

Atopic Dermatitis Debate Patch Testing is Underutilized in AD patients



**Luz Fonacier MD, FACAAI, FAAAAI
Professor of Medicine
Section Head of Allergy
Program Director, Allergy and Immunology
NYU Long Island School of Medicine**

Learning Objective

1. Discuss why patch testing should be performed in AD patients suspected to have contact dermatitis
2. Be aware of allergens in AD treatment protocols, including lanolin, fragrances, preservatives, and corticosteroids

CD is common in AD!!!!

“preponderance of data supports a significant and clinically impactful incidence of ACD among atopic patients”

- Study of 48 adults & children with difficult-to-treat AD, 75% had a concomitant ACD, and 39% were polysensitized
- Most patients referred for patch testing with AD history had a final diagnosis of ACD
 - Patients with AD had a similar likelihood of a positive PT as those without AD history
 - Adults with AD history had a higher number of positive PT reactions

Silverberg JI, et al. Prevalence and Trend of Allergen Sensitization in Adults and Children with Atopic Dermatitis Referred for Patch Testing, North American Contact Dermatitis Group Data, 2001-2016. *J Allergy Clin Immunol Pract.* 2021 Jul;9(7):2853-2866. PMID: 33781959.
JAMA Dermatol. 2021 Nov 3:e214314.doi: 10.1001/jamadermatol.2021.4314.
Br J Dermatol. 2019 Feb;180(2):315-320. doi: 10.1111/bjd.17080. Epub 2018 Sep 30.
J Eur Acad Dermatol Venereol. 2017 Jun 19. doi: 10.1111/jdv.14423.
J Allergy Clin Immunol Pract. 2019 Jan;7(1):18-26. doi: 10.1016/j.jaip.2018.11.003.

Risk of ACD in AD

Dysfunctional skin barrier allows for increased penetration of chemicals

Increased exposure & chronic use of emollients and topical anti-inflammatory therapy

- survey of so called “hypoallergenic pediatric cosmetic products” in the US contained potent contact allergens such as fragrances and preservatives.
- children with AD often were sensitized to chemicals found in their emollients and topical medications

Bacterial colonization can activate inflammatory cells that are also involved in potentiating contact sensitization & ACD

- presence of bacteria has been suggested to promote both sensitization and elicitation of a murine contact allergic response

AD patients are more prone to irritant contact dermatitis even when their AD is quiescent

- resulting in further compromise of skin barrier and often precedes ACD
- irritant CD may also increase susceptibility to ACD through innate immune signaling.

Allergic Contact Dermatitis Mechanisms

Contact dermatitis pathogenesis is not the same across allergen groups:

- **nickel** promotes strong Th1/Th17 polarization
- **fragrance** causes Th2/Th22 skewing.
- **poison ivy** causes Th2/Th17 skewing
- Sensitization is hapten, host, concentration, and surface area dependent.

Experimental allergens

Initrofluorobenzene (DNFB)	Th1
Trinitrochlorobenzene (TNCB)	Th1
Fluorescein isothiocynate (FITC)	Th2
Urushiol	Th2
Oxazolone	Th1/Th2

Human allergens

Nickel	Th1/Th17 Th22 component
Fragrance	Th2/Th22 (weaker Th1/Th17 axis)
Poison ivy	Th2/Th17

Front. Allergy, 04 October 2021 <https://doi.org/10.3389/falgy.2021.702488>
Clin Rev Allergy Immunol. 2019 Feb;56(1):1-8.
Clin Immunol. 2019 Feb 14;201:1-3.
Structure. 2009 Oct 14; 17(10): 1398–1410.

ACD may complicate the course of AD

Who should you suspect to have ACD

- 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



TABLE 3. Potential Pitfalls in Patch Testing the AD Patient

- Irritant reactions to metals, especially chromium and cobalt, as well as fragrances, formaldehyde, and lanolin, are common in patients with AD and may be misinterpreted as allergic reactions.^{11,44,45}
- Personal rinse-off products may cause irritant reactions, especially if not appropriately diluted.
- Between patch readings, the typical “crescendo” pattern is not observed to the same degree in patients with AD.⁴⁴
- Patch testing at the time of an AD flare may decrease contact sensitization, leading to false negatives¹¹; additionally, this may also lead to increased irritancy.
- Concomitant systemic immunosuppressive therapy may result in false negatives⁴⁶; thus, this should be avoided whenever possible or reduced to the minimum necessary to clear the back. If patch testing a patient on systemic immunosuppressive medications is unavoidable, repeat patch testing should be considered in patients who are successfully tapered off of immunosuppression.
- AD patients are more susceptible to variations in climate that may affect the skin barrier and affect the rate of positive and irritant patch test reactions.^{11,44,45}

