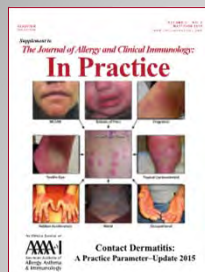


Pennsylvania Allergy, Asthma and Immunology Society  
June 25, 2017

## Contact Dermatitis: Update and Practical Advice

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## Disclosure

Research and Educational Grants (to Winthrop University Hospital)

Baxter

Genentech

Merck

Consultant

Church and Dwight, Co., Inc

Regeneron

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# 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

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**TABLE 3. Body Sites of Dermatitis and Final Diagnoses**

Characteristic	Primary, n (%)	Total of up to 3 Listed <sup>d</sup> , n (%) <sup>f</sup>
Dermatitis site <sup>b</sup>	n = 4854*	N = 4871
Hand	982 (20.2)	1180 (24.2)
Scattered/generalized	808 (16.6)	1039 (21.3)
Face	755 (15.5)	1094 (22.5)
Eyelids	514 (10.5)	626 (12.9)
Trunk	319 (6.6)	704 (14.5)
Arm	251 (5.2)	781 (16.0)
Leg	224 (4.6)	589 (12.1)
Scalp	210 (4.3)	314 (6.5)
Lips	187 (3.9)	253 (5.2)
Anal/genital	147 (3.0)	198 (4.1)
Foot	128 (2.6)	273 (5.6)
Other	85 (1.8)	112 (2.3)
Neck	82 (1.7)	464 (9.5)
Most exposed areas	56 (1.2)	66 (1.4)
Ears	54 (1.1)	122 (2.5)
Eyes	32 (0.7)	55 (1.1)
Only under clothes	17 (0.4)	23 (0.5)
Erythroderma	4 (0.1)	7 (0.1)
Nose	1 (0.0)	5 (0.1)

DeKoven JG, Warshaw EM, Belisio DV et al. North American Contact Dermatitis Group Patch Test Results 2013-2014. DERMATITIS, January/February, 2017 Vol 28, No 1 pp 33-46

\*Excludes 17 patients with no primary site listed.

<sup>b</sup>Total of percentages may exceed 100% because up to 3 sites/diagnoses per patient could be listed.

<sup>c</sup>Total of any of up to 3 sites or up to 3 diagnoses listed.

<sup>d</sup>Excludes 39 patients with no primary final diagnosis.

## **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 hair dressers
- 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)

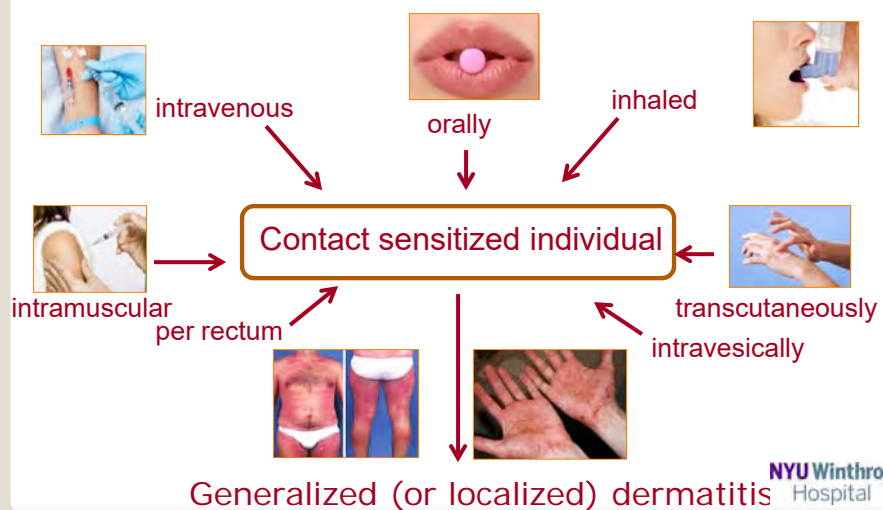
## Allergic Contact Dermatitis to Textile Formaldehyde Resin

- 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

Dermatitis: 2007, Vol 18 (1) 40-44  
doi: 10.2310/6620.2007.05003

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## Systemic Contact Dermatitis



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## 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

Am J Clin Dermatol 2011; 12 (3)

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## Dermatitis with Scattered Generalized Distribution



### Nickel



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=895mcg
- Figs: ~5=85 mcg
- Cocoa: 1 tbsp=147 mcg
- Lentils: ½ 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

