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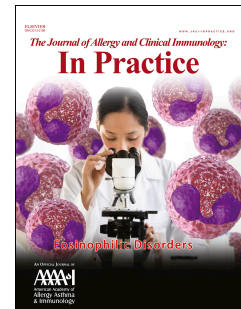
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1 A Hands-on Approach to Contact Dermatitis and Patch Testing

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Abstract:

Contact dermatitis (CD) is a common skin condition caused by contact with an exogenous agent that elicits an inflammatory response. While history and physical exam can be helpful in distinguishing between irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD), the gold standard for diagnosing ACD is patch testing. While the actual patch test (PT) procedure and application is relatively straightforward, the decisions involving which allergens to use, interpretation of results, determination of relevant allergens and subsequent patient management requires more skill and expertise. Often, the distribution of the presenting dermatitis can provide insight into the potential causative allergens and should be taken into account when selecting PT allergens. Commercially available PT panels and personal care products can be used for patch testing. Determining the clinical relevance of PT results is a critical component of the PT procedure. Patients must be educated on avoidance of relevant allergens and given guidance on alternative products available for use. Special populations, including children with ACD, occupational contact dermatitis (OCD), and patients with biomedical devices have unique allergen considerations and PT panels should be directed as such to address all potential allergens.

Key Words: contact dermatitis; allergic contact dermatitis; irritant contact dermatitis; patch testing; contact allergens; atopic dermatitis; occupational contact dermatitis; patch test procedure

46

47 Abbreviations:

48 CD: Contact dermatitis

49 ICD: Irritant contact dermatitis

50 ACD: allergic contact dermatitis

51 IL: Interleukin

52 TNF: Tumor necrosis factor

53 GM-CSF: Granulocyte-macrophage colony-stimulating factor

54 PT: Patch test

55 AD: Atopic dermatitis

56 TCS: Topical corticosteroids

57 TCI: topical calcineurin inhibitors

58 MI: methylisothiazolinone

59 FM: Fragrance mix

60 MCI: Methylchloroisothiazolinone

61 BOP: Balsam of Peru

62 PPD: p-phenylenediamine

63 NACDG: North American Contact Dermatitis Group

64 SCD: Systemic contact dermatitis

65 CAMP: Contact allergen management program

66 CARD: Contact allergen replacement database

67 ROAT: Repeat open application test

68 FDA: Food and Drug Administration
69 GCDG: German Contact Dermatitis Group
70 OCD: Occupational contact dermatitis
71 ISR: In-stent restenosis
72 PCI: Percutaneous coronary intervention

73

74 INTRODUCTION

75 Contact dermatitis (CD) is a common skin condition caused by contact with
76 an exogenous agent that elicits an inflammatory response. CD affects approximately
77 4.17% of the US population and the estimated cost associated with this condition
78 was over \$1.5 billion in 2013.¹ Acute CD presents as a pruritic, erythematous rash
79 with papules, vesicles, and crusted lesions while chronic CD is typically associated
80 with secondary skin changes including lichenification, fissuring, and scaling. The
81 two main types of CD are irritant contact dermatitis (ICD) and allergic contact
82 dermatitis (ACD). Irritant contact dermatitis (ICD) accounts for approximately 80%
83 of CD cases while allergic contact dermatitis (ACD) is less common. Chronic ACD
84 may be clinically indistinguishable from ICD.

85 ICD is a localized, non-immunologic inflammatory response to a substance
86 that results in direct cell damage, usually from chronic exposure to an irritant in the
87 setting of skin barrier disruption.² In comparison, ACD is a type IV-mediated
88 hypersensitivity reaction that occurs in susceptible individuals and requires prior
89 sensitization to a specific allergen. Upon re-exposure to an allergen, activated Th1
90 cells produce inflammatory cytokines, including interleukin (IL)-1 α , IL-1 β , IL-6, IL-8,

IL-13, tumor necrosis factor (TNF) α , and granulocyte-macrophage colony-stimulating factor (GM-CSF), which leads to mast cell and macrophage activation with subsequent inflammation, cellular destruction and repair.^{3,4} Historically, ACD was considered a Th1-dominated or a mixed Th1/Th2 response, but recent work on allergic sensitization to common allergens (*e.g.* nickel, fragrance) has shown that different allergens may have distinct molecular fingerprinting. For example, Dhingra, N. et al, showed that nickel demonstrates broad immune activation, involving innate immunity, Th2, activation, and Th17/Th1 polarization. Conversely, fragrance, and to a lesser extent, rubber, demonstrates a Th2 bias with some Th22 skewing and less Th1/Th17 contribution.⁵ These new data suggest that the unique allergen polarity in ACD may influence therapeutic decisions.

ICD affects only areas of skin that are in direct contact with the irritant whereas ACD can affect the areas where allergen comes in contact with the skin, and become more diffuse with the inflammation extending beyond areas of allergen contact. Allergen can be transferred ectopically to areas distant from the original skin sites. One example is transfer of allergen from nail polish or artificial nail (tosylamide and/or formaldehyde resin, methyl methacrylate, other nail hardeners and setting lacquers) to areas of the face, especially the eyelids and neck. Ectopically triggered ACD has also been reported with the transfer of allergen from partners and caregivers.

