Contact Dermatitis and Patch Testing: An Update for the Allergist

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Disclosure

- **Research and Educational Grants**
  - AAAAI ArTrust
  - Genentech
  - Dyax
  - Baxter

- **Speaker’s Bureau**
  - Baxter
AAAAl
Objectives

1. Discuss the clinical correlation of the patch test results
2. Develop a current understanding of allergic contact dermatitis and patch testing to cosmetics, medical devices and other allergens
3. Demonstrate the technique of application and interpretation of non standardized allergens as in personal products
Patterns of Cosmetic Contact Allergy

- Facial cosmetic dermatitis
  - Bilateral
  - Patchy
- Eyelid
- Neck
  - “run-off” pattern
  - Cosmetics applied to face, scalp or hair often initially affect the neck
  - Most affected site of ACD from nail varnish is the neck
- Lips
  - Consort/Connubial Dermatitis: primarily fragrance
Typical contact allergens tend to be clustered in a few important classes

- Fragrances
- Preservatives
- Excipients
- Glues
- Sun blocks
Fragrance Contact Allergen of 2007

- Most common cause of ACD from cosmetic
- >2800 fragrance ingredients used routinely in cosmetics
  - ~100 are known allergens
- ~10-25% of PT are positive to fragrance chemicals
  - 1.7-4% of general population
  - predominantly women

*Buckley DA et al. The frequency of fragrance allergy in a patch-test population over a 17 year period. Br J Dermatol 2000;142:203-4
Contact Dermatitis 2003 Dec;49(6):287-9
<table>
<thead>
<tr>
<th>Fragrance Mix I</th>
<th>Balsam of Peru</th>
<th>Fragrance Mix II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>Myroxylon pereirae</em></td>
<td></td>
</tr>
<tr>
<td>Cinnamic alcohol 1%</td>
<td>Cinnamic acid</td>
<td>Coumarin 2.5%</td>
</tr>
<tr>
<td>Cinnamic aldehyde 1%</td>
<td>Benzoyl Cinnamate</td>
<td>Hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyral) 2.5%</td>
</tr>
<tr>
<td>$\alpha$-Amyl cinnamaldehyde (amyl cinnamal) 1%</td>
<td>Benzoyl Benzoate</td>
<td>Citronellol 0.5%</td>
</tr>
<tr>
<td>Hydroxycitronellal 1%</td>
<td>Benzoic acid</td>
<td>Farnesol 2.5%</td>
</tr>
<tr>
<td>Geraniol 1%</td>
<td>Vanillin</td>
<td>Citral 1.0%</td>
</tr>
<tr>
<td>Isoeugenol 1%</td>
<td>Nerodilol</td>
<td>$\alpha$ Hexyl cinnamic aldehyde 5.0%</td>
</tr>
<tr>
<td>Eugenol 1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oak moss 1%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Other fragrance sensitizers: Lyral, jasmine, lavender, sandalwood, tea tree oil, ylang ylang oil, lemongrass oil, jasmine, Narcissus
Fragrance Contact Allergen of 2007

- Standard fragrance mix: Fragrance mix I & Balsam of Peru
  - pick up 60-70% of all ACD to fragrances at best
- (-) PT to FM I
  - ~35% had (+) PT to FM II
- (+) PT to FM II
  - ~1/3 had (+) PT to FM I

Buckley DA et al. The frequency of fragrance allergy in a patch-test population over a 17 year period. Br J Dermatol 2000;142:203-4
Fragrance Mix Patch Test

- Low specificity
  - Mild Irritant potential, caution with weak positive reactions

- Increased probability of a relevant FM patch-test
  - Increased strength of test reaction
  - Repeated (+) reaction on retest
  - (+) to one of its ingredients

Tricky Aspects of Fragrance Allergy

- New fragrance chemicals are constantly introduced
- Regulation of fragrance ingredients in cosmetics exempts fragrance formulas as “trade secrets”
- Some manufacturers do not consider essential oils to be fragrance
  - Tree tea oil (Melaleuca alternifolia)
  - Ylang-ylang oil (Cananga odorata)
  - Jasmine flower oil (Jasminum officinale)
  - Peppermint oil (Mentha piperita)
  - Lavender oil (Lavandula angustifolia)
  - Citrus oil (limonene)
- “Covert fragrances”- used for other than for aroma (ie preservatives) can be added to “fragrance free” products
  - Bensaldehyde
  - Benzyl alcohol
  - Bisabolol
  - Citrus oil
  - Unspecified essential oils

