Contact Dermatitis: Update and Practical Advice

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Disclosure

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- Baxter
- Genentech
- Merck
Consultant
- Church and Dwight, Co., Inc
- Regeneron
Learning Objective

Upon completion of this session, participants should be able to:

1. Identify causes of contact dermatitis
2. Describe appropriate and effective patch testing methods and their role in evaluating allergic contact dermatitis

Dermatitis with Scattered Generalized Distribution

- Allergic Contact Dermatitis with Diffuse Contact
- Systemic Contact Dermatitis
  - Baboon syndrome
  - Metals
  - Plants
- Drug-elicited Systemic Allergic Dermatitis
  - Drug related Baboon syndrome
  - Symmetric drug related intertriginous and flexural exanthema (SDRIFE)
- Protein contact dermatitis
- Atopic Dermatitis

Allergic Contact Dermatitis with Diffuse Contact: Textile

- Irritant CD
  - Rough material (wool, burlap)
  - Occlusive materials (polyester, nylon)
- Allergic CD
  - Dyes
  - Formaldehyde Resin (wool, rayon)
  - Rubber chemicals (elastic fibers)
  - Chromates (leather)
  - Cobalt (clothes with metallic dyes)
  - Medications trapped in clothing (corticosteroids, lanolin, propylene glycol, neomycin)
Textile ACD

- Most common textile allergens
  - Disperse Dyes
  - Formaldehyde Resin
- Distribution affected by areas with greatest contact
  - ACD to bed linens & furniture: upper back & posterior thighs
  - ACD to apparel: antecubital folds, popliteal folds, medial thighs, anterior & posterior axillary lines, waistbands, posterior neck, upper back
- Confounding factors: perspiration & friction
  - Moisture facilitates release of dyes and resins from fabrics

Allergic Contact Dermatitis to Textile Dyes

- Primary sensitization: occupational exposure to cross-reacting chemicals
  - PPD in hairdressers
- Disperse dyes accounts 2/3 of textiles ACD
  - TT™ contains only Disperse blue 106
- High False (-) to PT to pieces of clothing (usage conditions may not be replicated)
Allergic Contact Dermatitis to Textile Formaldehyde Resin

- Primary sensitization via occupational exposure to formaldehyde in health care workers, embalmers, cabinetmakers
- Common in highly finished garments (wrinkle free, permanent press, reduce shrinking, increase strength)
  - uniforms (water-resistant laboratory coats)
  - zip-up greens worn by machinists
  - military wool garments
  - vintage clothing
  - furniture cotton upholstery

Systemic Contact Dermatitis

- intravenous
- orally
- inhaled
- intramuscular
- per rectum
- transcutaneously
- intravesically

Contact sensitized individual

Generalized (or localized) dermatitis
**Baboon Syndrome**

Most recognizable form of SCD with diffuse, well demarcated erythema of the buttocks, upper inner thighs, and axillae

Involvement of the buttocks is a suggestive clinical feature in baboon syndrome.

Two most common allergens:
- Nickel
- Balsam of Peru

**Dermatitis with Scattered Generalized Distribution**

Estimated SCD following oral nickel in nickel allergic patients

- 1% to 0.3 - 0.6 mg/d (normal diet)
- 10% to 0.55 - 0.89 mg of nickel
- ~ 50% to 2.5 mg nickel

Approximate nickel content of foods
- Soybean: ~ 1 cup=895 mcg
- Figs: ~5=85 mcg
- Cocoa: 1 tbsp=147 mcg
- Lentils: ⅓ cup cooked=61 mcg
- Cashew: ~ 18 nuts=143 mcg
- Raspberry: 56 mcg
- Vegetables: ½ cup canned=40 mcg
- Lobster: 3 oz=30 mcg
- Oat Flakes: 2/3 cup=25 mcg
- Peas Frozen: ½ cup=27 mcg
Nickel

- 10% of population are nickel allergic
- Increasing sensitization in North America
  - New sources of nickel ACD: cell phones, laptops

