03%) Cobalt Chloride (12.9%) Potassium Dichromate (9.4%) Fragrance Mix (4.7%) |

Table 1. Prevalence of Allergic Contact Dermatitis in Selected (Symptomatic) Populations (Studies with > 250 patients)

Fewer studies have been completed that investigate the prevalence of allergic contact dermatitis in the general, asymptomatic population (Table 2). One study reported positive

Study	No.	Age	Positive Patch Test	Most Frequent Allergens
Weston et al. (1986)	314	<18 yo	20%	Neomycin (8.1%) Nickel (7.6%) Dichromate (7.6%) Thimerosal (3.5%) Balsam of peru (1.5%) Formaldehyde (1.5%)
Barros et al. (1991)	562	Schoolchildren	13.3%	Neomycin Thimerosal PTBPF resin Fragrance Mix
Dotterud & Falk (1995)	424	7-12 yo	23.3%	Nickel (14.9%) Cobalt (5.7%) Kathon CG (5.2%) Lanolin (1.7%) Neomycin (1.4%)
Bruckner et al. (2000)	85	6 mo–5 yo	24.5%	Nickel (12.9%) Thimerosal (9.4%) Kathon CG (2.4%) Neomycin (1.2%) Cobalt (1.2%) *p-tert*-butylphenol (1.2%)
Mortz et al. (2002)	1146	13 yo	15.2%	Nickel (8.6%) Fragrance Mix (1.8%) Colophony (1%) Cobalt Chloride (1%) Thimerosal (1%)

Table 2. Prevalence of Allergic Contact Dermatitis in Unselected (Asymptomatic) Populations

patch test results in 13.3% of 562 schoolchildren. Using this data, investigators suggested that allergic contact dermatitis may be more common than previously suspected (Barros et al., 1991). Weston showed that of 314 healthy children, 20% had at least one positive patch test (Weston et al., 1986). Finally, Bruckner has reported the highest overall prevalence at 24.5% when evaluating 85 healthy patients who presented for routine well-child care visits. In this study, subjects were 6 months to 5 years old, further supporting that young children are not uncommonly sensitized (Bruckner et al., 2000). The most common allergens detected in unselected populations are nickel, thimerosal, neomycin, cobalt, fragrances and Kathon CG (Table 2).

2.3 Prevalence in females versus males

Studies are not consistent with regard to prevalence of pediatric allergic contact dermatitis varying between the sexes. Many suggest that there is no difference (Barros et al., 1991; Bruckner et al., 2000; Weston et al., 1986). Other researchers report that the disease is more prevalent in females (Clayton et al., 2006). Mortz and colleagues reported positive patch tests in 19.4% of unaffected females and 10.35% of unaffected males (Mortz et al., 2002). Giordano-Labadie et al. remark that males and females have a similar overall prevalence of allergic contact dermatitis but that females more commonly show sensitization to nickel in comparison to males (Giordano-Labadie et al., 1999). This sentiment is echoed in other studies, and Beattie reports that up to 82% of positive patch tests to nickel in symptomatic patients occur in females (Beattie et al., 2007; Brasch & Geier, 1997). One reason for this difference between the sexes is likely allergen exposure. Jewelry that contains nickel is more commonly worn by female rather than male children (Modjtahedi et al., 2004). In fact, Jensen and colleagues demonstrated that young Danish girls who had their ears pierced prior to a Danish law that regulated nickel exposure were 3.3 times more likely to display sensitization to nickel compared to females without pierced ears. After regulation, patients were only 1.2 times more likely to be sensitized to nickel if their ears were pierced (Jensen et al., 2002).

2.4 Prevalence as related to culture

When evaluating a patient with suspected allergic contact dermatitis, it is important to consider cultural context. Allergen exposure and age of exposure may vary depending on cultural practices. For example, in a study of 70 symptomatic Indian children, the second-most common allergen was potassium dichromate. Investigators attributed this high prevalence to the frequent use of leather footwear without socks. Another cited cause is the trend towards urbanization in India, which has resulted in exposure to potassium dichromate found in cement and metals. The same article suggests that children may be sensitized to nickel early on due to jewelry that is worn at a young age for religious reasons (Sarma & Ghosh, 2010).

Obtaining the appropriate level of suspicion for an allergic contact dermatitis does not depend on a clinician's complete understanding of a patient's lifestyle or culture, but rather, the clinician's ability to ask the proper questions. Social factors such as job-related exposures are still relevant in the pediatric adolescent population. In one German study, higher rates of sensitization were discovered in adolescents aged 13-18 who worked as hair dressers or in the healthcare field (Heine et al., 2004). Another consideration is the child's hobbies and

extracurricular activities. Consider the case of an 11-year-old female cellist with a three year history of an eruption on the right first, second and third digits. She patch tested positive to para-phenylenediamine, which the manufacturer of her bow verified was present in the bow stain (O'Hagan and Bingham, 2001).

