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A DERMATOLOGIST'S APPROACH TO PATCH TESTING: INDICATIONS, PITFALLS AND BENEFITS

INTRODUCTION:

Allergic contact dermatitis (ACD) is a T-cell mediated delayed type IV hypersensitivity reaction that occurs after topical or systemic exposure to an allergen. Patch testing is the gold standard in diagnosing ACD. Acquiring a detailed history from the patient including their medical history, occupational history, hobbies, topical and oral exposures, and site(s) of involvement while having knowledge of the common allergens allows the clinician to create a targeted and personalized approach thus increasing the diagnostic yield of patch testing for each patient.

Indications and approach:

Important indications for patch testing include: a) an acute onset of new dermatitis b) an acute flare of chronic dermatitis and c) dermatitis that is unresponsive to standard topical or systemic therapies. There are key common sites of ACD including eyelids, lips, hands, feet and a widespread distribution that drive most referrals. These particular sites are also commonly associated with specific allergens (**Table 1**) which underscores the rationale for taking a regional approach to patch testing. Although these sites are more common, it is important to remember that ACD can affect any site on the body. Most patients suffering from chronic hand dermatitis should be patch tested as the etiology is often multifactorial including endogenous atopic dermatitis, irritant contact dermatitis (e.g. wet work, hand washing) and superimposed ACD all potentially playing a role.

Some clinicians may benefit from providing the patient with a comprehensive questionnaire prior to their assessment. Although questionnaires can be helpful they can also gather information that is not relevant to the patient's complaint. Questioning should be targeted with a regional approach and requires familiarity with key allergen sources that cause ACD at specific sites. Pertinent details to obtain include: the patient's age, sex, co-morbidities (with special attention to history of atopy including eczema, asthma and seasonal allergies), medications (including over the counter preparations, medical devices, and herbal remedies), underlying medical conditions including previously diagnosed ACD, occupation, and hobbies (including use of sports equipment, specialized gear, cosmetics, grooming practices etc.).

The initial flare of ACD is often described as a pruritic erythematous papulo-vesicular spreading eruption which resolves with scaling. The morphology of ACD varies depending on the site of involvement (**Table 2**) and the stage of the dermatitis (i.e. acute vs chronic). The clinician should ask the patient to specify which sites of the body are affected. It is helpful if the patient has photographs of their dermatitis especially if it has resolved by the time they are seen. It is also important to establish the clinical course of their eruption. ACD typically has a delayed onset after exposure (6-48 hrs) to the allergen and may last for days to weeks, whereas an urticarial reaction will usually occur within minutes to hours of exposure and individual lesions resolve within 24 hours. Other dermatoses such as urticaria, irritant contact dermatitis, scabies, rosacea, seborrheic dermatitis, psoriasis, and lichen planus can be mistaken for ACD and generate unnecessary referrals for patch testing. Performing a pre-assessment

of cases referred by non-dermatologists may help screen these patients, avoid unnecessary patch testing and allow for proper management.

When considering potential allergens that are linked to occupational exposures the patient should be asked if they flare at work and whether improvement is seen during weekends and holidays.

A hairstylist and a mechanic for example will have very different work environments and exposures and therefore it is important for the clinician to recognize key potential allergens that are relevant to each occupational group.