### TABLE 2. Constituents of Food on the BOP Diet

<table>
<thead>
<tr>
<th>Constituent</th>
<th>Bugenic</th>
<th>Cinnamates</th>
<th>Butenolic Acid</th>
<th>Vanillin</th>
<th>Ferulic Acid</th>
<th>Coniferyl</th>
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<tbody>
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<td>Citrus peel</td>
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<td>Vanilla</td>
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<td></td>
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<td>Synthetic vanilla</td>
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<td>Cilantro</td>
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<td>Bay leaves and basil</td>
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<td>Curry powder</td>
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<td>Spiced condiments</td>
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<td>Perfumed tea and tobacco</td>
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<td>x</td>
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<td>x</td>
<td></td>
<td></td>
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<tr>
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<td></td>
<td></td>
<td>x</td>
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<tr>
<td>Gin</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Vermouth</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
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<td></td>
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<tr>
<td>Whiskey</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Spiced Liquors</td>
<td>x</td>
<td>x</td>
<td>x</td>
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</tr>
<tr>
<td>Beets</td>
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<tr>
<td>Asparagus</td>
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<td></td>
<td>x</td>
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<tr>
<td>Wheat and rye</td>
<td></td>
<td>p</td>
<td></td>
<td>x</td>
<td></td>
<td>(product of fermentation)</td>
</tr>
<tr>
<td>Brewer's yeast</td>
<td>p</td>
<td>p</td>
<td>(product of fermentation)</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Food with benzene</td>
<td>p</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>preservation</td>
</tr>
</tbody>
</table>

*denotes the food may be additionally contained in these foods but must be added as a preservation. x, present; p = may not be present.
The make-up used by children
- sold in toy stores
- not suitably controlled
- often contaminated by nickel
- can cause eyelid dermatitis (mascara, eye-liners, eye shadow)

MAC Cosmetics teamed up with Mattel toy to launch a new line, “Barbie inspired” MAC Barbie Line cosmetics.

Average adult apply 12 personal hygiene products daily
- These 12 products exposes one to 168 discrete chemicals

Cosmetics
-爱尔

Face: bilateral & patchy
- Central face: make-up, moisturizers
- Peripheral face: shampoo, conditioner, facial cleanser

Neck
- "run-off" pattern
- cosmetics applied to face, scalp or hair often initially affect the neck
- Ectopic transfer of toluene sulfonamide formaldehyde resin in nail polish

Lip
- Irritant CD 36%
- Allergic CD 25%
- Fragrance mix
- Oral hygiene products, cosmetics, gums, foods, flavorings
- Nickel trace in lip cosmetics, containers, ectopic reactions

Eyelid
- Allergic CD 55-72%
- Fragrance (FMI & BOP)
- Gold sodium thiosulfate
- Nickel sulfate
Typical contact allergens tend to be clustered in a few important classes

- Fragrances
- Preservatives
- Excipients
- Glues
- Sun blocks

Fragrance Mix I & Balsam of Peru (in TT) pick up 60-70% of all ACD to fragrances at best
Fragrance Mix Patch Test

- Low specificity
  - Mild Irritant, caution with weak (+) reactions
- Increased probability of a relevant FM patch-test
  - Increased strength of test reaction
  - Repeated (+) reaction on retest
  - (+) to one of its ingredients


Cosmetic Preservatives

- ~1:6 stay-on cosmetics & 1:4 rinse-off products contain a formaldehyde releaser (FDA Voluntary Cosmetic Registration Program Database)

<table>
<thead>
<tr>
<th>Preservative</th>
<th>(+) PT*</th>
<th>Non Preservative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formaldehyde</td>
<td>6.6%</td>
<td>Iodopropynylbutylcarbamate</td>
</tr>
<tr>
<td>Quarternium 15</td>
<td>6.4%</td>
<td>Methyldibromoglutaronitrile (Euxyl K 400)</td>
</tr>
<tr>
<td>Diazolidinyl urea (Germall II)</td>
<td>2.1%</td>
<td>MCI/MI</td>
</tr>
<tr>
<td>Imidazolidinyl urea (Germall)</td>
<td>1.6%</td>
<td>Parabens</td>
</tr>
<tr>
<td>Bromonitropropane (Bronopol)</td>
<td>1.6%</td>
<td>Chloroxylenol</td>
</tr>
<tr>
<td>DMDM Hydantoin (Glydant)</td>
<td>1.6%</td>
<td></td>
</tr>
</tbody>
</table>