2.5 Atopic dermatitis

The association between atopic dermatitis and allergic contact dermatitis remains somewhat unclear. Several older studies that specifically investigated the prevalence of positive patch testing in children with atopic dermatitis suggested that contact allergy is less common in this population (Angelini & Meneghini, 1977). Jones et al. investigated sensitivity to Rhus in atopic and non-atopic patients. Patch tests to Rhus were positive in 61% of healthy patients and only 15% of those with atopic dermatitis (Jones et al., 1973). This correlation may be explained, as contact allergy is a Th1 response and atopic dermatitis patients have a decreased Th1 response (Mortz & Anderson, 1999). Alternatively, some studies suggest that allergic contact dermatitis is more frequent in atopic patients. Epstein and colleagues evaluated the frequency of positive patch tests in patients with atopic dermatitis versus those with psoriasis. Twenty-eight percent of those with atopic dermatitis had positive reactions versus 9% of those with psoriasis (Epstein & Mohajerin, 1964). Another study showed that patch tests were more frequently positive in those with atopic dermatitis versus controls without atopic dermatitis but with other allergic disease including allergic conjunctivitis and asthma (Lammintausta et al., 1992). Dotterud and Falk reported positive tests were significantly more common in schoolchildren with atopic dermatitis, 28.8%, versus 17.9% in controls (Dotterud & Falk, 1995). One explanation for increased risk in atopic patients is their defective skin barrier, which allows for increased exposure to antigens. Also, atopic patients may become sensitized to more allergens given their frequent use of topical agents including emollients, which often contain fragrances and preservatives (Mortz and Anderson, 1999). It should also be considered that atopic skin is readily irritated, which may lead to false positive patch testing results, especially in the case of metals (Dotterud & Falk, 1994). The latter concept is important as some recent studies did not detect a difference in the prevalence of positive patch testing between children with and without atopic dermatitis (Balato et al., 1989; Motolese et al., 1995).

3. Common causes of contact dermatitis in children

3.1 Irritant dermatitis

There are two categories of contact dermatitis that affect the pediatric population: irritant and allergic contact dermatitis. Irritant dermatoses have been diagnosed in children for many years, particularly diaper dermatitis.

3.1.1 Diaper dermatitis

The term 'diaper dermatitis' refers to a multifactorial eruption in the region of the diaper and should not be confused with other diseases that are aggravated by diapers or occur in the same distribution (Scheinfeld, 2005). Factors contributing to primary diaper dermatitis include increased skin moisture and wetness, which create a warm and humid environment that makes infant skin more susceptible to breakdown and more permeable to chemicals

and enzymes. An elevated pH results when bacterial ureases split urea in the urine to release ammonia, and this predisposes infant skin to dermatitis. Friction may also play a role, though this is likely a predisposing or exacerbating rather than dominant factor. Fecal enzymes including proteases and lipases have direct irritant action on the skin and their effects are increased by an alkaline environment. Finally, microorganisms, particularly candida, but also staphylococcus, peptostreptococcus, bacteroides, herpes virus, and dermatophytes can worsen irritant diaper dermatitis (Prasad et al., 2003; Wolf et al., 2000).

Other causes of dermatitis in the diaper region include seborrheic dermatitis, psoriasis, atopic dermatitis, congenital syphilis, acrodermatitis enteropathica (zinc deficiency), scabies, child abuse and miliaria. Finally, dermatitis of the diaper area may also be allergic contact dermatitis. Allergens to consider in this setting include sorbitansesquioleate, fragrances (mix I and balsam of peru), disperse dye, cyclohexlthiopthalimide, mercaptobenzothiazole, iodopropylcarbamate, bronopol and *p-tertiary*-butyl-phenol-formaldehyde (Smith & Jacob, 2009).

Prevention and management of irritant diaper dermatitis revolves around keeping the occluded skin dry and limiting the amount of time that the skin is exposed to urine and feces. Removing diapers is one of the oldest and most effective measures in preventing and treating this condition. Frequent diaper changes are most helpful if done immediately after urination and bowel movements (every hour in neonates and every 3-4 hours in infants). Some experts recommend washing the area with mild soap, while others suggest that rinsing the area in lukewarm water is sufficient. New technology has allowed diapers to be much more absorbent and effective in keeping skin dry and with a normal pH. In terms of topical treatments, low potency steroids can be effective for inflamed skin. However, even if these are applied for a short time to acute disease, a waterproof emollient should be placed over them as a barrier to protect the skin. Ideally, emollients should be reapplied after every diaper change. Emollients effective in this setting are usually made of a large quantity of fine powder, such as zinc oxide, suspended in a greasy vehicle. For those eruptions which are superinfected with candida, topical antifungals may also be required (Wolf et al., 2000).

