Allergic contact dermatitis (ACD) is increasingly recognized as a significant problem in children. It has been estimated that 20 percent of all pediatric dermatitis is due to ACD; however, this could be an underestimation, as many cases may be overlooked without patch testing, especially in the very young and when it is a contributing factor in atopic dermatitis (AD). The international literature over the last decade reports a significantly increased risk for ACD in female adolescents when compared to their male counterparts for certain allergens such as nickel-containing piercings, cosmetics, and fragrances. More recent studies demonstrate an even distribution of allergens across all pediatric age groups with no gender bias. 2008 marked the first reported patch test studies in US-based populations. These studies confirmed that contact dermatitis was equally prevalent in the pediatric population as in adults, and patch testing was safe and efficacious.

What is Contact Dermatitis?
Contact dermatitis is an umbrella term that refers to a group of dermatoses that are considered related to an external agent. There are two main types, namely, irritant and allergic contact dermatitis. Irritant contact dermatitis (ICD) is the most common form and is not an immunologic reaction but is secondary to contact with a substance that is irritating to the skin, such as urine in diaper dermatitis, saliva in lip licking dermatitis, and soap in hand dermatitis. Any substance could potentially be an irritant in certain clinical scenarios.
such as a mildly caustic substance in contact with sensitive skin for a long period of time. In general, the severity of an irritant reaction will likely be directly proportional to the concentration and time of exposure to the instigating agent.\textsuperscript{1} The patient usually can identify by the distribution of the dermatitis and the temporal association with the caustic agent (short time line from contact to rash) that they have an irritation (ICD) from a particular source. This means that in general they will avoid an exposure in the future.

Allergic contact dermatitis (ACD) is the second most common form of contact dermatitis and is characterized by a complex immunologic event that presents as a delayed (48-96 hours) Type IV hypersensitivity reaction. The pathogenesis of ACD includes two main stages: sensitization followed by elicitation. Impairment in the skin barrier facilitates the entry of allergens into the epidermis where they are processed on keratinocytes into haptens. Dendritic cells then process these haptens and present them to naïve T-cells, which results in clonal expansion of memory T-cells.\textsuperscript{1,2} This phase constitutes sensitization. Rates of sensitization in the pediatric population may be on the rise due to greater contact with an increasing number of chemicals in the environment from jewelry and cosmetic and personal hygiene products to sporting gear and toys.\textsuperscript{3}

The second phase of ACD is elicitation, which occurs after repeated exposure to an environmental allergen to which memory T cells have been cloned to remember. ACD is the clinical state of hypersensitivity, in which T helper cells dominate; whereas if suppressor cells dominate, a state of relative or complete tolerance is produced.\textsuperscript{2} In contrast to ICD, the patient usually cannot identify a temporal association with a source, as the reaction is delayed and the distribution of the dermatitis may be diffuse. Oftentimes the patient will, in fact, disbelieve the source, as it may be something they have used repeatedly for years without a problem. For this reason, it is important to explain to the patient the concept of threshold of sensitization (a.k.a., the limit point at which the immune system lets you know that it can no longer take seeing that chemical again). In clinic we explain that for every chemical in every patient there is a potential threshold point at which rashes develop with exposure and we give examples of how keys, jean snaps, spinach and chocolate all contain one common ingredient, namely nickel. Each exposure counts and we teach avoidance to get beneath the threshold in the rash-free zone.

It is important to differentiate the Type IV delayed immunologic reaction, ACD, from that of contact urticaria, which is mediated by an immediate IgE Type I immunologic reaction. Type I hypersensitivity is often tested for by RAST (radioallergosorbent test) or prick testing, usually by an allergist. An allergist is then able to attempt desensitization, which is not possible with Type IV reactions.\textsuperscript{2}

\section*{Clinical Presentation}

Clinically, ACD often appears as pruritic, eczematous plaques that can be difficult to distinguish from irritant...
contact dermatitis (ICD) or atopic dermatitis (AD).2