It can be difficult to differentiate allergic from irritant CD using skin biopsy findings alone as both forms of CD demonstrate spongiosis with varying degrees of

acanthosis and superficial perivascular, lymphohistiocytic infiltrates.⁶ Some distinguishing histological features of ACD, in addition to marked spongiosis, include intraepidermal vesicles as well as a mixed dermal inflammatory infiltrate with varying numbers of eosinophils.⁶ Conversely, ICD typically shows necrotic keratinocytes in the epidermis with less spongiosis than what is seen with ACD.²

Patch testing remains the gold standard for diagnosing ACD and identifying the contact allergen responsible for the dermatitis.⁷ While a thorough history and physical examination are key components to diagnosing and managing ACD, it has been reported that even experienced physicians accurately predict the sensitizer in only 10-20% of cases when relying solely on history and physical exam.⁸ Additionally, a self-reported history of nickel allergy has only a 60% positive predictive value in determining actual nickel hypersensitivity confirmed with positive patch testing.⁹ While the actual patch test (PT) procedure and application is relatively straightforward, the decisions involving which allergens to use, interpretation of results, determination of relevant allergens and subsequent patient management requires more skill and expertise. When managing patients with chronic dermatitis, or when there is concern for ACD, patch testing is a vital diagnostic tool available to allergists and dermatologists in clinical practice.

INDICATIONS FOR PATCH TESTING

Patch testing should be considered in patients with a localized or diffuse

chronic, pruritic, eczematous, vesicular, or lichenified dermatitis. CD can present in an acute, sub-acute, or chronic manner so having a strong clinical suspicion is an important first step in correctly identifying patients that may benefit from PT. Historically, it was believed that atopic dermatitis (AD) patients were at lower risk for developing ACD as compared to the general population; however, multiple subsequent studies suggest that patients with AD are at increased risk of developing contact sensitization compared to non-atopic individuals.¹⁰⁻¹⁴ Despite the controversy surrounding the frequency of ACD in AD, it is now generally accepted that ACD can worsen the clinical course of children with AD. This is likely due to the impaired skin barrier increasing exposure and enhanced absorption of topically applied substances.¹⁵ Increased exposure to allergens in personal products, ointments and creams used for treating chronic AD contain sensitizers can predispose AD patients to developing ACD. Therefore, patch testing is indicated to rule out concomitant ACD in any patient with AD that does not improve with the usual treatment, initially improves and then exacerbates, worsens with topical therapy, or has a change in their typical dermatitis pattern.

CONTRAINDICATIONS TO PATCH TESTING

Patients with active generalized dermatitis or dermatitis located in areas where the PT will be applied should not undergo patch testing until their underlying dermatitis is controlled. Immunosuppressant agents can interfere with PT interpretation due to attenuated skin responsiveness. If patch testing is medically indicated in patients who are taking systemic corticosteroids, cyclosporine, or other

immunosuppressive medications, dose adjustments of the medications may be warranted to improve patch test validity. In cases where oral corticosteroids cannot be discontinued, studies have shown that doses of prednisone less than 20mg/day and low doses of cyclosporine (2-3mg/kg/day) may still yield clinically relevant patch test results.¹⁶⁻¹⁸ If patch testing yields a negative result in a patient on systemic immunosuppressive agents and the clinical suspicion of ACD is high, repeat testing when immunosuppressant doses can be lowered should be considered.⁶

Another consideration when determining when to do the PT is the use of topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI). Studies have shown that medium to high potency TCS (betamethasone dipropionate 0.05%) applied topically to PT sites for 3 successive days suppress the 48-hour response to contact allergens.¹⁹ Additionally, topical 0.1% tacrolimus applied to PT sites for 2 days suppressed 48-hour responses to 5% nickel sulfate.²⁰ As a result, it is recommended that the PT site should have no potent TCS or TCI applied for 5 to 7 days before testing.^{21,22}

Dupilumab, a human monoclonal antibody that inhibits the IL-4 receptor alpha subunit (IL-4R α) and targets Th2 inflammation by inhibiting the signaling of IL-4 and IL-13, is approved for treatment of moderate-to-severe AD. While there are several recent case reports and series demonstrating that patients on dupilumab can mount clinically significant positive PT,²³⁻²⁵ other studies show a variable modifying effect of dupilumab on PT results, with the some patients showing loss of prior contact sensitization while on dupilumab.^{26,27} These inconsistencies suggest

that different contact allergens may elicit responses via diverse immune pathways. If there is a strong clinical suspicion for ACD despite negative patch testing, repeat testing should be considered if dupilumab therapy is discontinued.

