

Patch Testing: Another Steroid-Sparing Agent to Consider in Children

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Abstract: The burden of children suffering from chronic severe dermatitis and especially from undiagnosed confounding allergic contact dermatitis can be overwhelming for not only the patients and their families but also for their dermatologists. We report our protocol for pediatric patch testing and three pediatric cases, with severe and recalcitrant dermatitis unresponsive to systemic therapies, in whom comprehensive patch testing played a key role in management. Comprehensive patch testing allowed for the culprit allergens to be detected and subsequently avoided. With strict compliance, we were able to cease the use of systemic immunosuppressive therapy. These cases illustrate the importance of patch testing in recalcitrant dermatitis within the pediatric population.

In 2004 the Society for Investigative Dermatology and American Academy of Dermatology conducted a burden of skin disease study in which it was estimated, from the peer-reviewed literature, that 15.2 million Americans suffer from atopic dermatitis (AD) and 72.3 million from contact dermatitis (CD). The costs associated with these conditions are estimated at \$1 billion and \$1.6 billion, respectively (1). However, the total “cost” of these diseases to the patient is not only the dollar amount of medications and loss of productivity but it includes a reduction in their quality of life. For those children suffering from chronic severe dermatitis and especially from undiagnosed confounding allergic contact dermatitis (ACD), the consequence of their condition to the family subunit can be devastating. Intrusions include sleepless nights secondary to pruritus, loss of productivity at work, feelings of helplessness and irritability, and arguments among family members.

The National Institute of Arthritis and Musculoskeletal and Skin Diseases estimates that 10–20% of all children are affected by AD; however, it has been suggested that this is probably an underestimation, given that milder cases may go unrecognized or underreported (2). Most children with chronic dermatitis are not patch tested, although current opinions state that they should be, which leads to ambiguity as far as the exact prevalence of endogenous dermatosis worsened by ACD in children is concerned (3–6).

For the most part AD is accepted as describing a hypersensitive state with enhanced ability to respond to a variety of antigens (7). While the association of the atopic diathesis triad (atopic skin disease, asthma, and rhinitis) with a familial tendency is well accepted, the relationship between ACD and AD is still controversial. In a recent patch test study, Seguardo Rodriguez et al found that a family history of AD (85%), female sex (74%), and age 11–16 (63%) were predisposing risk factors to

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TABLE 1. *Insightful Clinical Clues Which Heighten the Index of Suspicion for ACD*

New-onset dermatitis
Progressing or deteriorating dermatitis (atopic dermatitis/psoriasis) such as increasing total body surface area (TBSA)
involvement or involvement of specific body sites (i.e., face/eyelids/hands/neck folds)
Recalcitrant dermatitis by standard therapies (clearing only with suprapotent topical steroids or oral steroids)
Clinical presentation of dyshidrosis

ACD, allergic contact dermatitis.

sensitization (8). On the other hand, Giordano-Labadie et al systematically evaluated contact sensitization in a series of atopic pediatric patients (9). It was observed that 43% of the 114 children who were patch tested had positive reactions without association with AS; however, the authors did not comment on the relevance of these reactions.

The point at which to suspect that ACD is confounding an underlying endogenous dermatosis is vague. This being said, several insightful clinical clues heighten the index for suspicion (Table 1). The three cases presented in this study reflect upon the utility of the patch test tool in the diagnosis of ACD in pediatric patients and the ability to use this tool to bring the child's endogenous dermatitis into a manageable state, ultimately sparing the need for systemic immunosuppressants.

PROTOCOL FOR PATCH TESTING

In general, patients are referred to the pediatric contact dermatitis clinic from pediatric dermatologists. At the initial visit, detailed environmental histories are taken including: (i) the patient's personal hygiene environment (i.e., shampoo, soap, diaper balms, diaper wipes, lotions, and creams); (ii) medical and medicament history; and (iii) home and caregiver environment (i.e., parent personal hygiene products, household products, and prominent articles/toys room by room) (Table 2). This

TABLE 2. *Demographic and Environmental History Gathered in the Initial Consult*

Baseline patient demographics (i.e., age, gender)
Patient's past medical history (atopy, asthma, hay fever, etc.)
Patient's medicament history (topical and systemic)
Patient's personal hygiene and personal effects environment (i.e., soap, diaper wipes, bubble bath, socks, shoes, school uniform including color)
Patient's school/daycare/caregivers' environment (i.e., sleep mats, cleansers)
Patient's connubial environment (i.e., parents'/caregivers' personal hygiene products)
Patient's home environment (room by room contents)
Patient's avocation/hobbies (i.e., painting, drawing, bicycling)

information is then correlated with the geographic distribution of the patients' dermatitis, leading to the selection of a customized set of allergens for each patient.

