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Contact Dermatitis in Atopic Dermatitis Children—Past, Present, and Future

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Abstract

Allergic contact dermatitis (ACD) used to be considered a rarity in children, but recently has been estimated to effect 4.4 million children in the USA alone, with a notable rise in investigative research in the field of pediatric ACD. Researchers have shown that patch testing is safe and effective in afflicted children and that those with atopic dermatitis (AD) have similar sensitization rates, although they have a higher sensitization to certain allergens, thought to be related to the inflammatory (IL-4) milieu. Patch testing assessment guidelines in children include five key considerations: if a patient's dermatitis worsens, changes distribution, fails to improve with topical therapy, or immediately rebounds after removal of topical treatments; if a patient has a particular distribution of dermatitis; if a working patient has hand eczema that fails to improve with therapy; if the patient has AD that started in adolescence or adulthood with definitely no history of childhood eczema; and importantly, if a patient has severe or widespread atopic dermatitis that will require immunosuppressive systemic medication.

Keywords Pediatric · Allergic contact dermatitis · Atopic dermatitis · Sensitization · Review

Abbreviations

CD	Contact dermatitis
ICD	Irritant contact dermatitis
ACD	Allergic contact dermatitis
PPTR	Positive patch test reaction
AD	Atopic dermatitis
RPPT	Relevant positive patch test
NACDG	The North American Contact Dermatitis Group
PCDR	The Pediatric Contact Dermatitis Registry
TEWL	Transepidermal water loss
E.A.S.I.	Eczema area and severity index
AOY	Allergen of the Year
TCS	topical corticosteroids

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Introduction

Contact dermatitis (CD) is a descriptive name for a group of skin diseases that develop as a result of contact with an exogenous agent. The American Academy of Dermatology estimated that 4.17% of the US population suffers from contact dermatitis and the estimated cost associated with this condition was over $1.5 billion in 2013 [1]. There are two main types of contact dermatitis that are characterized by the etiologic inciting agent, irritant and allergic. Irritant contact dermatitis (ICD) results when a caustic chemical contactant disrupts the skin barrier. It usually presents as a well-demarcated, erythematous lesion, localized to the area of contact by the substance and classically occurs within hours after exposure. This is by far the more common type of contact dermatitis. Allergic contact dermatitis (ACD), on the other hand, is a cell-mediated (type IV) hypersensitivity reaction that occurs following repeated cutaneous exposure to an allergen. This cutaneous reaction usually extends beyond the area of contact with the allergen and may take hours to several days after exposure to develop clinical signs in the skin. Notably, ACD was listed as the fifth most prevalent skin disease; this disease affects approximately 13 million people in the USA, and remarkably 4.4 million of those affected are children [1]. This number is staggering considering that less than a decade ago, contact

dermatitis in children (other than irritant diaper dermatitis) was considered to be a rarity [2, 3].

The Discovery of CD in Infants and Children

Inducible contact sensitization was first described as an experimental model in children by Straus in 1931 [4]. Straus applied poison ivy extract to the back of newborns, 1 to 4 days old, and noted the absence of cutaneous reactions [4]. Straus then retested them at 2 to 4 weeks of age and found 70% demonstrated sensitization on provocation and developed a delayed type hypersensitivity reaction to poison ivy [4]. Subsequently, in 1960s, investigators demonstrated that afflicted children could be evaluated for allergic contact dermatitis via patch testing [2, 3, 5–11].

In 1963, investigators in Sweden aggregated data from patients with dermatitis who were subsequently patch tested over a 3-year period. They found that the incidence of a positive reaction in children (46%) was not significantly different from that of the adult population that they tested (50%) [11]. Moreover, 24% of these children with dermatitis were found to have a positive patch test reaction (PPTR) to balsam of Peru, statistically significantly higher as compared to only 6% positive rate of the adult cohort [11]. This was one of the earlier studies that confirmed children may have positive patch reactions just as frequently as adults and that patch testing with balsam of Peru was particularly important in children. Another early study that included pediatric patients involved a cohort of children and adults with atopic dermatitis (AD) and compared the incidence of contact dermatitis to patients with psoriasis. The authors found an incidence of contact dermatitis in 28% of patients with AD as compared to 9% in patients with psoriasis [12]. This study suggested that the prevalence of ACD in AD was higher than in those with other chronic inflammatory skin conditions such as psoriasis.

Hammershoy et al. reported patch test results from 3225 consecutive Danish patients in 1980 and found that 1038 patients reacted to one or more allergen [7]. The study included adult patients, but found children had positive reactions to five of the six different allergens [7]. With an increasing amount of data showing children with PPTR, subsequent investigators began to perform sub-analysis studies on pediatric cohorts. In 1983, Weston et al. found that 42% of the children studied had a contact allergy to a shoe-related allergen; the clinical relevance was assigned if the subject had dermatitis involving the dorsum of the feet. Those children who avoided their identified allergens remained dermatitis-free for the 2 years of follow-up of the study [8]. In 1984, Penvy et al. published the results of a 10-year study of patch testing done in German children with suspected ACD between the ages of 3 and 16 years old and found that 71% were positive to at least one substance [6, 10].

Sensitization Studies in Pediatric Patients Without Dermatitis

A pivotal paper by Weston et al. estimated the prevalence rate of a positive patch test result to be 20% in healthy children aged 6 months to 5 years old [13]. This study provided further evidence that contact sensitization likely occurred in early childhood and refuted the belief that infants have less exposure and sensitization rates to allergens than adults [13]. Supporting evidence for this high incidence of sensitization in children without dermatitis was also noted by Barros et al. who also found that 13.3% of healthy Portuguese children aged 5 to 14 years old had a positive patch test to one or more contact allergens [14]. Subsequent to this, Bruckner et al. evaluated the efficacy of a newly available patch test kit in asymptomatic children less than 5 years of age and found a positive rate comparable to that of Weston et al.'s study, at 24.5% [15]. Notably, 45% of the children who had a positive reaction were less than 18 months of age [15].

