Getting to the Root of ACD

A practical approach to dermatitis in young and old.

BY LAUREN A. IVEY, MS; JANNA M. VASSANTACHART, MD; AND SHARON E. JACOB, MD

Allergic contact dermatitis (ACD) affects more than 13 million Americans annually.¹ The complex pathogenesis involves delayed type IV hypersensitivity with re-exposure to an allergen causing activation of TH1 cells and release of inflammatory cytokines in a previously sensitized individual.² ACD can be acute, as seen in linear blisters secondary to poison ivy exposure, or chronic, secondary to a wide range of allergens from fragrances to nickel-releasing jewelry to sun-activated compounds. Atopic and irritant contact dermatitis can occur concurrently with ACD.

Given the numerous allergen sources and delayed dermatitis expression after allergen exposure, determination of the cause of ACD can be challenging by history alone. Patch testing is therefore an important diagnostic tool used to identify potential allergens of contact sensitization. By connecting the history and clinical findings and evaluating the relevance of positive patch test findings, a diagnosis of ACD can be confirmed and allergen sources identified. Those suffering from ACD can reach remission with proper diagnostic testing and interpretation, leading to identification and avoidance of the culprit allergen.

WHEN TO INVESTIGATE AND EVALUATE FOR ACD

ACD should be suspected in patients with the following profiles (see Flow Chart):

1. Patients with new onset recalcitrant dermatitis lasting more than two months that is non-responsive to standard-of-care treatments, either requiring increasing strength or number of refills of topical corticosteroid.³ Delays in diagnostic patch testing can increase the potential for polysensitization or the risk of development of a more widespread generalized distribution of the primary dermatitis.⁴

2. Patients with a history of dermatitis who have a change in the dermatitis pattern. The acute change in a previously stable patient may indicate a compounding factor, such as ACD.

3. Patients with dermatitis involving greater than 25-40 percent body surface area (BSA).

The top three clues suggesting the diagnosis of ACD over other disorders include:

1. Anatomical predilection of the dermatitis for specific geographical areas or distinct linear or geometric shape, suggest the origin could be “an outside affair” (see Table 1). For example, dermatitis presenting at the earlobes may suggest contact allergy from an earring, whereas involvement of the bilateral lateral neck may indicate allergy secondary to a perfume. Because ACD can spread from the point of contact, a full-body examination should be conducted before inferring the allergen based on the pattern of distribution.⁵

2. A temporal association between exposure to an allergen source and flare of the dermatitis.

3. Improvement with time away from the activity where the allergen is contacted.

**TABLE 1: ACD SAMPLE INTERVIEW QUESTIONS**

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approximate onset and site of dermatitis (rash)</td>
<td></td>
</tr>
<tr>
<td>Please describe your symptoms</td>
<td></td>
</tr>
<tr>
<td>What do you think is causing your rash?</td>
<td></td>
</tr>
<tr>
<td>Do you notice any periods (i.e. during work, vacation, etc.) of spontaneous clearing or exacerbation?</td>
<td></td>
</tr>
<tr>
<td>What is your occupation? Avocation?</td>
<td></td>
</tr>
<tr>
<td>Do you think your rash could be work related?</td>
<td></td>
</tr>
<tr>
<td>Have you had a reaction to pierced areas or inexpensive jewelry?</td>
<td></td>
</tr>
<tr>
<td>Do you have any prior history of allergy testing?</td>
<td></td>
</tr>
<tr>
<td>What topical medications you are using/have used?</td>
<td></td>
</tr>
<tr>
<td>List your personal hygiene products</td>
<td></td>
</tr>
</tbody>
</table>
Flow Chart

Eczematous Dermatitis

(History & Questionnaire*)

New onset unremitting dermatitis
requiring increasing no. of refills or strength of corticosteroid

Change in dermatitis pattern in patient
with history of dermatitis (increased BSA); new areas

25-40% BSA†

Biopsy + PEAS†

45-80% BSA†

Biopsy + Systemic tx + PEAS†

Improvement

Stable

No Patch Test indicated

Standard series patch test
+ supplemental
+ PHP as indicated

Patch placement (visit dates; M-W-F-W-F-M)
Removal at 24 hrs (8 yrs & younger)§
Removal at 48 hrs (8 yrs & older)