False
Positive
Patch
Results

False
Negative
Patch
Results

Patch testing remains the criterion standard for diagnosing ACD

Failure to PT when appropriate may overlook an important and potentially curable complicating comorbidity (DERMATITIS, 2016; Vol 27: No 4)

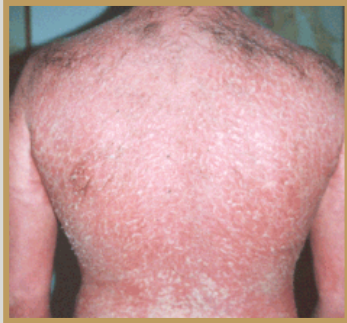
*THE GREATEST ABUSE OF PATCH TESTING
IS
FAILURE TO USE THE TEST*

Colman, 1982

- **The diagnosis of ACD made solely by history is under suspected, under diagnosed or misdiagnosed when compared with those patch tested** (Sherbets EF. Controversies in contact dermatitis. Am J Contact Dermat 1994;5:130-135)
- **Relief of symptoms average 143 days sooner on patch tested vs. non patch tested patients** (Rajagopalan R et al. Cutis 1996;57:360-364)

Nightmares of Patch Testing

The eczema flare



PT during a flare may

- decrease contact sensitization, leading to false (-)
- lead to increased irritancy

The Medications

- Topical Corticosteroids
- UV therapy
- Systemic corticosteroids
- Dupilumab
- Other immunosuppressants

The oily back

- no emollients on day of PT for good adherence



?????



PT during systemic therapy

- It is recommended that patients with AD undergo PTs before starting systemic therapy
- In clinical practice, PTs in moderate-to-severe AD is often difficult to perform because of AD severity or skin reactivity

Mufti A, Lu JD, Sachdeva M, et al. Patch testing during immunosuppressive therapy: a systematic review. *Dermatitis*.2021;32(6):365-374

Some consensus guidelines

Days	Mean	Median	Range
Minimum withdrawal after TCI	7.5 (5.1)	7	0-21
Minimum withdrawal after TCS	8.2 (5.3)	7	0-28
Minimum withdrawal after UV light exposure	15 (10.2)	14	0-42
Minimum withdrawal after IM Corticosteroids	29.7 (15.4)	28	0-90
Highest dose of Prednisone acceptable (mg)	10.5	10	0-20

Immunomodulatory Agents & Patch testing

Positive PT reactions during therapy	Medications with high probability of impacting PT results
Prednisone <10 mg/d, (relative dosing for pediatric patients)	Prednisone >10 mg/d
Methotrexate (<0.25 mg/kg per week)	Cyclosporine (>2 mg/kg per day)
Dupilumab (variable)	JAK Inhibitors
Omalizumab	Mycophenolate (dose dependent)
Antihistamines	

Assess the risks & benefits of patch testing given the impact of ACD on patient quality of life.

Mufti A, Lu JD, Sachdeva M, et al. Patch testing during immunosuppressive therapy: a systematic review. *Dermatitis*. 2021;32(6):365-374
Fowler JF Jr, Maibach HI, Zirwas M, et al. Effects of immunomodulatory agents on patch testing: expert opinion 2012. *Dermatitis* 2012;23(6):301-303.)

Impact of dupilumab on PT results and ACD: A prospective multicenter study

Prospective, multicenter study of 76 Dupi-treated patients who underwent PT

- Thirty-six (47%) patients had ≥ 1 positive & clinically relevant PT reaction
- Only 8 patients had uninterpretable PTs because of angry back syndrome

Conclusion

- **PT are often positive and relevant for Dupi-treated AD patients**
- PT reproducibility during Dupi therapy seems to be preserved
- Dupi does not always effectively treat ACD
- Therefore, it is important to perform PT on all Dupi-treated patients
 - with partial responses or worsening eczema
 - during treatment to look for ACD, especially on head and neck, eyelids, and hands

Bocquel et al. J Am Acad Dermatol 2024;90:512-20.