In general, patients should avoid excessive sun exposure and sunbed use 2-4 weeks before patch testing as studies have shown that ultraviolet radiation can reduce the allergic response, evidenced by a study showing pretreatment of skin test sites with UV irradiation produced dose-related suppression of erythema at 48 hours after application of nickel sulfate in nickel-sensitized subjects.²⁸ This suppression can be prevented by UVA and UVB blocking sunscreen products.²⁹ Because there is insufficient data on patch testing in pregnant or breastfeeding women, it is generally not recommended. Current evidence indicates that systemic antihistamines do not inhibit patch test responses and do not need to be withheld prior to patch testing.³⁰

COMMON CONTACT ALLERGENS

While any chemical ingredient that encounters the skin can cause sensitization and elicit an allergic response, certain products such as jewelry, personal care products, cosmetics, dyes, preservatives, detergents and adhesives are most commonly implicated in ACD. According to the most recent North American study, the most frequent specific allergens identified on patch testing in patients with suspected ACD are nickel (17.5%), methylisothiazolinone (MI) (13.4%), fragrance mix (FM) I (11.3%), formaldehyde 2% (8.4%), methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) (7.3%), balsam of

Peru (BOP, *Myroxylon pereirae*) (7.0%), neomycin (7.0%), bacitracin (6.9%), formaldehyde 1% (6.4%), and p-phenylenediamine (PPD) (6.4%).³¹ Natural botanical extracts, such as tea tree oil, propolis, and essential oils, are gaining popularity and are increasingly used in personal-care products. These plant-based products have sensitizing properties and are potential causes of ACD. Case reports of contact dermatitis and positive patch-test reactions to cucumber, eucalyptus, rosemary, sage, witch hazel, and chamomile have been reported.^{32,33}

DISTRIBUTION

Often, the distribution of the presenting dermatitis can provide insight into the potential causative allergens, as demonstrated in Table I. According to the North American Contact Dermatitis Group (NACDG), the most common primary geographic sites for CD are the hands, scattered/generalized distribution pattern, and face.³⁴

Hand dermatitis is usually caused by repetitive exposure to irritants (ICD). Certain workers such as hairdressers, beauticians, and health care workers are at increased risk for ACD due to frequent exposure to known sensitizers.³⁵ Hairdressers are exposed to PPD allergen in hair dye and beauticians handle cosmetics containing quarternium-15 (a preservative), formaldehyde, BOP, nickel, and fragrances.³⁶ Health care workers can develop sensitization to topical antibiotics such as neomycin and bacitracin and rubber chemicals contained in rubber gloves (thiuram, carbamates, and mercaptobenzothiazole).⁶

ACD involving the face, including periorbital and perioral involvement, is commonly seen in women who wear cosmetics and other personal care products (lotions, creams) that contain botanical ingredients, FM, BOP, nickel, preservatives, and excipients.⁶ Although less common than direct exposure to the face, ectopic transfer of allergens contained in nail polish (tosylamide and formaldehyde resin), artificial nails (methyl methacrylate) and jewelry (nickel) to the face and eyelids can cause facial and/or eyelid dermatitis.³⁷ Consort and ectopic dermatitis should be considered if the history suggests the absence of direct and/or personal exposure to the allergen. Allergic contact cheilitis often involves the lip vermillion border and extends to contiguous skin with concomitant perioral dermatitis but typically spares the oral mucosa.⁶ Oral hygiene products such as toothpaste and mouthwash flavorings contain flavoring chemicals such as spearmint and menthol that are sensitizing agents. Cosmetics and lip products that contain FM, BOP, lanolin, coconut oil, and vitamin E are all potential sensitizers.³⁸ Patients that present with scalp and neck dermatitis should be evaluated for allergy to products contained in hair care products and cosmetics, such as FM, BOP, quaternium-15, cocoamidopropyl betaine (surfactant), acrylates (hairspray), botanicals, as well as PPD (hair dye) and glyceryl thioglycolate (permanent wave solutions).⁶

In AD patients with an unusual distribution of dermatitis, such as a head and neck predominance, a hand or foot involvement, eyelid predominance, and chelitis/perioral predominance, PT should be highly considered.^{39,40}

In patients presenting with a more scattered or generalized pattern, it may be more difficult to determine the source of allergen exposure based on

presentation alone, which further highlights the importance of using patch testing to confirm the diagnosis of ACD. A dermatitis that involves clothing-covered areas are more commonly related to formaldehyde or textile dyes (disperse blue dye) in clothing.⁶ Rarely, systemic contact dermatitis (SCD) can present as a generalized dermatitis if a patient gets a systemic exposure (ingestion, transcutaneous exposure, or infusion) to a known contact sensitizer. The most common allergens that can cause SCD are metals, such as nickel, mercury, and gold, medications including topical antibacterials, corticosteroids, and plants or herbal products containing the Compositae and Anacardiaceae plant families and BOP (see Table II).^{41,42} Patients that are sensitized to BOP can experience SCD with ingestion of foods and flavoring agents that are contained in BOP, including citrus products, ice cream, cinnamon, chutney, cola, vanilla, curry, ketchup and tomatoes.⁶ There are case reports of patients sensitized to formaldehyde that experience SCD with ingestion of the artificial sweetener aspartame, as formaldehyde is a by-product of aspartame metabolism.^{43,44}

DIFFERENT TYPES OF PT PANELS AVAILABLE

There are several commercial providers of PT panels available to clinicians, including standard and expanded or specific series. The NACDG uses 50-80 allergens to evaluate patients with suspected ACD in North America and Canada.⁴⁵ The American Contact Dermatitis society has a suggested core series of 80 allergens. There are also PT series that are targeted at specific populations, including cosmetic,

hairdressing, and metal series that contain allergens that are not included in the general panels.