Further inquiries should be targeted to understand the patient's

SITE	COMMON ALLERGENS	COMMON SOURCES
Eyelids	MCI/MI, MI fragrance, balsam of peru, nickel, neomycin, , Quaternium-15, cobalt, DMDM hydantoin, amidoamine, CAPB, thiuram mix, bacitracin, cinnamic aldehyde, tocoperol acetate, tosylamide formaldehyde, propylene glycol, ethyl acrylate, MMA, colophony, ylang ylang, lanolin, gold, hyperoxides of linalool and lemonene[4] Ophthalmic medications such as antibiotics (especially aminoglycosides), neomycin, tobramycin, corticosteroids, tixocortol-21-pivalate, Budesonide, hydrocortisone butyrate, HEMA, Benzalkonium chloride[5]	Shampoos, conditioners, makeup, moisturizers, cleansers, eye cream, wet wipes, jewelry, topical medicaments, artificial nails, glues/adhesives, perfumes[4] eyelash curler, glasses, tweezers, makeup applicators, contact lenses (HEMA), medicated eyedrops[5]
Lips	MCI/MI, rosin, propolis, fragrance mix, balsam of peru, nickel, neomycin, cobalt, propylene glycol, lanolin, gallates, peppermint, cinnamic aldehyde, bacitracin, benzophenone-3, tea tree oil, budesonide, formaldehyde, potassium dichromate, tosylamide formaldehyde[6]	Lip balms, lipstick, makeup, cosmetic products, moisturizers, sunscreens, oral hygiene products, dentistry products, artificial nails, topical medications[6]
Hands	Nickel, MCI/MI, formaldehyde, Quaternium-15, fragrance, neomycin, bacitracin, balsam of peru, cobalt, carba mix, thiuram mix, PPD, potassium dichromate, diphenyl guanidine, HEMA, benzalkonium chloride, propylene glycol, lanolin[7]	Gloves, soaps/cleansers, jewelry, electronic devices, coins, tools[7], moisturizer, personal care products, topical medicaments, acrylic nails.
Feet	Potassium dichromate, PTBFR, thiuram mix, dialkylthioureas, carba mix, colophony, mercaptobenzothiazole, PPD, IPBC, black rubber mix[8]	Rubber shoe linings/insoles, shoe adhesive, leather tanning agent, fabric dyes in footwear, socks and hosiery[9]
Other	**Vulva** Fragrances, preservatives (eg. Quaternium-15, paraben mix, MCI/MI, ethylenediamine dihydrochloride), medicaments (eg. neomycin, bacitracin, clotrimazole, tixocortal-21-pivalate, benzocaine), metals (nickel, cobalt), plant extracts, flavours (eg. peppermint), emollients/vehicles (eg. propylene glycol, lanolin, glycerin), acrylates, rubber accelerators[10]	Topical medicaments, cleansers, condoms, douches, personal hygiene products, sanitary napkins, wipes, cosmetic products[10]
	Occupational contact dermatitis (commonly hands/face) Carba mix, thiuram mix, MI, bisphenol A epoxy resin, formaldehyde, nickel, PPD[11] *Occupations:* Service workers, machine operators/assemblers/inspectors, precision production workers, mechanics/repairers, health professionals, hair dressers[11]	Gloves, safety equipment (masks, respirators), adhesives, glues, bonding agents, paint, metalworking fluid, cutting oils, tools, cement, hair dye, soaps, moisturizers[11]
	Pediatric Nickel, cobalt, neomycin, bacitracin, balsam of peru, fragrances, formaldehyde, MCI/MI, lanolin, propylene glycol, CAPB[12]	Jewelry, toys, electronics, topical antibiotics, sports equipment, personal care products, perfume, cleaning products, toys, glue, slime, moisturizer, lip balm, packaged foods[12]
	Diabetic devices IBOA, MMA, DMAA, cyanoacrylates, epoxy resin, colophonium[13]	Insulin pump and glucose monitor devices specifically the adhesives, circuit boards, plastics, and tubing[13]
	Scalp PPD, fragrance, nickel, balsam of peru, cinnamic aldehyde, MCI/MI, IPBC, oleamidopropyl dimethylamine, MDBGN/PE[14]	Shampoos/conditioners, hair dyes, hair styling products, hair appliances, jewelry, glasses[14]
	Photoallergic contact dermatitis Oxybenzone, ketoprofen, avobenzone, fragrance (sandalwood), benzophenone-4, padimate O, oxtyl methoxycinnamate, PABA, triclosan, chlorhexidine, SQL, thiourea[15]	Sunscreen, medications, anti-microbials, plant extracts, fragranced products