3.1.2 Perianal dermatitis

An entity that is distinct from diaper dermatitis is perianal dermatitis. Fecal components including fecal lipase and bile acids can cause degradation of the skin barrier perianally, leading to an erythematous irritant dermatitis limited to perianal skin (Ruselet-van Embden et al., 2004). There are several less common diagnoses that are thought to be related to irritant perianal dermatitis and some believe that these exist on a spectrum of one disease. These entities include granuloma gluteale infantum, pseudoverrucous papules and Jacquet's erosive dermatitis.

Granuloma gluteale infantum is thought to be multifactorial and related to occlusion, powder, topical halogenated steroids, *Candida* infection, urine and feces. It classically appears as oval, red-purple granulomatous nodules at sites of occlusion (Robson et al., 2006). This condition will improve with removal of inciting agents (Al-Faraidy & Al-Natour, 2010). Pseudoverrucous papules and nodules is a less common condition and was first reported in association with urostomy sites but may also be seen in children in a perianal distribution. Lesions are shiny, smooth, red, moist, flat-topped and round and may be

mistaken for condyloma (Robson et al., 2006). Finally, Jacquet's erosive diaper dermatitis describes perianal papules that are well-demarcated, sometimes umbilicated and red-purple in color (2-5mm diameter). They evolve into slow-healing erosions and ulcers (Paradisi et al., 2009) and may have elevated borders (Robson et al., 2006). This usually occurs in infants older than six months. Treatment of this entity can be difficult, but therapeutic options include topical treatment with antibiotics, miconazole, zinc oxide and non-steroidal ant-inflammatory drugs (Paradisi et al., 2009).

3.1.3 Lip-licker's dermatitis

Another relatively common form of irritant dermatitis in children is lip-licker's dermatitis. This presents as erythematous, scaly, thin plaques in a perioral distribution. Characteristically, the vermillion border is involved. It is caused by habitual licking of the lips and skin around the mouth and the irritant in this case is saliva. Atopy, wind and cold weather are predisposing factors. It is managed well with behavioral modification and topical emollients (i.e. petrolatum) acting as barriers from saliva. This entity should be differentiated from perioral dermatitis, which is an eruption of pink scaly papules that generally spares the skin involving the vermillion (Leung & Robson, 2005).

3.2 Allergic contact dermatitis

As mentioned previously, the diagnosis of allergic dermatitis is more frequently being made in children. Tables 1 and 2 list the most common allergens detected in a series of investigations. A recent review evaluates 49 studies, most of which included symptomatic patients, finding the five most common allergens to be nickel sulfate, ammonium persulfate, gold sodium thiosulfate, thimerosal and toluene-2,5-diamine (Bonitsis et al., 2011). Table 3 provides prevalence rates of common allergens.

Allergen	Prevalence
Nickel	**5-40**% (Goon et al., 2006; Seidenari et al., 2005)
Mercury	**6.4-25.3**% (Romaguera & Vilaplana, 1998; Wohrl et al., 2003)
Thimerosal	**8.5-23**% (Manzini et al., 1998; Romaguera & Vilaplana, 1998)
Potassium dichromate	**8-21**% (Roul et al., 1999; Wilkowska et al., 1996)
Fragrance	**4.3-19**% (Rademaker & Forsyth, 1989; Romaguera & Vilaplana, 1998)
Cobalt	**3.6-17.9**% (Shah et al., 1997; Zug et al., 2008)
Wool alcohols	**3.58-10.1**% (Manzini et al., 1998; Seidenari et al., 2005)
Rubber chemicals (including carba mix & thiuram)	**4-10**% (Beattie et al., 2007; Fernandez Vozmediano & Armario Hita, 2005)
Balsam of peru	**2.6-8**% (Clayton et al., 2006; Giordano-Labadie et al., 1999)

Table 3. Prevalence of Common Allergens in Selected Populations

3.2.1 Metals

Nickel

Nickel is the most widespread allergen in the general population (Heim & McKean, 2009; Johnke et al., 2004) and is most often identified as the leading allergen in children (Tables 1 & 2). It accounts for up to 14.9% of positive patch tests (Dotterud and Falk, 1995) in asymptomatic children and is generally more frequent in females (Beattie et al., 2007; Brasch & Geier, 1997; Giordano-Labadie et al., 1999). Importantly, young infants may also be sensitized to nickel. In a study of 543 infants followed from birth to age 18 months, 8.6% showed a reproducible positive reaction to this metal (Johnke et al., 2004). Ear piercing is often considered the major risk factor for becoming sensitized to nickel (Smith-Sivertsen et al., 1999). Other sources include everyday items such as jewelry, eyeglass frames, belt buckles, jean snaps, zippers, coins, keys and even cell phones (Hsu et al., 2010). Another potential cause for sensitization is orthodontic devices (Temesvari & Racz, 1988; Veien et al., 1994). In this setting, the allergic contact dermatitis can present as cheilitis, perioral eczema and stomatitis. Other metals are also implicated in this setting including potassium dichromate (Veien et al., 1994). Typical locations for nickel dermatitis include the face, earlobes, wrist, neck and periumbilical skin with the last site being most common (Hsu et al., 2010).