These studies established that patch testing could safely be performed on asymptomatic, healthy children and also confirmed that clinically unaffected infants and young children could demonstrate a cutaneous delayed hypersensitivity response through patch test provocation [16]. The rates described in the literature for asymptomatic children are consistently lower than reported rates in symptomatic pediatric populations referred for patch testing, as expected.

Sensitization Studies in Pediatric Patients with Dermatitis

In Europe and South America, several large studies examined the sensitization rates in children. In the United Kingdom (UK), Buckley et al. determined the frequency of fragrance allergy was low in the first 20 years of life, ranging from 2.5–3.4%, with the youngest patients being only 2 years of age [17]. In France, children with a suspected diagnosis of ACD, aged 1 to 15 years old, had a PPT rate of 66%, so the authors recommended using an abbreviated series of patch tests in children less than 6 years [18]. A Brazilian study found a prevalence rate of 56% for positive patch test results for patients between the ages of 10 and 19 years old who were suspected of having contact dermatitis [19]. Another UK study demonstrated that children 3 to 15 years of age with uncontrolled dermatitis had a 54% rate of positive patch test reactions [20].

Pediatric Studies with Relevant Positive Patch Test Allergens

A more recent study from Poland tested a group of children with eczema at 7 and 16 years of age [21]. The 7-year-olds had a PPTR rate of 43.8% while the 16-year-olds had a 52.6% rate

[21]. The relevant positive patch test (RPPT) rates were 36% and 26%, for the 7- and 16-year-olds, respectively [21].

The first two multi-center North American studies on patch testing in affected children were published in 2008 marking a significant milestone in the field [22, 23]. These groundbreaking studies showed the usefulness of patch testing in the affected pediatric population and found that the PPTR rates were similar to those of evaluated adults. Jacob et al. found a PPTR rate of 83% in children between 1 and 18 years old and of those, 77% had clinically relevant reactions. While Zug et al. found that there was no significant difference between children (51.2%) and adults (54.1%) in the frequency of at least one RPPT, children were found be more likely to have a comorbid diagnosis of AD. The commercially available screening kit is proposed to have detected 61.5% of all relevant positive reactions and 15.1% of children had at least one relevant positive reaction to a non-North American Contact Dermatitis Group (NACDG) screening panel allergen, which was the test used in this study [23].

More recent studies have further defined the prevalence rates in children with suspected ACD, which have ranged from 46.7 to 65%, with about half of those cases having a RPPT. Zug et al. showed consistent rates with previously reported literature of 62.3% of children having a PPTR and 56.7% of children having a RPPT [24]. The percentage of RPPT did not differ significantly from adults; however, the RPPT for 27 allergens was significantly different between the children and adults [24]. Another recent large, single-center study from Italy found similar prevalence rates of PPTR with 46.7% of children having at least one positive reaction of which 49.7% were clinically relevant [25]. In 2016, Goldenberg et al. quantified patch test results from the first US national registry of pediatric CD cases and found 65% of cases had one or more positive patch test with 48% having a RPPT, corroborating the findings of the previously mentioned studies [26].

Increased Risk Factors in Children

Despite early studies by Straus in poison ivy on infants, it was largely accepted that children had either less exposure to contact allergens compared to adults (in terms of lifetime cumulative dose) and/or that their immune systems were less responsive to contact allergens as compared to adults [2, 3, 27, 28]. This was confounded by the co-existence of AD in a significant portion of the pediatric recalcitrant dermatitis population which inadvertently led to an increased threshold to patch test [2, 10].

And yet, it is believed that newborns and infants may have a higher risk of sensitization due to their developing skin being thinner with a potentially more absorbent surface and there being a larger surface area to body weight ratio [29]. Additionally, children have a thinner stratum corneum as compared to adults and the other layers of the epidermis are not fully formed until puberty [29].

Of interest, data from the Pediatric Contact Dermatitis Registry (PCDR), in which 49% of the population had AD, elucidated further differences between AD children and non-AD children. AD children were likely to be younger when patch tested and had different reaction profiles, notably to their skin care treatments, as compared to non-AD children suggesting that the treatment with topical skin care regimens may increase the risk of sensitization to allergens in their products [30].

ACD develops secondary to absorption and metabolism of an immune priming hapten (aka allergen). In AD patients, there is an impaired skin barrier function, thus having the potential for greater allergen absorption and for systemic effects [31]. AD impairing skin barrier is demonstrated through an increase in transepidermal water loss (TEWL). A European study demonstrated that penetration of 1% sodium laurel sulfate was higher in the AD group along with increased TEWL as compared to healthy controls [32]. Moreover, mutations in the filaggrin gene have been reported in AD patients, and the filaggrin gene mutations have also been implicated in chronic irritant CD, which contributes to the impaired skin barrier and has been associated with a higher risk factor to contact sensitization to nickel [33–36].

The Issue of Underlying AD

AD pathophysiology is complex and multifactorial in that a defective skin barrier, bacterial colonization, and immune dysregulation all contribute to the dermatitis [37, 38]. AD inflammatory response is primarily mediated by T helper (Th) cell 2 activity, with the involvement of Th1, Th17, and Th22 lymphocytes as well [37, 39]. ACD pathophysiology is primarily driven by T cytotoxic (Tc)1/Th1 inflammatory cells, but Th2, Th17, and Th22 may also play a role in the inflammatory response [37, 39, 40]. The inflammatory response is somewhat dependent upon the allergen causing the dermatitis [40]. Because of this division of inflammatory response mediators, it was previously thought that the Th2-skewed immune response in AD patients resulted in less contact dermatitis reactivity when exposed to an allergen [41].