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

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* % Prevalence PT reaction based on NACDG 2011-2012
Methylisothiazolinone

- Preservative in cosmetics and toiletries
  MI (singly or MCI/MI) was used in 1125 cosmetic products in the US (US FDA Voluntary Cosmetic Ingredient Registration Program)
  - 24% (n = 275) in shampoos
  - 18% (n = 206) in conditioners
  - 10% (n = 117) in baby soaps & detergents
- Household products: dishwashing liquid, soaps, laundry detergents, stain removers, fabric softeners,
- Tested with MCI/MI mix
  - MCI/MI trade names: Kathon CG
  - Mix misses ~ 40% of allergy to MI (low concentration of MI in mix)

Castanedo-Tardana & Zug. Contact Allergen of the Year 2013 Dermatitis, 24 (1)

Lanolin (wool wax alcohols)

- Ointment base for topical medicaments: antibiotics, corticosteroids, analgesics
- Personal care products: moisturizers, creams, lipsticks, shampoos, soaps
- Complex mixture: test actual lanolin
- Lanolin Paradox:
  - sensitivity low in normal skin
  - moderate in atopic
  - high in stasis eczema & ulcers

Cocoamidopropyl betaine

- Amphoteric surfactant in shampoos, bath products, eye & facial cleaners, liquid detergents, surface cleaners, roll-on deodorants, pet products
- Second most common allergen in shampoo
- Areas of Involvement
  - Face: 30.2%
  - Neck: 14.3%
  - Hands: 12.7%
  - Eyelids: 9.5%
  - Scalp: 4.8%
  - Scattered: 23.8%
- Positive reactions to this allergen are often clinically relevant

Contact Dermatitis in Atopics

Atopic Dermatitis
- Exposed to numerous creams, ointments & medications
- Impaired skin barrier function
  - Increase allergen penetration
  - Amplifies effects of irritants & allergens
- Contact sensitization in AD is underestimated
  - AD is an important risk factor for development of ACD in children (34.0%) > in adults (11.2%)
- Contact sensitization may worsen the skin of AD and influence the course of atopic disease

References:
Consider CD in AD patients who have:
- Dermatitis that
  - worsens
  - changes distribution
  - fails to improve
  - immediately rebounds
- Atypical distribution/pattern
  - head predominance
  - hand or foot
  - eyelid predominance
  - cheilitis/perioral predominance
- Therapy-resistant hand eczema
- Adult- or adolescent-onset AD w/o childhood eczema
- Severe or widespread dermatitis before initiating systemic immunosuppressant

Consider the following allergens in AD
- Metals (nickel, cobalt, potassium dichromate)
- Fragrances (FM, Balsam of Peru)
- Preservatives
- Topical emollients, corticosteroids, antibiotics, antiseptics
- Patient's products

Corticosteroids
- Affects 0.5%-5.8% of suspected of ACD
- Increased risk/suspect:
  - Chronic venous leg ulcers/ stasis derm
  - Contact dermatitis
  - When dermatitis fails to respond to CS
  - When dermatitis worsens with treatment
Steroid Classifications

• **Potency**
  - Class 1-2: thickened, lichenified, severe & acutely inflamed skin
  - Class 6-7: face, eyelids neck, genitalia, axilla, intertriginous areas

• **Allergenicity**
  - Cross reactivity based on 2 immune recognition sites - C6/9 & C16/17 substitutions
  - Groups A, B, C, D-1, D-2

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**Steroid Group A**
- Structure: Has C17 or C21 short chain ester
- Examples: Hydrocortisone acetate, Prednisone, Tixocortol (marker Group A)
- Cross Reactions: Cross reacts with Group D

**Steroid Group B**
- Structure: Has C16 C17 cis-ketal or –diol additions
- Examples: Triamcinolone, Desonide, Flucinonide

**Steroid Group C**
- Structure: C16 methyl group
- Examples: Desoximetasone, Clocortolone, Fludrocortisone

**Steroid Group D1**
- Structure: C16 methyl group & halogenated B ring (labile esters w/o C16 methyl nor B ring halogen substitution)
- Examples: Betamethasone dipropionate, Mometasone furoate

