

ALLERGIC CONTACT DERMATITIS IN ATOPIC DERMATITIS

While there has been a heightened awareness of allergic contact dermatitis in the last decade, the true prevalence is likely grossly underestimated as it is often overlooked, especially in very young patients.

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Figure 1. Female with allergy to numerous essential oils. Oil use was stopped and her dermatitis was treated. Her symptoms resolved and did not return.

Atopic dermatitis (AD) is a chronic skin disorder with a complex etiology and presentation. Characteristic features of AD include immune dysregulation and skin barrier dysfunction.^{1,2} These features lead to pruritic and erythematous lesions in the acute phase, and xerotic lichenified lesions in the late stages.³

The prevalence of AD has been increasing worldwide,⁴ with cases documented in the United States in up to 20% of children and up to 10% of adults.^{5,6} AD has traditionally been considered a disease mostly limited to childhood with studies noting persistence

into adulthood in only 1% to 3%.⁶ Recently, however, data from a very large AD patient registry of 7157 patients showed that more than 80% of AD patients aged 2 to 26 years had symptoms of AD and were using medication to treat it. By age 20, about 50% of these patients had finally attained only one 6-month period with no symptoms.⁷ In cases of recalcitrant AD, allergic contact dermatitis (ACD) is often an underrecognized problem and should be considered in all patients with a chronic dermatitis even when confirmed AD exists.

One important entity that can worsen and complicate the course of AD

is ACD, which is a delayed (type IV) T-cell mediated hypersensitivity reaction that develops following cutaneous re-exposure to a culprit allergen in sensitized individuals. Contact dermatitis is an important disease estimated to notably affect more than 72 million Americans each year.⁸ The economic impact of this disease is high in regards to patient morbidity and quality of life, missed work days and loss of income, not to mention significant expenditures for visits to health care providers and for medications. Correctly diagnosing ACD results in improvement, prevention, or “cure” of the dermatitis and decreases overall costs to the health care system.⁹ Once patch testing is performed and a culprit has been identified, education becomes the critical intervention to ensure adherence to an avoidance regimen.

With allergen avoidance, remission of the dermatitis ensues. If patients are unable to comply with the avoidance regimen, they become at risk for recurrent or sustained dermatitis or progression to a systematized presentation.¹⁰ The evaluation of ACD fits well with therapeutic theory, individualized therapy combining diagnostics and therapeutic intervention, as the patch test evaluation is used to dictate a personalized avoidance strategy for the management of each patient. Although ACD is not “curable,” many individuals will achieve complete remission with meticulous avoidance. This article highlights ACD in AD patients and explores top relevant allergens, pathophysiological factors, as well as clinical tips and pearls for diagnosis and treatment. ACD should be considered in any patient with chronic recalcitrant dermatitis.



Figure 2. Nine year old girl with life long history of atopic dermatitis and ichthyosis vulgaris had been using bacitracin on all of the open sores of her eczema. Patch testing showed she is allergic to bacitracin. She was treated with a compound of flucinonide in TrueLipids cream followed by TrueLipids ointment BID. After 3 to 4 months she was able to stop all steroids and stay on maintenance with these emollients.

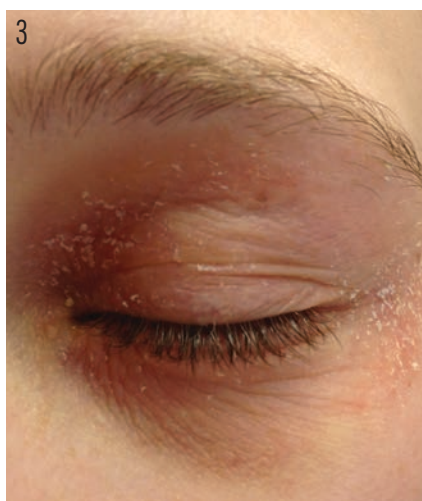


Figure 3 and 4. Eyelid dermatitis due to methchloroisothiazolinone found in Versa base compounding base (Figure 3). Resolved with treatment with TrueLipids 1% hydrocortisone cream after 2 weeks (Figure 4).