**MI: methylisothiazindone, PPD: paraphenylenediamine, NSAID: non-steroidal anti-inflammatory drug, HEMA: 2-hydroxyethyl-methacrylate, PTBPFR: Para tertiary butylphenol formaldehyde resin, CAPB: cocamidopropyl betaine, MCI/MI: methylchloroisothiazolinone/methylisothiazolinone, IPBC: 3-iodo-2-propynyl-butylcarbamate, SQL: sesquiterpene lactone, MMA: methyl methacrylate, IBOA: isobornyl acrylate, DMAA: dimethylacrylamide, PABA: para-aminobenzoic acid*

Table 1. Examples of common allergens based on site of involvement; courtesy of Veillet-Lemay and Pratt

SITE	CLINICAL PRESENTATION
Hands	Papulovesicular eruption of palmar surface of hand and fingers spreading onto dorsal and lateral fingers as well as dorsal hand. There is often extension of dermatitis onto the ventral and dorsal forearms
Eyelids	Papulovesicular and/or edematous eruption +/- scale affecting both the upper and lower eyelids
Lips	Papulovesicular and/or scaly dermatitis affecting both the upper and lower lips extending onto the perioral region
Feet	Papulovesicular eruption and/or scaly dermatitis affecting the dorsal forefoot as well as dorsal great toe in addition to plantar surface
Widespread	Episodic and vesicular and/or scaly dermatiti explosive episodes that last weeks to months. Some variants include: photo distributed, airborne contact dermatitis, systemic contact dermatitis, symmetric erythema of gluteal and inguinal area and other flexural sites[16]

Table 2. Clinical presentation of allergic contact dermatitis based on site; courtesy of Veillet-Lemay and Pratt

potential allergen exposures and some examples of questions might include: Does the patient use or diffuse essential oils at home? Has the patient tried to treat their dermatitis with an over-the-counter antimicrobial cream or herbal remedy? What exposures does the patient have in the workplace? Do their hobbies require special equipment (gloves, goggles, sports equipment, paints, etc.)?

Patients should be encouraged to bring their personal care products to their appointment (or a photograph of the product including the ingredients) or provide a printed list. These include shampoos, conditioners, soaps, moisturizers, dish and laundry detergents, cosmetics, topical medicaments, etc. The clinician should review the ingredients of each product to identify potential allergens. This process will help target the approach to patch testing and help to better counsel and educate the patient once the final test results have been received. With experience, this process can become very efficient. In some cases it may also be appropriate to patch test the patient to their own products. Leave on products (e.g. moisturizers and topical medicaments) are applied to the skin as is, whereas rinse off products (eg. shampoo, conditioner, soaps) are applied with a semi-open technique. The "semi-open" technique is performed by using a cotton swab to apply a thin layer of the product to a small, marked area on the skin then allowing the product to air dry and then covering with Scanpor tape. Occupational allergens (such as epoxy resins, acrylates, isocyanates etc.) must be appropriately diluted prior to application. A comprehensive textbook written by De Groot can be referenced to find the appropriate dilution concentration and vehicle of various chemicals for patch testing[1]. Finally, testing solid products such as sports equipment, gloves, glucose monitors, stoma devices, dressings, textiles or shoes is performed by cutting a small piece of the material into an approximately 1 inch square, placing it on the patient's skin and covering it with Scanpor tape. After four to five days the product can be removed and the patch test results can be interpreted. After patch testing is completed and a patient is diagnosed with ACD a confirmatory "usage test" or ROAT (repeated open application test can be performed. The "usage test" is performed by applying a product that is known to contain the patient's allergen to a small circular area (approximately 1 inch in diameter) on the volar forearm twice daily for 2 weeks in an attempt to reproduce the initial ACD eruption.