While a localized contact dermatitis is most expected with nickel, id reactions may not be uncommon. Id reaction refers to involvement of skin lacking direct contact with the allergen, resulting from auto-sensitization from circulating immune cells. Such eruptions, sometimes confused with atopic dermatitis, present as pruritic papules distributed on the upper arms, thighs, knees and elbows. They tend to be more persistent than localized contact dermatitis, lasting up to months after localized plaques have cleared (Hsu et al., 2010). Silverberg and colleagues examined 30 pediatric patients with personal history of umbilical or wrist dermatitis or a family history of nickel allergic contact dermatitis. All patients developed a positive patch test to nickel and 50% of patients were reported to develop id reactions (Silverberg et al., 2002). Systemic contact dermatitis has also been reported with nickel. It may present as a generalized dermatitis despite contact with nickel at a limited body site. In some cases, it may result from oral ingestion of nickel, including the small amount that is present in foods and tap water (Hsu et al., 2010).

Cobalt

While a significant percentage of positive patch test results in children are attributed to cobalt, it should be recognized that this metal often co-sensitizes with other metals, particularly nickel and potassium dichromate (Goon & Goh, 2006; Lisi et al., 2003). At times, contamination of cobalt patch tests with nickel may also lead to false positive tests (Lisi et al., 2003). Yet, cobalt itself remains relevant for allergic contact dermatitis. One study attributes 2 of 17 cases of pediatric hand dermatitis to cobalt (Beattie et al., 2007). In 1971, a case was reported of an 11-year-old boy who presented with eczematous lesions at the site of his eyeglass frames, wrists and mouth. His dermatitis was attributed to cobalt in his watch, glasses and the ball point pen that he chewed (Grimm, 1971).

Potassium dichromate

A common source for potassium dichromate exposure in children is its use in tanning leather, particularly in shoes (Sarma and Ghosh, 2010; Weston et al., 1986). In such cases, the

distribution of dermatitis is typically located at the dorsal feet and occasionally at the plantar surfaces. Though, if only the plantar surfaces are involved, the diagnosis of juvenile plantar dermatosis should also be considered. Other items that contain potassium dichromate include cement, matches, bleaches, antirust compounds, varnishes, yellow paints, spackling compounds and certain glues (Fisher et al., 2008). While many of these items are encountered more so in occupational exposures, these items could potentially exist in a child's home environment or relate to adolescent hobbies.

Mercury

Sensitization to mercury is relatively common. It is also thought to cross react with thimerosal, a compound that contains mercury. Sources of exposure include shoes in which mercury is used as a preservative, and more classically antiseptic solutions (Fernandez Vozmediano & Armario Hita, 2005). Other items that may contain mercurial agents are eye drops, depigmenting creams, pediculosis preparations, vaccines, broken thermometers, amalgam fillings, contact lens solutions and pesticides (Goossens & Morren, 2004). Another presentation for mercury contact allergy is' baboon syndrome'. This entity was described by Andersen et al. in 1984 and is characterized by a systemic contact dermatitis that involves a pruritic and confluent macular and papular light-red eruption localized to the gluteal cleft and major flexures. It can result from contact with various allergens, but mercury is a classic cause. The most common exposure to mercury has been via inhalation from broken thermometers (Lerch & Bircher, 2004). The use of such thermometers has greatly diminished over the years.

Other metals

Less common metal allergens include aluminum, iron, copper and palladium. The development of pruritic nodules at hyposensitization therapy injection sites has been attributed to aluminum. In one study, 8 of 37 children who underwent this therapy showed a contact allergy to aluminum (Netterlid et al., 2009). Iron is considered a rare cause of allergic contact dermatitis, though one case describing a 7-year-old boy with an iron allergy related to his orthopedic prosthesis has been reported (Hemmer et al., 1996). Copper is also an infrequent allergen, but dental amalgam has been associated with positive copper patch testing thought to be clinically relevant (Wohrl et al., 2003). Allergy to palladium may be attributed to jewelry (Goossens, 2008). In a 1996 study, 7% of 700 adolescents had positive patch tests to palladium. Except for three subjects, they demonstrated positive testing to nickel as well, suggesting co- or cross-sensitization (Kanerva et al., 1996). The importance of palladium alone as a relevant contact allergen is controversial. Similarly, despite a review reporting gold sodium thiosulfate to be a common allergen resulting in positive patch testing, its clinical relevance is debated (Bonitsis et al., 2011). Many who test positive to this allergen can wear gold jewelry without developing a reaction (Andersen & Jensen, 2007).