A longitudinal study demonstrated that severe and moderate AD patients elicited a sensitization to dinitrochlorobenzene (DNCB) in 33% and 95% of cases, respectively, but when the nonreactor AD subjects were re-challenged when their AD was well controlled after 1 month, 18 out of those 20 subjects tested had positive reactions [41]. This suggests that the Th2-driven inflammatory response of AD may decrease the ACD Th1 response to strong haptens, while the AD is active in these patients. Newell et al. studied immunological sensitization by the skin in AD non-lesional skin compared to healthy controls.

AD individuals with filaggrin gene mutation, AD subjects without the mutation, and controls were sensitized to DNCB. One month after sensitization, AD subjects (with and without filaggrin mutation) were re-challenged at a different skin site and had reduced contact hypersensitivity responses as compared to the healthy control group as measured by reduced skinfold thickness and erythema. While systemic Th1 responses were noted in both the control and AD groups, only the AD group mounted a significant Th2 response. There was no significant difference between the AD filaggrin gene mutation groups. Four months post-sensitization, the DNCB Th2 cell responses were persistent in the AD group whereas the Th1 cell responses were persistent in the control group. This is important because this suggests that AD patients have an attenuated skin immunologic response to certain allergens, which is driven by Th2, independent of their filaggrin gene mutation status [42].

Interleukin 4 (IL-4) is a cytokine that induces differentiation of naive helper T cells to Th2 cells. IL-4 acts as a proinflammatory mediator in contact hypersensitivity, possibly favoring the accumulation of mononuclear cells at the site of inflammation. Mouse studies showed that IL-4 knockout mice had preserved ability to elicit contact sensitivity to oxazolone but not to 2,3,6-trinitrochlorobenzene which is a contact allergen that triggers a predominantly Th-2-mediated sensitization [43]. Dupilumab is a monoclonal antibody against the alpha subunit of IL-4 which has been recently approved to treat moderate to severe AD. Through blockade of IL-4 receptor alpha, both IL4 and IL13 pathways are modulated leading to decreased levels of Th2 bio-markers. A recent study by Machler et al. reported 15 adult patients, mostly with a history of childhood AD and concurrent ACD, who had a 70–100% improvement of their dermatitis after dupilumab treatment. This study highlights the potential of IL-4 blockade in the treatment of recalcitrant dermatitis in patients with concurrent AD and ACD [44].

Genetic differences may also help distinguish AD and ACD. Correa da Rosa et al. studied the gene expression and immunohistochemistry patterns of biopsied skin taken from allergen-reactive patches (e.g., nickel, fragrance, and rubber), versus expression in non-AD controls [45]. The non-AD group had a higher magnitude of inflammatory genes expressed and a larger number of unique differentially expressed genes as compared to the AD group; the inflammatory genes included T cells, Th1, Th17, and matrix metalloproteinases [45]. Th17 promotes inflammation and T cell recruitment, while Th22 maintains skin homeostasis via induction of epithelial cell proliferation and migration [46]. A significantly stronger expression of Th1 and Th2 genes were detected in the non-AD group in their reaction to nickel and PCR data demonstrated an attenuated immune response in AD skin as compared to controls [45]. AD skin had an increased expression of Th2, Th17, and negative regulator levels at baseline as compared to non-AD skin; this may attenuate the Th1 component of ACD leading to decreased magnitude of response in patients with AD [45].

Although in the classic sense, the immune function by which ACD develops (Th1) opposes the AD inflammatory response (Th2), AD patients may actually have an increased risk of ACD or at least comparable to non-AD population [47]. Th17 and Th22 are a newly discovered class of tissue-signaling T cells that protect the skin from pathogens and are also implicated in acute AD skin disease and ACD [46]. Th22 may heighten the immune response in inflamed skin, such as AD, by enhancing the production TNF alpha cytokines and chemokines, potentially contributing to increased sensitization of allergens [46]. The barrier disruption in AD may lead to enhanced immune signals that then allow for sensitization to low potency allergens such as propylene glycol, cocamidopropyl betaine (CAPB), and vanillin [48]. Weak sensitizers may trigger ACD in AD skin because of the altered skin barrier that potentially allows for greater absorption of these allergens and responds differently [48]. This was demonstrated by Kohli et al., and in a cohort patch tested for 80 standard screening allergens, those with a history of AD were more likely to react to weak allergens than other patients [48]. They concluded that weak antigens may be more allergenic to the skin with a Th2-skewed immune response based on a hypothesis that the disrupted skin barrier enhances cutaneous sensitization via the allergens molecular pattern [48].

Rajka and Hanifin conducted a landmark study assessing for immune dysfunction in AD patients (Fig. 1) [49]. They evaluated various immunological abnormalities in 14 AD patients and specifically showed that AD patients with repeated exposure to DNCB developed a delayed hypersensitivity reaction at a rate of 33% whereas the antigens would be expected to produce a PPTR in at least 80% of non-AD population [49]. Some studies have shown that ACD frequency is increased in patients with mild AD, but there is a decreased rate in severe AD patients, while other studies have shown an increase in the number of PPTR to be associated with patients having an eczema area and severity index (E.A.S.I.) score higher than 10 [50–52]. Rees et al. also observed that fewer atopic patients became sensitized to DNCB compared to non-atopic patients, leading to the theory that the inflammatory mediators of AD may attenuate the hypersensitivity inflammatory reaction [53, 54]. Forsbeck et al. found similar findings when evaluating DNCB and NDMA (p-nitrosodimethylamine), in that those patients with severe dermatitis were sensitized only 52% of the time while those with mild dermatitis had a 84% sensitization rate [55]. In the most recent study with this allergen, as discussed above by Newell et al., DNCB penetration was equivalent among patients with AD with and without filaggrin mutation and healthy controls, but when re-challenged with DNCB, AD patients had a decreased frequency of hypersensitivity [42].

