Allergic Contact Dermatitis
Patch Testing Beyond the TRUE Test

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ABSTRACT

Epicutaneous patch testing is the gold standard method for the diagnosis of allergic contact dermatitis. Despite this knowledge, many clinical dermatologists do not offer patch testing in their offices or offer testing with only a limited number of allergens. Introduced in 1995, the Thin-Layer Rapid Use Epicutaneous Test originally contained 23 allergens and one control. In 2007, five additional allergens were added. This United States Food and Drug Administration-approved patch testing system made patch testing more convenient, and after its introduction, more dermatologists offered patch testing services. However, the number of allergens in the Thin-Layer Rapid Use Epicutaneous Test remains relatively low. Every two years, the North American Contact Dermatitis Group collects and reports the data from patch testing among its members to a standardized series of allergens. In 2005-2006, the Group used a series of 65 allergens. Of the top 30 allergens reported in 2005-2006, 10 were not included in the Thin-Layer Rapid Use Epicutaneous Test. Knowledge of and testing for additional allergens such as these may increase patch testing yield.

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CONTACT DERMATITIS

Contact dermatitis is a common problem encountered in dermatology clinics. Of all contact dermatitis cases, 80 percent are caused by irritant contact dermatitis (ICD) and 20 percent are caused by allergic contact dermatitis (ACD). These two different forms of contact dermatitis can be difficult to distinguish. Although epicutaneous patch testing is the gold standard method for the diagnosis of ACD, many dermatology clinics do not offer patch testing at all or offer testing to only a limited number of allergens.

REVIEW OF ALLERGIC CONTACT DERMATITIS

ACD is an immunological reaction that occurs in genetically susceptible people who have been previously sensitized to an allergen. This is in contrast to ICD, which can occur in any person if the amount and duration of irritant exposure are sufficient to cause direct epidermal keratinocyte damage.1

When a genetically susceptible person’s skin comes into contact with an allergen for the first time, the allergen enters the stratum corneum and binds to carrier proteins. The allergen-protein complex is engulfed by Langerhans cells in the epidermis and subsequently processed. The Langerhans cells then travel to nearby lymph nodes and present the processed allergen-protein complex to naive Th1 cells. This presentation leads to the release of interleukin-1 and 2, which initiate clonal proliferation of newly sensitized Th1 cells as well as the release of memory Th1 cells into the circulation. Upon re-exposure to the allergen, the circulating memory Th1 cells use their skin-specific homing receptors to enter the skin at the site of allergen exposure and release inflammatory cytokines that lead to the spongiosis and inflammatory infiltrate typically seen in ACD.1

Patients with ACD usually present with a well-demarcated eczematous dermatitis. The hands and face are the most common localized areas.2 There is almost always significant associated pruritus. If the process is acute, there may be vesicles and bullae. If the process is chronic, there may be scaling and lichenification. Typically, but not always, the process is confined to the site of cutaneous exposure. Systemic and photosensitive ACD are less commonly encountered presentations.2

USE OF PATCH TESTING IN DERMATOLOGY CLINICS

The use of patch testing to diagnose ACD was first

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developed by Josef Jadassohn in 1895. Sulzberger brought the technique to the United States in the 1930s. Over the past 40 years, the pathophysiological understanding of ACD and the technique of patch testing have been expanded and redefined.

More than 3,000 chemicals are known to cause ACD. When a diagnosis of ACD is suspected in a dermatologist’s office, this number is indeed daunting. Certainly patch testing 3,000 chemicals is not practical. Thankfully, a small percentage of these 3,000 chemicals account for a large percentage of cases of ACD. Knowledge of the most commonly implicated allergens and a thoughtful patient history including personal care products, exposures, occupation, and hobbies as well as response of dermatitis to time away from work and hobbies can guide appropriate allergen selection for patch testing.

In 1990, the American Academy of Dermatology sponsored a survey on the use of patch testing among its members. Questionnaires were mailed to all members and 42 percent (2,453 members) responded. At that time (20 years ago), 27 percent of responders did not perform any patch testing and 54 percent patch tested less than one patient per week. Reasons for not testing included the following: 1) the belief that the diagnosis of ACD could be made on history alone, 2) patch testing was too time consuming, and 3) reimbursement was too low.