Preliminary reading at patch test removal

Delayed reading at 72, 96, 120 hrs

Positive patch test = contact sensitization

Review of pre-patch history, current personal hygiene products & avocations

Predict possible relevance

Patient education and counseling

Strategic avoidance of products, sources, and allergens guided by CAMP®

Follow-up in 8-12 wks

Assign relevance & review efficacy of avoidance protocol & adherence; evaluate for clinical improvement

* See Table 1 (Questionnaire)
† BSA = “Body surface area”
‡ PEAS = “Preemptive Avoidance Strategy”
§ PHP = “Personal hygiene products”
# CAMP = “Contact Allergen Management Program”
△ See Table 2 (Relevance)
**TABLE 2: CAUSATIVE ALLERGENS BASED ON ANATOMIC RELEVANCE, ADAPTED FROM BERNSTEIN, 2010**

<table>
<thead>
<tr>
<th>Geographical location</th>
<th>Source of sensitization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scalp &amp; neckline</td>
<td>Styling products, fragrance, essential oils, jewelry</td>
</tr>
<tr>
<td>Periorbital, face, lips,</td>
<td>Cosmetics, beauty preparations, fragrance, hair products, jewelry, topical medicine transfer, lip and oral hygiene products</td>
</tr>
<tr>
<td>Chest &amp; abdomen</td>
<td>Sun exposure, sunscreens, belts, tattoos</td>
</tr>
<tr>
<td>Arms &amp; wrists</td>
<td>Jewelry, watches, tattoos,</td>
</tr>
<tr>
<td>Anogenital region</td>
<td>TCS, contraceptives, personal hygiene sprays, perfumes, powders, baby wipes, personal lubricants</td>
</tr>
<tr>
<td>Hands</td>
<td>Nail polish, rubber gloves, cosmetics and personal care products</td>
</tr>
<tr>
<td>Legs</td>
<td>Plants, topical preparations for leg ulcers,</td>
</tr>
<tr>
<td>Ankles &amp; feet</td>
<td>Shoe materials or chemicals, including rubber, adhesives, and chromates</td>
</tr>
</tbody>
</table>

**TABLE 3: ACD SYSTEMIC TREATMENT OPTIONS**

<table>
<thead>
<tr>
<th>Systemic treatment</th>
<th>Recommended dosage</th>
<th>Monitoring Parameters &amp; Precautions</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>0.5-1mg/kg/day orally</td>
<td>BP; weight; chest x-ray and DEXA scan if prolonged treatment</td>
<td>Dose tapered down over 3 weeks SE: weight gain, acne, mood changes</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>3-5mg/kg/day orally given in 2 divided doses</td>
<td>Baseline: B/Px2, BUN/Cr, CBC, LFTs, K+, Mg, lipids, uric acid Monitor: BP and BUN/Cr, Mg, q2wk x2mo, then if stable, qmo; more frequently if adjusting dose</td>
<td>Course limited due to risk of renal complications SE: HTN, hyperkalemia, hypertrichosis, gingival hyperplasia</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>2mg/kg/day orally given in 2 divided doses</td>
<td>Baseline: Cr, LFTs Monitor: CBC qwk x4, then q2wk x4, then qmo or more frequently if adjusting dose</td>
<td>TPMT genotyping prior to initiating treatment SE: nausea, vomiting, leukopenia, infections</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>7.5-25mg orally/ subcutaneously weekly</td>
<td>Baseline: CBC w/diff, BUN/Cr, LFTs, viral hepatitis panel Monitor: CBC w/ diff, BUN/Cr, LFTs weekly for 1 mo then gradually decrease to 3-4 mo</td>
<td>Monitor closely when therapy is initiated. Folate supplementation on non-MTX days SE: nausea, vomiting, pancytopenia</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>4-5mg/kg daily in younger children 3-4mg/kg daily for adolescents</td>
<td>Baseline: Cr Monitor: CBC qwk x1mo, then 2x/mo x2mo, then qmo during 1st year of tx</td>
<td>SE: diarrhea, abdominal pain, nausea, vomiting</td>
</tr>
</tbody>
</table>

Key: BP – blood pressure; SE – side effects; CBC - complete blood count; BUN/Cr – Blood Urea Nitrogen/creatinine; LFTs- Liver function test; K+ - potassium; Mg – magnesium; mo – month; wk – week; HTN – hypertension; TPMT - Thiopurine methyltransferase; tx- treatment.
THE ART OF PATCH TESTING

Patch testing is the gold standard diagnostic test for confirming allergens to which an individual is sensitized. Due to the overwhelming number of potential allergens a person can encounter daily, the pre-patch test history-taking consultation should be streamlined yet broad; many centers have a pre-test questionnaire that they include as part of the initial evaluation (see Table 2). Patch testing should be performed in a systematic fashion and include a delayed reading. A positive patch test indicates that the patient is sensitized to the tested allergen. Sensitization to an allergen however does not necessarily mean that the patient’s current clinical presentation is caused by the allergen demonstrating patch test positivity. Causality between allergen and clinical presentation is established in light of the cross-examination history. The steps of patch testing are shown in the Flow Chart on the previous page.