Table 3 lists the basic pediatric series, which we developed at the University of Miami starting from the North American Contact Dermatitis Group Standard Allergen Panel as a primary base. It is important to note that new products with potentially sensitizing chemicals are continuously being introduced and exposures do vary per individual (10), thus this base screening panel is constantly revised. Furthermore, additional allergens deemed to be potentially clinically pertinent are individually selected for each patient from our extended specialty panels (including fragrances, vehicles, textiles, bakery, shoe and plastics, and glues series).

Children are then tested only if they meet the clinical indications and satisfy the testing criteria of our protocol. The primary indications include: (i) uncontrollable or worsening chronic dermatitis of greater than 2 months duration; (ii) failure to improve following a preliminary avoidance regimen (a.k.a. *the super skin regimen*), which eliminates exposure to fragrance and formaldehyde, as these are significant allergens found to be prevalent in children's personal hygiene products. This serves two purposes, one of which is to perform a trial avoidance and the other is to estimate family compliance. Patch testing is not performed on pediatric patients whose caregivers refuse to comply, have too limited a testing area due to severe dermatitis, or if informed consent is not received from the legal guardian.

Of note, during the period January 10, 2005 to May 25, 2006, 60 patients were evaluated, 45 patients were patch tested, four did not meet criteria because of extensive dermatitis (too limited a test area), patch testing was deferred in two because of parental noncompliance, and patch testing was deferred by nine families (15%), as the patients dramatically improved on the supersensitive skin regimen (unpublished data).

A formal education session, including disclosure that the procedure has not received Food and Drug Administration indication in pediatric patients, is conducted with all parents/legal guardians prior to patch testing. After the preemptive avoidance period (4–6 weeks), the patient is re-evaluated and the decision is made with the parents/guardian on whether to proceed with the patch test. A less than 50% improvement with preemptive avoidance meets criteria for patch testing to be performed.

Allergens and supplies (IQ Chambers on Scanpore tape) were obtained from Dormer Diagnostics/Chemotechnique Diagnostics (Malmö, Sweden). Customized patch tests were made for each individual patient. Per center protocol, in children under 6 years of age, a high

TABLE 3. Base Screen for Pediatric Patients

	Allergen	Exposure source
1	Bacitracin 20% pet	Antibiotic ointment
2	Balsam of Peru (<i>Myroxylon pereirae</i>) 25%	Fragrance, flavor agent, tomato ("nature identical"), sunscreens, calamine lotion, toothpaste, and lozenges
3	Benzocaine 5% pet	Teething rings (anesthetic)
4	Benzophenone-3 3% pet	Soaps, sunscreens
5	Benzyl alcohol 1% pet	Fragrances, medical creams (preservative)
6	Bronopol (2-bromo-2-nitropropane-1,3-diol) 0.5% pet	Diaper wipes, shampoos, liquid soaps—formaldehyde-releasing preservative (FRP)
7	Budesonide 0.1% pet	Class B steroid screening agent (corticosteroid)
8	Carba mix 3% pet*	Diaper, toys, underwear—rubber (accelerator)
9	Cinnamic aldehyde 1% pet	Chewing gum, toothpaste (flavorant)
10	Cobalt chloride hexadrate 1% pet	Button snaps, braces, vitamin (metal)
11	Cocamidopropyl betaine 1% aq	Shampoos, soaps, toothpaste (surfactant)
12	Colophony 20% pet	Band-aids, adhesives, chewing gum
13	Compositae Mix 6% pet	Shampoos, soaps, "green" personal hygiene products
14	Diazolidinyl urea 2% pet	Lotion, liquid soap (FRP)
15	Disperse Blue 124/106 mix 1% pet	Clothing, diapers (textile dye)
16	Disperse Yellow 3/9 mix disperse dye 1% pet	Textile clothing (textile dye)
17	DMDM hydantoin 1% pet	Lotions, shampoos, liquid soap (FRP)
18	Epoxy 1% pet	Plastics and glues
19	Ethylenediamine dihydrochloride 1% pet	Mycolog cream, antihistamines (cross reacts with atarax/zyrtec)
20	Euxyl k400 [Methyldibromoglutaronitrile phenoxyethanol] 2% pet	Moisturizer and paper (preservative)
21	Formaldehyde 1% aq*	Preservative and plastic resin
22	Fragrance Mix I 8% pet	Baby lotions, soaps, "cosmetics," toys
23	Fragrance Mix II 14% pet	Lotions, soaps, "cosmetics"
24	Imidazolidinyl urea 2% pet	Lotions, soaps—FRP
25	Lanolin 30% pet	Lotion, ointment, creams, medicaments (emollients)
26	Mercaptobenzothiazole 1% pet*	Shoes, toys—rubber (accelerator)
27	Mercapto mix 1% pet*	Shoes, toys—rubber (accelerator)
28	Methylchloroisothiazolone/methylisothiazolone 100ppm aq	Lotions, liquid soaps, shampoos (preservative)
29	Neomycin sulfate 20% pet	Neosporin, polysporin, triple antibiotic ointment
30	Nickel sulfate 5% pet*	Jean snaps, buckles, orthodontics, eyeglasses, school chair sign, some vitamins (metal)
31	Para-tertiary-butylphenol-formaldehyde resin 1% pet	Shoe glue
32	Paraben mix 12% pet	Lotions, soaps, creams, medicaments (preservative)
33	Para-phenylenediamine 1% pet*	Dye, temporary tattoos (rubber antioxidant)
34	Potassium dichromate 0.25% pet	Leather tanning, vitamins (metal)
35	Propolis (beeglue) 10% pet	Green cosmetics, salves, lip balm, chewable vitamins
36	Propylene glycol 30% aq	Lubrication in moisturizers
37	Quaternium-15 2% pet	Shampoo, liquid soaps (FRP)
38	Thiuram 1% pet*	Rubber gloves, toys, shoes (accelerator)
39	Tixocortol-21 pivalate 0.1% pet	Class A steroid for hydrocortisone-type allergies (cortisone)
40	Tosylamide formaldehyde 10% pet	Nail polish