In 1995, the United States Food and Drug Administration (FDA) approved the first ready-to-use patch testing system. The introduction of the Thin-Layer Rapid Use Epicutaneous Test (TRUE Test) suddenly made patch testing much more convenient. The original TRUE Test consisted of 23 allergens and one control that could be applied to the patient’s back with little additional preparation for the physician or physician’s assistant.

In 1997, a second survey was done that assessed for changes in patch testing practices since the approval of the TRUE Test. One-third of American Academy of Dermatology members were surveyed and 43 percent responded (1,372 members). Eighty-three percent of respondents stated they were performing patch testing in their offices (as compared to 73% in 1990 prior to the availability of the TRUE Test). Among the 83 percent that were patch testing, 74 percent were using the TRUE Test and of those 74 percent, 44 percent were using the TRUE Test because it was less time consuming. Of note, less than 20 percent of the American Academy of Dermatology’s membership was represented in this survey.

Finally, in August 2008 the 600 members of the American Contact Dermatitis Society (ACDS) were surveyed regarding their patch testing practices. One-hundred of the members responded. Sixty-eight percent used a modified North American Contact Dermatitis Group (NACDG) series, 18 percent used the standard NACDG tray, and nine percent used only the TRUE Test. The most common reason cited for not using the TRUE Test was the relative lower number of allergens. The ACDS members used an average of 61.6 allergens in their trays, which is double the number of allergens in the TRUE Test.

CONVENIENCE AND THE TRUE TEST

Although patch testing remains the gold standard for the diagnosis of ACD, the actual procedure involves several steps. Selection of an appropriate series of allergens requires the physician to have sufficient knowledge of numerous allergens and to have them on hand in his or her clinic. Obtaining a history of the patient’s exposures both at home and work is vital and takes time during an office visit. Even if only using the TRUE Test, taking a careful exposure history is important. For example, if the patient is a hygienist or dentist, he or she should be referred to a patch testing specialist who has a dental panel rather than simply applying the TRUE Test, which may miss obvious allergens. If using a series other than the TRUE Test, the preparation of the patch test panels can be time consuming, but can be done ahead of time. Patients need appointments both for the application as well as first and second readings. When reading a patch test, correctly identifying a positive allergic versus irritant reaction requires skill. When patch testing is complete, identifying clinical significance of the positive allergen in the patient’s environment requires detective work and patient education. All of these factors may contribute to a dermatologist’s decision to not offer patch testing in his or her office. However, patch testing remains a very useful tool.

As discussed above, the approval by the FDA of the TRUE Test in 1995 made patch testing much more convenient for those either converting over to the TRUE Test or just starting to patch test. The original 23 allergens and one control were embedded into two panels each containing 12 allergens. Indeed, survey results showed more dermatologists were patch testing and most were using the TRUE Test. In 2007, the TRUE Test was expanded to include five additional allergens. Currently, there are plans to expand the TRUE Test even further to include three full panels (35 allergens and one control) (Table 1).

As the TRUE Test continues to gain more allergens, the diagnostic utility of this commercially available patch testing system will continue to improve. However, two of the biggest shortfalls of using the TRUE Test are the still limited number of allergens and the inability to customize the panel to potential allergens encountered in an individual patient’s workplace and hobbies. Only 25 to 30 percent of patients with ACD are completely diagnosed with the TRUE Test and 50 percent of allergens causing occupational dermatitis are missed. Although patch testing beyond the TRUE Test does not have FDA approval, many dermatology referral centers routinely use an expanded allergen series of 50 to 80 allergens, such as the NACDG Screen Series. The ACDS has also put forth a screening series that is similar to the NACDG’s series. In addition, smaller series are added depending on an individual patient’s exposures, such as a baker, dental hygienist, hairdresser, or nail technician. Dermatologists wanting to expand patch testing beyond the currently available commercial trays may use these expanded trays (either the NACDG or ACDS tray) as a starting point.
COMMONLY MISSED ALLERGENS

One way for dermatologists currently using the TRUE Test to increase sensitivity of patch testing for their patients is to be knowledgeable of which allergens are most likely to be missed by the TRUE Test. In a busy clinical practice, the TRUE Test is certainly a good starting point when addressing the need for patch testing. However, clinicians need to be familiar with its limitations as stated above. Adding another 10 to 30 of the most common allergens (either through a standard additional series or customized to the patient) can increase diagnostic yield of the patch test for the patient.