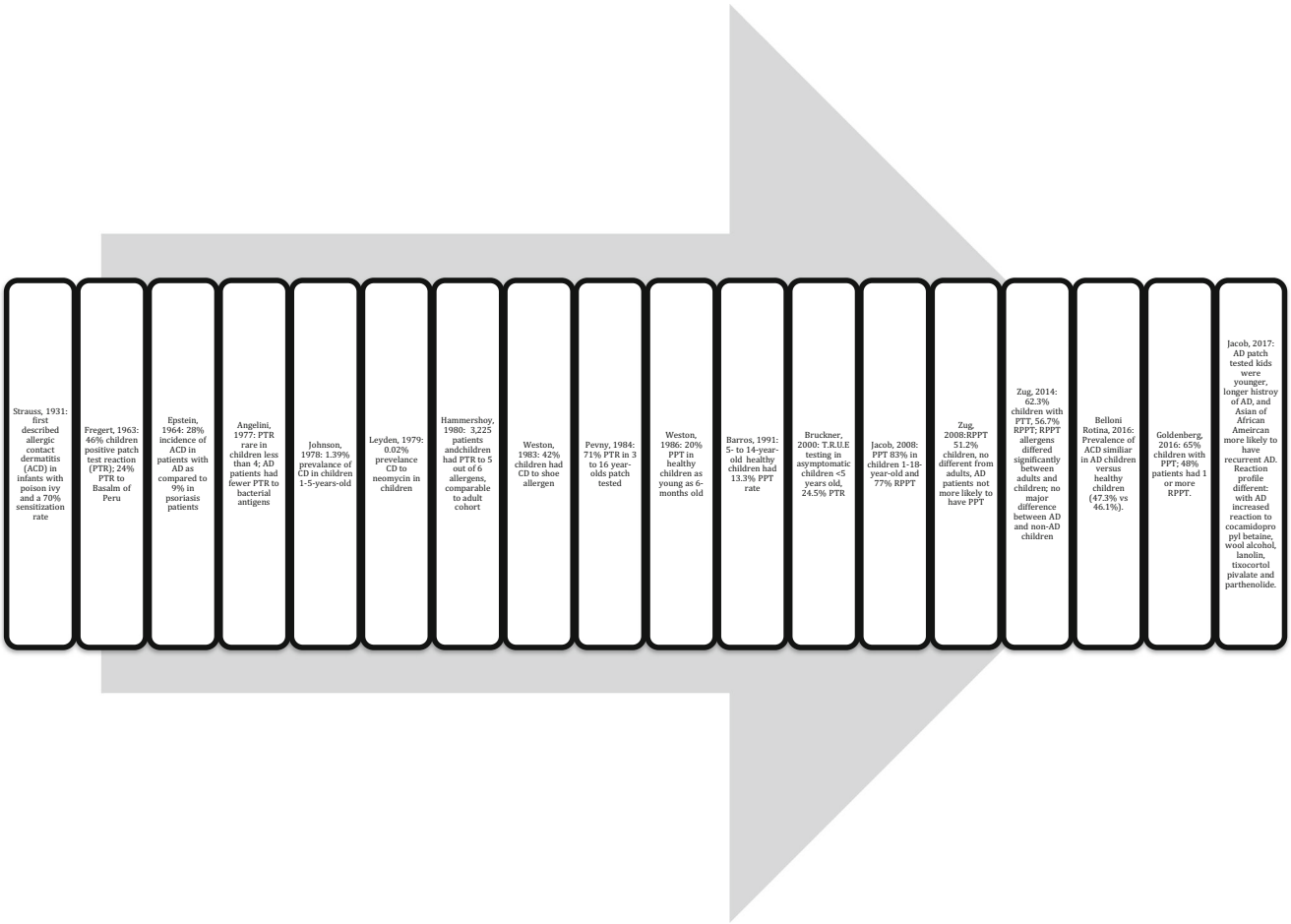

Fig. 1 Timeline of landmark studies on ACD in children from the 1930s

This attenuated response to sensitizers is also supported by the work of Jones et al. who performed two sets of patch tests on a group of AD and non-AD controls, to test if the first patch test had a sensitization effect. After the first patch test, 61% of controls versus only 15% of AD patients had a PPTR to *Rhus* oleoresin. After the second patch test in a subset of patients, only 6% of AD patients had an ACD to *Rhus* plant while significantly more, 33%, of healthy controls had *Rhus* dermatitis [56]. Similarly, Jacob et al. showed that strong sensitizers in personal care products, such as methylisothiazolinone (MI), had a higher frequency in causing PPTR in patients without AD than AD patients [30].

Furthermore, AD patients are exposed to many topical treatments such as emollients and topical therapeutics and can develop sensitization to the vehicle excipients or active agents used to treat the inflammation [47]. A recent study found that 89% of 187 surveyed products labeled as "hypoallergenic," "dermatologist recommended/tested," "fragrance-free," or "paraben-free" contained at least one contact allergen [57]. Moreover, another large study demonstrated that AD patients are more likely to be sensitized to their topical emollient treatment and antiseptics [58]. Contrary to previous studies, severe AD patients were more likely to be sensitized to topical treatments as compared to moderate AD patients [58]. The authors suggest that the topical treatments of antiseptics and emollients should be included in the standard patch testing series in AD children when ACD is suspected [58]. Moreover, AD patients are colonized with varying bacterial organisms that have been shown to contribute to the inflammatory response affected by contact sensitization and ACD [32, 59].