The T.R.U.E Test™, approved for ages 6 and above, comes in ready-to-use thin-layer PT panels that are pre-loaded and contains 35 allergens and 1 negative control. The T.R.U.E. Test™ is currently the only FDA approved PT antigens in the United States and is easy to apply. Because the panels are pre-loaded with a limited number of allergens, testing cannot be easily modified or individualized based on clinical history or patient necessity. While these T.R.U.E test™ or other standardized series may be convenient for clinical use, relying solely on these may result in failure to identify causative allergens. Recent studies published by the NACDG show that 21-26% of patients demonstrated a clinically relevant positive PT to an allergen not included in a standard 70-antigen panel.^{31,34,46,47} To address this limitation, clinicians should also consider selecting test allergens from supplemental allergen panels, such as a cosmetic series, metal series, sunscreen series, or dental screening series, customized on specific patient exposures and clinical history. An overview of commercially available PT panels as well as supplement allergen series is listed in Table III.

PT METHODOLOGY AND TECHNIQUE

Patch tests are prepared by placing allergens into chambers. Chambers are generally flat cavities, either circular or square shaped, and are mounted onto rectangular strips of tape.⁴⁸ Generally, each PT strip contains 10 individual

chambers. Various chambers are commercially available and differ in size, depth and material. No particular chamber is known to be superior to others.⁴⁸

Allergens are available in petrolatum at standard concentrations or in aqueous vehicles (usually water or alcohol).⁴⁸ Allergens that cannot be dispersed in petrolatum due to chemical stability, such as formaldehyde, propylene glycol, methylisothiazolinone, and cocamidopropylbetaine, are supplied in the aqueous form. The majority of PT allergens should be stored in the refrigerator to maintain stability of the allergen. However, hydrocortisone-17-butyrate in an alcohol vehicle has been shown to degrade even if refrigerated, and is recommended to be stored in a freezer.⁴⁹ There are different loading chambers currently available in varying sizes, shapes, and materials. Square chambers, such as AllergEAZE, Van der Bend, and IQ Ultra, and round Finn Chambers have comparable efficacy. Some Finn Chambers however need a paper disc to absorb liquid allergens while others have filter papers built into the chambers.¹⁵ The allergens are dispensed into the chambers, with an ideal volume of approximately 20uL (Figure 1).⁵⁰ In addition to standardized test kits, personal products can be tested by placing them into individual chambers, although responses should be interpreted cautiously due to unknown irritant effects of certain products. Personal “leave on” products, such as moisturizers, deodorant, and cosmetic products, can be applied directly into the chambers. It is important that personal products that are normally washed off, such as shampoo, conditioner, and body/face washes should be diluted (1:10 to 1:1000) before use.⁵¹

Patch test chambers should ideally be loaded at the time they are applied to prevent false-negative results. Any substances in an aqueous vehicle should be loaded into chambers and placed on the patient immediately before drying can occur. Most substances in a petrolatum base may be prepared 24-48 hours prior to the application of the patch test.⁵¹ Exceptions include acrylates and fragrances, which should not be preloaded. All allergens in an aqueous vehicle should be prepared at the time of visit and applied to the skin immediately.

Patch tests should be applied to the upper back, in an area free of hair, lesions or emollients. Patch tests should not be applied over the vertebrae, as movement may displace the patches and because irritant reactions can occur from doing so.⁴⁸ To affix the PT onto the patient's back, the patient should be facing away from the physician with a slightly hunched over position. The PT strip should be applied to the patient's upper or mid-back from the bottom-up (Figure 2).⁵⁰ Chambers should be pressed from below to expel any air from the chambers and ensure a tight seal. Once the entire strip is on the back, the physician should press lightly over each individual chamber to evenly distribute the allergen against the skin.⁴⁸ Proper technique is essential in ensuring an appropriate seal. This process is repeated for each PT strip until all of the chambers have been applied to the patient's back. To reinforce all strips to the skin, adhesive tape (Scanpor tape) can be applied over the chambers. Once all of the PT have been applied, each strip should be outlined on the skin with an indelible marker. Patients should be warned that overlying clothing may be stained. The patient should be instructed not to wet

or rub their back, swim, exercise or excessively sweat once the patch tests have been applied.

PT READING AND INTERPRETATION

Approximately 48 hours after placement, the patient returns to the clinic for the initial reading.⁵² At this visit, all of the PT panels should be removed, and all markings/numberings should be re-done. Tests should be read approximately 30 minutes after removing all of the panels, to allow for any irritation/erythema from the adhesive materials to subside. A second reading should be done at 72 to 96 hours after placement. This reading is considered most clinically relevant. Approximately one third of allergens negative at the 48-hour reading become positive in 72-96 hours.⁶ The same physician ideally performs each reading. A standardized grading system should be used at each reading. The International Contact Dermatitis Research Group's scoring system is widely used and recognized (Figure 3).⁶

A number of allergens are associated with late reactions and a delayed reading at 7 to 10 days after PT application should be considered for these allergens. Table IV shows common allergens that are associated with late reactions and include metals (nickel, gold, palladium, potassium dichromate, cobalt), topical antibiotics (neomycin, bacitracin), topical corticosteroids and dyes (PPD).² Thus, it is common practice to perform a delayed read at 7-10 days with metal panels and topical corticosteroids. In contrast, reactions to certain fragrances and preservatives are prominent on day 5 but may disappear by day 7 (see Table V).⁶

Irritant reactions can be distinguished from allergic reactions based on the timing of the reaction. Irritant reactions tend to appear within the first 48 hours and then disappear by 96 hours (decrescendo). In contrast, allergic reactions tend to increase in nature as time lapses (crescendo).² Some allergens are associated with early peak reactions at 48 hours and should not be confused with irritant reactions (see Table VI).