TABLE 3. Strength of Reactions/Clinical Relevance

Substance	n	% Positive	Positive Reactions
Nickel sulfate hexahydrate, 2.5% pet	4937	16.2	803
MI, 0.2% aq (2000 ppm)	4938	15.3	756
MCI/MI, 0.02% aq (200 ppm)	4940	11.0	543
Fragrance mix I, 8.0% pet	4944	9.2	456
Hydroperoxides of linalool, 1% pet	4934	8.9	439
Formaldehyde, 2.0% aq	4928	7.4	367
BIT, 0.1 % pet	4946	7.3	359
<i>Myroxylon pereirae</i> resin (balsam of Peru), 25.0% pet	4940	7.1	350
Cobalt (ii) chloride hexahydrate, 1.0% pet	4946	6.7	331
4-Phenylenediamine, 1.0% pet	4926	5.6	279
Bacitracin, 20.0% pet	4937	5.5	274
Neomycin sulfate, 20.0% pet	4938	5.4	269
Formaldehyde, 1.0% aq	4938	5.4	267
Propolis, 10.0% pet	4939	4.7	234
Fragrance mix II, 14.0% pet	4944	4.4	219

*Isothiazolinone family

Selecting Allergens

The top 15 most frequently positive allergens

- 2 metals
 - nickel & cobalt
- 2 antibiotics
 - neomycin & bacitracin
- 4 fragrances
 - FM I, **FM II**, *M. pereirae* (BOP), **hydroperoxides of linalool**
- 4 preservatives
 - **MI***, MCI/MI*, **Benzisothiazolinone***, formaldehyde
- p-phenylenediamine
- propolis

Not in the True Test ®

Therefore, if used, add supplemental testing whenever possible

- Children >12 years may be patch tested similarly to adults.
- Patch Test Recommendations for Children 6-12 y.o.

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

SPECIFIC CONTACT ALLERGENS IN AD

Atopics were at greater risk of positive reactions to supplementary allergens

Consider the following allergens in AD

- Metals (nickel, cobalt, potassium dichromate)
- Fragrances (FM, Balsam of Peru)
- Preservatives (methylisothiazolinone, formaldehyde)
- **Medication-induced ACD in AD** (allergens AD treatment products)
 - Emollients (most common) (lanolin)
 - Topical Antibiotics/Antiseptics
 - Topical Corticosteroids
- Compositae
 - Herbal medicaments & cosmetics
 - Higher prevalence of (+) PT to compositae in children



Silverberg JI, et al. Prevalence and Trend of Allergen Sensitization in Adults and Children with Atopic Dermatitis Referred for Patch Testing, North American Contact Dermatitis Group Data, 2001-2016. *J Allergy Clin Immunol Pract.* 2021 Jul;9(7):2853-2866. PMID: 33781959.
Mailhol C, Lauwers-Cances V, Rancé F, Paul C, Giordano-Labadie F. Prevalence and risk factors for allergic contact dermatitis to topical treatment in atopic dermatitis: a study in 641 children. *Allergy.* 2009;64:801-6. doi: 10.1111/j.1398-9995.2008.01890.x
Paulsen E, Otkjaer A, Andersen KE. Sesquiterpene lactone dermatitis in the young: is atopy a risk factor? *Contact Dermatitis.* 2008;59(1):1-6.

Characterize Reactions

Irritant Morphology

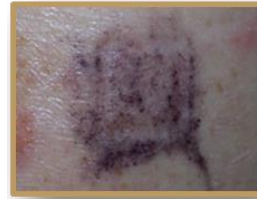
- Pustules, Dry Skin, Scaling
- Petechiae, Shiny Skin,
- Cigarette Paper Appearance



Expected Discoloration

- Dye retention

PPD



Disperse
Dyes



Allergic Morphology

- Erythema, infiltration & edema filling application site
- Papules
- Vesicles, Bullae



False Positive reactions to Metals



Pustular patch reaction

- **Common in atopics**
- Nickel, copper, arsenic & mercuric chloride
- Minimal pruritus



Cobalt

- false (+) cobalt “poral” reaction
- punctate erythema, almost petechial
- probably toxic effect of cobalt on acrosyngium (superficial portion of sweat duct)