A challenge exists in maintaining a sensitive threshold to test AD patients for ACD as oftentimes, these conditions involve similar areas of the body including the lips, eyelids, hands, and flexural areas [60]. The preferential involvement of flexural areas of AD may be secondary to changes in pH, skin thickness, and types of microorganisms and antimicrobial peptides in those areas [61]. Since it is easier for haptens to penetrate the skin in these areas of occlusion, it has been shown that even with generalized topical exposure to a substance, subjects continued to develop a predisposition for flexural specific ACD [62–64]. Furthermore, when atopic patients are in flare (their dermatitis is very active), the false-negative rates of patch testing appear higher, whereas when the patients are under control there is a greater likelihood of true positive test.

For this reason, optimizing the skin barrier and reducing inflammation through utilization of aggressive peri-patch test

treatments such as intense moisturization, use of wet wraps, adequate corticosteroid regimens as well as acidification protocols through bathing and moisturizing regimens, and *S. aureus* control with bleach baths, in atopic patients, lead to more efficacious patch test outcomes and clinical improvement (SEJ and CM personal observation) [65, 66].

Sensitization Studies in Patients with AD

Historically, it was believed that AD patients were at lower risk for developing ACD as compared to the general population [67]. Maihol et al. showed the frequency of sensitization to topical treatments of AD in 641 children who were patch tested with seven common topical treatment agents to be 6.2% ($n = 41$) [58]. The most frequent allergens were found to be emollients at 47.5%. In this group, increased risk of sensitization was associated with AD severity, onset of AD at less than 6 months of age, and IgE-mediated sensitization [58].

Another study by Belloni Fortina et al. evaluated contact sensitization in patients less than 3 years old by distributing patch testing with a series of 30 allergens [68]. Two-hundred children (62.3%) had a positive reaction to at least one allergen and the prevalence was similar between subjects with (61.3%) and without (63%) AD [68]. A recent large, single-center study from Italy found similar prevalence rates of PPTR with 46.7% of children having at least one positive reaction of which 49.7% were clinically relevant [25]. The prevalence of sensitization was similar between children with and without AD, although AD patients had higher sensitization rate to certain allergens (potassium dichromate, Compositae mix, and disperse blue) [25]. Another large-scale study used the standard NACDG screening series in patients of which 12.89% had AD [69]. They found that the incidence of a PPTR was significantly higher in pediatric AD patients, and they were more likely to develop a hypersensitivity reaction to metal allergens [69]. A retrospective analysis of the PREA-1 data found that 89% of the pediatric AD patients compared to 66% of non-AD patients had a positive allergen sensitivity using the T.R.U.E. Test™ [52]. In this review, there was a significantly higher PPTR to fragrance mix and balsam of Peru [52].

Several studies have not only looked at the higher prevalence of ACD in AD but also at the relevant positive patch tests reactions. A study of AD patients of all ages found a RPPT in 38% of subjects [70]. They found that PPTR were correlated with severity of AD [70]. A review of the current literature showed that the frequency of PPTR in children with "suspected ACD, recalcitrant AD, or eczema," ranged from 27 to 96%, with RPPT ranged from 52 to 100% [71]. The rates of PPTR between the non-AD patients and AD patients were 55% and 56%, respectively, which confirms prior evidence [71]. Based on the studies mentioned above, AD patients have the same or higher rates of developing ACD compared to non-AD patients.

Most recently, Jacob et al. retrospectively reviewed 1142 patch test cases of patients less than 18 years old and found that those with AD were younger at the age of patch testing than those without a history of AD had almost five times the odds of having generalized distribution of dermatitis and also found that Asian and African American patch tested children were more likely to have AD [30]. Despite the controversy surrounding the frequency of ACD in AD, it is now generally accepted that ACD can worsen the clinical course of children with AD [42, 61, 72, 73].

Current Consensus on Approach to Evaluation of Patients Suspected with ACD

Patch testing (PT) is the gold standard in diagnosing ACD [74]. PT is recommended when there is a clinical suspicion for contact dermatitis and where children have a history of deteriorating or chronic recalcitrant dermatitis lasting longer than 2 months, worsening dermatitis despite a preliminary treatment with a pre-emptive avoidance strategy (P.E.A.S.), or dermatitis involving highly susceptible locations such as the eyelids, genitals, hands, and feet [72, 75]. In a recent work by Hill et al., the five most recent pediatric patch test studies were reviewed and the top ten prevalent allergens in children were identified. Following an avoidance strategy of these top ten allergens, 30% of patients were able to improve their dermatitis [76].

As indicated by the patient's environmental exposure history, the health care provider will make a clinical care decision as to whether patch testing is indicated and whether to screen the patient with the commercially available patch test kit or generate a customized comprehensive patch test to the allergens based on this initial assessment of likely exposed substances. The currently commercially available patch test kit (Thin-layer Rapid Use Test ™, SmartPractice, Phoenix, AZ) recently received FDA indication for use in the 6- to 18-year-old population [77]. Based on the P.E.A.S. data, the commercially available kit is thought to capture 64% of the most common allergens [76].