Acute ACD and AD can be hard to differentiate because of their similar morphologic presentation. Furthermore, ACD can complicate the diagnosis of AD, as they may occur simultaneously. The National Institute of Arthritis and Musculoskeletal and Skin Diseases estimates that 10-20 percent of all children experience AD.7 This number is likely to be an underestimate, as milder cases may go unrecognized or unreported.8 Some believe that children affected by AD are at higher risk for developing ACD, as their skin barrier is already compromised, allowing for allergens to more easily penetrate the skin.8,9 Acute ICD and acute ACD can often be distinguished by time course and character. ICD usually appears as a well-demarcated, erythematous and sometimes follicular reaction confined to areas of contact exposure. ACD is marked by induration, and papulovesicular eruptions and often expands beyond the area of contact. Furthermore, ICD tends to burn, while ACD tends to itch. In addition, ICD tends to occur within 24 hours of exposure, with earlier presentations corresponding to higher concentrations of the offending agent. On the other hand, ACD is a delayed hypersensitivity, whereby the reaction tends to present 48-96 hours after exposure to the allergen, but even further delays up to three weeks have been noted.2,10 Chronic ICD and chronic ACD, however, can be extremely difficult to differentiate as the inflammatory areas become poorly demarcated and lichenified. Importantly, ICD reactions may be seen during patch testing, and generally these resolve by 72-96 hours, while again ACD may just be peaking in intensity at that time.

An investigative history and diagnostic clues can help guide a clinician to the proper diagnosis. Examples will be used to illustrate below.

### Diagnosis

At times, the diagnosis of ACD can be difficult to make because there are instances when the location of the dermatitis is not directly related to the site of exposure. For example, one can see what is termed ectopic ACD, when there is transfer of the allergen into an area where it otherwise would not be found. Examples of ectopic ACD are when sites of AD flare from contact with nail polish from scratching9 or a cashier who rubs his/her eyelids after handling money. Furthermore, idiopathic reactions may also be seen in which there are non-specific widespread eruptions when the patient contacts their allergen.1,2

As mentioned above, distinguishing between ACD and AD can be a more difficult challenge, especially

<table>
<thead>
<tr>
<th>Table 1: Top 21 Allergens in US Children</th>
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<tbody>
<tr>
<td><strong>Allergen</strong></td>
</tr>
<tr>
<td>Nickel sulfate</td>
</tr>
<tr>
<td>Cobalt chloride</td>
</tr>
<tr>
<td>Thimerosal</td>
</tr>
<tr>
<td>Gold</td>
</tr>
<tr>
<td>Fragrance Mix</td>
</tr>
<tr>
<td>Neomycin</td>
</tr>
<tr>
<td>Myroxylon pereirae (balsam of Peru)</td>
</tr>
<tr>
<td>Colophony</td>
</tr>
<tr>
<td>Formaldehyde</td>
</tr>
<tr>
<td>Lanolin</td>
</tr>
<tr>
<td>Quaternium 15</td>
</tr>
<tr>
<td>Benzalkonium chloride</td>
</tr>
<tr>
<td>Potassium dichromate</td>
</tr>
<tr>
<td>p-Phenylenediamine</td>
</tr>
<tr>
<td>Bacitracin</td>
</tr>
<tr>
<td>Cucumispropyl betaine</td>
</tr>
<tr>
<td>Carbamates</td>
</tr>
<tr>
<td>Disperses dye</td>
</tr>
<tr>
<td>Propylene glycol</td>
</tr>
<tr>
<td>Indazolidinyl urea</td>
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<tr>
<td>Cinamic aldehyde</td>
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</tbody>
</table>

This composite list was compiled based on data from Jacob 2008, Zieg 2008, Hopelien 2008, and Hammond 2009.
when the two are confounding diagnoses. There are clinical clues that can heighten the index of suspicion for ACD, such as new-onset, and/or a progressing or deteriorating dermatitis that is recalcitrant to standard therapies. The gold standard of diagnosis for ACD is epicutaneous patch testing. When children are referred for patch testing, there is usually a high index of suspicion for ACD based on the clinical clues above. Given the high prevalence of dermatitis in pediatric populations and the limited access to comprehensive patch testing, the patients most likely to benefit from patch testing are those with a minimum of two months of uncontrollable or worsening dermatitis and those who have failed standard treatments and not improved on super sensitive skin regimens. The main limitation to patch testing in children is the relatively smaller surface area available for patch testing (especially in dermatitic patients). This correlates with an increased need for selectivity regarding which causative allergens to consider evaluating.

Unfortunately, there are some patients who may be so extensively affected that there is too limited an area to test and may still need to be controlled on systemic immunosuppressives.

The first step in evaluating the patient with presumed ACD is eliciting a thorough history from the patient and family to determine which allergens have the greatest potential to be culprits. This includes information about the patient’s personal hygiene and home environment, as well as their medical history. A review of their caregiver’s environment is also necessary as patients may be exposed either directly or indirectly (from transfer from a caregiver), producing a connubial dermatitis. Clues regarding which allergens the patient may be reacting to can also be found by examining the geographic locations of the reaction and reviewing his/her products/habits to determine which allergens are repeated in seemingly unrelated sources. For example, a child who presents with a periumbilical dermatitis despite no longer wearing pants with nickel-containing snaps or buttons, but who eats chocolate four times per week, as it is high in nickel.