3.2.2 Pharmaceuticals

Thimerosal

Thimerosal is composed of two allergenic compounds, mercury and thiosalicylic acid, and is among the most common causes for positive patch testing in pediatric studies (Tables 1 & 2). It is used as a preservative in vaccines, antitoxins, ophthalmic preparations, contact lens

solutions and eardrops. However, its clinical relevance is often questioned, as most sensitized patients deny a history of dermatitis. High rates of sensitization are likely due to the presence of this compound in mandatory vaccines that were used in the past (Osawa et al., 1991; Schafer et al., 1995). Possibly, thimerosal sensitization is relevant in a subset of children affected by atopic dermatitis. Patrizi and colleagues described a series of five children who developed diffuse atopic dermatitis flares, starting at injection sites, within days of vaccination with thimerosal-containing vaccines. External contamination of the needles is often blamed as a cause for sensitization (Patrizi et al., 1999).

Neomycin

Neomycin is present in many topical preparations including ear and eye drops that are used to treat bacterial infections. In 1979, Leyden and Kligman reported that intermittent use of the agent was not associated with excessive sensitization, as only 1 of 653 subjects less than 12 years old was sensitive to neomycin (Leyden & Kligman, 1979). Since then, however, others have supported its status as a relevant contact allergen (Mortz & Andersen, 1999). In 1986, Weston identified it as the most common allergen causing positive patch test results and attributed this to the prominent use of this agent for bacterial infections and diaper dermatitis (Weston et al., 1986).

Other pharmaceuticals

A number of other pharmaceutical agents and preservatives have been implicated in allergic contact dermatitis, though to a lesser degree than thimerosal and neomycin. These include ethylenediamine, a chemical stabilizer used in Mycolog cream (nystatin and triamcinolone cream) used to treat various skin conditions including diaper dermatitis. It too has been reported as one of the most common causes of positive patch testing in children (Balato et al, 1989). Ethylenediamine can cross react with antihistamines to produce severe systemic reactions. Benzoyl Peroxide is occasionally found among lists of most common allergens (Table 1), but Heine et al. warn that when the adult concentrations of this agent are applied to children during patch testing, false positive reactions can occur due to the agent's irritant potential (Heine et al., 2004). Corticosteroids have been implicated in pediatric allergic contact dermatitis in multiple case reports (Cunha et al., 2003; Luigi et al., 2001). It is recommended that the standard corticosteroid series as well as any agents being used by the child be patch tested when allergic contact dermatitis is suspected in the setting of topical steroid use (Luigi et al., 2001). Less common pharmaceutical allergens have also been reported in children. In 2008, the first case of chlorhexadine allergic contact dermatitis was described in a 4-year-old boy (de Waard-van der Spek & Oranje, 2008). Another case of chlorhexadine contact dermatitis was reported in a 23-month-old with a wound cleaned with this agent. Interestingly, the patient's mother reported that chlorhexadine had been prescribed for umbilical cord care at birth. This case may suggest that sensitization occurred within days to weeks of birth (Le Corre et al., 2010).

3.2.3 Skin care products & fragrances

In present day, cosmetics are being marketed towards children (Kutting et al., 2004). Though industry guidelines exist regarding safe or hypoallergenic compounds, in some instances, these recommendations are not adhered to in made-for-children cosmetics (Rastogi et al.,

1999). Kohl and colleagues patch tested 70 children suspected of having allergic contact dermatitis. In total, 48.6% of them patch tested positive, with cosmetics being the number one cause for sensitization (Kohl et al., 2002). The specific allergens responsible for sensitization in cosmetics are diverse but include fragrances and dyes. Ammonium persulfate and toluene-2,5,diamine are allergens in hair dyes, and interestingly, children often patch test positive to these agents (Bonitsis et al., 2007). Preservatives, including formaldehyde and formaldehyde releasers, are also considered relevant allergens in cosmetics, with Kathon CG being the most common preservative to patch test positive in one study (Conti et al., 1997). Interestingly, not all of children's exposure to cosmetics is direct, but may be related to agents used by caretakers. Fisher reported a 7-year-old girl with an allergy to cinnamic aldehyde who presented with cheilitis and periorbital dermatitis caused by her mother's lipstick (Fisher, 1995).