Zug KA, Rietschel RL, Warshaw EM, et al. The value of patch testing patients with a scattered generalized distribution of dermatitis: Retrospective cross-sectional analyses of North American Contact Dermatitis Group data, 2001 to 2004. J Am Acad Dermatol 2008;59:426-431

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## 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<sup>6</sup>**

	Eugenol	Cinnamates	Benzoic Acid	Vanillin	Ferulic Acid	Coniferins
Citrus peel		x			x	
Sweet food	x	x	P	x		
Chocolate	x	x	x	x		
Vanilla			x	x		
Synthetic vanilla	+/-			x		
Cola	x	x	x	x	x	
Tomato	x	x			x	x
Cinnamon	x	x	x			
Cassia		x	x			
Cloves	x			x		
Nutmeg and mace	x					
Dill	x				x	
Allspice	x					
Anise	x	x	x			
Bay leaves and basil	x	x				
Curry powder	x	x		x		
Spiced condiments	x	x	x			
Pickles	x	x	x	x	x	
Pâte	x	x	x	x	x	
Perfumed tea and tobacco	x	x		x		
Wine		x		x	x	x
Beer	x	x		x		x (product of fermentation of brewer's yeast)
Gin	x	x			x	
Vermouth	x	x	x	x	x	
Whiskey	x			x	x	x
Spiced Liquors	x	x		x		
Beets						x
Asparagus				x		x
Wheat and rye					x	
Brewer's yeast			P			x (product of fermentation)
Food with benzoate preservatives			P			

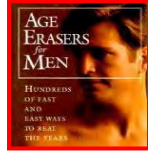
*P, benzoates are not intrinsically contained in these food but may be added as a preservative; x, present; +/-, may or may not be present.*

## COSMETICS



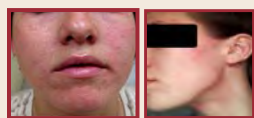
MAC Cosmetics teamed up with Mattel toy to launch a new line, "Barbie inspired" MAC Barbie Line cosmetics

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



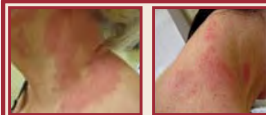
### The make-up used by children

- sold in toy stores
- not suitably controlled
- often contaminated by nickel
- can cause eyelid dermatitis (mascara, eye-liners, eye shadow)



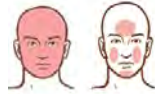
Face: bilateral & patchy

- 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



Eyelid

- Allergic CD 55-72 %
- Fragrance (FMI & BOP)
- Gold sodium thiosulfate
- Nickel sulfate



Lip

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



## The Science of Cosmetics

Typical contact allergens tend to be clustered in a few important classes

- Fragrances
- Preservatives
- Excipients
- Glues
- Sun blocks

Warshaw EM et al. North American Contact Dermatitis Group Patch Test Results for 2009-2010. DERMATITIS, 2013. Vol 24: 2:50-59

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## Fragrance

Fragrance Mix I	Balsam of Peru <i>Myroxylon pereirae</i>	Fragrance Mix II
Cinnamic alcohol 1%	Cinnamic acid	Coumarin 2.5%
Cinnamic aldehyde 1%	Benzoyl Cinnamate	Hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyral) 2.5%
$\alpha$ -Amyl cinnamaldehyde (amyl cinnamal) 1%	Benzoyl Benzoate	Citronellol 0.5%
Hydroxycitronellal 1%	Benzoic acid	Farnesol 2.5%
Geraniol 1%	Vanillin	Citral 1.0%
Isoeugenol 1%	Nerodilol	$\alpha$ Hexyl cinnamic aldehyde 5.0%
Eugenol 1%		
Oak moss 1%		

Other fragrance sensitizers: jasmine, lavender, sandalwood, tea tree oil, ylang ylang oil, lemongrass oil, jasmine, Narcissus

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

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## 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



Devos SA et al. Relevance of Positive Patch-Test Reactions to Fragrance Mix. Dermatitis, Vol 19, No 1, 2008: 43-47

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## Cosmetic Preservatives

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

Formaldehyde	(+) PT*	Non Formaldehyde	(+) PT*
Formaldehyde	6.6 %	Iodopropynylbutylcarbamate	4.2%
Quarternium 15	6.4%	Methyldibromoglutaronitrile (Euxyl K 400)	3.7 %
Diazolidinyl urea (Germall II)	2.1 %	MCI/MI	5.0 %
Imidazolidinyl urea (Germall)	1.6 %	Parabens	1.4 %
Bromonitropropane (Bronopol)	1.6 %	Chloroxlenol	0.5 %
DMDM Hydantoin (Glydant)	1.6 %		