INFLAMMATORY PATHWAYS ASSOCIATED WITH AD AND ACD

AD is a chronic condition that arises as a result of chronic immune dysregulation, skin barrier dysfunction, and susceptibility to infection or colonization with bacteria such as *Staphylococcus aureus*.^{1,2} The inflammation of AD is characterized by primarily the T-helper (Th) 2 cell phenotype, although there are also contributions from Th1, Th22, and Th17 cells.^{1,2}

With ACD the initial sensitization occurs when small haptens penetrate the skin and are processed by Langerhans cells or dermal dendritic-antigen pre-

senting cells. Subsequently, they are presented to naive T cells in the lymph nodes which in turn induce clonal expansion of the memory T cell.¹¹ Upon re-exposure to the allergen, the primed T cells mount an immunologic response, eliciting the clinical picture of ACD that include edema, erythema, and vesiculation. The inflammation of ACD is characterized by primarily a T cytotoxic (Tc)1/Th1 phenotype, although Th2, Th17, and Th22 cells may be activated as well.^{1,2,12}

Several inflammatory mechanisms may predispose AD patients to ACD. Irritant contact dermatitis (ICD) may induce an innate immune cascade that predisposes

to ACD.² In addition, AD in the chronic phase partially shifts to a more Th1 phenotype.² Finally, the presence of bacteria, common in AD, has been suggested to promote ACD, possibly through the up-regulation of similar inflammatory mediators to ACD, such as toll-like receptors and T-cell receptor Vbeta 17 region expansion.¹ A recent study also linked nickel allergy and *S aureus* infection specifically in AD. These investigators reported an elevated secretion of IL-2 under nickel sulfate stimulation in vitro exclusively in atopic patients with nickel allergy infected by *S aureus*.¹³ IL-2, in addition to its role in promoting the differentiation of T cells following antigen stimulation (geared to aid in fighting off infections), also plays a pivotal role in the development of contact sensitization.

IMPACT OF A DEFECTIVE SKIN BARRIER

The skin of AD patients notably shows increased transepidermal water loss, with decreased production of terminal differentiation proteins such as filaggrin, aberrations in skin lipid concentrations and ratios, and increased pH.^{1,14} Additionally, defective skin barrier acidification has been shown to lead to a myriad of other problems including decreased skin barrier lipid production, diminished production and secretion of cutaneous antimicrobial peptides, defective cellular differentiation, excessive inflammation, and the initiation of contact sensitization.¹⁵ Several studies have suggested that skin barrier acidification may be the missing link and the “master switch” in AD.^{16,17} Immune abnormalities may also contribute to the barrier dysfunction of AD. For example, the Th2 cytokines IL-4 and IL-13 have been shown to downregulate ceramides and the expression of epidermal differentiation complex genes.²

ACD SHOULD BE CONSIDERED IN AD PATIENTS

Strong evidence exists that the Th2 bias in AD may lower the risk of contact sensitization compared with healthy controls.¹ However, AD patients appear to be at similar or even increased risk of ACD as compared with the general population for several reasons.

First, the dysfunctional skin barrier in AD patients allows for increased penetration of chemicals, which may increase the

risk for sensitization and ACD.¹ Of note, this barrier defect also results in increased rates of ICD, which further compromises the skin barrier and magnifies this issue.

In addition, the mainstay of therapy in AD patients includes chronic emollients and topical anti-inflammatory therapy for treatment and maintenance, which may result in children with AD becoming sensitized to allergens found in their topical products.^{1,18} For example, many so-called hypoallergenic pediatric cosmetic products for sale in the United States contain potent contact allergens such as fragrances and preservatives.¹⁹ It has been suggested that skin barrier repair medicaments that do not contain any of the common allergens seen in AD may be helpful, although further research is required.¹⁴