**Steroid Group D2**
- Structure: C16 methyl group & halogenated B ring (labile esters w/o C16 methyl nor B ring halogen substitution)
- Examples: Hydrocortisone butyrate, Budesonide

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**Examples**
- Prednisone
- Desonide
- Clocortolone
- Betamethasone valerate
- Hydrocortisone valerate
- Dexamethasone
- Cloprednol
- Aminonide
- Fluocortolone
- Fluticasone
- Methylprednisolone acetate
- Budesonide
- Betamethasone sodium phosphate
- Mometasone
- Prednicarbate

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**Steroidal Classifications**

**Cross reactivity based on 2 immune recognition sites - C6/9 & C16/17 substitutions**

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Group D1</th>
<th>Group D2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>2.7%</td>
<td>1.5%</td>
<td>&lt;0.2%</td>
<td>0.8%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Structure</td>
<td>Has C17 or C21 short chain ester</td>
<td>Has C16 C17 cis-ketal or –diol additions</td>
<td>C16 methyl group</td>
<td>C16 methyl group &amp; halogenated B ring</td>
<td>(labile esters w/o C16 methyl nor B ring halogen substitution)</td>
</tr>
</tbody>
</table>

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**Cross Reactions**
- Cross reacts with D2
- Budesonide specifically cross reacts with D2
- Cross reacts Class A and Budesonide

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What agents should you test with?

- These three agents have been shown to detect > 90% of steroid allergy
  - Tixocortol Pivalate* (marker for Group A)
  - Budesonide* (Group B)
  - Hydrocortisone-17-Butyrate *(Class D2)
- Use of patient’s own CS product
- Vehicle etc
  - Propylene glycol: 64% (most common)
  - Sorbitan sesquioleate: 28% (second most common)
  - Formaldehyde-releasing preservatives
  - Parabens
  - Fragrance mix
  - MCI/MI
  - Lanolin
- If PT is not available: Class C steroid with a vehicle with no “common” allergens
  - Desoximetasone 0.25% ointment
  - Desoximetasone 0.05% gel
  - Tacrolimus Ointment (0.1%, 0.03%)

* all in TT®

Issues to patch testing with steroids

- Late Reading
  - PT complicated by anti-inflammatory nature
  - Additional reading Day 7-10
  - ~30% of TCS allergy would be missed without late reading*
- Rim reactions
  - True positives
  - High concentration in center suppresses reaction
  - Lower concentration at edge does not suppress reaction

Gold

- Now included in TRUE Test (routine epicutaneous PT)
- ACDS suggest including gold sodium thiosulfate 2% stating potential relevance in specific targeted patients
  1. suspected jewelry allergy
  2. patients with facial or eyelid dermatitis
  3. exposure through gold dental restorations

Gold Allergy Pearls

- Gold is largely inert unless in the presence of specific factors
  i.e., cysteine in some body fluids/sweat; microabrasives such as titanium dioxide; copper in lower-karat gold alloys
- Screening for gold allergy is most helpful when evaluating patients
  ◦ with facial and eyelid dermatitis
  ◦ when jewelry allergy is suspected
  ◦ when there is involvement of the ears, hands, and neck
  ◦ history of current exposure to gold dental materials
- Reactions are often delayed (up to 3 weeks) & long lasting
- Positive gold reactions are often not clinically relevant.
- Trial of gold avoidance may be warranted if with + PT to gold
  ◦ Avoidance period for benefit is long & may only be partial
**Gold: 96 hours**

Persistent (+) reactions
- may persist from 7 days to months after application
- notorious is gold

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**Top (+) reactions to NACD Allergens**