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

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

\*\*Albert MR et al. Concomitant positive reactions to allergens in the patch testing standard from 1988-1997. Am J Contact Dermat 1999. 10:219-223  
Warshaw EM et al. North American Contact Dermatitis Group Patch Test Results for 2011-2012. DERMATITIS, March/April 2013. Vol 26:1:49-59

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## 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)



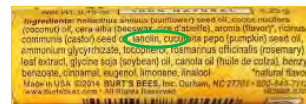
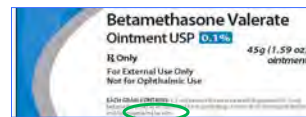
Castaneda-Tardana & Zug. Contact Allergen of the Year 2013 Dermatitis, 24 (1)

\* Lundov MD, Thyssen JP, Zachariae C, et al. Prevalence and cause of methylisothiazolinone contact allergy. Contact Dermatitis 2010;63:164-167

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## 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



Erin M. Warshaw et al. Positive Patch Test Reactions to Lanolin: Cross-Sectional Data from the North American Contact Dermatitis Group, 1994 to 2006. Dermatitis. April 2009. 20:2:79-88

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## 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

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## 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

Seidenari S, Giusti F, Pepe P, Mantovani L. Contact sensitization in 1094 children undergoing patch testing over a 7-year period. *Pediatr Dermatol* 2005;22:1-5.

\*Czarnobilska E, et al. Contact hypersensitivity and allergic contact dermatitis among schoolchildren and teenagers with eczema. *Contact Dermatitis* 2009; 60: 284-9. Position paper on diagnosis and treatment of atopic Dermatitis. Darsow, U et al 2005 European Academy of Dermatology and Venereology *JEADV* (2005) 19, 286-295

Manzini BM, Ferdani G, Simonetti V et al. Contact sensitization in children. *Contact Dermatitis* 1998; 15: 12-17.

Mortz CG, Andersen KE. Allergic contact dermatitis in children and adolescents. *Contact Dermatitis* 1999; 41: 121-130

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## Contact Dermatitis in Atopic Dermatitis

### 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

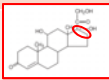
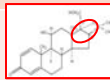
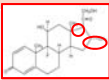
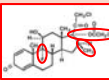
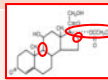
- Potency
  - Class 1-2: thickened, lichenified, severe & acutely inflamed skin
  - Class 6-7: face, eyelids neck, genitalia, axilla, intertriginous areas
- Allergenicity
  - Cross reactivity based on 2 immune recognition sites- C 6/9 & C16/17 substitutions
  - Groups A, B, C, D-1, D-2

Warner MR, Camisa C. Topical Corticosteroids. In: Wolverson SE, ed. Comprehensive Dermatologic Drug Therapy, 2nd ed. Saunders, 2007. p 595-624.  
 Berth-Jones J. Topical Therapy. In: Burns T, Breathnach S, Cox N, Griffiths C, eds. Rook's Textbook of Dermatology, 8th ed. Wiley-Blackwell. Ch. 75.

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### STRUCTURAL GROUPS OF CORTICOSTEROIDS

Cross reactivity based on 2 immune recognition sites- C 6/9 & C16/17 substitutions

Steroid	Group A	Group B	Group C	Group D1	Group D2
Prevalence	2.7%	1.5%	<0.2%	0.8%	0.8%
Structure					
	Has C17 or C21 short chain ester)	Has C16 C17 cis-ketal or -diol additions)	C16 methyl group	C16 methyl group & halogenated B ring	(labile esters w/o C16 methyl nor B ring halogen substitution
Examples	Hydrocortisone acetate Prednisone Tixocortol (marker Group A) Methylprednisolone acetate Cloprednol Fludrocortisone Prednisolone	Triamcinolone Desonide Fluocinonide Budesonide (may cross react with Group D) Aminonide Halcinonide Fluocinolone	Desoximetasone Clocortolone Dexamethasone Betamethasone sodium phosphate Fluocortolone	Betamethasone dipropionate Betamethasone valerate Clobetasol propionate Mometasone Fluticasone Aclomethasone	Hydrocortisone butyrate Hydrocortisone valerate Prednicarbate Hydrocortisone aceponate Methylprednisolone aceponate
Cross Reactions	Cross reacts with D2	Budesonide specifically cross reacts with D2			Cross reacts Class A and Budesonide