DETERMINING CLINICAL RELEVANCE

Once there is a positive PT result, the allergist is to determine the clinical relevance. The clinical relevance depends on the correlation between the patient's history in conjunction with the PT results. A positive PT can be clinically relevant, depending on the patient's current or past exposures to the allergen.

Clinical relevance can be broken down into 4 types of responses: (1) *Definite*, (2) *Probable*, (3) *Possible* and (4) *Past*.⁶ A *definite PT response* is defined by a positive confirmatory use test or challenge with the suspected material or product or a positive PT with the product. A *probable response* is when the PT is positive and the allergen is present in known skin contactants, and the patient's clinical presentation is consistent with that exposure. A *possible* response is when the PT is positive, and patient is in contact with materials that *likely* contain the suspected allergen.^{2,6} Past relevance is when the PT result is positive, but the patient no longer has a current exposure to the allergen, but did in the past.^{2,6}

When a positive PT reaction is deemed to be relevant (definite, probable or possible) by the physician, this information should be reviewed with the patient. A

list of products containing the allergen should be provided to the patient so that he or she may avoid the product. A “safe” list of alternative products that do not contain the allergen should also be provided to the patient.⁴⁸ There are currently 2 online databases available in the United States that list products free of the suspected allergen. They are the Contact Allergen Management Program (CAMP), which is available for members of the American Contact Dermatitis Society (www.contactderm.org), and the Mayo Clinic’s Contact Allergen Replacement Database (CARD), (www.AllergyFreeSkin.com).¹⁵ Providing lists of products that patient’s may use can increase compliance and make avoidance of allergens more feasible. Table VII illustrates key pearls and pitfalls with regards to patch testing.

FACTORS THAT AFFECT PT RESULTS

It is important for the physician to be cognizant that both false-positive and false-negative reactions can occur. A false-positive reaction can occur with application of substances at irritant concentrations, pressure from the filling chamber, “angry back syndrome”, or with patch testing on skin with active dermatitis/eczematous lesions.⁵³ “Angry back syndrome” occurs when erythema or papulation created by a large true-positive reaction extends beyond its application site to other adjacent antigen application sites causing adjacent skin inflammation/irritation. This should be suspected when there are more than 5 positive reactions in close proximity to each other.^{6,54}

False negative reactions are estimated to occur in approximately 30% of PT patients.^{6,55} False negative reactions can occur if inadequate allergen concentrations

are used in the testing chambers, thus standard concentrations should always be used if possible. False negative reactions may also occur if patients are on immunosuppressive therapies, or were recently exposed to ultraviolet light.⁵⁵ The application of topical corticosteroids to the test site or oral prednisone of 20mg/day or more may diminish results.^{6,56} In addition, testing errors can cause false-negative results such as insufficient occlusion of the chambers on the back, or too brief of an occlusion period (<48 hours). False negative reactions may also occur if incorrect allergen vehicles are used (aqueous versus solutions), or if a delayed 7 day reading is not performed (such as in the case of metals or topical corticosteroids).

REPEAT OPEN APPLICATION TEST AND USE TEST

Open techniques were developed to test products that may cause irritation to the skin and can be helpful when suspected allergens are personal care products and cosmetics. A “repeat open application test” (ROAT) can be helpful in patients with negative PT responses, when the clinical suspicion for contact dermatitis remains high. R.O.A.T. involves having the patient apply the suspected source of allergen (lotion, cream, etc) on their skin, two fingerbreadths away from the antecubital fossa twice a day for 7-14 days and observing for the development of dermatitis.⁶ A positive response is typically expected to emerge between days 2-4, at which point testing can be stopped once a positive reaction occurs. Of note, low potency allergens may require a minimum source product application twice a day for 7 days for a reaction to show. This type of test can be extremely helpful in

distinguishing an allergic from irritant response, as open testing is less likely to cause irritation than an occlusive PT.⁴⁸ A “usage test” is defined as the daily application of a product suspected to be an allergen, to the actual area of use to prove causation.^{6,57} As mentioned, this approach can be used to confirm the “definite” clinical relevance of a positive PT.