In order to proceed with patch testing, the patient must be advised to stop using all products that are potential sources of their ACD. This includes essential oils (scented candles, massage oils, diffusers), hair dyes, cosmetic products, fragrances etc. Patients are provided with a list of products (shampoo, conditioner, moisturizer, laundry detergent, dish soap etc) that are free of major allergens. If the ACD is thought to be related to their occupation, a medical letter can be provided to exempt them from work or to request the patient be placed in an alternate work environment until patch testing is done. If the patient requires topical treatment of their dermatitis as they await patch testing, we prefer to use ointments that are free of propylene glycol such as betamethasone valerate 0.1% ointment for the body (a group III steroid with lower risk of ACD) and tacrolimus 0.1% ointment for the face and skin folds.

Patch testing is a very valuable tool for both the adult and pediatric population. Patch testing in the pediatric population can be done at any age however is more practical for patients who are five years and older from a compliance perspective. A study examining the patch test results of 1,871 children and 41,699 adults revealed that the prevalence of ACD among children referred for patch testing is similar to adults (55.2% and 57.3% respectively). The most common allergens seen in children included nickel, hyperoxides of linalool, methylisothiazolinone, cobalt, and fragrance mix I. Approximately

20% of children were allergic to products that were not part of the North American Contact Dermatitis Group (NACDG) standard series, emphasizing the need for supplementary testing in some cases[2]. The risk of primary sensitization of children secondary to patch testing to the NACDG standard series is low and should not deter the clinician from proceeding with testing.

There are over 4,000 recognized allergens but a small subset of these are repeatedly seen in the clinic and have emerged as the most common allergens. The NACDG collect data from patch testing and compile the incidence of allergies to various compounds annually. We have summarized the twenty most common allergens from 2017-18 in **Table 3**[3]**.**

Pitfalls:

Although patch testing is a safe and non-invasive procedure, there are factors related to the test and to the patient that must be considered prior to proceeding.

Patient factors:

In order for patch testing to be successful the patient must be motivated and willing to follow instructions which can be difficult especially in the pediatric population. After the patches are applied, the patient is instructed to avoid vigorous activity and should only sponge bathe until after the final reading. Patches are removed after 48 hours, and a first reading is complete. The final reading is done at 96-168 hours (day 4 or 7) after patch test application. Failure to follow these instructions can lead to poor patch adherence and/or false negative results.

ALLERGEN (CONCENTRATION %)	POSITIVE PATCH TEST RESULT (%)
Nickel sulfate (2.5)	16.2
Methylisothiazolinone (0.2)	15.3
Methylchloroisothiazolinone/methylisothiazolinone (0.02)	11.0
Fragrance mix (8.0)	9.2
Hydroperoxide of linalool (1.0)	8.9
Formaldehyde (2.0)	7.4
Formaldehyde (1.0)	5.4
Benzisothiazolinone (0.10)	7.3
Balsam of Peru (25.0)	7.1
Cobalt chloride hexahydrate (1.0)	6.7
Phenylenediamine (1.0)	5.6
Bacitracin (20.0)	5.5
Neomycin sulfate (20.0)	5.4
Propolis (10.0)	4.7
Fragrance mix II (14.0)	4.4
Lanolin alcohol (50.0)	4.4
Propylene glycol (100)	3.8
Oleamidopropyl dimethylamine (0.1)	3.7
Carba mix (3.0)	3.4
Quaternium-15 (2.0)	3.4
Thiuram mix (1.0)	3.4

Table 3. Twenty most common positive patch test rates adapted from North American Contact Dermatitis Group Patch test results from 2017-2018 by DeKoven et al[3]; courtesy of Veillet-Lemay and Pratt

In most adult patients, the patches containing the allergens are applied to their back, however, there are some circumstances when this is not possible (for example if the patient has a large tattoo over their back) and an alternate location such as the upper outer arms are used. If the patient has active dermatitis on their back, due to atopic dermatitis, ACD, or a combination of both, they must be treated prior to patch testing as interpretation of results on already inflamed skin is both difficult and inaccurate.