Food-related contact dermatitis
Myroxilon pereirae, Fragrance Mix, Cinnamic Aldehyde

- **Myroxilon pereirae** (Balsam of Peru) (2nd)
- **Fragrance mix** (4th)
- **Cinnamic aldehyde** (6th)
  - Relatively specific (not very sensitive) marker for spice allergy
  - Flavoring in gums, mouthwashes, toothpaste
  - Sensitization to BOP in topical products may cause systemic CD from foods with BOP

Fragrance Systemic Contact Dermatitis

Foods to Avoid in Balsam-Restricted Diet

- **Citrus** fruits: oranges, lemons, grapefruit, tangerines
- Flavoring agents: pastries, bakery goods, candy, gum
- **Spices**: cinnamon, cloves, vanilla, curry, allspice, anise, ginger
- Spicy condiments: ketchup, chili sauce, barbecue sauce, chutney,
- Perfumed or flavored tea & tobacco
- Chocolate
- Certain cough medicines & lozenges
- Ice cream
- Cola, spiced soft drinks such as Dr Pepper
- **Tomatoes** & tomato-containing products
- Possible cross reactivity with Compositae (“natural” & “organic”) containing sesquiterpene lactones (chamomile, echinacea)

~ half of patients with (+) PT to MP who followed a low BOP diet had significant improvement of their dermatitis

Summary for Fragrance Allergy

- Wash on/wash off products: ? Relevance of brief exposure
  - Concentration of fragrance left on fabric is below threshold induction levels
- Testing to FM I & BOP picks up 60-70% of fragrance allergy*
- Many FM I PT reactions are weak, perhaps irritant & hard to reproduce
- Advising patients to avoid all fragranced products on the basis of a very weak (+) PT (? irritant) may deprive them of one of life's pleasures

Storrs F J. Fragrance. Dermatitis Volume 18, Issue 01, March 2007, Pages 3-7
*Larsen W et al. Fragrance contact dermatitis: a worldwide multicenter investigation (part III)> Contact Dermatitis 2002;46:141-4
Preservatives

- 945 PT patients at Mayo
  - 68.4% had at least 1 (+) reaction
  - 47.3% had at least 2 (+) reactions
  - 49.4% reacted to at least 1 preservative
  - 31.2% reacted to at least 1 fragrance/botanical additive
- Older individuals were 3.7x more likely to have (+) PT to common preservatives than children
### Cosmetic Preservatives

<table>
<thead>
<tr>
<th>Formaldehyde</th>
<th>(+) PT</th>
<th>Non Formaldehyde</th>
<th>(+) PT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formaldehyde*</td>
<td>8.4 %</td>
<td>Methylidibromoglutaronitrile (Euxyl K 400)</td>
<td>5.8 %</td>
</tr>
<tr>
<td>Quarternium 15*</td>
<td>9.3%</td>
<td>MCI/MI</td>
<td>2.3 %</td>
</tr>
<tr>
<td>Diazolidinyl urea* (Germall II)</td>
<td>3.2 %</td>
<td>Parabens*</td>
<td>0.5 %</td>
</tr>
<tr>
<td>Imidazolidinyl urea* (Germall)</td>
<td>3.0 %</td>
<td>Chloroxylenol</td>
<td>0.8 %</td>
</tr>
<tr>
<td>Bromonitropropane (Bronopol)</td>
<td>3.3 %</td>
<td>Iodopropynylbutylcarbamate</td>
<td>0.4%</td>
</tr>
<tr>
<td>DMDM Hydantoin (Glydant)</td>
<td>2.6 %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Paraben, quarternium-15 & formaldehyde preservatives are frequently combined & cosensitize ***

*Antigen present in the T.R.U.E. Test
** % Prevalence PT reaction based on NACDG or TT
Formaldehyde