Symptomatic children frequently exhibit positive patch testing to fragrances, as elucidated by several recent studies (Clayton et al., 2006; Hogeling & Pratt, 2008; Milingou et al., 2010; Zug et al., 2010). A particularly important diagnostic tool is the 'Fragrance Mix' patch test, which contains three cinnamic derivatives, two eugenol derivatives, geraniol, hydroxycitronellal and oak moss absolute extract. Fragrances are nearly ubiquitous, as they are present in many products including cosmetics, toiletries, soaps, laundry detergents, cleansers, rubber, plastic, paper and textiles (Johansen, 2002). Allergic contact dermatitis due to fragrances may present in either a localized or generalized distribution, and facial dermatitis is more common in those with fragrance contact allergy compared to those without. In adolescent patients, axillary exanthem may indicate a fragrance allergy due to use of deodorants (Johansen, 2002).

Balsam of peru is a plant-derived allergen that is present in many topical medications and cosmetics due to its aromatic properties. It has marginal bacteriocidal activity and is used in toothpastes, cough lozenges and dental cements. It is not an uncommon cause of sensitization in infants and children (Fisher et al., 2008) and is found to be one of the most frequent causes of positive patch testing in children (Kuiters et al., 1989; Jacob et al., 2008; Romaguera et al., 1998; Roul et al., 1999). The face is a common site of involvement (Edman, 1985).

Other rising causes of allergic contact dermatitis, which could be avoided in children, are natural remedies. Oftentimes, these agents are presumed safe because they are 'natural' but in fact, several have been linked to dermatitis (Kutting et al., 2004). For example, tea tree oil derived from the Melaleuca alternifolia cheel is considered a treatment for many skin conditions including infections and acne (Allen, 2001; Bedi & Shenefelt, 2002). It contains approximately 100 components which are generally in low enough concentrations so as not to induce allergy (Kutting et al., 2004). However, when photoaged, tea tree oil becomes a stronger sensitizer due to formation of monoterpene breakdown products (Hausen et al., 1999).

Another skin care product particularly pertinent to the field of dermatology is sunscreen. Much data regarding the allergic potential of sunscreens is in adults. However, there are multiple agents which are reported to cause contact allergy in children as well. Though photoallergy is generally uncommon in children, Cook and Freeman described a case of photoallergic contact dermatitis to two sunscreen agents, methoxycinnamate and

oxybenzone, in a 6-year-old (Cook & Freeman, 2002). Recently, octocrylene, a solar filter from the cinnamate family, has been used as a sunscreen against UVB and near-UVA range. It was initially considered to be non-allergenic (Delplace & Blondeel, 2006). But even this agent has caused positive patch tests in 10 of 11 children tested (Avenel-Audran et al., 2010). Not all sunscreen ingredients that can cause allergy are active ingredients. Chu and Sun reported a case of contact allergy to triethanolamine, an emulsifier in sunscreens, in an 8-year-old girl (Chu & Sun, 2001).

A somewhat controversial allergen in adults and children is lanolin, containing wool alcohols. It is found in many skin care products such as Aquaphor Healing Ointment ® (AHO), an emollient commonly used in atopic children. Though previously thought to be a pertinent allergen, in 1998, Kligman wrote that lanolin was "at most a weak contact allergen" and that many case reports represented false positives (Kligman, 1998). However, a few large scale epidemiologic studies list wool alcohols as one of the most common allergens in children (Tables 1 and 2). Epidemiologic data in adults suggests that over time, positive patch testing to lanolin is in fact decreasing (Warshaw et al., 2009). However, in 2010, Matiz and Jacob reported that at least two children who reported burning or irritation to AHO and tested negative to commercially prepared lanolin (one to the T.R.U.E. test and one to Allergeaze) also tested positive to lanolin 30% in petrolatum (Beiersdorf) and their own AHO product (Matiz & Jacob, 2010). These conflicting opinions may not be cause to stop recommending agents that contain lanolin, but rather, a reason for suspicion of allergy if parents report a reaction or if a patient's dermatitis is not improving.

3.2.4 Rubber chemicals

Natural rubber (latex) itself is most often associated with a type I hypersensitivity reaction, which is characterized by urticaria and, in severe cases, anaphylaxis. However, many rubber additives are responsible for type IV hypersensitivity in the form of allergic contact dermatitis. These include accelerators such as thiurams, carbamates, thioureas and mercaptobenzothiazoles (MBTs) and antioxidants such as para-phenylenediamine (PPD) derivatives, which retard environmental degradation (Fisher et al., 2008.) These additives can result in a variety of clinical presentations. The face may be affected after contact with balloons. Eruptions at the waistline have occurred in response to elastic underwear and rubber sponges. Balls and gloves may cause chronic hand eczema (Goossens & Morren, 2004).There is also at least one case report of co-existent type I and type IV sensitivity to rubber latex in a 6-year-old dental patient (Placucci et al., 1996)).

In Beattie et al's study, it was reported that thiuram mix and PPD were each responsible for one case of hand dermatitis (from a total of 17 cases). In the same study, of five cases of foot dermatitis with relevant positive patch tests, two were attributed to mercapto mix and MBT and one to PPD. Such dermatoses are attributed to the presence of these agents in rubber shoe components. Shoe dermatitis that is attributed to allergic contact typically presents as a pruritic papular exanthem on the dorsum of the toes, sparing the webspaces (Sharma &Asati, 2010).