Many patients that are referred for patch testing have already been prescribed topical or systemic immunomodulating therapies to control their dermatitis which could potentially cause false negative results. Ideally, patients would be patch tested while not utilizing any immunomodulating drugs however this is not always possible. The NACDG released their expert opinion regarding effects of various agents (both topical and systemic) on patch testing which is summarized in **Table 4**[17]. A more recent review article also found that patch testing generally benefits patients receiving dupilumab, low dose prednisone (<10 mg/day) and cyclosporine for the treatment of dermatitis and TNF-$\propto$ inhibitors, ustekinumab and methotrexate for the treatment of psoriasis[18]. Patient's on these medications can still develop positive patch test results therefore it can still be beneficial to investigate if discontinuation of systemic therapies is warranted prior to patch testing. Newer systemic agents for the treatment of atopic dermatitis such as tralokinumab (IL-13 inhibitor), abrocitinib (JAK inhibitor) and upadacitinib (JAK inhibitor) are on the market in North America however we do not yet have data on their impact on patch testing; hopefully over time this data will become available.

Finally, while patch testing during pregnancy and lactation is not known to cause harm it is generally avoided as a precaution[19].

Patch testing specific factors:

An important drawback of patch testing is that it is not readily available in some centers and access can be associated with long wait times. When patch testing is available, there are some circumstances where testing must be delayed. As discussed above, if the patient has active dermatitis on the back, the patient should be treated prior to patch testing to ensure accuracy of results. If the patient does not bring their belongings/products to the initial consult and it is felt to be relevant to their disease manifestation, testing may be delayed (ex: shoes, textiles, dressings, equipment, etc.). There are some circumstances, especially occupational cases, when the suspected allergen is not part of a standard series and must be prepared in advance which may also delay testing.

After many years of experience performing patch testing, the clinician will become familiar with which allergens cause irritant reactions or false positive results. Real-world experience has shown that this can be seen with gallates, formaldehyde, linalool, chromium, methyldibromo glutaronitrile, benzalkonium chloride as well as gold, to name a few. The clinician will also come across equivocal reactions. Interpreting these results in the context of the clinical history requires experience and expertise. **Table 5** summaries how patch test results are interpreted as per the NACDG morphology codes and **Figures 1-4** provides examples.

Lastly, patch testing is a multiple day commitment for the patient

Agent	Consensus opinion
Topical corticosteroids on test site	Avoid between 3-7 days
Ultraviolet exposure at test site	Avoid for one week
Oral prednisone	Can test at 10 mg or less however best to discontinue completely prior to patch testing, by 2 weeks
Intramuscular triamcinolone (40 mg)	Delay patch testing until 4 weeks after injection
Methotrexate	Has little to no effect on patch test results
TNF-a inhibitors	Has little to no effect on patch test results
Ustekinumab	Has little to no effect on patch test results
Azathioprine	Dose dependent inhibition of results
Cyclosporine	Dose dependent inhibition of results
Mycophenolate mofetil	Dose dependent inhibition of results

Table 4. Summary of NACDG expert opinion on effects of various agents on patch test results adapted from Fowler et al.17; courtesy of Veillet-Lemay and Pratt

PATCH TEST RESULT	MORPHOLOGY
1 (+)	Weak (non-vesicular) reaction. Erythema, infiltration, possibly papules
2 (++)	Strong (edematous or vesicular) reaction
3 (+++)	Extreme (spreading, bullous, ulcerative) reaction
4	Macular erythema only
5	Irritant morphology
6 (-)	Negative reaction