COMPLICATIONS OF PT

Although generally safe, in rare instances patch testing may be associated with adverse effects. Most adverse effects are due to testing errors such as using too high a concentration of test substance instead of the standard concentration, and leaving the PT panels on the skin for a prolonged period.⁴⁸

Active sensitization has been reported to the allergen during the PT itself, but is rare.⁵⁸ Irritant reactions to PT materials are less frequent now with the use of commercial chambers and non-rubber adhesives. Irritant reactions to adhesive tapes are common, however these reactions tend to be minor, and resolve quickly.⁴⁸ The “edge effect” is a type of irritant reaction where a reaction is noted to be greatest at the periphery rather than the center. This effect tends to dissipate quickly after the removal of the PT. It should be noted that the “edge effect” with testing topical corticosteroids is NOT a false positive, and can represent true allergy, due to the anti-inflammatory nature of corticosteroids. The allergic reaction to topical corticosteroids may be suppressed at earlier readings, and may become positive once the anti-inflammatory effect of the corticosteroid decreases, thus a delayed reading should always be performed.

Other complications to be aware of include a flare of an already existing dermatitis, as well as hypopigmentation and hyperpigmentation of the skin.⁵⁹ Although exceedingly rare, case reports of anaphylactic reactions have been reported after testing to topical antibiotics, nitrogen mustard and latex.^{60,61} Necrosis, scarring, keloids, as well as bacterial/viral infections have also been reported as complications of patch testing.⁴⁸

SPECIAL POPULATIONS

ACD IN CHILDREN

ACD is a common pediatric condition that can easily be misdiagnosed and confused with other chronic dermatoses that present in childhood, such as AD, nummular dermatitis, and multiple other skin conditions. In the past, contact sensitization was thought to be rare in children due to an immature immune system, but studies have shown that sensitization can occur in children as young as 6 months,⁶² and the sensitization rate is around 15% in healthy schoolchildren.^{63,64} The sensitization rate in children with suspected ACD is much higher and the NACDG found a clinical relevant positive PT response in 51-57% of children depending on the year of the report.^{65,66}

As in the adult population, patch testing is the gold standard for diagnosing ACD in children and is a safe procedure for pediatric patients.⁶⁷ Currently, there is no Food and Drug Administration (FDA) approved PT device for patients under the age of 6 so it is common for providers to tailor patch testing to the specific history of the very young children. . The German Contact Dermatitis Group (GCDG)

recommends using only select allergens in children under 6 years of age who have a high clinical suspicion for ACD. The TRUE Test™ is approved for age 6 and above. Children over the age of 12 can be tested in the same manner as adults.⁶⁸ In general, the concentrations of patch testing reagents do not need to be adjusted for older children.^{14,69} but it has been suggested that in children younger than 6 years old, certain allergens should be diluted to avoid irritant false-positive reactions.^{70,71} Jacob et al recommend the following basic standard allergen series for screening children with suspected contact allergy, aged 6-12 years: Bacitracin 20% pet., Budesonide 0.1% pet., Carba mix 3% pet., Cobalt chloride 1% pet., Cocamidopropyl betaine 1% aq., Colophonium 20% pet., Compositae mix/dandelion extract 6% pet./2.5% pet., Disperse blue #124/106 1% pet./1% pet., Ethylenediamine 1% pet., Formaldehyde 1% aq., Fragrance mix 1 8% pet., Fragrance mix 2 14% pet., Lanolin alcohol 50% pet., Methylchlorisothiazolinone/Methylisothiazolinone (MCI/MI) (3:1) 0.01% aq., Myroxylon pereirae (BOP) 25% pet., Neomycin sulfate 20% pet., Nickel sulfate 2.5% pet., Potassium dichromate 0.25% pet., Quaternium 15 2% pet., and Tixocortol-21-pivalate 1% pet.⁷²

OCCUPATIONAL CONTACT DERMATITIS (OCD)

OCD is the most common form of occupational skin disorder and is estimated to exceed \$1 billion in costs annually.⁷³ It is seen at significantly higher rates in individuals with mining or manufacturing jobs, with the most common causes arising from soaps and cleaners.² Most cases of OCD are due to ICD and are associated with exposures to wet work, solvents, alcohols, cleaning agents and

disinfectants.⁶ Workers exposed to metal, rubber-related materials, epoxies, resins and acrylics, dyes, plants, foods, and medications are predisposed to developing ACD.⁷⁴ Patients with suspected OCD should undergo a thorough history of all work-related exposures and complete physical exam. Patch testing to work-related substances may be feasible depending on the availability of safe and commercially available test antigens in order to confirm a diagnosis of occupational ACD.

PATIENTS WITH BIOMEDICAL DEVICES

PRE-IMPLANTATION PATCH TESTING FOR METAL AND CEMENT ALLERGY

Pre-operative patch testing to metal allergens can be considered in patients with high clinical suspicion for metal allergy before orthopedic or other surgeries requiring alloy implantation. Metal is a common sensitizer, and nickel is actually the most common cause of ACD worldwide affecting close to 12% of the general population.⁷⁵ Hypersensitivity reactions to implanted devices can manifest in various degrees, from local cutaneous reactions overlying device placement, to generalized cutaneous dermatitis, to local reactions and complications associated with device failure. Data suggests that the average rate of implant failure is approximately 10% of all joint replacements done in the United States.⁷⁶ Metal hypersensitivity has been associated with device failure, but should be suspected only when more common causes of failure, such as infection and mechanical issues have been excluded. Additionally, case reports of patients experiencing neurologic complications related to metal containing surgical clips have been reported.^{77,78} Studies also suggest there is an increased incidence of chronic refractory in-stent

restenosis (ISR) in patients with positive metal patch testing receiving bare metal stents during percutaneous coronary intervention (PCI).⁷⁹