<table>
<thead>
<tr>
<th>Rank</th>
<th>Allergen</th>
<th>NACD %</th>
<th>T.R.U.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nickel Sulfate</td>
<td>18.5</td>
<td>x</td>
</tr>
<tr>
<td>2</td>
<td>Fragrance Mix I</td>
<td>12.1</td>
<td>x</td>
</tr>
<tr>
<td>3</td>
<td>Neomycin</td>
<td>9.1</td>
<td>x</td>
</tr>
<tr>
<td>4</td>
<td>Balsam of Peru</td>
<td>7.9</td>
<td>x</td>
</tr>
<tr>
<td>5</td>
<td>Bacitracin</td>
<td>7.6</td>
<td>x</td>
</tr>
<tr>
<td>6</td>
<td>Cobalt Chloride</td>
<td>7.3</td>
<td>x</td>
</tr>
<tr>
<td>7</td>
<td>Formaldehyde</td>
<td>6.6</td>
<td>x</td>
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<tr>
<td>8</td>
<td>Quaternium 15</td>
<td>6.4</td>
<td>x</td>
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<tr>
<td>9</td>
<td>PPD</td>
<td>6.3</td>
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<tr>
<td>10</td>
<td>Fragrance Mix II</td>
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<td>11</td>
<td>MC/MI</td>
<td>5.0</td>
<td>x</td>
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<tr>
<td>12</td>
<td>Carba Mix</td>
<td>4.7</td>
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<td>13</td>
<td>Lanolin (Wool Alcohol)</td>
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<tr>
<td>14</td>
<td>Iodopropynyl Butylcarbamate</td>
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<td>15</td>
<td>Cinnamic Aldehyde</td>
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<td>in FMI</td>
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<td>Methyl Dibromoglutaronitrile/phenoxycetanol</td>
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<td>17</td>
<td>Carmine</td>
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<td>18</td>
<td>Thioram</td>
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<td>x</td>
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<td>19</td>
<td>Propylene Glycol</td>
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<td>x</td>
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<tr>
<td>20</td>
<td>Tixocortol Pivalate</td>
<td>2.3</td>
<td>x</td>
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</tbody>
</table>

**Top (+) reactions to NACD Allergens**

<table>
<thead>
<tr>
<th>Rank</th>
<th>Allergen</th>
<th>NACD %</th>
<th>T.R.U.E.</th>
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<tbody>
<tr>
<td>21</td>
<td>Diamidopropyl dimethylamine</td>
<td>2.3</td>
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<tr>
<td>22</td>
<td>Colophony</td>
<td>2.2</td>
<td>x</td>
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<tr>
<td>23</td>
<td>Diazolidinylurea Pet</td>
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<td>x</td>
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<td>24</td>
<td>Hydroxyethylnmethacrylate</td>
<td>2.0</td>
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<td>25</td>
<td>Compostae Mix</td>
<td>1.9</td>
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</tr>
<tr>
<td>26</td>
<td>Propolis</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>Imidazolidinylurea pet</td>
<td>1.6</td>
<td>x</td>
</tr>
<tr>
<td>28</td>
<td>Potassium Dichromate</td>
<td>1.6</td>
<td>x</td>
</tr>
<tr>
<td>29</td>
<td>2-Bromo-2-nitro-1,3- propanediol</td>
<td>1.6</td>
<td>x</td>
</tr>
<tr>
<td>30</td>
<td>DMDM Hydantoin</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>Decyl glucoside</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>Shellac</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>Glutaral 1%</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>Dimethyaminopropylamine</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>Epoxy resin</td>
<td>1.5</td>
<td>x</td>
</tr>
<tr>
<td>36</td>
<td>Cocamidopropyl betaine</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>Benzocaine</td>
<td>1.4</td>
<td>Caïne Mix</td>
</tr>
<tr>
<td>38</td>
<td>Paraben</td>
<td>1.4</td>
<td>x</td>
</tr>
<tr>
<td>39</td>
<td>Ethylenediamine dihydrochloride</td>
<td>1.3</td>
<td>x</td>
</tr>
<tr>
<td>40</td>
<td>Majantol</td>
<td>1.3</td>
<td></td>
</tr>
</tbody>
</table>

Allergens not in the T.R.U.E. Test ®

DERMATITIS, Vol 28, No 1, January/February, 2015
T.R.U.E. TEST® (36) vs. NACDG Screening Series

- Hypothetical detection rate of TT® vs. NACDG: 69.7% - 75.1%
- Antigens on TT® not on NACDG screening series
  - Thimerosal, gold, quinoline mix
- Individual components vs. “mixes”
  - caine mix (TT®) vs. benzocaine & dibucaine (NACDG)
  - parthenolide (TT®) vs. sesquiterpene lactone mix & compositae mix (NACDG)
- TT®: higher false (-) to neomycin, thiuram mix, BOP, fragrance mix, cobalt, lanolin

Antigens in top 40 NACDG not on TT
- fragrance mix II
- carmine
- propolis
- shellac
- decyl glucoside
- majantol
- DMDM hydantoin
- iodopropyl butylcarbamate
- propylene glycol
- dimethylaminopropylamine
- hydroxyethylmethacrylate
- oleamidopropyldimethylamine
- cocamidopropyl betaine
- glutaral

Other important non-TT allergens
- tosylamide formaldehyde resin
- amidoamine
- acrylates/methylacrylates
- tea tree oil
- benzophenone-3
- mixed dialkyl thioureas

Patch Test Recommendations for Children 6-12 y.o.