Most common potential source of exposure

- **Cosmetics**
  - Rarely on ingredient label, direct use forbidden in some countries
  - Contain formaldehyde releasers

- **Permanent press textiles**
  - Increase strength, prevent shrinking, resist wrinkling (permanent press) of cellulose and rayon fibers

Formaldehyde Resins

- Dermatitis pattern in areas where clothing fit tightly
  - posterior neck
  - upper back
  - lateral thorax
  - anterior & posterior axillary folds (spares axillary vault)
  - waistband (spares undergarment areas)
  - flexor

- Importance of pressure, friction, heat, perspiration
Subacute and chronic dermatitis

Formaldehyde testing alone identifies only ~70% of formaldehyde resin allergic patients
  • PT with resins as well

Slow resolution of dermatitis even with careful avoidance
  • As much as 50% still had constant dermatitis *

Occasional exposure to “Dress clothes” on weekends is enough to maintain dermatitis

Treatment for Formaldehyde Resin Allergic Contact Dermatitis

- Use 100% silk, polyester, acrylic, nylon
  - Linen & denim if soft & wrinkle easily
- Avoid “easy care,” “permanent press,” or “wrinkle free”
- Some experts also recommend avoidance of formaldehyde-releasing preservatives in personal products*
- AVOID FORMALDEHYDE RESINS AT ALL TIMES. Even exposure once a month is enough to cause a rash to continue

SCD in formaldehyde-sensitive patients after ingesting aspartame (artificial sweetener) in food, medicaments, vitamins

- Monteleukast chewable tablets (contain aspartame)
  - granule does not

Aspartame $\rightarrow$ metabolized to phenylalanine, aspartic acid, & aspartic acid methyl ester $\rightarrow$ methanol $\rightarrow$ transported to liver

Liver: methanol oxidized formaldehyde
Quarternium 15

- Most common cosmetic preservative allergen
- Most sensitization is caused by formaldehyde releaser
- Most Q 15 allergic patients are also allergic to formaldehyde

Most commonly used cosmetic ingredient next to water (87-93%)

Average total paraben exposure per person in the US is ~ 76 mg/day
- Cosmetics & personal products: 50 mg per day
- Foods: paraben is usually less than 1%

Weak sensitizers in cosmetics

Paraben-sensitive individuals often tolerate paraben-containing cosmetics on normal intact skin but not damaged skin

“Paraben paradox”: only sites of healed dermatitis flare when sensitizer is applied

Cosmetic vehicles, emulsifiers & additives

Lanolin (Wool wax alcohols)

- Most common sources: moisturizer, creams, cosmetics & topical medications
- Male sex, atopic dermatitis, & co-reactivity to other allergens were higher in lanolin-positive patients
- Complex mixture therefore test actual lanolin used
- Lanolin Paradox:
  - sensitivity low in normal skin
  - moderate in atopic
  - high in stasis eczema & ulcers
Most common patterns of dermatitis in PG (single reactors)
- Dermatitis on the face
- Scattered or generalized dermatitis

Uses
- solvent, vehicle, emulsifier or humectant
- thickening agent in many foods (concentration may be too low to cause skin reactions)

Most common source of allergy
- Personal care products
- Topical medicaments, especially topical CS
Food-related irritant and allergic contact dermatitis
Specific Allergens: Propylene Glycol

- Used in food colorings, foods thickening agent in cake mixes, salad dressings, soft drinks, popcorn
- Concentration in foods is likely too low to cause a reaction
  - but there are reports of flares from ingestion of foods containing propylene glycol by sensitized patients
  - flares following oral provocation (15 mL of propylene glycol)

P-phenylenediamine (PPD)
Contact Allergen of 2006

Permanent Hair Dye

- Theoretically, does not cause reaction if fully oxidized
- In reality, it is likely that PPD is never completely oxidized
New Route of Exposure

- Body painting & temporary tattooing (until stratum corneum is shed)

- Clinical course
  1. Acute intense eczematous response within 1-2 days of tattooing
  2. Subacute response: lichenoid eruptions within 1-2 week
     - Most likely causative agent is PPD

- PPD sensitization is likely lifelong; may react to first attempts at hair coloring