In addition to metal allergy, there are case reports of patients developing aseptic loosening of total knee prostheses who demonstrate positive PT reactions to various components of bone cements, including acrylates, or additives such as benzoyl peroxide, and dimethyl-paratoluidine, hydroquinone, or antibiotics (especially gentamicin) after surgery.⁸⁰ One patient with positive patch testing to all methacrylates included in T.R.U.E. Test underwent successful revision surgery using a noncemented metallic prosthesis with good tolerance to the new prosthesis at long-term follow-up.⁸⁰ As with metal allergy, any person who has a clinical history concerning for adhesive or cement hypersensitivity, such as issues with prior dental work, skin glues, and artificial nails, should consider pre-operative patch testing evaluation. There are numerous PT allergens commercially available for pre-operative testing, and some examples are shown in Table VIII. Ultimately, the patient's clinical history and the known constituents of the potential implant should direct the selection of which metal and adhesive allergens are included in the pre-operative evaluation.

While there are patients with a documented sensitization to nickel or cement components that tolerate implants without issue, there is no way to identify patients at risk for post-operative complications related to metal or cement hypersensitivity. Additionally, data suggests that individuals who have undergone joint replacement therapy have a higher frequency of positive patch testing compared to the normal population but the predictive value of metal contact sensitization on long term

clinical outcomes in unknown.⁸¹ Conversely, pre-operative testing is not generally indicated in patients without a history of metal or cement and adhesive hypersensitivity because the results can be difficult to interpret and can lead to undue anxiety and stress for patients as well as unnecessary, costly selections of alternative surgical hardware.

POST-IMPLANTATION PATCH TESTING FOR METAL AND CEMENT ALLERGY

The risk of de novo sensitization to metal constituents of an implanted device is unknown although anecdotal cases have been reported.⁸² Additionally, post-implantation patch testing to metal or cement components should be considered in any patient who develops implant failure, when the common causes of infection and mechanical mismatch have been ruled out, or new-onset dermatitis or vesicular rash near site of alloy implantation when other etiologies have been ruled out.⁷⁶ Post-implant patch testing to metal and implant components, such as methacrylates and topical antibiotics, may be helpful to the clinician to document specific sensitization and to help select alternatives in patients requiring revision surgery.⁷⁶

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772 **Table I: Common Allergens Associated with ACD by Distribution**

Hand Dermatitis	Para-phenylenediamine Formaldehyde BOP Nickel Fragrance mix Topical antibiotics Rubber chemicals contained in rubber gloves (thiuram, carbamates, mercaptobenzothiazole)
Facial (including Periorbital and Perioral) Dermatitis	Botanical ingredients Fragrance mix BOP Nickel Ectopic transfer of tosylamide and formaldehyde resin, methyl methacrylate Lanolin
Scalp and Neck Dermatitis	FM BOP Quaternium-15 Cocamidopropyl betaine Acrylates Botanicals PPD Glyceryl thioglycolate
Generalized	Formaldehyde Textile dyes (disperse blue dye)

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782 **Table II: Causative Agents of SCD⁴¹**

	Drugs	Foods	Metals
Topical Inducers	Ampicillin Anesthetics Aminosalicylic acid Bufexamac Diclofenac Hydroxyquinoline	Aspartame Balsam of Peru Compositae plants (chamomile, Echinacea) Garlic Propylene Glycol Propolis	Chromate Cobalt Gold Mercury Nickel Zinc
Systemic Inducers	Amoxicillin Cephalosporins Corticosteroids Erythromycin Estrogen Ethylenediamine Gentamycin Neomycin Nystatin		Mercury Gold

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799 **Table III: Patch Test (PT) Allergens**

Consider PT panels tailored to the specific exposure history to improve diagnostic accuracy.	
A. Standardized test kits	
	T.R.U.E Test Allergeaze allergEAZE®:(www.smartpractice.com) SmartPractice 3400 E. McDowell Road Phoenix, AZ 85008-7899 Ph: 800.522.0800 info@smartpractice.com
	Dormer laboratories®: (http://www.dormer.com) 91 Kelfield Street #5 5040 Toronto, ON M9W CANADA Ph: 866.976.7637
B. Personal items	
C. Allergens from the cosmetic industry	
D. Supplemental allergen panels	
	Special Occupational PT Allergen Panels: Bakery Dental screening – health care providers Dental screening – patients Hairdressing Photographic chemicals
	Allergen Panels Based Upon Specific Exposures: Cosmetics Epoxy series Eyelid dermatitis Footwear/shoes Fragrance/perfumes Isocyanates Methacrylate series: adhesives, dental, nails, and others Photoallergens Photochemical/photopatch Plastics and glues Rubber additives/chemicals Sunscreens Textile colors/finish

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Medications, Treatments, and Food Panels:

Antibiotics/antimycotics
 Corticosteroids
 Local anesthetics
 Medicinal substances
 Antimicrobials/preservatives
 External agents/emulsifiers
 Food additives
 Leg ulcer
 Metal compounds and implants
 Plants/compounds of natural origin