Currently, while there is a commercially available prepackaged allergen panel kit available for screening purposes, namely the Thin Rapid Use Epicutaneous test (T.R.U.E. Test™, Mekos Laboratories A/S), it is currently only approved by the FDA for use in patients greater than 18 years of age. It is important to note that this test includes 29 of the most commonly found allergens in adult populations and may need additional consideration when used in children.

Comprehensive patch testing, on the other hand, is when individual allergen panels are tailored to the patients’ specific environmental exposures. This specialized technique allows for customized testing for specific agents suspected of causing ACD. The allergens are placed into individual chambers that are then applied to unaffected regions of the child’s back in linear configurations under occlusion (Image 1) and secured with hypafix tape™ (Smith & Nephew). The chambers are left on the skin under occlusion for 24-48 hours, but should be removed before 48 hours to

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**Figure 1: Treatment algorithm for chronic allergic contact dermatitis.**

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reduce irritant reactions. Upon removal, the initial reading is performed, noting any erythema, induration, papules, or blistering. The patient is also asked to return for a 72-120 hour read, as some cutaneous reactions may be delayed. This delayed reading also helps to distinguish between allergic and irritant contact reactions. In general, ICD type reactions are seen early (at the time of allergen removal) and are usually in the healing-resolution phase by 72-96 hours. ACD reactions, on the other hand, continue to worsen over the duration of the patch test procedure.

Following the final patch test reading, a second retrospective history is obtained to further delineate the clinical relevance of the positive reactions noted and to investigate for potential exposure sources. This is necessary as all positive patch test results may not be relevant to the patient’s environment and reaction history. Determining relevance is crucial before unnecessarily restricting the patients’ daily routine.

Once clinical relevance is determined, the patient and their family are provided with comprehensive education regarding which chemicals and products to avoid based on which allergens are pertinent. In our clinic, the families are given both literature on these specific chemicals and a list of alternative products derived from the American Contact Dermatitis Society-Mayo Clinic Contact Allergen Replacement Database [CARD]. As products on the CARD list may contain chemicals that have not been tested individually on a given patient, it is important to instruct families on how to perform a provocative use test on the inner arm of the patient. To perform the provocative use test a small amount of the product should be applied twice a day for seven days, to a 2.5 cm circle drawn on the inner arm, proximal to the antecubital fossa. The patient is told to discontinue use of the product if burning, redness or irritation develops and most importantly, the patient should return to their physician for evaluation of the application site at the end of the test period if reactions occur.

**Top 10 Offending Allergens**
Recent publications have reported a striking similarity between the common allergens that cause ACD in children and adults. Table 1 lists a compilation of the top 21 allergens that have been reported to be most prevalent in US children at the present time.

### Table 2: Common Nickel Containing Objects

<table>
<thead>
<tr>
<th>Jewelry items - including watches, hairpins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cosmetic items - including powder compacts, lipstick holders, razors</td>
</tr>
<tr>
<td>Clothing items - including zippers, buttons, suspenders, belt clips, jean clips/snaps</td>
</tr>
<tr>
<td>Kitchen items - including knives, utensils, appliances, scissors</td>
</tr>
<tr>
<td>Office items - Pens, pins, paper-clips, scissors, type-writer</td>
</tr>
<tr>
<td>Mobile phones</td>
</tr>
<tr>
<td>Eye-glass frames</td>
</tr>
<tr>
<td>Cigarette lighters</td>
</tr>
<tr>
<td>Keys and key rings</td>
</tr>
<tr>
<td>Coin money</td>
</tr>
<tr>
<td>Music Instruments - especially wind instruments</td>
</tr>
<tr>
<td>Foods including canned items: vegetables- beans, peas, spinach; fruits- and raspberries, figs, pineapples, prunes; grains- buckwheat, oatmeal, wheat bran and other fiber products; chocolate</td>
</tr>
</tbody>
</table>

1. **Nickel**

   In 2008, nickel was designated the “Allergen of the Year” by the American Contact Dermatitis Society (ACDS). For the last three decades, nickel has held the first place position as the top allergen found in patch-tested populations. More recently, however, a significant trending upwards in the prevalence was noted. The classic presentation relates to contact with jewelry, i.e., earlobes, neck, wrists, and from contact with jean snaps, i.e., inframammary. Notably, nickel is present in a significant number of products (Table 2). The presentation clinically can be complex, as the dermatitis is not always limited to the distribution of contact with an item containing the allergen. There is the potential for both ectopic dermatitis (as has been reported from cell phones) and generalized eruptions. Systemic contact dermatitis with food-related triggers have also been reported.