Every two years, the NACDG collects and reports the data from patch testing among its members to a standardized series of allergens. In the years 2005 to 2006, the NACDG standard series consisted of 65 allergens. It is important to note some of the 65 allergens in the NACDG’s panel were selected for research purposes. During this timeframe, 4,454 patients were patch tested. The 30 most common allergens from this report are listed in Table 2. Of the top 30 most frequently positive allergens, 10 are not included in the TRUE Test. Thus, these 10 allergens could be considered some of the most likely allergens to be missed by patch testing utilizing only the TRUE Test. Dermatologists currently using the TRUE Test who want to increase the sensitivity of patch testing, but do not want to apply an expanded tray, such as the NACDG standard tray, should be familiar with additional common allergens. The allergens reviewed below could be considered among others when physicians are contemplating expanding their patch testing services.

BACITRACIN

Bacitracin was the sixth most common allergen in the

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### Table 1. TRUE Test Allergens

<table>
<thead>
<tr>
<th>ORIGINAL ALLERGENS</th>
<th>ADDITIONAL ALLERGENS</th>
<th>FUTURE ADDITIONAL ALLERGENS</th>
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<tbody>
<tr>
<td>Nickel sulfate</td>
<td>Diazolidinyl urea</td>
<td>Bacitracin</td>
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<tr>
<td>Wool alcohols</td>
<td>Imidazolidinyl</td>
<td>2-Bromo-2-nitropropane-1,3-diol</td>
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<tr>
<td>Neomycin sulfate</td>
<td>Budesonide</td>
<td>Methyl dibromogluaronitrile</td>
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<tr>
<td>Potassium dichromate</td>
<td>Tixocortol-21-pivalate</td>
<td>Disperse blue 106</td>
</tr>
<tr>
<td>Caine mix</td>
<td>Quinolone mix</td>
<td>Hydrocortisone 17 butyrate</td>
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<tr>
<td>Fragrance mix</td>
<td></td>
<td>Parthenolide</td>
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<tr>
<td>Clophophy</td>
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<td>Gold sodium thiosulfate</td>
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<td>Paraben mix</td>
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<tr>
<td>Balsum of Peru</td>
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<tr>
<td>Ethylenediamine dihydrochloride</td>
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<td>Cobalt dichloride</td>
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<td>p-tert-butylphenol formaldehyde resin</td>
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<td>Epoxy resin</td>
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<tr>
<td>Carba mix</td>
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<tr>
<td>Black rubber mix</td>
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<tr>
<td>C+ Me- isothiazolinone (MO/MI)</td>
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<tr>
<td>Quaternium-15</td>
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<td></td>
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<tr>
<td>Mercaptoperothizole</td>
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<tr>
<td>p-Phenylenediamine</td>
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<tr>
<td>Formaldehde</td>
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<tr>
<td>Mercapo mix</td>
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<tr>
<td>Thimerosol</td>
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<tr>
<td>Thiuram mix</td>
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</tbody>
</table>

* FDA-approved in 1995; ^FDA-approved in 2007; †Personal communication, Curt Hamann, 4/29/10
Bacitracin is an antibiotic produced from the Tracy I strain of *Bacillus subtilis* and was discovered in 1943. Due to nephrotoxicity, its use is restricted to topical use only. It is available in both a “plain” bacitracin formulation as well as a zinc bacitracin formulation. Available vehicles include ointments, powders, and aerosols. Bacitracin is available over the counter and is widely used by the public for minor cuts and scrapes. Some of the more recognized bacitracin-containing antibiotics readily available to consumers are Neosporin (Johnson & Johnson), Polysporin (Johnson & Johnson), Baciguent (Shire US Inc), Cortisporin (Alcon Manufacturing), and Mycitracin (Upjohn). In the past, many dermatologists recommended routine use of bacitracin in post-biopsy wound care. However, during the 1990s, ACD to bacitracin became a well-known clinical entity. Furthermore, there have been multiple reports of anaphylaxis due to topical use of bacitracin. A large study comparing the use of bacitracin versus white petrolatum for routine post-biopsy wound care showed no increased infection rate for white petrolatum while at the same time reporting patients with ACD from bacitracin. In the past decade, many dermatology centers have changed their practice to the use of white petrolatum for routine post-biopsy wound care. When patch testing with bacitracin, it is important to note the following two facts: 1) Although bacitracin and neomycin are chemically unrelated, the two often co-react during patch testing, probably due to patients being exposed to both medications through combination ointments and 2) around 50 percent of positive bacitracin patch test readings are seen only at the 96-hour reading, indicating a delayed reaction in many patients.