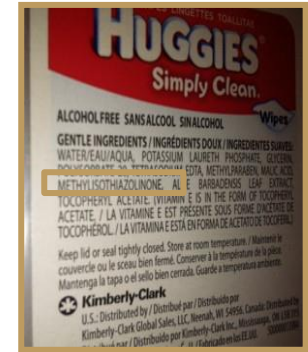
Determine relevance

Potential Pitfalls in Patch Testing the AD Patient

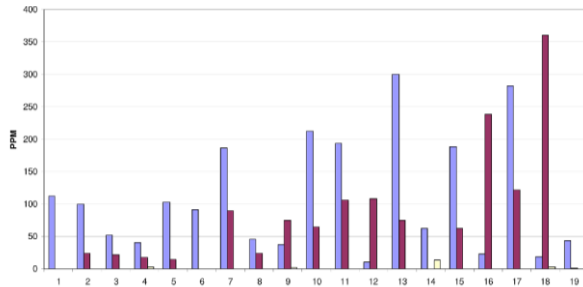
- **Mild irritant reactions** may occur more commonly to
 - metals, (chromium, cobalt)
 - fragrances
 - formaldehyde
 - lanolin
 - personal rinse-off products
- Between readings, the typical “crescendo” pattern is not observed to the same degree in AD patients.
- Patch testing during an AD flare may decrease contact sensitization, leading to false (-) & increased irritancy.
- AD patients are more susceptible to variations in climate that may affect skin barrier and affect the rate of positive and irritant patch test reactions.

Methylisothiazolinone

- “Epidemic” of ACD
 - PT positivity rate 13.8% (2nd only to nickel)
 - **personal care** (cosmetics and toiletries)
 - **household** (dishwashing liquid, soaps, laundry detergents, fabric softeners)
 - **industrial products** (water-based paints)
- high clinical relevance
- MCI/MI mix (Trade name: Kathon CG) at 3:1



Mix misses ~ 40% of allergy to MI



Concentration of methylisothiazolinone (MI), benzisothiazolinone (BIT), and methylchlorisothiazolinone (MCI) in the 19 different paints analyzed.



Daily Mail 2014
 “Mother-of-two breaks out in a rash every time she walks into her lounge after B&Q paint job”

DeKoven et al. NACDG Patch Test Results:2017–2018 March 2021.DERMATITIS

Lundov MD et al. Emission of isothiazolinones from water-based paints. Environ Sci Technol. 2014 Jun 17;48(12):6989-94.PMID: 24869638.

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

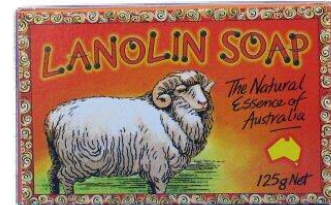
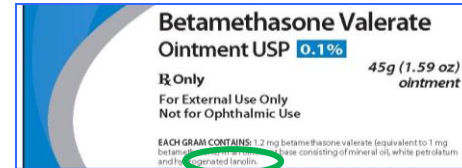
Natural is not hypoallergenic

- Common “natural sensitizers”, Lanolin, shellac, propolis, BOP

Contact Dermatitis. 2017 Mar;76(3):151-159. doi: 10.1111/cod.12711. Epub 2016 Nov 11.
Contact Dermatitis. 2017 Feb 14. doi: 10.1111/cod.12763. Contact Dermatitis. 2016 Nov 11.

Lanolin (wool wax alcohols)

- **Ointment base for topical medicaments:** antibiotics, corticosteroids, analgesics
- **Personal care products:** moisturizers, creams, lipsticks, shampoos, soaps
- **Children with AD reacted more often to lanolin alcohol & Amerchol L-101**
(12.6 v 5.3% - $p = 0.030$)
- **Lanolin Paradox:**
 - sensitivity low in normal skin
 - moderate in atopic
 - high in stasis eczema & ulcers



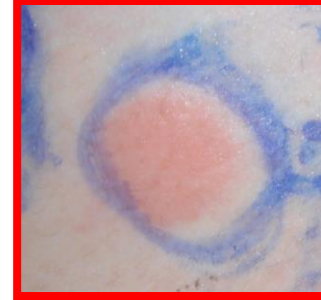
Cocoamidopropyl betaine

- Amphoteric surfactant in shampoos, bath products, eye & facial cleaners, liquid detergents, surface cleaners, 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





Budesonide 0.1%
in Petrolatum
72 hours



Product: 7 days

TOPICAL CORTICOSTEROID (TCS) HYPERSENSITIVITY

- Overall, between 0.2% - 5% of all dermatitis patients have TCS allergy
 - 85% of these patients have multiple TCS allergies