Table 5. Interpretation of patch test results

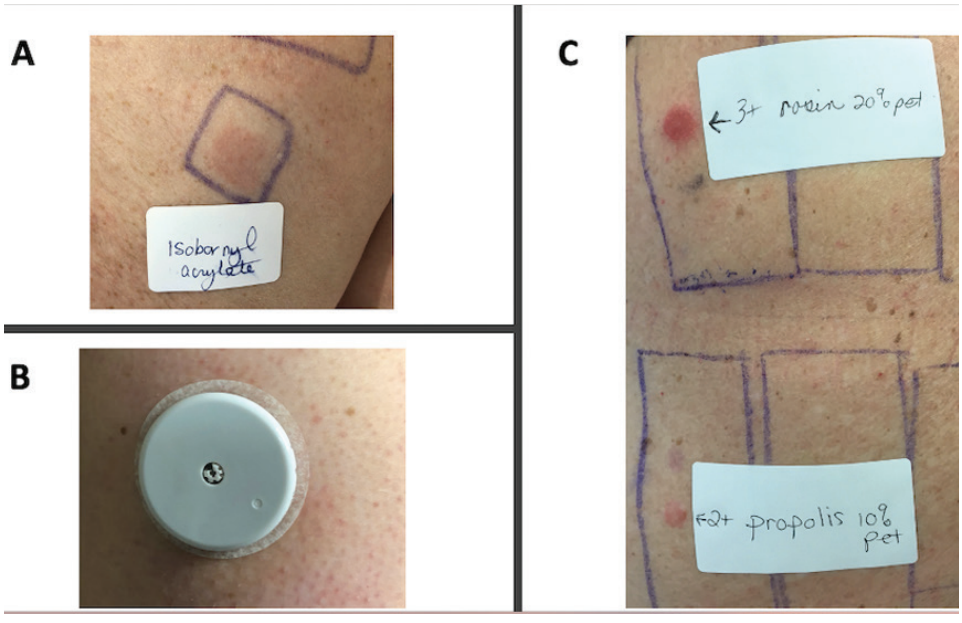

Figure 1. A) and B) An example of a 2+ reaction to isobornyl acrylate found in the adhesive of a glucose monitor. C) Example of a 3+ reaction to rosin in 20% petrolatum and 2+ reaction to propolis 10% in petrolatum.

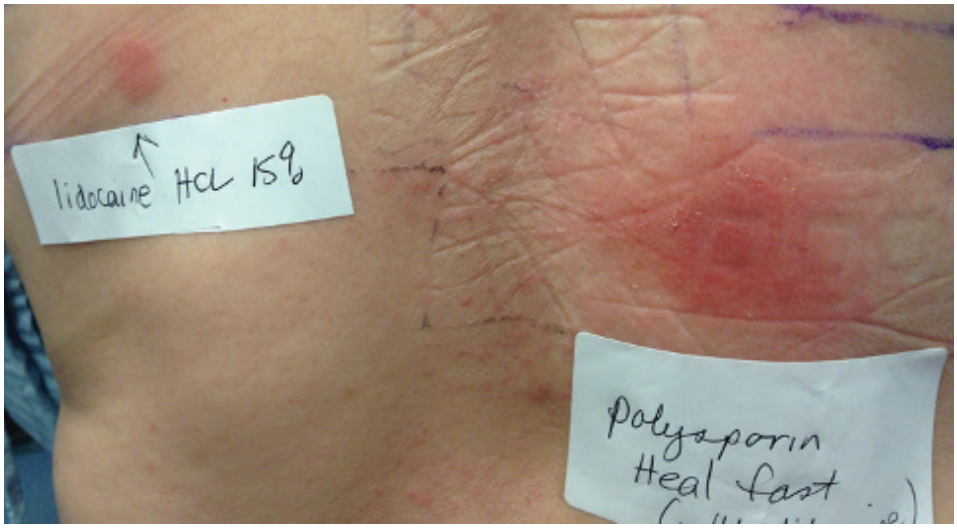

Figure 2. An example of a 2+ reaction to lidocaine hcl 15% and a 3+ reaction to Polysporin ∝ containing lidocaine