**METHYLDIBROMOGLUTARONITRILE**

Methyldibromoglutaronitrile (MDGN) was the ninth most common allergen in the 2005-2006 NACDG standard series. MDGN is a preservative used in personal care products as well as latex paints, adhesives, and metalworking fluids. MDGN is also known as dibromodicyanobutane. It is often used in combination with phenoxyethanol (PE) in a MDGN:PE ratio of 1:4. This combination of PE and MDGN is called Euxyl K400. The great majority of sensitization to Euxyl K400 is due to MDGN, not PE. When patch testing for MDGN, one can either use MDGN alone with a recommended concentration of 0.5% or use the combination MDGN/PE in a concentration of 2.5%. Using concentrations less than these have resulted in false-negative patch test results.

MDGN was first used in Europe in the 1980s and later incorporated into products in the United States. By the early 1990s, the frequency of contact allergy to MDGN in Europe rose rapidly. This prompted the allergen to be banned from leave-on products in Europe in 2005. This ban was extended in 2007 to include rinse-off products as well. A study comparing the frequency of positive patch tests to MDGN in Denmark before and after this ban showed a decrease from 4.6 percent in 2003 to 2.6 percent in 2007. In another study from Denmark, the most common source of relevant MDGN allergy was to creams and lotions (31%) followed by liquid soaps (23%). Hand dermatitis is a frequent presentation of MDGN allergy. Of note, MDGN is used less commonly now as a preservative in the United States and depending on the concentration used in patch testing, MDGN can lead to false positives.

**2-BROMO-2-NITROPROPANE-1,3-DIOL**

2-bromo-2-nitropropane-1,3-diol (BNPD) was the 15th most common allergen in the 2005-2006 NACDG standard series. BNPD is also known as bronopol. BNPD is a preservative most commonly used in cosmetics. It can also cause occupational dermatitis as a preservative in coolants. BNPD is usually used in concentrations less than 0.1%.

![Table 2. 30 Most Common Allergens in the 2005–2006 NACDG Panel](image)
which is the highest permitted concentration in Europe. It has broad antimicrobial activities against gram-positive bacteria, gram-negative bacteria, fungi, and yeast. It is particularly active against *Pseudomonas aeruginosa*. BNPD is degraded to formaldehyde. Because it is an irritant, patch testing should not be done at concentrations greater than 0.5%.10

**CINNAMIC ALDEHYDE**

Cinnamic aldehyde was the sixteenth most common allergen in the 2005-2006 NACDG standard series. Cinnamic aldehyde is commonly used as a flavoring agent and fragrance. It is found in cola beverages, vermouths, chewing gums, mouthwashes, soaps, and toothpastes. Cross reactions with balsam of Peru and benzoin can be seen. Cinnamic aldehyde is one of the most common causes of allergic stomatitis. If a patient has allergic stomatitis and positive patch test to balsam of Peru, cinnamic aldehyde-containing flavorings should be avoided. Cinnamic aldehyde is also a cause of contact urticaria. When a person with contact urticaria to cinnamic aldehyde has patch tests applied, there may be an immediate stinging sensation that resolves within a few hours.10