Dickel H et al. Comparison of patch test with standard series among white and black racial groups. Am J Contact Dermat 2001;12:77-82
Prevention

- Home test appear to be predictive and could provide secondary prevention if properly used
- New hair dyes (semipermanent) contain FD & C and D & C dyes that appear to have very low cross reactivity with PPD
  - Elumen Hair Color
    - (Goldwell cosmetics Linthicum Heights, MD)
  - Clairol Basic Instincts-Loving Care
    - (The Proctor & Gamble Company, Cincinnati, OH)

Krasteva et al. Contact Sensitivity to hair dye can be detected by the consumer open test. Eur J Dermatol 2002;12:322-6
Cocoamidopropyl betaine
Contract Allergen of 2004

- Second most common allergen in shampoo
- Less irritating than older surfactants (sodium lauryl sulfate) but more sensitizing
- Positive PT are often clinically relevant
- Areas of Involvement
  - Face: 30.2%
  - Neck: 14.3%
  - Hands: 12.7%
  - Eyelids: 9.5%
  - Scalp: 4.8%
  - Scattered: 23.8%

Fowler JF. Cocamidopropyl Betaine. Dermatitis 2004;15:3-4
Shampoos

Typically composed of 10-30 ingredients

<table>
<thead>
<tr>
<th>Allergen</th>
<th>No. of Products Containing Allergen</th>
<th>% of Products Containing Allergen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fragrance</td>
<td>170/179</td>
<td>95.0</td>
</tr>
<tr>
<td>Cocamidopropyl betaine</td>
<td>95/179</td>
<td>53.0</td>
</tr>
<tr>
<td>Methylchloroisothiazolinone/methylisothiazolinone</td>
<td>92/179</td>
<td>51.0</td>
</tr>
<tr>
<td>Formaldehyde-releasing preservatives</td>
<td>87/179</td>
<td>48.0</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>68/179</td>
<td>38.0</td>
</tr>
<tr>
<td>Vitamin E (tocopherol)</td>
<td>51/179</td>
<td>28.0</td>
</tr>
<tr>
<td>Parabens</td>
<td>43/179</td>
<td>24.0</td>
</tr>
</tbody>
</table>

Only 5 products in the Walgreens database were truly fragrance free
Of 9 with no fragrance, 4 had fragrance related ingredients, 3 had botanical ingredients, 1 had benzyl alcohol

Table 2. Low-Allergenicity Shampoos

<table>
<thead>
<tr>
<th>Product</th>
<th>Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFM Safe Choice Hair and Body Shampoo*</td>
<td>Purified water, sodium laureth sulfate, cocamide MEA, citric acid</td>
</tr>
<tr>
<td>Free &amp; Clear Shampoo†</td>
<td>Purified water, disodium cocamphodiacetate, disodium laureth sulfosuccinate, sodium chloride, cocamidopropylamine oxide, PEG-150 pentaerythrityl tetrastearate, citric acid, PEG-12 dimethicone, disodium EDTA, potassium sorbate</td>
</tr>
</tbody>
</table>

Emergent and Unusual Allergens in Cosmetics

- ACD from cosmetics is a common problem, the formulation of cosmetic products is constantly changing
  - Shellac (lacca or gomme-laque): found in pump or aerosol hair sprays, shampoos, eyeliners, mascaras, nail lacquers, lipsticks
  - Lipsticks
    - Various D&C dyes & inorganic pigments in D&C yellow 11 and D&C red 7
    - Oily base: Castor oil (ricinus oil): suspends pigment
    - Additives (ie. emollients), antioxidants (ie gallates), sunscreens

- Old allergens learn new tricks while new allergens emerge to challenge our quest for a definitive diagnosis

Issues with Contact Dermatitis

- History not always accurate
- Physician’s guess is almost always wrong
- Changing landscape of cosmetics
- **NEW Products** (New fragrance chemicals constantly introduced)
  - New bottles of old products
  - New and improved products
  - Natural products can cause allergies
- Poor Regulation of cosmetics industry
  - Fragrance formulas are “trade secrets”
  - Some manufacturers do not consider essential oils to be fragrance (Tree tea oil, Ylang-ylang oil, Jasmine, Peppermint, Lavender, Citrus oil)
  - “Covert fragrances”- used for other than for aroma (i.e. preservatives)
- Labels difficult to read or Incomplete
- Cross-reactivity and Co-reactivity
- Test for personal products especially for facial, eyelid and lip dermatitis
Nickel in Biomedical Devices