A new pattern for allergic contact dermatitis has been attributed to anti-leak diapers, which feature elastic bands at the thighs that are quite tight. These diapers cause a characteristic distribution of dermatitis at the outer buttocks and hips in toddlers, which resembles a

gunbelt holster. The term 'Lucky Luke' is used to describe this entity that has been attributed to MBT, BPF (Roul et al., 1998) and recently cyclohexylthiophathalimide, which is used as a vulcanization retarder in rubber (Belhadjali et al., 2001).

3.2.5 Plants

Plants, particularly those of the Rhus family, are often thought of in the context of allergic contact dermatitis, though they are infrequently within the top five allergens detected in children (Table 1). Up to 85% of the population is sensitized to plants within the Toxicodendron genus, which includes poison ivy, and most patients are sensitized between ages 8 and 14 years old (Koo et al., 2010). Plant allergy can often be identified by history and distribution generally at exposed sites. *Rhus verniiciflua* (Japanese lacquer tree) has been reported in children to cause severe allergic contact dermatitis, which can be mistaken for cellulitis. Many reported patients required systemic steroids due to severity of rash (Gach et al., 2006; Rademaker & Duffill, 1995).

Compositae (Asteraceae) is the second largest plant family and is a well-recognized cause for contact allergy in gardeners, florists and farmers due to the sesquiterpene lactone component. For some time, it was rarely considered a clinically relevant allergen in children. However, there are several cases described in the literature. Flohr and colleagues described hand dermatitis in three children aged 3-8 years old, each of whom had frequent exposure to plants and tested positive to Compositae (Flohr et al., 2008). Paulsen et al. suggest that this particular allergy may be more common in atopic patients (Paulsen et al., 2008.) and Belloni Fortina et al. propose it should be added to the pediatric screening series when investigating airborne dermatitis in atopic children. They made this recommendation after finding 12 of 641 children sensitized to this antigen (Belloni Fortina et al., 2005).

3.2.6 Henna tattoos with para-phenylenediamine (PPD)

Henna (*Lawsoniainermis*) is a plant from the Lythraceae family. Henna dye is a dark green powder made from the leaves of this plant and used for hair dyeing and for temporary body tattooing. PPD is added to henna dye in order to make the color darker and speed the dyeing process (Jovanovic & Slavkovi-Jovanovic, 2009). This tattooing practice is becoming more popular in the pediatric population. PPD is a potent sensitizer and the literature is peppered with case reports regarding sensitization to PPD after henna tattooing in children (Jovanovic & Slavkovi-Jovanovic, 2009; Sidwell et al., 2008). As this exposure is becoming more prevalent in the pediatric population, some are calling for increased regulations (Sidwell et al., 2008).

4. Utility of patch testing

With increasing recognition of allergic contact dermatitis in the pediatric population, patch testing is becoming more important in this age group. Relative to the total number of studies investigating the prevalence of positive patch testing, those which address clinical relevance of results are fewer. However, a number of epidemiologic studies reflect upon the significance of positive tests, supporting the use of this diagnostic modality in pediatrics. In 1989, Kuiter reported that over 23% of positive tests were clinically relevant, while

Rademaker purported that the value was as high at 92% (Kuiters et al., 1989; Rademaker et al., 1989). A review of studies that report on relevance suggests that the value is probably around 60% (Table 1). Many authors specifically endorse the use of patch testing in children (Jacob et al., 2008; Worm et al., 2007). In the past, it was recommended that the concentration of patch tests be reduced in children (Fisher, 1975; Hjorth, 1981). For example, Fisher recommended using half the recommended concentration (Fisher, 1975). This was due the concern that children are at higher risk of developing irritant reactions and thus, false positive tests (Mortz & Andersen, 1999). However, recent studies suggest that the incidence of irritant reactions is low. Brasch and Geier reported a 9% incidence of irritant reactions (Brasch & Geier, 1997). Most experts recommend the use of the same allergen concentration in children as in adults (Brasch & Geier, 1997; Mortz & Andersen, 1999; Roul et al., 1997; Worm, 2006).