**PROPYLENE GLYCOL**

Propylene glycol was the 18th most common allergen in the 2005-2006 NACDG standard series. Propylene glycol is widely used as a vehicle for topical medications, cosmetics, and body lotions. In some products, the amount of propylene glycol is 70% or higher. In these high concentrations, propylene glycol also acts as a preservative. It is especially important to think of propylene glycol allergy in cases of contact dermatitis from deodorant. Some topical steroids also contain propylene glycol as a vehicle so patch testing should be considered in cases of dermatitis not responding to or becoming worse with topical steroids. One study found propylene glycol listed as an ingredient in 28 of 46 brand name and 78 of 120 generic name topical steroids used in the United States.17 Other topical products containing propylene glycol are some forms of ear drops, personal lubricants, and electrocardiogram (ECG) gels. Propylene glycol is also used in industry as an ingredient in brake fluid and antifreeze and as a humectant in tobacco products. Systemic contact dermatitis can be due to propylene glycol found in foods, especially salad dressings. The NACDG uses a 30% concentration when patch testing propylene glycol. This relatively high concentration will yield some transient irritant responses. However, using lower concentrations can produce false-negative results.10

**DIMETHYLOL DIMETHYL HYDANTOIN**

DMDMH was the 21st most common allergen in the 2005-2006 NACDG standard series. DMDMH is a preservative that contains 0.5% to 2% free formaldehyde and over 17% combined formaldehyde.18 Although not all patients who are formaldehyde allergic need to avoid all formaldehyde releasers, DMDMH contains a significant amount of formaldehyde and thus should be avoided in all formaldehyde allergic patients. In clinically relevant positive patch tests, it is found most commonly in cosmetics (30%) and topical drugs (22%).19 DMDMH has been patch tested in the past using either a petrolatum or aqueous vehicle or both. The petrolatum vehicle has been found to be more sensitive to diagnose DMDMH allergy and should be used if only one vehicle is chosen.19

**IODOPROPYNYL BUTYLCARBAMATE**

Iodopropynyl butylcarbamate (IPBC) was the 22nd most common allergen in the 2005-2006 NACDG standard series. IPBC is a preservative that was approved for use in the United States in 1996. It was originally used for wood preservation and before it was approved for use in cosmetics, IPBC was known as a cause of ACD from cutting oils. It is now found in a wide variety of household products, including moistened toilet tissue, shampoos, lotions, powders, makeup, baby products, and contact lenses.20 It has particularly good activity against fungi. The trade names of IPBC are Troysan Polyphase (Troy Corp), Biodocarb (Milker & Gruning), and Glycasil (Lonza Ltd). A small study has shown possible cross-reactivity between IPBC and thiuram mix.21

**ETHYLENE UREA MELAMINE FORMALDEHYDE**

Ethylene urea melamine formaldehyde (EMF) was the 25th most common allergen in the 2005-2006 NACDG standard series. EMF resins are used as textile finishes, in tableware, as surface coatings, and in glues in the furniture and wood industries. As a textile finish, they are used to make wrinkle-resistant or permanent-press clothing. Any wrinkle-resistant fabric, shrink-proof wool, rayon, or corduroy may contain this allergen.10 Patients allergic to EMF are often also allergic to formaldehyde.22

**DISPERSE BLUE 106**

Disperse Blue 106 was the 26th most common allergen in the 2005-2006 NACDG standard series. Disperse blue 106 is a textile dye used in clothing. Along with disperse blue 124, it has been recommended to be used as a screening allergen for textile dye dermatitis.23 Patients with a positive result need to avoid synthetic fibers in general, not just “blue clothing.”24 Patients allergic to dyes in shirts often present with dermatitis of the axillary borders, but sparing of the axillary vault. If a patient is allergic to a dye in pants, the anterior thighs will often be affected first, followed by posterior thighs and popliteal fossae.19

**AMIDOAMINE**

Amidoamine was the 27th most common allergen in the 2005-2006 NACDG standard series. Amidoamine is a contaminant found in the manufacture of cocamidopropyl betaine (CAPB). CAPB is used as a surfactant in many personal care products such as shampoos, contact lens solutions, toothpastes, makeup removers, and liquid soaps.25 CAPB was introduced in the 1970s and has mostly replaced the use of other surfactants due to its low irritancy. CAPB and amidoamine allergy often present as scalp/face
Since few patients react to both allergens, patch testing, both allergens should be tested separately to increase the sensitivity of the test. Knowledge of the 10 most common allergens not included in the TRUE Test as identified by the NACDG is a good next step for dermatologists already utilizing the TRUE Test allergens. Once the clinician is familiar with other common allergens, he or she can choose additional allergens, including but not limited to the allergens reviewed above, to increase the sensitivity of patch testing for ACD.

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