Wilkinson SM Corticosteroid cross reactions: an alternative view. Contact dermatitis 2000;42:59-63

## 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®

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## 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



\*Issaksson M et al. Patch testing with corticosteroid mixes in Europe. Contact Dermatitis 2000;42:27-35

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## 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



Gold: 3 months later

**Persistent (+) reactions**

- may persist from 7 days to months after application
- notorious is gold

	Top (+) reactions to NACD Allergens	NACD %	T.R.U.E.
1	Nickel Sulfate	18.5	x
2	Fragrance Mix I	12.1	x
3	Neomycin	9.1	x
4	Balsam of Peru	7.9	x
5	Bacitracin	7.8	x
6	Cobalt Chloride	7.3	x
7	Formaldehyde	6.6	x
8	Quarternium 15	6.4	x
9	PPD	6.3	x
10	Fragrance Mix II	5.2	
11	MCI/MI	5.0	x
12	Carba Mix	4.7	x
13	Lanolin (Wool Alcohol)	4.6	x
14	Iodopropynyl Butylcarbamate	4.2	
15	Cinnamic Aldehyde	3.9	In FMI
16	Methyl Dibromoglutarate Nitrile/ phenoxyethanol	3.7	x
17	Carmines	3.1	
18	Thiuram	2.9	x
19	Propylene Glycol	2.6	
20	Tixocortol Pivalate	2.3	x

	Top (+) reactions to NACD Allergens	NACD %	T.R.U.E.
21	Oleamidopropyl dimethylamine	2.3	
22	Colophony	2.2	x
23	Diazolidinylurea Pet	2.1	x
24	Hydroxyethylmethacrylate	2.0	
25	Compositae Mix	1.9	Parthenonide
26	Propolis	1.8	
27	Imidazolidinylurea pet	1.6	x
28	Potassium Dichromate	1.6	x
29	2-Bromo-2-nitro-1,3-propanediol	1.6	x
30	DMDM Hydantoin	1.6	
31	Decyl glucoside	1.6	
32	Shellac	1.6	
33	Glutaral 1%	1.5	
34	Dimethylaminopropylamine	1.5	
35	Epoxy resin	1.5	x
36	Cocamidopropyl betaine	1.4	
37	Benzocaine	1.4	Caine Mix
38	Paraben	1.4	x
39	Ethylenediamine dihydrochloride	1.3	x
40	Majantol	1.3	

Allergens not in the T.R.U.E. Test ®

## 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** - iodopropyl butylcarbamate
- carmine - propylene glycol
- propolis - dimethylaminopropylamine
- shellac - **hydroxyethylmethacrylate**
- decyl glucoside - oleamidopropyldimethylamine
- majantol - **cocamidopropyl betaine**
- DMDM hydantoin - glutaral

### Other important non-TT allergens

- **tosylamide formaldehyde resin**
- amidoamine
- **acrylates/methacrylates**
- tea tree oil
- benzophenone-3
- mixed dialkyl thioureas

DERMATITIS, Vol 26 | No 1 | January/February, 2015

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

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

Jacob SE, Brod B, Crawford GH. Clinically relevant patch test reactions in children—a United States based study. *Pediatr Dermatol*. 2008 Sep-Oct;25(5):52

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## Pre Loading Allergens



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.

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## The "Right Time to Read"

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
- Methylidibromogluteroni trile/phenoxyethanol
- Octyl gallate

### Delayed Patch Test Reactions after 5 days

- Metals
  - Gold
  - Potassium Dichromate
  - Nickel
  - Cobalt
- Topical Antibiotics
  - Neomycin
  - Bacitracin
- Topical Corticosteroids
- PPD

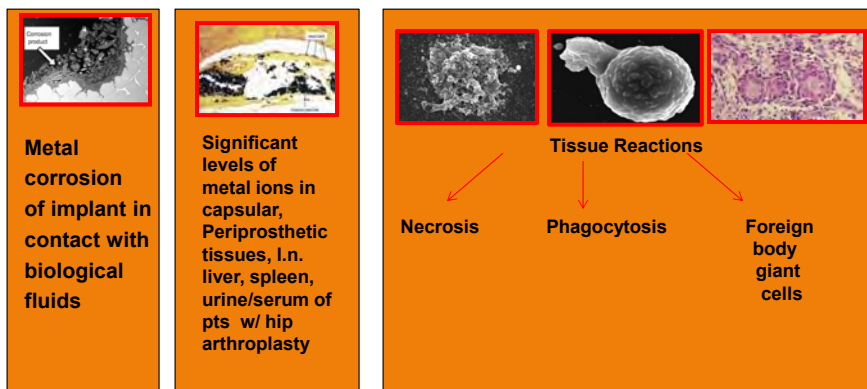
Davis M et al. Delayed Patch Test reading after 5 days : the Mayo Clinic Experience. JAAD Aug 2008; 59 (2):225-233  
Higgins et al. The relevance of 7-day patch test reading. Dermatitis. 24(5):237-240, 2013.