This table serves as a primary base from which we select allergens for pediatric patients. Selection is driven by the clinical picture and history as not all allergens are appropriate for all patients.

*These allergens are diluted to half concentration if they are selected for testing in children under 5 years old.

suspicion of clinical relevance for an allergen had to be demonstrated before patch testing with that allergen was performed. Furthermore, while current patch test data sources suggest that the same test concentrations as adults should be used (11), reports do exist of "atypical" irritant reactions, especially in the very young (12).

In an attempt to reduce false-positive readings of irritant reactions, Fisher recommended that allergen concentration for specific chemicals—namely formaldehyde and nickel—be reduced to half when testing in children under the age of 8 years (13). Our protocol alters the Fisher recommendations to children under 5, and

additionally halves the concentration of rubber additives (accelerators and antioxidants). These changes have been made based on relevant positive reactions in individuals tested at these lower concentrations at our testing site.

In the contact dermatitis specialty clinic the allergens were placed on the patient's back and removed and evaluated after 48 hours of epicutaneous exposure (all with the assistance of video distraction assist) (14). In addition, patients return to the clinic for a 72- and 96-hour postplacement reading by the contact dermatitis specialist. Of note, because no difference was noted between the 72- and 96-hour read time points in all the

pediatric patients tested between 2004 and 2006, our center protocol has opted to not continue with the additional 96-hour read, consistent with the German protocol (15).

Following final patch test results, a 1- to 2-hour postprocedure education session is conducted with the patient's family to review common allergen locations, potential cross-reactors, and potential exposure sources within the child's environment. The family is provided with a list of alternative personal hygiene products derived from the American Contact Dermatitis Society-Mayo Clinic Contact Allergen Replacement Database available at <http://www.contactderm.org> (16). In addition, in the event that a new product is to be introduced to the patient, the caregiver is instructed on how to perform the provocative use test on their child, whereby a pea-sized amount of a "leave-on" product is applied to a 2.5 cm circle drawn on the inner arm (away from the antecubital fossa) twice daily for 7 days. Instructions are given to return to the clinic for evaluation of these reactions.

CASE EXAMPLES

Patient 1

A 3-year-old white Latin boy presented to the pediatric dermatology clinic with an 18-month history of severe and recalcitrant AD involving his face, arms, and trunk (Fig. 1). Previous therapies had included multiple topical creams. Despite repeat negative bacterial skin cultures performed on the facial erosions, the patient was treated empirically with multiple rounds of antibiotics. In addition, he was treated with a multitude of systemic antihistamines (including diphenhydramine, hydroxyzine,



Figure 1. Prepatch test examination of the face revealing erythematous plaques with scale, crust, and erosions.

certirizine, and doxepin) and ketotifen (a mast cell stabilizer), and three courses of systemic steroids. These aforementioned medications provided the patient only minimal and temporary relief. His past medical history was also significant for allergic rhinitis, IgE-based allergies to casein and dog dander, and a positive family history of asthma and allergic rhinitis.