<table>
<thead>
<tr>
<th>Primary Allergens</th>
<th>Secondary Allergens</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Bacitracin</td>
<td>1 black rubber mix</td>
</tr>
<tr>
<td>2 Budesonide</td>
<td>2 dialkyl thioureas</td>
</tr>
<tr>
<td>3 Carba mix</td>
<td>3 mercaptobenzothiazole</td>
</tr>
<tr>
<td>4 Cobalt chloride</td>
<td>4 para-phenylenediamine</td>
</tr>
<tr>
<td>5 Cocamidopropyl betaine</td>
<td>5 p-tert butyl phenol formaldehyde resin</td>
</tr>
<tr>
<td>6 Colophonium</td>
<td></td>
</tr>
<tr>
<td>7 Compositae mix/dandelion extract</td>
<td></td>
</tr>
<tr>
<td>8 Disperse blue</td>
<td></td>
</tr>
<tr>
<td>9 Ethylenediamine</td>
<td></td>
</tr>
<tr>
<td>10 Formaldehyde</td>
<td></td>
</tr>
<tr>
<td>11 Fragrance mix 1</td>
<td></td>
</tr>
<tr>
<td>12 Fragrance mix 2</td>
<td></td>
</tr>
<tr>
<td>13 Lanolin alcohol</td>
<td></td>
</tr>
<tr>
<td>14 MCI/MI</td>
<td></td>
</tr>
<tr>
<td>15 Myroxylon pereirae (Balsam of Peru)</td>
<td></td>
</tr>
<tr>
<td>16 Neomycin sulfate</td>
<td></td>
</tr>
<tr>
<td>17 Nickel sulphate</td>
<td></td>
</tr>
<tr>
<td>18 Potassium dichromate</td>
<td></td>
</tr>
<tr>
<td>19 Quaternium 15</td>
<td></td>
</tr>
<tr>
<td>20 Tixocortol-1-pivalate</td>
<td></td>
</tr>
</tbody>
</table>

Ideally tests would be prepared at the time they are placed.

Allergen in Petrolatum can be prepared ahead of time except....

Avoid early preparation of acrylates, fragrances, and all allergens in aqueous vehicle.

Most true allergic reactions occur between 72-96 hours.

Allergens that may peak early
- thiuram mix
- carba mix
- balsam of Peru

Allergens that Disappear after 5 Days
- Balsam of Peru
- Benzoic Acid
- Disperse Blue #124
- Fragrance mix
- Mercury
- Methylidibromogluteronitrile/phenoxethanol
- Octyl gallate

Delayed Patch Test Reactions after 5 days
- Metals
  - Gold
  - Potassium Dichromate
  - Nickel
  - Cobalt
- Topical Antibiotics
  - Neomycin
  - Bacitracin
- Topical Corticosteroids
- PPD

Reported manifestation of implant allergy
1. Dermatitis
2. Implant failure

Peri-implant immune environment

- Metal corrosion of implant in contact with biological fluids
- Significant levels of metal ions in capsular, periprosthetic tissues, l.n. liver, spleen, urine/serum of pts w/ hip arthroplasty
- Necrosis
- Phagocytosis
- Foreign body giant cells

- Cutaneous reactions above implant: primarily T cell-mediated type IV rxns
- Peri-implant environment
  - Type 4 delayed response likely a component but not the only cause
  - TH1 dominant with increased IL-2, IL-6, IL-17, IFNg

Which subgroups have increased risk of complications with metal implants?