Multiple groups recommend abbreviated series in children, in part due to smaller body surface area of normal skin on which to perform the testing. The German Contact Dermatitis Research Group suggests that in children aged 6-12 years old, the following allergens should be tested: nickel sulfate, thiuram mix, colophony, mercaptobenzothiazole, fragrance mix I, fragrance mix II, mercapto mix, bufexamac, dibromodicyanobutane, chlor-methylisothiazolinone, neomycin and Compositae mix. Potassium dichromate, wool alcohols, disperse blue mix, para-phenylenediamine and *p-tert*.-butylphenol-formaldehyde resin may be added if clinically indicated (Worm et al., 2007). Brasch and Geier advocate for a shorter series that includes nickel, cobalt, dichromate, thimerosal, fragrance allergens, wool wax alcohols and Kathon CG. Their analysis was conducted in Germany, and they suggest that since different geographic locations may show varying rates of sensitization to allergens, local experience should be considered when choosing patch testing series for children (Brasch & Geier, 1997). Finally, Seidenari et al. advise clinicians to use patch testing in children but warn that due to frequent changes in relevant allergen exposures, periodic evaluations of the appropriate testing trays should be done for the pediatric population (Seidenari et al., 2005).

Of note, it should be mentioned that while patch testing often yields positive results to relevant allergens, it is unclear that finding a positive allergen is associated with improved clinical outcome. This is generally due to lack of data. Moustafa et al. recently published retrospective data supporting the relevance of positive patch tests in 44% of 110 children. Unfortunately, finding a positive allergen was not associated with improved clinical outcome in this population (Moustafa et al., 2011).

In adults, it has been shown that performing delayed patch test readings often yields more positive results. Matiz and colleagues have recently proposed that this is true in children as well. In 38 children aged 6 -17 years old, patch tests were evaluated after 48 hours, 72-96 hours and again at 7-9 days. 50% of children revealed positive reactions at the 7-9 day mark and 13% of the total number of children revealed new late delayed reactions. 4 of 6 late delayed allergens were considered clinically relevant including quaternium 15, formaldehyde, diazolidinyl urea and *p-tert*-butylphenol formaldehyde resin (Matiz et al., 2011). While this may not be a feasible approach to patch testing in all patients, it is a useful pearl in children for whom a diagnosis of allergic contact dermatitis is highly suspected.

Perioral	Nickel, potassium dichromate, cobalt, amalgam fillings (mercury), flavoring agents (cinnamic aldehyde)
Periorbital	Ophthalmic preparations (mercury, thimerosal)
Face	Topical pharmaceuticals (benzoyl peroxide, sunscreen allergens), fragrances including balsam of peru, nickel
Ears	Otic preparations (thimerosal, neomycin), nickel, cobalt
Neck	Nickel, fragrance
Wrists	Nickel, cobalt, potassium dichromate
Hands	Nickel, cobalt, rubber additives (including thiuram and PPD), plants (Rhus)
Arms	Vaccines (mercury, thimerosal), hyposensitization therapy (aluminum), sunscreen allergens
Feet	Potassium dichromate
Periumbilical	Nickel
Diaper area	Topical pharmaceuticals (neomycin, ethylenediamine), rubber additives
Trunk, Extremities	PPD, clothing dyes, sunscreen allergens, plants

Table 4. Patterns of Localization of Allergic Contact Dermatitis and Their Respective Allergens.

5. Conclusion

As clinicians begin to recognize the diagnosis of allergic contact dermatitis in children, they should also appreciate that the approach to this disease must be different than in adults. The allergens to which children are exposed are often not the same as those that can affect adults. The use of patch testing may be helpful in this age group, but may need to be modified to evaluate for the most clinically relevant allergens. The body of research that is conducted in this area of dermatology continues to grow and it seems likely that our understanding of allergic contact dermatitis in children will continue to advance as will our ability to diagnose and manage this condition. In particular, further epidemiologic studies in asymptomatic patients that focus on the relevance of positive patch test results will be helpful.

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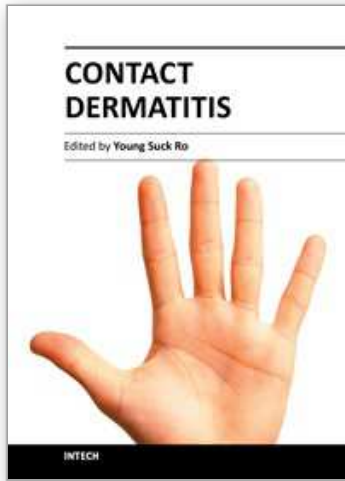
This book centralizes on the subject of contact dermatitis. It aims to provide the dermatologist with a sound base of clinical wisdom and key scientific findings to make an accurate diagnosis and management plan. SPECIAL FEATURES: - Describes numerous possible allergens that cause contact dermatitis. - Provides details of research in the basic sciences to help our readers understand more about contact dermatitis. - Provides a comprehensive description of recently developed methods that have evolved for the diagnosis of contact dermatitis. - Provides a concise, clinically focused, user-friendly format, which can rapidly improve your knowledge of the disease. The past decade has seen significant changes in contact dermatitis. Our understanding of the pathophysiology, our diagnostic approaches, and management of the disease has evolved. In this volume, some of the world's most highly regarded experts discuss areas that have seen significant improvement, as well as areas for future development.

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