Table IV: Allergens associated with late reactions⁶

Dyes	Para-phenylenediamine
Medications	Caine mix Neomycin Topical corticosteroids
Metals	Chromate Cobalt Gold Nickel Palladium
Preservatives and glues	Dodecyl gallate Epoxy resin Ethylenediamine dihydrochloride Mercapto mix Methylchloroisothiazolinone p-Tert-butyl phenol formaldehyde resin Thimerosol

812 Table V: Allergens associated with reaction on day 5, resolved day 7⁶

Balsam of Peru
Benzalkonium chloride
Benzoic acid
Disperse blue #124
Fragrance mix
Methyl dibromo glutaronitrile phenoxy ethanol
Octyl Gallate

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820 Table VI: Allergens associated with early reactions⁶

Balsam of Peru
Benzoyl peroxide
Carba mix
Cinnamic alcohol
Cocamidopropyl betaine
Fragrance mix
Imidazolidinyl urea
Thiuram mix
Wool alcohols

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833 **Table VII: Pearls and Pitfalls of Patch Testing**

Pearls:

1. Load acrylates, fragrances and allergens in aqueous vehicles immediately before application of PT
2. Delayed PT readings are common to:
 - metals
 - topical antibiotics
 - topical corticosteroids
3. (+) Gold reactions are often not clinically relevant. Trial of gold avoidance may be warranted with + PT to gold in:
 - suspected jewelry allergy
 - facial or eyelid dermatitis
 - exposure through gold dental restorations
4. Consider contact dermatitis in patients with atopic dermatitis who have worsening of dermatitis, changes in distribution, fail to improve, immediately rebound, have atypical pattern and therapy-resistant hand eczema

Pitfalls:

1. Avoid testing patients with an acute and/or severe dermatitis
 2. Avoid testing patients on systemic corticosteroids
 3. Avoid TCS, TCI and ultraviolet light exposure of the test site for 5-7 days before PT
 4. Avoid placing testing panels along the spine, due to poor adhesion
 5. Fragrances are mild irritants, be cautious with weak (+) reactions
 6. Pustular patch reactions are common in AD and to allergens such as nickel, copper, arsenic and mercury. These reactions are false positive reactions
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835 **Table VIII: PT allergens commercially available for pre-operative testing**

Aluminum
Aluminum Chloride Hexahydrate
Chromium (III) chloride
Cobalt (II) Chloride Hexahydrate
Copper sulphate pentahydrate
Ethyl Acrylate
Manganese chloride
Methyl Methacrylate
Molybdenum
Nickelsulfate Hexahydrate
Palladium Chloride
Potassium Dichromate
Titanium Oxide
Vanadium
Vanadium (III) Chloride
Zirconium Chloride

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838 **Figure Legends**

839 **Figure 1.** Loading the patch test chambers (NYU Winthrop Hospital)

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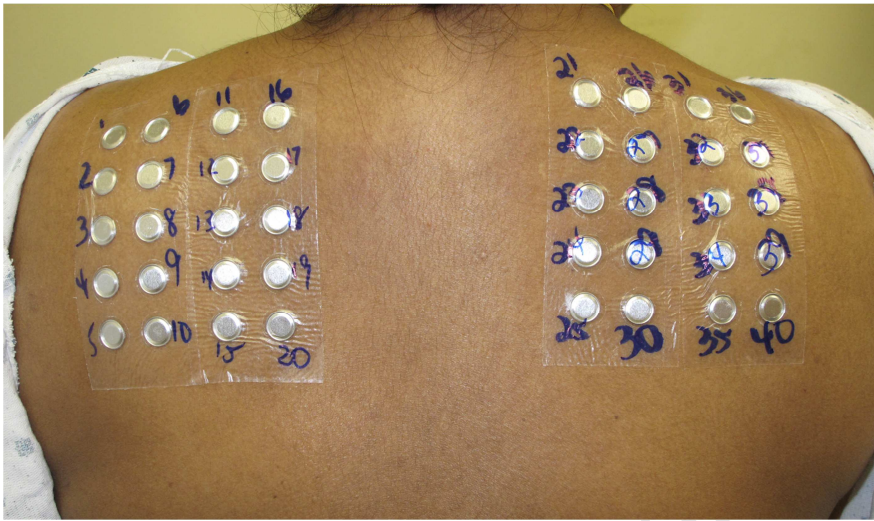
841 **Figure 2.** Application of the patch test (NYU Winthrop Hospital).

842

843 **Figure 3.** Grading System for PT Interpretation⁶

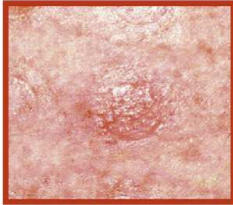
844







(-) Negative reaction



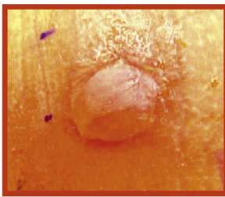
(?+) Doubtful reaction with faint erythema only



(1+) Weak positive reaction with nonvesicular erythema, infiltration, possible papules



(2+) Strong positive reaction with vesicular erythema, infiltration and papules



(3+) Extreme positive reaction with intense erythema and infiltration, coalescing vesicles, bullous reaction



(IR) Irritant reaction