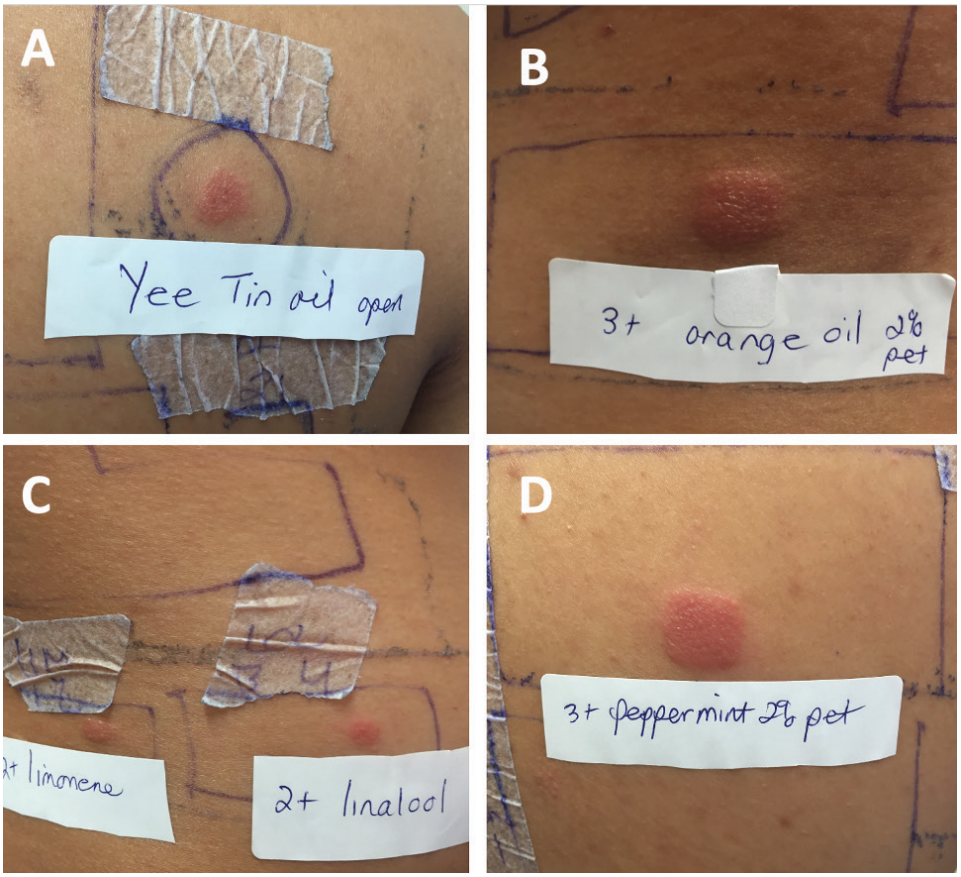

Figure 3. a) An example of an "open patch test" 3+ reaction to Yee Tin oil which is known to contain orange oil, peppermint oil, and limonene and linalool. b) Same patient with a 3+ reaction to orange peel oil 2% in petrolatum. c) Same patient with a 2+ reaction to both hydroperoxide of limonene and hydroperoxide of linalool. d) Same patient with a 3+ reaction to peppermint oil 2% in petrolatum.

which often requires time away from work and recreational activities. Furthermore, patch testing has been associated with reports of itch, sleep difficulty, pain and worsening of rash[20] which is often observed as a recall dermatitis. The patient must understand the level of involvement and be motivated to proceed in order for patch testing to be successful.

Benefits:

Many patients who suffer from allergic contact dermatitis experience a significant improvement in their quality of life after patch testing[21]. There is also value in patch testing patients, both adult and pediatric, with atopic dermatitis. A study looking at 36,834 patch test results from 2001-2016 revealed that most adults (56%) and children (52.8%) with a history of atopic dermatitis that were referred for patch testing had a final diagnosis of ACD. Patch testing and allergen avoidance in these cases can help clarify the etiology of the patient's dermatitis and allow for proper management[22].