On physical examination, erythematous plaques with scale, crust, and erosions were noted on his face, trunk, arms, and legs. Laboratory analysis demonstrated an IgG level that was low at 465 mg/dL (normal values 533–1078 mg/dL) and an IgE level that was elevated at 783 mg/dL (normal 15–700 mg/dL). Radioallergosorbent testing was significantly elevated for dog dander (174% or 1.02 KU/L) and casein (103% or 0.50 KU/L). There were no aberrancies noted in his T and B cell subset analyses.

Despite administration of prednisone, the patient continued to worsen and was hospitalized due to a recalcitrant flare and bacterial superinfection. On admission, he was started on cyclosporine (4mg/kg/day), intravenous vancomycin for presumed methicillin-resistant *Staphylococcus aureus*, and doxepin (0.2 mg/kg/day). One week later, he was discharged home on cyclosporine (4 mg/kg/day) and doxepin (0.2 mg/kg/day). Still showing no improvement at his 2-week follow-up appointment, his cyclosporine dose was increased to 5 mg/kg/day. The patient was then referred to the pediatric contact dermatitis clinic for evaluation.

As per protocol, this patient was patch tested. Of note, he maintained his dose of cyclosporine at 3 mg/kg/day during the patch test. At 72 hours, clinically relevant positive reactions were noted to: formaldehyde [1 +], the formaldehyde-releaser, bronopol [1 +] (in the patient's CVS brand unscented soft cloth baby wipes), balsam of Peru (*Myroxylon pereirae*) [1 +], geraniol [1 +] (in fragranced soaps, shampoos, and household cleansers), sodium benzoate [1 +], and isopropyl myristate [1 +] (in the patient's hydrocortisone 2.5% cream, desonide lotion, fluocinolone acetonide topical oil, and fluticasone propionate cream). A clinically irrelevant positive reaction was also noted to thimerosal [1 +], which likely represents sensitization through vaccination, and cobalt.

Based on the knowledge of his allergens an allergen-free treatment option was prescribed, which included a selected dietary avoidance of tomato products, cola, chocolate, and sodium benzoate (17). Topically the patient was prescribed hydrocortisone butyrate 0.1% ointment to the body and tacrolimus 0.1% ointment for his face, axilla, and groin. With strict adherence to his avoidance regimen protocol significant improvement of his dermatitis was seen at the 1-month follow-up visit



Figure 2. Postpatch test examination of the face revealing significant improvement in dermatitis.

(Fig. 2). Furthermore, discontinuation of cyclosporine became possible within 3 months after patch testing.

Eight months since the patch test, our patient has intermittently presented with mild erythematous, finely scaled plaques of his trunk, arms, and legs, which is consistent with his history of AD. Of note, these lesions have been controllable with allergen-free topical emollients and low-potency topical cortisone cream. Periodically, such as in association with upper respiratory infections, mid-potency topical steroids have been used for flares in the “atopic areas” (hydrocortisone butyrate 0.1% ointment). Even during flares, he has had no evidence of erosions, and his facial eruption has remained clear following the discontinuation of baby wipes to his face.

Patient 2

Our second patient was a 10-month-old African American boy with past medical history significant for failure to thrive presenting with severe AD for 7 months duration. His topical treatments included: alclometasone dipropionate cream, triamcinolone acetonide 0.1% cream, hydrocortisone butyrate cream, and Aquaphor ointment. He was treated with numerous systemic agents including: hydroxyzine (2 mg/kg/day), three courses of cefalexin (100 mg/kg/day) for bacterial superinfection with *S. aureus*, and three courses of prednisone (1 mg/kg/day). Oral prednisone provided the most significant relief, but discontinuation both times after a 2-week taper resulted in a rebound flare. Throughout his course, morning cortisol levels were within normal limits. Topical steroids failed to appropriately control the disease. The patient was referred to the pediatric contact dermatitis clinic for evaluation.

On physical examination, the patient exhibited lichenified, scaly pink plaques on his face, predominantly affecting the eyelids, scalp, and extremities. Following the pre-emptive avoidance period (see Protocol for Patch Testing), the patient returned for evaluation with less than 50% improvement, and thus the decision was made to proceed with patch testing. At the 72 hour patch test reading, positive reactions were noted to cinnamic alcohol [1+], stearyl alcohol [1+], and cetyl alcohol [1+]. Stearyl and cetyl alcohol are fatty alcohols present in lanolin, the main ingredient in the emollient Aquaphor and notably also present in his topical corticosteroids (triamcinolone acetonide 0.1% cream plus cetyl alcohol and alclometasone dipropionate plus cetearyl alcohol). Irritant reactions were noted to both cocamidopropyl betaine and neomycin. A postpatch use test demonstrated sensitivity to Aquaphor.