   For those children with a known nickel allergy, caregivers can purchase a confirmatory nickel detection testing kit. The kit contains 1% dimethylglyoxime-ammonia (DMG-A). This can be applied to any product in question. If the product contains nickel in a
concentration of at least 1:10,000, a pink indicator color appears on the applicator tip. This simple detection kit helps guide patients and families in avoidance.

2. Cobalt chloride
Cobalt, a metal often found as an alloy with nickel or other metals, can be found in paints and dyes, metal-plated objects, braces, amalgams, and vitamins (B12). Not only do children have a high percentage of positive patch test results to cobalt, but they also have been found to have a high co-reactivity to nickel.1,3,5

3. Thimerosal
Thimerosal is the mercuric derivative of thiosalicylic acid that is used as a preservative and has received much attention recently for its use in vaccines. It also can be found in some cosmetics and ophthalmic medicaments.3,16 This allergen, however, is a good example of a chemical being prevalent, but not necessarily relevant. The North American Contact Dermatitis Group (NACDG), as well as many tertiary care centers, has removed it from their standard screening panels because of the high number of positive patch tests with little clinical relevance. Currently, the inactivated influenza vaccine is the only vaccine recommended for children below seven years of age that still contains thimerosal (N 1,16).

4. Gold
Gold is commonly found in jewelry and dentistry products and was named Contact Allergen of the Year in 2001. Interestingly, gold is associated with black dermographism which is the phenomenon of ‘black writing’ that appears on the skin with exposure to gold. Contact with gold doesn’t always correlate with the area of suspected ACD. In 2005, Nedorost and Wagman speculated that titanium dioxide in cosmetics absorbs gold particles from jewelry worn elsewhere resulting in a facial contact dermatitis where the product is applied.17 For this reason, the most clinically relevant presentations usually include eyelid involvement and stomatitis.3,18,19

5. Fragrance Mix
Fragrances can be found in virtually every product that contains scent, i.e., cosmetics, lotions, shampoos, candles, perfumes, etc., and notably some that are ‘unscented’.1,3,4 An essential clinical pearl relating to fragrance is patients must look for “fragrance free” products; the terms “unscented” and “scent-free” may indicate the presence of masking fragrances/scents.1 Given the large number of personal hygiene products for children that contain fragrances, the high prevalence of ACD to this allergen is expected. Regarding patch testing, pre-packaged fragrance mix 1 contains eight common fragrance chemicals and fragrance mix 2 contains six fragrance chemicals. The clinical presentation of fragrance-associated dermatitis can be both localized and generalized. Like nickel, oral provocation has been reported to induce systemic flares in some patients. For more information on fragrance, please refer to balsam of Peru section below.

6. Neomycin
For the last three decades, neomycin has been second only to nickel in the ranks of top allergens in adult populations. The rise of bacitracin use came with a dip in the prevalence of neomycin allergy. That being said, neomycin is still included in many over-the-counter antibiotic preparations from ointments and creams to medicated first aid plasters. In 2010, neomycin was designated Contact Allergen of the Year by the ACDS.3 A significant number of the patients with antibiotic allergy present with dermatitis at the site of application of the product containing neomycin.20 Notably, bacitracin, which is also over-the-counter in the US, has a high rate of sensitization as well. In children, the increased sensitization rates to antibiotics is likely associated with significant utilization of these products in this population for minor cuts and abrasions and potentially because many children with AD use antibiotic ointments to manage their atopic flares.1 Unfortunately, both neomycin and bacitracin have been reported to induce anaphylactic reactions by topical application.20,22,23

7. Balsam of Peru (Myroxylon pereirae)
Balsam of Peru (BOP) is a natural fragrance obtained from the bark of the tree Myroxylon balsamum; it contains over 400 different chemicals. These chemi-
cals or synthetically related chemicals are used as fragrances (to impart pleasant odors to products such as cosmetics, lotions, cleansers and perfumes) and flavorants in foods and personal hygiene products, such as toothpaste, floss, and mouthwash. Both local and systemic reactions to BOP have been described. Persons exquisitely sensitized to this allergen may benefit from a low-BOP diet. In a significant number of patients, dramatic improvement has been seen with the elimination of the foods containing the highest concentration of the related chemicals, namely tomato products (ketchup and pizza), all soda (both because of the flavorants and preservatives), chocolate, cinnamon, and vanilla extract.3 The low-BOP diet is not warranted for every patient, but may be of utility when topical avoidance measures suggest improvement.