PATCH TESTING PANELS

The Thin-Layer Rapid Use Epicutaneous (T.R.U.E) Patch Test* (SmartPractice) is FDA approved for persons aged six and older. This commercially available standardized pre-loaded kit contains 35 allergens and one negative vehicle control. This kit is able to capture up to ~70 percent of the positive reactions identified by the surveillance screening panel of the North American Contact Dermatitis Group (NACDG).6

In 2012, the American Contact Dermatitis Society (ACDS) published a Core Allergen Series, a screening series based on the top allergens, in order of prevalence. The core panel serves as an evidence-based reference point for initial screening. It should be recognized that testing with extended panels tailored to exposures and the patient’s own products can be essential, as this helps to confirm the relevance of the allergen exposure and potentially assists in the detection of uncharacterized antigens, which may be present in the product the patient is using. Notably, several studies have shown that comprehensive patch testing with both standard and supplemental series carries a much higher probability of confirming contact sensitization in a patient.8

PREPARING PATIENTS FOR A PATCH TEST

Ideally, the patch testing panels should be placed on a clean, dry, non-inflamed area of the skin. The most common location for the panels is the upper back away from the spine.9 Proper contact of the hapten to the skin reduces the risk of false negatives.

For some patients, you may want to advise them to remove hair (at home) in the area prior to placement of the panels. Instruct patients to avoid sun exposure for two to four weeks prior to testing and avoid topical cortico-

steroid or immune modulator application at the site for patch test placement or to the area for at least one week prior to testing.10 Antihistamines do not have to be discontinued, unless patch testing is being conducted to evaluate for contact urticaria.9,10 It’s also important to educate the patient that the patch test panels will need to be kept intact and dry until they are removed and evaluated at 48 hours, with no topical applications to the area until the final read.

Patients with generalized dermatitis or extensive back involvement may need to delay patch testing until the dermatitis is better controlled with a non-dermatitis skin area upon which to apply the patches. A trial of the Pre-Emptive (Allergen) Avoidance Strategy (P.E.A.S.) may be warranted in cases of restricted access to patch testing or for those whose dermatitis is so widespread that patch testing is unable to be performed.11 The 2017 P.E.A.S. update fragrance mix/balsam of Peru, neomycin/bacitracin, wool wax/lanolin, formaldehyde, methylisothiazolinone (MI)/methylchloroisothiazolinone (MCI), propylene glycol, cocamidopropyl betaine, glucosides, propolis, and compositae as the top prevalent allergens affecting pediatric patients in North America.12

PATCH TEST INTERPRETATION

Patch test reactions are graded based on International Contact Dermatitis Research Group (ICDRG) descriptive scoring system ranging from IR (-) negative reaction to (3+) extremely positive reaction. Doubtful and irritant reactions are also documented and reviewed for clinical relevance. Positive reactions, if present, must be interpreted in light of reflective history and clinical association.9 The setting of a dermatitis with a positive patch test that correlates with the exposure history and clears with avoidance of the positive allergen confirms the diagnosis of ACD. If after an avoidance period, the allergen is again encountered and the condition returns, the allergen can be deemed of definite clinical relevance.

“ACD has been demonstrated to affect patients’ quality of life, with a significant symptom burden, including sequelae of itching, pain, and sleep and mental health disturbances.”
SYSTEMIC TREATMENT TO DAMPEN DERMATITIS RESPONSE IN PREPARATION FOR PATCH TESTING

Recalcitrant dermatitis may necessitate a trial of systemic therapy (See Table 3). Presently there are no FDA-approved systemic treatments for ACD, however systemic corticosteroids and immune modulators have been shown to be effective for patients with recalcitrant ACD. Immune modulators include cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil.