We recommended the avoidance of the clinically relevant allergens and irritants in conjunction with hydrocortisone butyrate ointment twice daily to his body, with white petrolatum as an emollient, and the use of glycerin soap, and Free & Clear™ shampoo. Three months postpatch testing, the patient's dermatitis was much improved, requiring only minimal use of the hydrocortisone butyrate ointment. Furthermore, he has not been hospitalized since patch testing or required systemic prednisone, and his pruritus is significantly improved.

Patient 3

Our third patient was a 3-year-old Caucasian girl with a past medical history of eosinophilic gastroenteropathy, gastroesophageal reflux disease, and multiple IgE-associated food allergies. Specifically, radioallergosorbent testing was positive to casein, soybean, egg white, wheat, cheese mold, egg yolk, beef, and house dust mite. The patient presented with a history of severe pruritic hand and foot dermatitis for 2 years. Laboratory evaluation demonstrated no aberrancies in her T and B cell subsets. IgE was elevated at 6101 kU/L.

On physical examination, the patient had lichenified, erythematous plaques involving her palms and soles with fissures along the lateral margins. The patient was unable to walk or use her hands because of her disease severity. High-potency topical steroids used intermittently for several months had failed to provide adequate relief. Therefore, she was treated systemically with a course of prednisone (1 mg/kg/day), hydroxyzine (2 mg/kg/day), and doxepin (0.2 mg/kg). Reduction in the cortisone dose resulted in a rebound dermatitis, and thus, cyclosporine (3 mg/kg/day) was then prescribed along with

topical white petrolatum. These had a minimal effect on her dermatitis.

Patch testing was performed per our Contact Dermatitis Clinic protocol, while the patient was on cyclosporine. At the 72 hours patch test reading, clinically relevant positive reactions were noted to: n,n diphenylguanidine (carbamate) [1+] (in the patient's socks), paraben mix [1+] (in the patient's hydrocortisone 1% cream and Balmex™), sorbitan sesquioleate [1+] (in the patient's fluticasone ointment), cetyl alcohol [1+] (in the patient's fluticasone cream) ethylenediamine dihydrochloride [1+] (cross-reactor with hydroxyzine), balsam of Peru (*M. pereirae*) [1+] (in the flavoring of the patient's hydroxyzine [18], Balmex™, and ketchup), and cinnamic aldehyde [1+]. In addition, a questionably relevant positive reaction was noted to musk mix [1+].

The patient was placed on an avoidance regimen. Instructions were given to purchase carbamate-free socks (organic cotton socks: <http://www.rawganique.com>) and undergarments, and the parent was advised not use medicaments containing her allergens (including topical creams and cetirizine or hydroxyzine, which cross-react with ethylenediamine dihydrochloride). She was treated with acromethasone ointment twice daily to the hands and feet. At her 12-week follow-up, the patient demonstrated resolution of her dermatitis, which allowed discontinuation of all topical medicaments and cyclosporine. Furthermore, there has not been a recurrence of her hand and foot dermatitis (7 months duration at present time).

COMMENTS

Patch testing is the gold standard in the diagnosis of ACD. Once the culprit allergen is revealed, an appropriate avoidance regimen needs to be initiated. This ultimately decreases the severity of the patient's dermatitis and allows for controlled management of underlying endogenous dermatoses as was exhibited in two out of three cases with AD in the present study. In these cases, management was further confounded by source allergens being present in the medicaments used to treat the underlying condition, resulting in aggravation of the dermatitis. Recognizing potential pediatric patients with ACD either as the primary diagnosis or the confounding factor is crucial.

We presented our basic series (with our most recent incorporations) in that it may serve as a guideline to assist practitioners in the diagnostic workup of the child with delayed-type hypersensitivity reactions. However, we realize that not all these chemicals would be appropriate for patch testing for all children and provide this information with the caveat that substances should only be

tested when there is clinical suspicion and a suggestive history.

Institution of appropriate allergen avoidance is life altering for the child and family. Extrapolating from the adult data and our clinical experience, we have noted significant clinical improvement 8–12 weeks following the patch test, when there is compliance with a strict avoidance regimen. Furthermore, we have observed that in pediatric patients with moderate to severe dermatitis, correct use of patch testing can allow for cessation of systemic immunosuppressant therapies and ultimately be a steroid-sparing agent.

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