Suspect allergy (active molecule or vehicle)

- all patients who don't respond to TCS
- those who get worse with TCS
- those who improve initially, then flare



In this population TCS allergy is seen in:

- 19% - 22% of these adults
- 25% of these children

Issues to patch testing with steroids

Corticosteroid concentration

- Too high - pharmacologic effect suppresses the allergic reaction
- Too low - not enough steroid to elicit reaction

Vehicle
petrolatum base
penetrates less

- Late reactions
 - Additional reading Day 6-7
 - ~30% of TCS allergy would be missed without late reading*
- Rim reactions
 - True positives



Steroid Classifications

Potency

Potency & side effects are related to saturation of the GCRs in different cell types

- Class 1 → Class 7
- Super-, high-, moderate-, low-potency

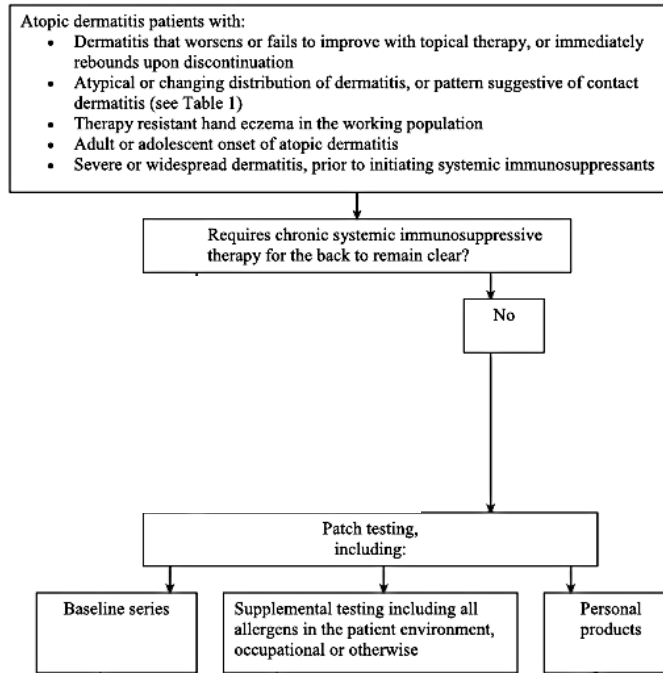
Allergenicity

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

- Reaction to more than one screening agent, reasonable to use a class C steroid

Steroid	Group A	Group B	Group C	Group D1	Group D2
Prevalence	2.7%	1.5%	<0.2%	0.8%	0.8%
Examples	Hydrocortisone acetate	Triamcinolone	Desoximetasone	Betamethasone dipropionate	Hydrocortisone butyrate
	Prednisone	Desonide	Clocortolone	Betamethasone valerate	Hydrocortisone valerate
	Tixocortol (marker Group A)	Fluocinonide	Dexamethasone	Clobetasol propionate	Prednicarbate
	Methylprednisolone acetate	Budesonide	Betamethasone sodium phosphate	Mometasone	Hydrocortisone aceponate
	Cloprednol	Amcinonide	Fluocortolone	Fluticasone	Methylprednisolone aceponate
	Fludrocortisone	Halcinonide		Aclomethasone	
	Prednisolone	Fluocinolone			

Suggested patch testing algorithm for AD patients



Pre-emptive Avoidance Strategy (P.E.A.S.) in Pediatric ACD

Allergen Avoidance

Estimate that 1/3 of children with ACD will potentially benefit from P.E.A.S.

Neomycin	Formaldehyde
Balsam of Peru	Corticosteroids
Fragrance Mix	MCI/MI
Lanolin	Propylene glycol
Cocamidopropylbetaine	Benzalkonium chloride

Low Contact Allergen Products

Recommendation Prior to Patch Testing

Eliminate most common allergens:

- Fragrance
 - Balsam of Peru
 - Fragrance Mix
 - Fragrance Mix II
- Formaldehyde Releasing Preservatives
 - Formaldehyde
 - Quaternium-15
 - Diazolidinyl Urea
 - Imidazolidinyl Urea
 - Bronopol
 - DMDM Hydantoin
- Non Formaldehyde Preservative
 - MDG/PE (Methyldibromo Glutaronitrile)
- MCI/MI and Methylisothiazolinone
- Lanolin
- Cocamidopropyl Betaine
- Benzophenone-3
- Paraphenylenediamine