Reports of dermatitis to biomedical devices lead to:

- Consults regarding safety of medical devices in nickel-sensitized patients
- High variability of care in terms of testing & recommendations
  - differences within and between countries
- Increased health care costs
- Medicolegal concerns contribute to testing
- Selection of more expensive & less durable option

As nickel allergy incidence increases, this problem will also increase

Pathophysiology of Metal Allergy and Implant Failure

**Immuneologic Level**

- Endothelial cell exposure induce **intercellular adhesion molecule 1 (ICAM-1)** expression
- Cutaneous reactions above implant are primarily **T cell-mediated type IV reactions**
- Tissues adjacent to implant in metal sensitive patients have **elevated immune cells/markers** (CD3⁺ T lymph, CD4⁺ cells, CD11c⁺ macrophages/dendritic cells & cells with abundant MHC class II)

Schalock1, et al Hypersensitivity reactions to metallic implants – diagnostic algorithm & suggested patch test series for clinical use. Contact Dermatitis, 66, 4–19
Orthopedic Implant Allergy

5% of orthopedic implant & up to 21% of patients with preop metal sensitivity may develop cutaneous allergic reactions on reexposure to the same metal

Clinical manifestations

• Cutaneous
  – localized: eczematous reaction overlying implant (urticaria & vasculitis reported)
  – generalized
  – both

Non Cutaneous Reactions

• Implant Failure

## Prospective Longitudinal Studies and Reviews

<table>
<thead>
<tr>
<th>Study</th>
<th>Pt</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carlsson &amp; Moller 1989</td>
<td>18</td>
<td>Metal allergic pts with confirmed allergy to metal in their device prior to stainless steel orthopedic implants had no issues (6-yr ff-up)</td>
</tr>
<tr>
<td>Thyssen et al, 2009</td>
<td>356</td>
<td>Risk of surgical revision not increased in patients with metal allergies</td>
</tr>
<tr>
<td>Niki et al 2006</td>
<td>92</td>
<td>26% had (+) LST tests to at least one metal (Ni, Co, Cr, Fe) 5% of total study developed cutaneous allergic reactions In metal (+) prior to implant: 21% developed dermatitis at site of implant (some widespread)</td>
</tr>
<tr>
<td>Eben et al 2010</td>
<td>92</td>
<td>66/92 had sx (pain, reduced motion, swelling) Rates of allergy: nickel: 24.2% vs 3.8% (no Sx); cobalt: 6.1%; vs 3.8% Symptomatic (31.8%) had allergic reaction to bone cement components</td>
</tr>
<tr>
<td>Braathen et al</td>
<td>16</td>
<td>81% of failed metal-on-metal implants had metal sensitivity (PT &amp;/or LTT)</td>
</tr>
<tr>
<td>Hallab N, et al 2001</td>
<td></td>
<td><strong>Accumulated reports in total hip arthroplasty: prevalence of metal allergy ~ 25% in well-functioning vs. ~ 60% in failed/poorly functioning implant</strong></td>
</tr>
</tbody>
</table>

Allergic Contact Dermatitis from bone cement components

Reported in 24.8% of patients (n = 239)*

<table>
<thead>
<tr>
<th>Common Bone Cement Allergen in Total Joint Arthroplasties</th>
<th>Use</th>
<th>Approx % (+) Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>N,N-dimethyl-p-toluidine (DPT)</td>
<td>Reaction initiator</td>
<td>10</td>
</tr>
<tr>
<td>Polymethyl methacrylate (MMA)</td>
<td>Cement Base</td>
<td>25</td>
</tr>
<tr>
<td>Benzoyl Peroxide</td>
<td>Activator</td>
<td>8-10</td>
</tr>
<tr>
<td>Hydroquinone</td>
<td>MMA Stabilization</td>
<td>5</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>Antibiotic</td>
<td>17-24</td>
</tr>
</tbody>
</table>