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## Reported manifestation of implant allergy

1. Dermatitis
2. Implant failure

## Peri-implant immune environment



- 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?

\* E. Frigerio, P. D. Pigatto, G. Guzzi, and G. Altomare, "Metal sensitivity in patients with orthopaedic implants: a prospective study," *Contact Dermatitis*, vol. 64, no. 5, pp. 273-279, 2011.  
\*\* N. Hallab, "Metal sensitivity in patients with orthopedic implants," *Journal of Clinical Rheumatology*, vol. 7, no. 4, pp. 215-218, 2001.  
\*\*\* D. Granchi, E. Cenni, D. Tigani, G. Trisolino, N. Baldini, and A. Giunti, "Sensitivity to implant materials in patients with total knee arthroplasties," *Biomaterials*, vol. 29, no. 10, pp. 1494-1500, 2008.

## 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

Schallock PC et al. Patch Testing for Evaluation of Hypersensitivity to Implanted Metal Devices: A Perspective From the American Contact Dermatitis Society. *Dermatitis*, Vol 27 | No 5 | September/October, 2016  
Thomas P. SchuHA, Ring J. et al. Orthopedic surgical implants and allergies: joint statement by the Implant Allergy Working Group (AK 20) of the DGOOC (German Association of Orthopedics and Orthopedic Surgery), DKG (German Contact Dermatitis Research Group) and DGAKI (German Society for Allergology and Clinical Immunology). *Orthopade* 2008;37:75Y88.

## Consensus Recommendations for Preimplantation



Allergy Practice  
Parameters



American Contact  
Dermatitis Society

Routine preimplant PT not recommended 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%)

Some studies show patients with high suspicion of metal allergy  
-- who had pre-operative PT that guided implant selection  
-- have improved outcomes

Fonacier L, Bernstein D, Pacheco K, Holness DL, et al. Contact Dermatitis: A Practice Parameter Update – 2015. Journal of Allergy and Clinical Immunology In Practice. Vol 3, No 3 May/June 2015. S1-39  
Schalock PC et al. Patch Testing for Evaluation of Hypersensitivity to Implanted Metal Devices: A Perspective From the American Contact Dermatitis Society. Dermatitis, Vol 27, No 5, September/October, 2016

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### 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

Schalock PC et al. Patch Testing for Evaluation of Hypersensitivity to Implanted Metal Devices: A Perspective From the American Contact Dermatitis Society. Dermatitis, Vol 27, No 5, September/October, 2016

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## 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

Schalock PC et al. Patch Testing for Evaluation of Hypersensitivity to Implanted Metal Devices: A Perspective From the American Contact Dermatitis Society. *Dermatitis*. Vol 27 ; No 5 ; September/October, 2016

Thomas P, Sumner B, Sander CA, et al. Intolerance of osteosynthesis material: evidence of dichromate contact allergy with concomitant oligoclonal T-cell infiltrate and TH1-type cytokine expression in the peri-implantar tissue. *Allergy* 2000;55:960/972

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## 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

Thysson JP et al. Pragmatic approach to the clinical work-up of patients with putative allergic disease to metallic orthopaedic implants before and after surgery. *Br J Dermatol*. 2011;164(3):473-8.

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## 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.