Enter in
CAMP (Contact Allergen
Management Program) of the
American Contact Dermatitis
Society to eliminate

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

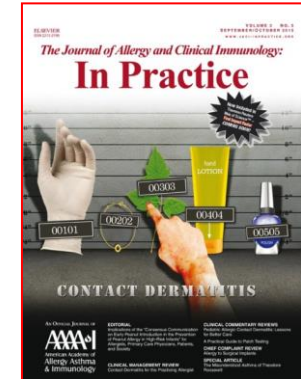
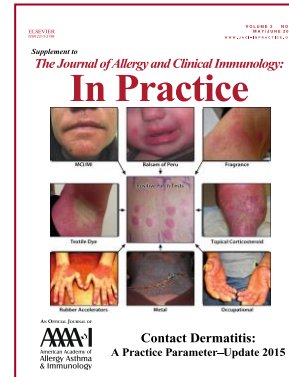
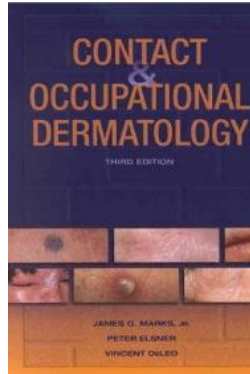
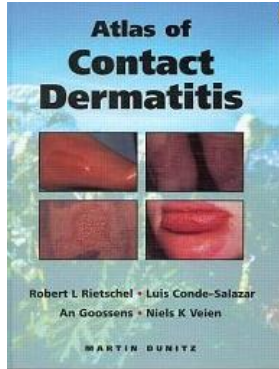
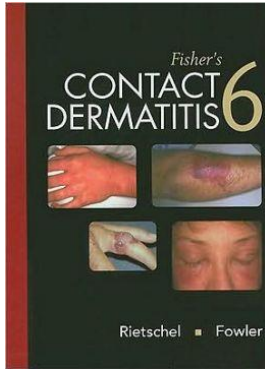
Topical Skin Care Product Databases

	CAMP Contact Allergen Management Program (American Contact Dermatitis Society)	CARD Contact Allergen Replacement Database (MAYO Clinic)
Web Address	www.contactderm.org	www.AllergyFreeSkin.com
Physician	<i>Requires ACDS Membership</i> Luz.fonacier@nyulangone.org	<i>No membership requirements</i> <i>Provider portal</i> <i>Patient portal</i> <i>Web and Smart Device</i>

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



Fonacier L 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

Fonacier L. 'A Practical Guide to Patch Testing'. Journal of Allergy and Clinical Immunology In Practice. Sept/Oct 2015; 3(5) 669-675

American Contact Dermatitis Society (www.contactderm.org)-requires membership
 Contact Dermatitis Institute (www.contactdermatitisinstitute.com/mypatchlink.php)
 NIH (<http://householdproducts.nlm.nih.gov/>) - list of products to avoid

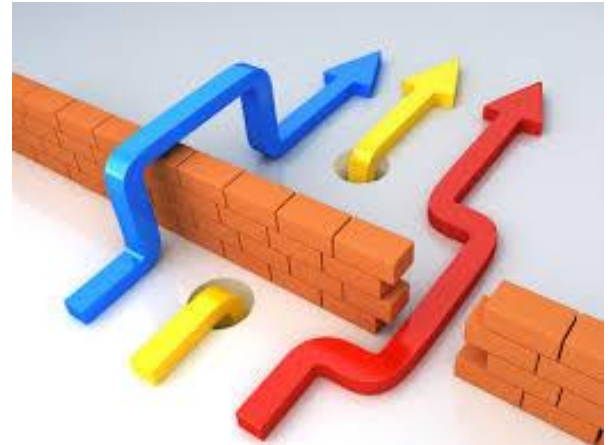
Rebuttal

Patch Testing is Underutilized in AD patients

- CD is common in AD
- ACD may complicate the course of AD,
- Addressing CD improves dermatitis in AD
- Failure to PT when appropriate may overlook an important and potentially curable complicating comorbidity