Systemic corticosteroids. Corticosteroids such as prednisone, methylprednisolone, and dexamethasone have been the pharmacologic mainstay of treatment for ACD while avoidance measures are being implemented. A brief course (five to seven days) of systemic glucocorticoids such as prednisone can provide rapid relief to patients with severe dermatitis. The short course should be followed by a tapering to 50 percent of the initial dosage before discontinuation to avoid rebound dermatitis.

Cyclosporine. Cyclosporine, a systemic calcineurin inhibitor, has been shown to be effective in the management of moderate to severe atopic dermatitis as well as ACD. Calcineurin is an intracytoplasmic phosphatase that regulates the activity of NF-AT, a transcription factor necessary for the synthesis of key inflammatory cytokines such as IL-2, IL-3, and IFN-γ. Cyclosporine binds to cyclophilin and prevents the activation of calcineurin, thus preventing T-cells from synthesizing the inflammatory factors necessary for their proliferation and activation following exposure to an antigen.

Azathioprine. Azathioprine is a systemic immunomodulatory agent that prevents both B- and T-cell division by depriving the cell of substrates necessary for DNA synthesis and thus, cell division. It has been recommended as a second-line treatment following cyclosporine in the use of immune-modulators for contact dermatitis.

Methotrexate. Methotrexate is a dihydrofolate reductase inhibitor demonstrated to have an efficacy similar to that of azathioprine in preventing both lymphocyte proliferation and decreasing disease severity in patients with CD.

Mycophenolate mofetil. Mycophenolate mofetil like azathioprine blocks the synthesis of purines, however does so via reversible inhibition of the enzyme inosine-5’-monophosphate (IMP) dehydrogenase, halting DNA and RNA synthesis in rapidly dividing cells. Mycophenolate has been shown to demonstrate similar efficacy in the treatment of atopic dermatitis refractory to treatment.

PREGNANCY CONSIDERATIONS FOR SYSTEMIC TREATMENTS

Cyclosporine carries the least risk of use during pregnancy (category C), while azathioprine and mycophenolate mofetil have evidence of risk and should be used with caution (category D). Methotrexate (category X) is contraindicated for use during pregnancy in the United States, however recent studies have shown minimal adverse outcomes in the third trimester. Methotrexate exposure pre-conception appears to carry the greatest association with birth defects.

PEDiatric CONSIDERATIONS

Although ACD in children was previously considered to be rare, there has been a recent flux of research in the field and the current estimate is that the condition affects up to four million US children each year. Patch testing has been shown to be safe and effective in children. As mentioned previously, the FDA approved use of the (T.R.U.E) Test™ in patients as young as six years old in 2017. Customizable patches and modifications of allergens and occlusion times have been suggested for younger patients. Patch testing in children has similar indications to adults, such as dermatitis that worsens or changes, involves highly susceptible areas such as the eyelids, hands or feet, and genitals, or will require immunosuppressive systemic medication. Other indications include refractory late-onset atopic dermatitis with no history of childhood eczema or refractory hand eczema. P.E.A.S. tailored to the allergens highly prevalent in pediatric patients can prove efficacious and may be given a trial where access to contact dermatitis evaluation is limited, where dermatitis is extensive, or to potentially dampen a dermatitis flare prior to patch testing.

HELPING PATIENTS MANAGE THEIR ACD

ACD can be not only an emotionally frustrating experience for the 20 percent of Americans who live with it, but is also estimated to have a societal cost upwards of $2 billion annually. ACD has been demonstrated to affect patients’ quality of life, with a significant symptom burden, including sequelae of itching, pain, and sleep and mental health disturbances.

Remission of ACD may be attained through avoidance of a known allergen(s) to which a person has become sensitized. Early screening and knowledge of how to avoid the causative allergen can significantly improve quality of life for the afflicted and reduce the cost to both the individual and medical costs to the society. It is vital that sensitized persons are aware of the common and not-so-common sources where they could come into contact with their allergen. Not all sources of contact are intuitive: formaldehyde, for example, can be found in permanent press or wrinkle-free fabrics. (Continued on page 63)
(Continued from page 56)

Electronic database tools, such as the Contact Allergen Management Program (CAMP), which is a benefit of membership in the American Contact Dermatitis Society, can be helpful in providing patient resources on allergen avoidance, for creating product list(s) devoid of allergens, and because they provide important cross-reactivity resources. Additional resources include mypatchlink.com and the Contact Allergen Replacement Database (CARD).29

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