On the other hand, customizable basic patch testing series have specifically been suggested for pediatric patients to serve as a minimum screening set for evaluating recalcitrant dermatitis in this population [78, 79]. Modifications to the allergen concentrations or time of occlusion has been suggested in younger patients (less than 5 years of age) and those with endogenous dermatitis to avoid irritant reactions that could potentially lead to a false-positive reading [78]. Notably, efficacy of patch testing is seen when the patient's own topical corticosteroids, antiseptics, antibiotics, and emollients are tested for alongside the patch testing panel [80].

The top allergens in the most recent large US-only PCDR study are listed by substance in descending order of frequency in Table 1. CAPB, propylene glycol, fragrance mix 2, MI as a single substrate, and Compositae mix are only available through custom-comprehensive patch testing [30]. Of note, parthenolide, a sesquiterpene lactone, is included as a component of the commercially available kit to screen for Compositae allergy, while MI is included in the MCI/MI component at a concentration of 100 ppm. Recent studies have shown that failure to test for MI alone could lead to a false-negative rate as high as 51% for MI allergy [81]. This underscores the notion of the importance of patch testing with supplemental allergens beyond the standard screening panel, as 23.6% of children had a positive reaction to a supplemental allergen and 28.4% of those allergens would not have been identified with the standard series [24].

Guidelines for Testing for ACD in AD Patients

Clinical guidelines based on expert consensus for the diagnosis of ACD in patients with AD were recently published to aid in the evaluation and management of patients with AD suspected of having ACD [47]. The guidelines were published by a working group of experts in the fields of AD and ACD [47]. Five key considerations to patch test children with AD are made: (i) if a patient's dermatitis worsens, changes distribution, fails to improve with topical therapy, or immediately rebounds after removal of topical treatments; (ii) if a patient has an abnormal distribution of dermatitis, such as a head and neck predominance, a hand or foot involvement, eyelid predominance, and cheilitis/perioral predominance; (iii) if a working patient has hand eczema that fails to improve with therapy; (iv) if the patient has AD that started in adolescence or adulthood with definitely no history of childhood eczema; and (v) if a patient has severe or widespread dermatitis that will require immunosuppressive systemic medication [82]. The authors suggest that patch testing is unlikely to be useful in the setting of stable AD, a flare, recent exposure to systemic immunosuppressive treatment or ultraviolet radiation or if only a limited patch test battery is used [82]. Immunosuppressive medications utilized during patch testing may decrease the sensitivity of the testing, although the inhibitory response is likely dose-dependent [47]. Therefore, slightly positive tests may be missed due to the immunosuppression [47, 83]. The clinical recommendations concede that there is a lack of data to establish a definitive recommendation on the use of systemic immunosuppressive medications and patch testing in children.

Table 1 Top allergens in AD cohort

1	Nickel sulfate
2	Fragrance mix 1
3	Balsam of Peru
4	Bacitracin
5	Formaldehyde
6	Cocamidopropyl betaine
7	Propylene glycol
8	Wool alcohol
9	Lanolin
10	Bronopol
11	Neomycin sulfate
12	Quaternium 15
13	Colophony
14	Tixocortol-21-pivalate
15	MCI/MI and MI
16	Cobalt
17	Fragrance mix 2
18	Potassium dichromate
19	Compositae mix
20	Parthenolide

Adapted from [30]

Allergens Prevalent in AD Patients

Several studies have demonstrated that children with AD have higher sensitization rates to certain allergens including: potassium dichromate, Compositae mix, disperse blue, balsam of Peru, fragrance mix, and lanolin [25, 52, 84]. The generalizability of these findings is limited due to the fact that the studies were either small in size or limited in their geographic area.

The PCDR gathered data on pediatric ACD from across the USA [30]. Jacob et al. used this data of 1142 pediatric patch test cases with 49% of the cases having a history of AD [30]. The study tabulated the most common 21 allergens with a positive patch test in the AD population compared to the rest of the study sample [30]. AD patients had a somewhat different reaction profile to certain allergens than non-AD patients [30].

Notably, patients with AD were more likely to have a RPPT to cocamidopropyl betaine (CAPB), wool alcohol, lanolin, tixocortol pivalate, and parthenolide (a sesqueterpene lactone component of feverfew, *Tanacetum parthenium*, a member of the Compositae family) [30]. These substances were often found to be relevant with exposures localizing to the skin care regimen of AD patients.

Allergen Discussion

Cocamidopropyl betaine (CAPB) is a surfactant found in shampoos and other cleansers. Synthetic CAPB was first patented in 1967 as a no-tear detergent for infants [82]. It is

composed of a coconut oil derivative in addition to dimethylaminopropylamine and monochloroacetic acid. The American Contact Dermatitis Society (ACDS) called it the "Allergen of the Year" (AOY) in 2004 as it had a rapidly developing prevalence as an allergen associated with increased utilization in products, especially those marketed for younger children [25, 85]. It often presents as dermatitis on the eyelids, face, scalp, and neck, but is also known to cause diffuse dermatitis, especially in AD [86]. Some authors have proposed that "health care practitioners counsel their atopic patients to minimize cutaneous contact with personal care products containing these surfactants," specifically CAPB [87]. The recent PCDR study is consistent with other recent findings that atopic patients are more likely to have a hypersensitivity reaction to CAPB or its precursor, amidoamine [25]. Again, CAPB is currently only available as an individual testing agent.

Lanolin is an oil-based compound extracted from natural wool by using solvents or detergents and is used in many topical skin products [88]. It functions as an emollient, moisturizer, emulsifier, adhesive, and plasticizer and is therefore contained in many products used to moisturize skin of AD patients [24, 88]. Lanolin is a natural substance and each product it is used in may have a different composition of the compound based on the natural wool source and the solvents or detergents used to make the lanolin. Therefore, some patients may develop a contact allergy to some lanolin-containing products and not others [89]. Wool alcohols can be removed from the lanolin compound, which has been shown to cause less reactivity in some patients [86].