Common causes of failure: infection, recurrent dislocation, aseptic osteolysis, fractures

## Endovascular stent & In-stent restenosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Positive Findings</th>
<th>Negative Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Köster R, et al 2000 Prospective study</td>
<td>Coronary in-stent restenosis 6 mos post stent &amp; PT 2 mo after angioplasty</td>
<td>(+) PT in 10/131 (8%) - All 10 (100%) had in-stent restenosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>However, 57% of (-) PT had ISR</td>
</tr>
<tr>
<td>Iijima R, et al 2005 Prospective study</td>
<td>174 stented patients -109 (initial placement) - 65 (restenosis)</td>
<td>Recurrence of ISR: higher (+) PT to metals (39% vs.12%; p =0.02) Predictors of recurrent restenosis: (+) patch test (OR 4.39, p =0.02)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Initial stent implantation not significantly different between with or w/o restenosis (10% vs 9%)</td>
</tr>
<tr>
<td>Thyssen, et al 2012 Linkage Study</td>
<td>149/18,794 (0.8%) PT prior to metal stent placement</td>
<td>14% (21/149) had ISR - Only 11.8% (2/21) had metal allergy</td>
</tr>
</tbody>
</table>

**Gold-plated stents (thought to be inert), subsequently showed that gold in cardiac stents was a strong risk factor for ISR, especially in those with prior gold allergy**

*Svedman C et al. A correlation found between contact allergy to stent material and restenosis of the coronary arteries. Contact Dermatitis 2009: 60: 158–164*
Pacemakers/Defibrillators

- Majority of reactions are infections
- Allergic complications rare: ~30 cases reported in literature

  - Ti alloy shell: most frequent
  - Manifestations:
    - dermatitis localized above implant
    - impaired wound healing
    - generalized or remote dermatitis (uncommon)

Schalock et al Hypersensitivity reactions to metallic implants – diagnostic algorithm and suggested patch test series for clinical use. *Contact Dermatitis*, 66, 4–19
Dental Implants & Orthodontic Devices

- Potential allergen groups
  - Ni–palladium &/or Ti alloys
  - CoCrMo alloys
  - Epoxy & epoxy-acrylate preparations
  - Anesthetics & flavorings

- Flexible titanium-nickel arch wires release more nickel compared to stainless steel
  - Nickel: most common contact allergen to orthodontics

Gynaecological devices

- Mostly from contraceptive devices
  - contain copper

- Reports of systemic allergic dermatitis resolving with IUCD removal

- Contraindication to placement
  - Copper allergy in Copper IUCDs (Paragard)*
  - Ni allergy in Nitinol (Essure)**

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Should allergy screening be performed?

- Patients with no history of metal hypersensitivity need not be screened prior to implantation.
- Pre-implantation PT identifies metal-allergic individuals*
  - Screening prior to surgery is recommended for those with history of metal sensitivity of a magnitude sufficient to cause concern to the patient or healthcare provider **
- Post-implantation PT: joint pain, implant loosening, or unexplained cutaneous reaction at the implant site with a question of metal hypersensitivity

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Reed K B, et al. Retrospective evaluation of patch testing before or after metal device implantation. Arch Dermatol 2008: 144; 999–1007

What is the benefit of the medical history?  
An alternative view

➢ The validity of self reported nickel allergy*
  • Sensitivity: 37–82%
  • Specificity: 77–87%

➢ Suggests that patient’s history is not sufficiently predictive to warrant PT & that the prevalence of reactions is high enough to warrant pre-implant evaluation **

“…requires all patient who will undergo pectus surgery to be tested for allergies to the metallic component of the implanted surgical stainless steel pectus bar”

*Schalock et al Hypersensitivity reactions to metallic implants – diagnostic algorithm & suggested patch test series for clinical use. *Contact Dermatitis*, 66, 4–19
Patch Testing vs. Lymphocyte Transformation Test

- Measures lymphocyte proliferation (stimulation index) after 7 days incubation +/- allergen
  - Limited allergens, availability & rapid decay of T cells (rapid transportation)
- LTT better reflect immune reactions within the body, whereas PT reflects cutaneous reactivity
- May be useful in questionable cases
  - 54/56 patients with Ti implants, (-) PT & (+) Ti LTT whose systemic symptoms resolved after implant removal
- Needs Validation