Thyssen JP et al. Pragmatic approach to the clinical work-up of patients with putative allergic disease to metallic orthopaedic implants before and after surgery. Br J Dermatol. 2011;164(3):473-8.  
Schalock PC et al. Patch Testing for Evaluation of Hypersensitivity to Implanted Metal Devices: A Perspective From the American Contact Dermatitis Society. Dermatitis. Vol 27 | No 5 | September/October, 2016

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## 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:

- specialty trays appropriate for the clinical history and an extended series
- Extended NACD series
- International Comprehensive Baseline series

Beswick AD, Wylde V, Goberman-Hill R, et al. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. BMJ Open 2012;22(2):e000435

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

Substances or alloy <sup>a</sup>	Implant or device					
	Dental	Orthopaedic		Intravascular	Pacemaker and ICD	Gynaecological
		Pre-implant	Post-implant			
Aluminium	x	x	x	—	x	—
Beryllium	x	—	—	—	—	—
Cadmium	x	—	—	—	—	—
Chromium	x	x	x	x	x	x
Cobalt	x	x	x	x	x	—
Copper	x	—	—	—	—	x
Gold	x	—	—	x	—	—
Iridium	x	—	—	—	—	—
Iodine	—	—	—	—	x	x
Iron	x	x	x	x	—	—
Manganese	x	x	x	x	—	x
Mercury	x	—	—	—	x	—
Molybdenum	x	x	x	x	x	—
Nickel	x	x	x	x	x	x
Niobium	x	x	x	—	—	—
Palladium	x	—	—	—	—	—
Phosphorus	x	x	x	—	—	—
Platinum	x	—	—	—	x	x
Rhodium	x	—	—	—	—	—
Ruthenium	x	—	—	—	—	—
Silicon	—	x	x	—	—	—
Silver	—	—	—	—	x	x
Tantalum	—	x	x	—	x	—
Tin	x	—	—	—	—	x
Titanium	x	x	x	x	x	x
Tungsten	—	x	—	x	—	—
Vanadium	x	x	x	—	x	—
Zinc	x	—	—	—	—	x
Zirconium	x	x	x	—	—	—
Custom-made disc of relevant alloy	x	x	x	x	x	—

Schaiock1, et al Hypersensitivity reactions to metallic implants – diagnostic algorithm and suggested patch test series for clinical use. *Contact Dermatitis*, 2011, 66, 4–19

## Bone cement components

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

All manufacturers use similar components

Thomas P, Schuh A, Eben R, et al. Allergy to bone cement components. *Orthopaedics* 2008;37:117–20  
 Haddad FS, Cobb AG, Bentley G, et al. Hypersensitivity in aseptic loosening of total hip replacements. The role of constituents of bone cement. *J Bone Joint Surg Br* 1996;78:546–9  
 Kuehn KD, Ege W, Gopp U. Acrylic bone cements: composition and properties. *Orthop Clin North Am* 2005;36:17–28

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## Patch Testing vs Lymphocyte Transformation Test

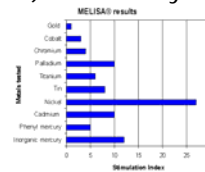


**Practice Parameters:**  
The clinical relevance of commercially available blood tests to diagnose metal sensitization have not been determined



**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)  
Muller K E, Valentine-Thon E. Hypersensitivity to titanium: clinical & laboratory evidence. *Neuro Endocrinol Lett* 2006; 27: 311-313

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## What to do with a Positive Patch Test:



**Practice Parameters:**  
**Highlights:**

- 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.**

Fonacier L, Bernstein D, Pacheco K, Holness DL, et al. Contact Dermatitis: A Practice Parameter Update – 2015. *Journal of Allergy and Clinical Immunology In Practice*. Vol 3, No 3 May/June 2015. S1-S9

Schalock PC et al. Patch Testing for Evaluation of Hypersensitivity to Implanted Metal Devices: A Perspective From the American Contact Dermatitis Society. *Dermatitis*, Vol 27 | No 5 | September/October, 2016

## 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

\* Rajagopalan R et al. Cutis 1996;57:360-364)

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## 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

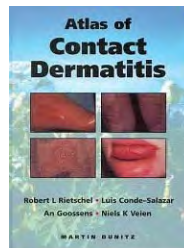
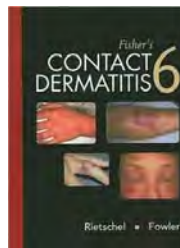
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## Coding & Reimbursement:

- 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**

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## 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))

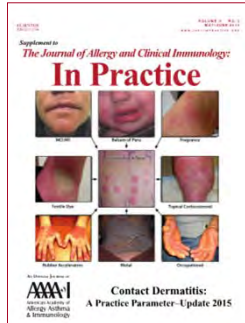
- Patient handouts, webinars

**Contact Allergen Replacement Database** ([www.AllergyFreeSkin.com](http://www.AllergyFreeSkin.com))

**NIH** (<http://householdproducts.nlm.nih.gov/> )

- List of products to avoid

**Thank you**



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**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.**