Tixocortol pivalate is the patch testing substance used as a marker for allergy to corticosteroids of the class A. Class A corticosteroids include the commonly used over the counter topical corticosteroid (TCS) medication hydrocortisone acetate. Corticosteroids are used across multiple disciplines in medicine. A failure to improve or worsening of dermatitis requiring longer courses of higher potency TCS suggests a potential underlying ACD [86]. Since corticosteroids are innately anti-inflammatory, patch testing may result in false-negative readings and it is recommended to check for delayed reactions at day 7 of patch testing [90]. Class A corticosteroids can cross react with class D2 which includes hydrocortisone butyrate and hydrocortisone valerate [88].

Parthenolide (a sesquiterpene lactone [SQL]) is a component of feverfew a member of the Compositae plant family. SLQs are found in other family members such as ragweed, dandelions, sunflowers, and daises [88, 91]. People are likely exposed to this substance from nature, especially when these plants are blooming in spring and summer. The dermatitis distribution may follow that of an airborne-pattern or may be localized to the area of exposure from the SQL-containing skin care product [91]. The prevalence rate in children tested for suspected ACD to parthenolide has been reported at 2.6% [30, 91]. Jacob et al.'s study found that parthenolide positive patch was significantly higher in AD patients [92]. Importantly, children who have had PPTR to dandelion extract may not react to SQL and Compositae mix and thus could demonstrate false negativity to Compositae on patch testing [93]. It has been suggested to test dandelion extract in children with chronic dermatitis as a supplement, as it is thought that the dandelion does not cross react with the other SQL allergens and therefore may be overlooked in the ACD diagnosis [93].

Nickel is ubiquitous in the modern day environment, from utilization in adornments (jewelry, clothing snaps, belt buckles) to other everyday household items such as, coins, toys, electronics, and razors [82]. Quite notably, some of the uses are necessary, for example, "nickel is vital in modern battery technology," and to protect against radiation. Stainless steel made with nickel is part of reinforcement arches that withstand extreme climate conditions and can withstand long-lasting radioactivity. This stainless steel nickel will help end the degradation of the current cover on the old Chernobyl nuclear reactor unit 4 [94]. In fact, every day, it is the nickel in cell phone coatings that protects the brain from the radiation emitted from cell phones [94]. Furthermore, "as much as 40% of the global population is affected by potable water shortages" and nickel alloys and nickel-containing high-alloy stainless steels are playing a key role in handling, storage, and processing of water [94]. Nickel stainless steel alloys have the right combination of metals to resist the extremely corrosive conditions that prevail in desalination plants [94]. However, nickel is then present in the water supply, which can then sensitize users.

The Nickel Institute states that "it is not the total amount of metal present in, for example a river or stream, that is most important, as some of the metal will be bound to dissolved organic compounds and other ions. [rather, it is the] remaining fraction of total metal that actually interacts with the aquatic organisms [or the skin that] is called the bioavailable metal" [94]. The bioavailability of the metal (as in the release of nickel reactive ions from nickel-containing alloys) should be the focus, as utilization of low release metals could be a pivotal component in prevention of contact sensitization [94]. Due to high exposure of the skin to high release nickel alloys, nickel has become the number one confirmed allergen by patch testing worldwide [23]. In 2008, nickel was designated the AOY to highlight is longstanding top allergen position and rising prevalence rates in patients referred to US tertiary care centers [30].

Nickel has become also the top allergen among children with and without AD. In 22% of children with AD, a PPTR was noted, and there was a 2.38 times odds of having an RPPT to nickel compared to the non-AD subjects [95]. The cutaneous response to nickel can be variable, localized, with an id response to a systemic response as it can be present in food or implantable devices [88]. Id reactions to nickel have been

observed in up to 50% of patients presenting with nickel allergy and tends to present in a generalized distribution [96]. Systemic response can be triggered by oral ingestion of nickel leading to a generalized dermatitis in almost 50% of food-related ACD cases [97].

Cobalt is a metal commonly most used in jewelry, dental and orthopedic hardware, and belt buckles [98]. It has also been used to color goods such as porcelain, glass, watercolor paints, crayons, blue tattoos, leather goods, and hair dye [98]. It is often contained in alloys with other metals such as nickel, and therefore, the allergy to cobalt has been linked to exposure of nickel; however, new evidence has indicated that up to 40% of patients positive to cobalt were negative to nickel on patch testing [98]. However, once isolated, it is seen as an independent allergen, so much so that in 2016 the ACDS named it AOY [98].

Potassium dichromate is used in manufacturing and construction. It is used as a pigment in several goods such as in tattoos, green felt fabric, cosmetics, and dental and orthopedic hardware [25, 30]. Sensitization oftentimes occurs in textile workers, leather tanners, and construction workers who are in contact with cement. However, in children, the allergy develops likely after contact with the pigment. There is inconsistent data on potassium dichromate allergy prevalence among AD patients as Jacob et al. showed that it was significantly less prevalent while Belloni Fortina et al. showed a significantly higher prevalence in AD children, which may reflect regional variations and sources of the allergen [99].