*(MELISA test: Health Diagnostics and Research Institute, South Amboy, NJ)
What to test with

PT with limited allergens is not recommended as there may be multiple causes of the dermatitis

- **Baseline series** [NACD, ACDS, European Baseline Series etc]
- **Extended series & specialty trays**
  - Extended NA standard series (Chemotechnique or Allergeaze; SmartPractice, Calgary, AB, Canada)
  - International Comprehensive Baseline series (Chemotechnique)
- **Metals**

Mayo Clinic PT Protocol for patients about to or have undergone device implantation

Rationale:
1. Implanted devices contain metals
   • nickel, cobalt, chromium, titanium
2. ~ 10% of the general population have cutaneous metal hypersensitivity
3. Cutaneous reactions to metal implants have been documented
4. Hip prostheses have a shorter lifespan in patients with documented sensitization to bone cement
5. Pre implantation PT may guide the choice of the device implanted

Table 6. Substances that may be present in different types of implant or device and that potentially should be considered for diagnostic patch testing

<table>
<thead>
<tr>
<th>Substances or alloy</th>
<th>Dental</th>
<th>Pre-implant</th>
<th>Post-implant</th>
<th>Intravascular</th>
<th>Pacemaker and ICD</th>
<th>Gynaecological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminium</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>—</td>
<td>x</td>
<td>—</td>
</tr>
<tr>
<td>Beryllium</td>
<td>x</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cadmium</td>
<td>x</td>
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<td>Zirconium</td>
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Suspect Orthopedic Metal Implant Allergy

Pre Implant

- No Hx of Dermatitis → No Concern for Hyper-sensitivity Reaction → No Testing
- Hx of Dermatitis → Possible Hyper-sensitivity Reaction → Baseline Series Metals: Aluminum, Chromium, Cobalt, Iron, Manganese, Molybdenum, Nickel, Niobium, Silicon, Phosphorus, Tantalum, Titanium, Tungsten, Vanadium, Zirconium, Gold

Post Implant

- No Symptoms → No Testing
- Symptoms → Extended Series Metals Bone Cement Implant Test Disc LTT?

Orthopedic Metal Implant Allergy

+ Metal Test

No Symptoms

No Intervention

+ Symptoms

No

Is Device Removal Necessary?

Yes

Is removal safe and reasonable

Yes

Options
- Remove Implant
- Replace w/ non allergenic alloy
- Coat metal w/ polytetrafluoroethylene

No

No surgical intervention

(+') dermatitis: consider 21 day course of tapered oral prednisone

METAL IMPLANT “ALLERGY”
What do we know

- Metal implant release metal ions and elicit an immune response
- Most reactions to metal implants are based on case reports or relatively small cohorts
- ~5% developed eczematous reactions directly associated with metallic implants
  - Proven cases incriminate nickel, cobalt, chromium, copper
- The temporal & physical evidence leaves little doubt that a considerable number of patients develop metal sensitivity & cutaneous allergic dermatitis in association with metallic orthopedic implants

METAL IMPLANT “ALLERGY”
What do we know about Patch Testing

- Need for patch testing is controversial, poorly reliable in predicting or confirming implant reaction
  - Preimplantation PT: Consider if history of metal sensitivity is of sufficient cause of concern to patient or healthcare provider **
  - Post cutaneous eruption PT: consider with an appropriate series

(-) PT is reassuring for absence of delayed hypersensitivity
A (+) PT does not prove relevance
If relevant allergens are identified & corticosteroid therapy is insufficient to clear eruption, removal of implant may be considered
What we do NOT know about Metal Implant Allergy

- Whether risk of allergic reaction to orthopedic implants increase in metal sensitized individuals
- Whether supposed allergies to implanted devices really cause problems such as loosening or dermatitis
- How to identify the subgroup of metal allergic patients with increased risk of complications from metal implant
- Whether PT can truly detect reactions to implanted devices
- Patch Testing vs. Lymphocyte Transformation Test

Based on the complex findings, it is difficult to make general principles for good clinical practice & prospective longitudinal studies are strongly needed