Patch Testing is Underutilized in AD patients

- There are challenges but they can be overcome
 - Clearing the eczema
 - Systemic antihistamine therapy has no effect on patch test results
 - Guidelines of discontinuation of topical medications
 - TCS and TCI for 7 days
 - UV exposure 14 days
 - IM steroid 28 days
 - Other areas aside from the back (abdomen, thigh, upper arms)
 - When possible, reduce dose of immunomodulatory medications prior to PT
 - PT on Biologics and other medications
 - Most experts will consider PT on Prednisone < 10 mg/day
 - PT are often positive and relevant for Dupilumab-treated AD patients
 - Interpret results with caution
 - Consider Repeat Application Test (ROAT)



Allergens

- Atopics were at greater risk of positive reactions to supplementary allergens, therefore, if used, add supplemental testing whenever possible.
 - Some relevant contact allergens are not in the True Test ®.
- Delayed Patch Test readings are common to:
 - metals
 - topical antibiotics
 - topical corticosteroids
- Testing with MCI/MI mix (3:1 TT) alone will miss ~ 40% of allergy to MI
- Mild irritant reactions may occur more commonly to
 - metals, (chromium, cobalt)
 - fragrances
 - formaldehyde
 - lanolin
 - personal rinse-off products

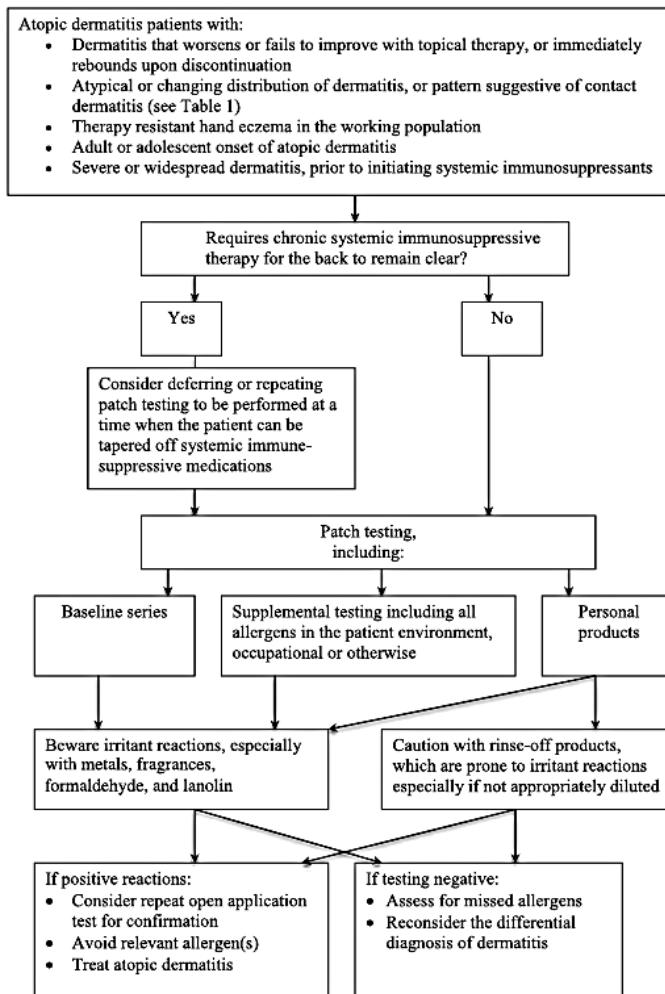
When not to PT the AD patient:

- The stable and well-controlled AD patient
- Patient experiencing an AD flare and/or active dermatitis involving the back and other potential sites of application for PT
- Current or recent use of systemic immunosuppressive medications
 - following medications were at high risk for leading to false negative PT results: prednisone >10 mg/d and intramuscular triamcinolone (avoid for 4 weeks), topical corticosteroids or calcineurin inhibitors at patch test application sites (avoid for 1 week), azathioprine, cyclosporine, mycophenolate mofetil, and systemic tacrolimus¹
 - considered generally acceptable for patients during PT: methotrexate, prednisone <10 mg/d, TNF α inhibitors, ustekinumab, and antihistamines¹
 - There is no consensus regarding avoidance of newer agents: crisaborole, Janus kinase inhibitors, or dupilumab²
- Recent exposure to UV therapy or excessive solar radiation
 - recommended to be avoided for 1 week prior to testing¹



1. Fowler JF Jr, et al. *Dermatitis* 2012 Nov-Dec;23(6):301-3.
2. Own JL, et al. *Am J Clin Dermatol.* 2018 Jun;19(3):293-302.

Suggested patch testing algorithm for AD patients





Patch me if you can !



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



Thank you