- Unknown...
  Sensitization to metals increased 6.5% following arthroplasty*

  Hip arthroplasty: sensitization to nickel, cobalt or chromium
  - 25% in well-functioning implants (>2x general population)**
  - 60% in failed or failing prosthesis (6x general population)**

  Total knee arthroplasty: metal sensitization rate
  - 20% in pts w/ no implant
  - 48.1% in pts w/ stable implant
  - 59.6% in unstable implant group***

- Available evidence indicates a correlation between metallic orthopaedic implants, development of metal hypersensitivity and implant loosening

  Does loosening cause hypersensitivity or does hypersensitivity cause loosening?

---


Should allergy screening be performed? (Preimplantation Patch Test)

- There is an increasing volume of malpractice cases related to implants and allegations of inadequate preoperative allergy assessment.
- Search on google.com returned 396,000 hits for “metal allergy malpractice.”

**The German Implant Allergy Working Group** of the German Association of Orthopedics & Orthopedic Surgery, German Contact Dermatitis Research Group & German Society for Allergology and Clinical Immunology

- Do not require preimplant testing
- Recommend titanium-based materials for patients reporting metal reactions
- Recommend have written consent before placement of a potentially allergenic articulation, if that device is preferred
Consensus Recommendations for Preimplantation

Allergy Practice Parameters
American Contact Dermatitis Society

Routine preimplant PT not recommended for individuals who deny a history of cutaneous reactions to metals and deny previous implant-related adverse events.

Consider pre-operative evaluation for metal sensitization in patients with a significant history of metal allergy.

Patients with clear self-reported history of metal reactions should be evaluated by PT before device implant.

-Self-reported intolerance to jewelry alone is not an adequate screen for cutaneous metal allergy (+ predictive value 59-60%)

Preimplantation: What to test with

- Standardized, commercially available materials when possible
  - Metals
  - Bone Cement components
  - Abbreviated Series
- Manufacturer-provided metal discs testing has limited utility
- (+) PT or LTT does not consistently predict in vivo metal-induced complications from metal implants
- (-) PT is only indicative of current state of allergy

If preimplantation testing is not possible or refused, titanium- or oxinium-containing devices are preferable.
Issues to address with a positive Pre-implantation patch test

1. Which implant/device will give the best outcome (functionality/durability)
   - Role of patient’s surgeon
2. Does a positive PT to metal found in the ‘best’ device warrant using an inferior device?
   - Role of allergist/dermatologist
   - Identify metal/s with positive PT
   - Give guidance on safe materials for implantation (i.e. negative reactions with metal screening series)

Retrospective case–control study prior to total hip replacement
• (+) PT to metals and history of metal hypersensitivity had significantly shorter life spans of their implants
• (+) PT to bone cement components, none had stable implant at a 10-year endpoint

Post Implantation PT:

Patients with no symptoms after implantation do not require PT

• Joint Failure: joint loosening, pain
  - Infection & biomechanical issues have been ruled out
• Dermatitis (above site of implant)
  - beginning weeks to months after implantation
  - resistant to medical therapy
Joint Failure: Post Implantation Patch Test

- ~10% of patients with joint replacements will fail (pain, swelling, itching/burning, and/or ↓ range of motion)
- Metal sensitivity rates are higher in patients with failed implants
- More common Causes
  - Infection
  - Biomechanical issues
  - Metallosis – a toxic/necrotic reaction to metal wear particles
  - DVT / hemarthroses

There is increasing evidence to support PT as the next step in evaluating patients as the cause of joint failure when other causes have been ruled out.

What to test with

- **Metal and Bone Cement components**
- **Baseline series** (Review examining metal device implantation suggested some form of baseline screening for all patients*)
- Manufacturer provided metal disc testing: unreliable
  - Irritant reactions, false negatives, and false positives are common.