Methylisothiazolinone (MI) is a common preservative in cosmetic products and detergents and is a well-known ingredient in baby wipes and moist towelettes [100, 101]. It has become popular in cosmetic products because of its antimicrobial properties and it remains active over a wide range of skin pH [102]. Its use has been restricted in Europe because of its heightened sensitization as a potent allergen [103]. While reactivity to potent sensitizers may be attenuated in AD, there have been reports of ACD in AD patients caused by MI in wall paint at a concentration of only 53 ppm [104]. New data has emerged that suggests the rate of sensitization may be dramatically underestimated because of under detection of MI on patch testing. Recent recommendations advocate for the testing of MI at a concentration of 2000 ppm [105, 106]. There has been more evidence that MI sensitization is on the rise, up to 7.2% in Belgium in 2013 [104]. The rise in sensitization is thought to be largely due to increased exposure in personal care products, but improved detection sensitivity may also be a factor as dermatologists started to test MI on patch testing at a higher concentration of 500 or even 2000 ppm [2]. This epidemic trend in sensitization can be generalized to other allergens and illustrates the necessity for more stringent regulations on the utilizations of strong allergens such as MI and the necessity for adjustment of the allergy testing concentration in order to improve the sensitivity of the test.

The Effect of pH on Skin Microbes

Normal skin pH tends to be acidic, with normal values ranging from a pH of 4–6 [107]. The acidification of the stratum corneum is necessary to protect the body from microbes and ensure the maturation and structural integrity of the stratum corneum. Dermal exposure to alkaline agents may lead to more severe skin barrier impairment in atopic dermatitis and be a pathogenetically relevant factor for development of chronic irritant contact dermatitis [108]. Acidification of the stratum corneum is maintained in several ways: by the secretory phospholipase A2, the sodium-hydrogen exchanger 1(NHE1) protein, and the processing of filaggrin amino acids [109]. These mechanisms help generate acids such as free fatty acids, lactic acid, and *cis*-urocanic acid in the epidermis [110]. Phospholipase A2 and NHE1 are capable of being upregulated in response to a loss of function filaggrin mutation, present in many AD patients; however, the buffering capacity of the skin is derived from filaggrin byproducts, which are necessary to protect the skin from environmental insults [111, 112].

As previously mentioned, the skin's antimicrobial properties function optimally at an acidic pH, and so the growth of *Staphylococcus* and other bacteria is inhibited at the skin's natural pH [113, 114]. Several enzymes that are involved in keratinocyte antimicrobial function and desquamation also function best at an acidic pH, such as cathelicidins, defensins, and dermcidin, and are important for antimicrobial function [115, 116]. Moreover, ceramides are dependent on an acidic pH to maintain barrier function of the skin [117].

Table 2 pH values of common skin care products [125, 126]

Product	pH
Vanicream light moisturizing lotion	3.73
Neutrogena Deep Clean Facial Cleanser	3.8–4.6
Vanicream moisturizing skin cream	4.27
Vaseline body lotion	4.30
Aquanil lotion	5.19
CeraVe moisturizing cream	5.49
Aveeno daily moisturizing lotion	5.62
Cetaphil daily advance ultrahydrating lotion	5.65
Eucerin original dry skin therapy lotion	5.97
Dove day lotion	6.47
Johnson & Johnson Baby Wash	6.5–7.0
Dove bar soap	7
Eucerin original dry skin therapy cream	8.01
Eucerin intensive repair body lotion	8.19
Lever 2000	9
Dial bar soap	9.5
Irish Spring soap	9.5

Of note, an alkaline stratum corneum causes activation of serine proteases which then destroy barrier proteins, leading to abnormal lipid organization and metabolism of the epidermis [118]. Moreover, these serine proteases help regulate the stratum corneum layer, and at a basic pH, there is then increased shedding of this layer, allowing for decreased barrier function and increased Th2 inflammation [116, 119].

Targeting acidification in AD patients could improve the barrier function and antimicrobial function of the skin. Bathing and moisturizing treatments have been studied for the management of AD in an effort to acidify the skin pH; however, these topical treatments can also unfortunately cause a hypersensitivity allergy in these patients. It has been shown that alkaline soaps can increase the pH of skin by up to pH 3 units, which may aggravate AD, and therefore should be avoided [120]. The use of moisturizers, including colloidal products, may be utilized as adjunct therapies to normalize the skin pH to the acidic range [121]. However, the pH of currently available over the counter and prescription medications is oftentimes commercially inaccessible (Table 2) [122].

Future Direction

The standardization of AD diagnosis is key to ensure consistency among research studies and clinical practice. Currently, intra- and inter-provider diagnoses of AD and ACD overlap leading to misclassification bias which ultimately drives study hypotheses to the null and further increases the complexity of analyzing and developing quantifiable studies of ACD and AD. It has been suggested that marker proteins may be used to help differentiate inflammatory skin conditions such as psoriasis, AD, ACD, and ICD [123]. Several studies have found that genetic signatures of protein expression differ between ACD and AD. For instance, Riis et al. showed that AD exhibits strong expression of neuron-specific Nel-like protein 2, while ACD expresses CCL17 and CXCL10 mRNA as compared to control subjects [124]. Batra et al. found a difference between AD and ACD in the expression of fast and slow acetylators, suggesting that *N*-acetylation expression could be a genetic maker for identifying AD. These studies suggest that AD and ACD may be more objectively defined using a molecular or genetic level; however, large validation studies would be necessary to prove the definitions to be clinically relevant.

Conclusion

This review article outlines the most up-to-date literature of ACD in AD patients. While much has been done in the last 10 years to further define the intersection of these diseases, there is still more work to be done. Recent evidence suggests that AD patients may have a heightened risk of sensitization to certain chemicals, especially those ones in their regular topical regimens and it is therefore important for physicians to "play detective" and ensure that patch testing includes the chemicals found in high frequency in the patient's environment. With new products constantly being introduced for the treatment of AD, it is important for patients, clinicians, the pharmaceutical industry, and lawmakers to work together and continue to research ACD in this population to prevent morbidity and disease in our pediatric population.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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