8. Colophony
Colophony, also known as rosin, is a resin that comes from pine and spruce trees. It is a common allergen found in adhesives, eyebrow wax, cosmetics (mascaras, lipsticks, eyeshadows, concealer creams, nail polish), and diapers (top-layer pad). There is thought to be a cross-reactivity among patients allergic to fragrances, BOP, and colophony.24 Its clinical presentation is directly related to the site of contact or can be systemic in nature. A significant number of patients react to both colophony and balsam of Peru, as these substances are related—they are commonly used in fragrances and components of both naturally occur together. For example, tomatoes contain coniferyl alcohol (a main substrate in colophony) and cinnamic alcohol (a main substituent of balsam of Peru).3,5

9. Formaldehyde
Formaldehyde is a preservative with antimicrobial properties found in many personal hygiene products, as well as clothing and building materials.1,25 Not only is formaldehyde an extremely sensitizing agent, but it is listed by the US Environmental Protection Agency (EPA) as a “probable carcinogen.”05 In 1939, Paul Bonnevieve included formaldehyde in his standard series for patch testing and more than 70 years later, it is still a top allergen and importantly one that is causing significant problems in children.26 A substantial number of children’s products contain formaldehyde-releasing preservatives (FRP’s), which include but are not limited to quaterium-15, imidazolidinyl urea, diazolidinyl urea, dimethylol-dimethyl hydantoin, bronopol, and sodium hydroxymethyl glycinate. These are inexpensive compounds that slowly release formaldehyde over time. The most sensitizing of these is Quaternium-15, which has been noted to cause about four percent of ACD in pediatric patients referred for patch testing in two different studies.45 (See Table 1.)

Formaldehyde is another allergen that can have a varied presentation, from localized reactions to generalized and systemic with idiopathic response. In addition to personal hygiene products, formaldehyde derivatives are found in sporting gear, wrinkle free clothing, rayon and corduroy. P-tert-butylphenol formaldehyde resin (PTBP-F-R), specifically has been associated with reactions due to shin guards (shins), swimming goggles (periocular), and wet suits.5,27

10. Lanolin
Lanolin is a chemical derived from sheep sebum commonly used as an emollient in personal hygiene products, medications and industrial products. It is among the most common offenders causing ACD in children.3,4,5,28

Management
The mainstay of treatment for ACD is avoidance of the chemicals to which the patient is confirmed sensitized to on patch testing.8,29 There are instances, however, when an allergen may not be identified or avoidance is not possible, and pharmacotherapy needs to be employed. Emollients, such as petrolatum, and barrier creams can be used as management/prophylactic options, but one must be careful to determine patients’ reactivity to ingredients in these products as well.1,29 A therapeutic algorithm can then be followed, beginning with topical corticosteroids (Figure 1). These are not meant for long-term or widespread use as patients, especially children, may experience cutaneous atrophy, hirsutism, acne, striae, telangiectasia, and changes in pigmentation, along with systemic and endocrine side effects. Caution must be used if perior-
Allergic Contact Dermatitis

bital application is indicated, as chronic use can precipitate glaucoma and/or cataracts. With chronic use of topical steroids, patients are more at risk for developing sensitization to the steroid itself or a vehicle ingredient such as sorbitans, preservatives or propylene glycol. A number of reports show this to indeed be the case in patients with endogenous dermatoses on long-term topical medications. 1,29

As topical steroids are not long-term options, topical immune-modulators may need to be employed, such as tacrolimus and pimecrolimus, especially on areas of thin skin, such as the face or eyelids. As significant pruritus is associated with ACD (burning is more associated with ICD), oral antihistamines, such as diphenhydramine and hydroxyzine, may be indicated. 29

Acute, severe, or widespread reactions may require systemic corticosteroids, such as oral prednisone, tapered after symptoms are controlled. Again, steroid use is not indicated for chronic cases as systemic side effects from long-term use include osteoporosis, hyperglycemia, hypertension, immunosuppression, and hypothalamic-pituitary-adrenal axis suppression. For glyceremia, hypertension, immunosuppression, and hypoglycemia, children should taper after symptoms are controlled. Again, steroid use is not indicated for chronic cases as systemic side effects from long-term use include osteoporosis, hyperglycemia, hypertension, immunosuppression, and hypothalamic-pituitary-adrenal axis suppression. For glyceremia, hypertension, immunosuppression, and hypoglycemia, patients are more at risk for developing sensitization to the steroid itself or a vehicle ingredient such as sorbitans, preservatives or propylene glycol. A number of reports show this to indeed be the case in patients with endogenous dermatoses on long-term topical medications. 1,29

Dr. Jacob was principal investigator on the PREA trial evaluating the TRUE Test™ safety and efficacy in children and is a speaker for Coria. Drs. Herro and Russell have no relevant disclosures.