Clinical studies show that AD patients are as much at risk for ACD as the general population. One study found that 89% of AD patients and 66% of non-AD patients with suspected ACD and chronic eczema were patch test positive.²⁰ In another study, Czarnobilska and colleagues²¹ found that 44% of 7-year-old children and 53% of 16 year-olds with a history of chronic eczema were patch test positive. When the study was repeated in atopic children only, 67% of 7 to 8 year olds and 58% of 16 to 17 year olds were patch test positive.²² Common allergens in these age groups included nickel (35.9% and 19.4%, respectively), propolis (16.5% and 5.4%, respectively), cobalt (9.7% and 6.5%, respectively), fragrance mix I (6.8% and 3.2%, respectively), chromium (6.8% and 3.2%, respectively), and fragrance mix II (5.8% and 2.2%, respectively).²²

While there has been a heightened awareness of ACD in the last decade, the true prevalence is likely grossly underestimated as it is often overlooked, especially in very young patients. ACD has been reported to occur even in those who are as young as 6 months.¹¹

Many studies show rates of ACD in AD are lower during flares and higher during periods of disease quiescence.²³ In a dinitrochlorobenzene sensitization study, 33% of severe, 95% of moderate, and 100% of mild atopics could be sensitized.²³ When nonresponders were rechallenged at a time of disease quiescence, almost all demonstrated an ACD response.



Figure 5. Thirteen-year-old girl with 3-year history of dermatitis that began on her leg and then spread to her face. She was treated with 2.5% hydrocortison butyrate, which would improve and then exacerbate the dermatitis. Patch testing revealed she was allergic to fixocortol pivalate, nickel sulfate, neomycin sulfate, and thimerosal. All hydrocortisone was removed from her treatment plan and she was treated with TrueLipids. Cream plus TrueLipids ointment BID for 3 weeks. She recovered completely.

In another study, when adolescent and adult AD patients were patch tested during a period of quiescence, 48% of patients had an allergic reaction to at least 1 European Standard Series allergen, and 12.8% of patients had an allergic reaction to at least 1 corticosteroid.²⁴ This finding underscores the importance of concomitant therapies aimed at barrier repair in the atopic patient, which ultimately decrease the utilization of topical corticosteroids and thus may reduce the risk of sensitization. Notably, the most common allergens in this study were nickel sulfate (28.2%), potassium dichromate (20.5%), cobalt chloride (12.8%), and phenylenediamine, budesonide, betamethasone, clobetasol, and dexamethasone (7.7% each).

ACD can be localized or distant from the site of exposure and may also predominantly involve the flexures, due to exposure patterns or local factors such as friction, occlusion, and maceration.²⁵ This is often confused for a flare of AD. Various factors may affect the thresholds for sensitization among individuals in-

cluding age, type of allergen, degree of skin barrier dysfunction, and frequency and duration of exposure.¹ Some patients require repeated exposure to the allergen to develop ACD while other more potent allergens may elicit earlier and more intense reactions.

As it may be difficult to differentiate ACD from AD, minimization of allergens that have been shown to be statistically significantly more common in AD (**Table**) may be prudent in all children who have any form of chronic eczema.²⁶⁻²⁸

CLINICAL CLUES TO ACD IN AD

Many distinctive clinical clues can help one to discern ACD from AD. Beattie and colleagues²⁹ found that eyelid, hand, and vulvar involvement were more commonly associated with ACD in patients with AD. In addition, Schena and colleagues³⁰ determined that body location of ACD was more often widespread in AD patients (30% vs 7.9%), or localized to the face (28.4% vs 16.3%), while localization on the trunk was less common (2.4% vs 14.4%).

Table. ALLERGENS REPORTED TO BE STATISTICALLY SIGNIFICANTLY MORE COMMON IN AD COMPARED WITH NON-AD DERMATITIS

Allergen	Details D
Fragrance mix 1 ^{20,40}	Mix of 8 fragrances, cinnamic alcohol, cinnamic aldehyde, eugenol, isoeugenol, feraniol, hydroxycitronellal, oak moss absolute, and amylcinnamaldehyde. Found in essential oils and personal care products
Disperse dyes ⁴¹	Aniline dye
Potassium dichromate ³⁰	Metal derived from chromium, often found in cement, leather, pigments, and cutting oils
Lanolin ⁴²	Emollient
Tixocortol-21-pivalate ⁴³	Corticosteroid (Class A)
Formaldehyde-releasing preservatives (quaternium-15, imidazolidinyl urea, DMDM hydantoin, and 2-bromo-2-nitropropane-1,3-diol) ²⁷	Preservatives used in cosmetics and occupational products
Cocamidopropyl betaine ²⁸	Detergent, surfactant
Myroxylon pereirae ²⁰	Fragrance/Flavorant — tree resin (naturally cross reacts with chemicals in tomatoes/ketchup)
Compositae ⁴⁴	Daisy (ragweed) family allergens