In order to reap the benefits of patch testing, the patient must be educated regarding the disease and the sources of their allergens so that they can be avoided in the future. A common misconception among patients and some physicians is that if a product has been used for many months or years, it is unlikely for it to be the cause of the patient's ACD. It is therefore imperative that the patient understand that contact allergies are acquired and can occur even after using a product for years. Once sensitization occurs, future exposures to the allergen will trigger ACD at the site of exposure which, if severe, can become widespread. Patients can be provided with comprehensive handouts detailing their positive allergens and clinicians should consider revisiting the patient's own products to identify any that contain their allergens so that they can be replaced with safer alternatives.

At the initial assessment, patients may be provided with a short list

of products that are low in irritants and allergens and that are safe to use while waiting for the patch testing procedure. For patients who have many allergens or use a wide variety of products, the CAMP database (Contact Allergy Management Program), which is a free resource for members of the American Contact Dermatitis Society (ACDS), may be used. The CAMP database allows users to enter all relevant allergens and generate a list of products free of these same ingredients. Patients are also encouraged to read product ingredient labels or to research ingredients online prior to finalizing a purchase.

Conclusion:

Patch testing is a safe and beneficial procedure when applied to the appropriate patient population. When ACD is suspected, even the most skilled and knowledgeable dermatologist cannot guess what specific allergen is causing the dermatitis as there are hundreds of possibilities. For this reason, patch testing with an informed and systematic regional approach is imperative to the diagnosis and management of ACD. The more familiar a dermatologist becomes with common allergen exposures as well as occupational allergens, the higher the likelihood of successful outcomes in the management of ACD.

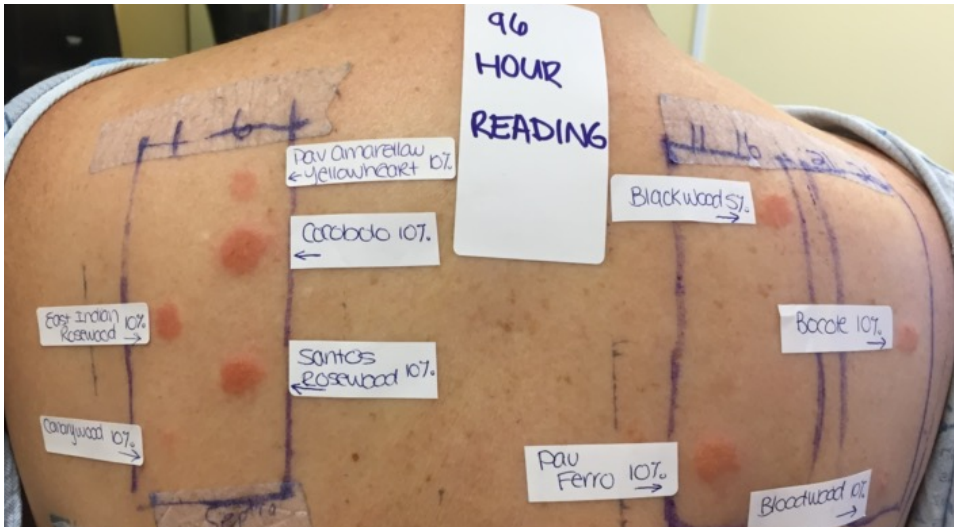

Figure 4. This patient is a wood shop worker and was found to be allergic to numerous exotic woods which were all diluted to 10% in petrolatum except Blackwood which was diluted to 5% in petrolatum. They had a 3+ reaction to Cocobolo, Santos Rosewood, East Indian Rosewood, Blackwood, Pau ferro and Bocole. They had a 2+ reaction to Pau Amarello and Bloodwood and a 1+ reaction to Canary Wood. The common allergen found in all of these woods is quinone.

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