**Joint failure w/o dermatitis:**
- **abbreviated series**
  - TRUE TEST™
  - European baseline series
  - NACDG Standard series of 50 allergens
  - American Contact Dermatitis Society’s Core Panel

**Those with dermatitis:**
- specially trays appropriate for the clinical history and an extended series
  - Extended NACD series
  - International Comprehensive Baseline series

---


Common Bone Cement Allergen in Total Joint Arthroplasties

<table>
<thead>
<tr>
<th>Allergen</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>

All manufacturers use similar components.
**Patch Testing vs Lymphocyte Transformation Test**

**Practice Parameters:**
- The clinical relevance of commercially available blood tests to diagnose metal sensitization have not been determined

**ACDS:**
- The LTT is not widely available, not standardized, expensive, subject to variability, may be overly sensitive (false-positive reactions)

- **Measures lymphocyte proliferation** (stimulation index) after 7 days incubation +/- allergen
  - Limited allergens
  - Rapid decay of T cells (rapid transportation)*
- May be useful in questionable cases
  - (-) PT & persistent concerns about metal allergy
  - 54/56 patients with Ti implants, (-) PT & (+) Ti LTT whose systemic symptoms resolved after implant removal

* MELISA test: Health Diagnostics and Research Institute, South Amboy, NJ


**What to do with a Positive Patch Test:**

**Practice Parameters:**
- Sensitization to metals were significantly higher in patients with failed than with well-functioning or without an implant.
- The likelihood that implant allergy is the cause of implant failure is higher when other causes of implant failure (infection and biomechanical issues) have been ruled out.
- There are no current recommendations for symptomatic patients with (+) PT to metals or bone cement components.
- The decision on implant revision following (+) PT results can only be made after a thorough discussion between the patient, the allergist or dermatologist, and the orthopedic surgeon.

**American Contact Dermatitis Society**
- A positive metal test does not prove causality of symptoms.
- Other causes of implant failure treatable without device removal should be carefully considered.
- Fixed devices with poor healing or eruptions above or adjacent to the incision site are more indicative of potential MHR.
- Replacement with nonallergenic alternative may be helpful, but must be individualized
- There is not enough evidence at this time to make overreaching recommendation.
- The decision to remove an implanted device must include assessment of all clinical factors and a thorough risk benefit analysis by the treating physician(s) and patient.


Relief of symptoms average 143 days sooner on patch tested vs. non patch tested patients*

Identification & avoidance of contact with the offending agent(s) is key to the success of ICD and ACD treatment.

Traditional approach
• Give name of allergen
• Patient reviews package labeling

Typical allergen names are
• long
• difficult to spell
• numerous complex synonyms
• intimidating

Poor compliance with allergen avoidance

• Generate list of allergens to avoid and
• Comprehensive list of products free of identified allergens

• Increase compliance
• Faster resolution of disease
• Decrease required physician patient education

Recommendation Prior to Patch Testing
“Lo.C.A.L. (Low contact allergen) Skin Diet (Zug KA)

Eliminates most common allergens:
• Fragrance
• Formaldehyde Releasing Preservatives
• MCI/MI
• MDG/PE
• Lanolin
• CAPB
• Benzophenone-3

• Cover girl clean fragrance free liquid make-up
• Clinique blushing blush powder blush
• Clinique soft pressed eye shadow
• Max factor vivid impact lip liner-all shades
• Almay hypoallergenic roll-on anti-perspirant/deodorant
• Cerave moisturizing lotion/ vanicream
• Cetaphil gentle skin cleanser
• Free & Clear shampoo
• Free & Clear hair spray - firm hold
Coding & Reimbursement:

- **Visit 1**
  - E/M service
  - Bill # of patches placed: CPT code 95044
  - No E/M if visit is only for application of PT
  - Determine maximum allowable tests per beneficiary per year.
  - Medicare pays $7.29/patch

- **Visit 2 and 3**
  - E/M Level 2-3 for follow up visits with supporting documentation

- **ICD-10 Codes for E/M visits**
  - Allergic Contact Dermatitis, Metals L23.0
  - Allergic Contact Dermatitis, Cosmetics L23.2
  - Allergic Contact Dermatitis, Unspecified L23.9

Useful Resources

- **American Contact Dermatitis Society** ([www.contactderm.org](http://www.contactderm.org))
  - requires membership

- **Contact Dermatitis Institute** ([www.contactdermatitisinstitute.com/mypatchlink.php](http://www.contactdermatitisinstitute.com/mypatchlink.php))
  - Patient handouts, webinars

- **Contact Allergen Replacement Database** ([www.AllergyFreeSkin.com](http://www.AllergyFreeSkin.com))
  - List of products to avoid
This parameter was developed by the Joint Task Force on Practice Parameters, which represents the American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology.

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Thank you