ACD can be localized or distant from the site of exposure and may also predominantly involve the flexures, due to exposure patterns or local factors such as friction, occlusion, and maceration.

The following can also be indicative of ACD: a new onset dermatitis; worsening dermatitis; change in distribution or distribution involving areas more suggestive of ACD (ie, face, eyelids, hands, neck folds); recalcitrant disease that clears only with ultrapotent topical or oral steroids; adult or adolescent onset of AD; and a clinical presentation of chronic vesicular hand dermatitis, especially in the working population.³¹ Recently, consensus guidelines have been created regarding when it is most appropriate to patch test patients with AD. The consensus paper has been submitted for publication to *Dermatitis*.

CONFIRMING CONTACT SENSITIZATION AND DIAGNOSING ACD

The gold standard for the diagnosis of ACD is epicutaneous patch testing. The FDA has approved this commercially available screening tool for individuals aged 18 years and older.

To date, the FDA has not approved patch testing for the pediatric population despite numerous studies both in the United States and internationally that demonstrate the safety and efficacy of patch testing in this population.^{32,33} As

many patients with AD are children, this is a crucial point to address. Experts agree that patch testing is indicated in children with chronic recalcitrant or worsening dermatitis, or dermatitis involving the hands and face in all age groups.³¹ A detailed history is imperative to help select allergens to be included in the testing especially in the pediatric population who has a smaller surface area for testing. This week-long testing can be cumbersome; therefore, consideration of the child and family's ability to tolerate the testing and follow-up is also important. For this reason, a preemptive avoidance strategy may be warranted.³⁴

When performing patch testing, allergens/chemicals are placed on the unaffected skin of the back or inner arm and placed under occlusion. The patches are removed and the first reading of symptoms is performed at 48 hours, although some have suggested that 24 hours may be sufficient in the pediatric population.³⁵ Delayed reads should also be performed at 72 hours and, in some cases, at up to 168 hours (7 days) after initial placement, as the first reading may miss up to 33% or more of the reactions.³⁶

Irritant reactions occurring within the first 48 hours are also typically resolved by the delayed readings.

After the reactions have been observed and documented, it is important to determine the clinical relevance of any positive patch test reactions. Not all positives will have clinical relevance. Once clinical relevance has been established, it is important to perform a thorough investigation of exposure risk of each relevant allergen. Avoidance measures can then be recommended for the patient and family.

Of note, certain allergens are so potent that they cause a more immediate and intense reaction that is easily identified by the patient, such as oleoresin in poison ivy and poison oak. These types of reactions often do not require patch testing for culprit identification and resolution of dermatitis. However, many allergens are ubiquitous and/or found in low concentrations in daily use preparations such as hygiene products or medications, and the association may not be as apparent. The most common allergen, nickel, can be found in objects including clothing fasteners, belts, electronics, medical implants, stainless steel cookware, nuts, and chocolate.^{37,38} Knowing where common allergens are found is imperative as it is important to educate patients on where hidden exposures might be occurring.

CONCLUSION

ACD is a significant and often under-recognized problem in the AD population and should be considered in all patients with a chronic dermatitis even when confirmed atopy exists.³⁹ Undiagnosed ACD can be devastating to both the patient and the caregiver and often results in years of therapy resistant disease. It is important to consider patch testing even in young children who have chronic recalcitrant eczema or a distribution suggestive of ACD.

Allergen avoidance, topical emollients, and anti-inflammatory therapies are central to the treatment of AD and ACD. Understanding sources of exposure and educating patients and family members is imperative. ■

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