

Best of the Literature

Matthew Zirwas
DOCS Dermatology

Industry Relationships

- Abbvie, Acrotech, Advanced Derm Solutions, Aldeyra, Henkel, Amgen, Anaptys Bio, Apogee, Arcutis, Beiersdorf, Biocon, Boehringer, Bristol Myers Squibb, Cara, Celldex, Organon, Evelo, Evommune, Galderma, Google, Incyte, Janssen, L'Oreal, Leo, Lilly, LUUM, Meta, Nimbus, Novartis, Pelthos, Pfizer, Q32 Bio, Regeneron, Sanofi, Sun, Supernus, Takeda, UCB, Verrica, Zai Labs

Compliance Tips

- Nobody (literally) is 80% adherent with topical therapy, even if one cream once a day to a small area
 - Likelihood of adherence goes down by 50% if two creams or twice a day
- You're recommending moisturizer too much in dermatitis patients – it doesn't help much and makes compliance with stuff that does work go down
- Eczema action plans don't work – too complicated
 - Just prescribe something simple and highly effective

An exploratory study of adherence to topical benzoyl peroxide in patients with acne vulgaris

A sticky mess—Are moisturizers overused in dermatitis care?

Adherence to oral and topical medications among dermatology patients

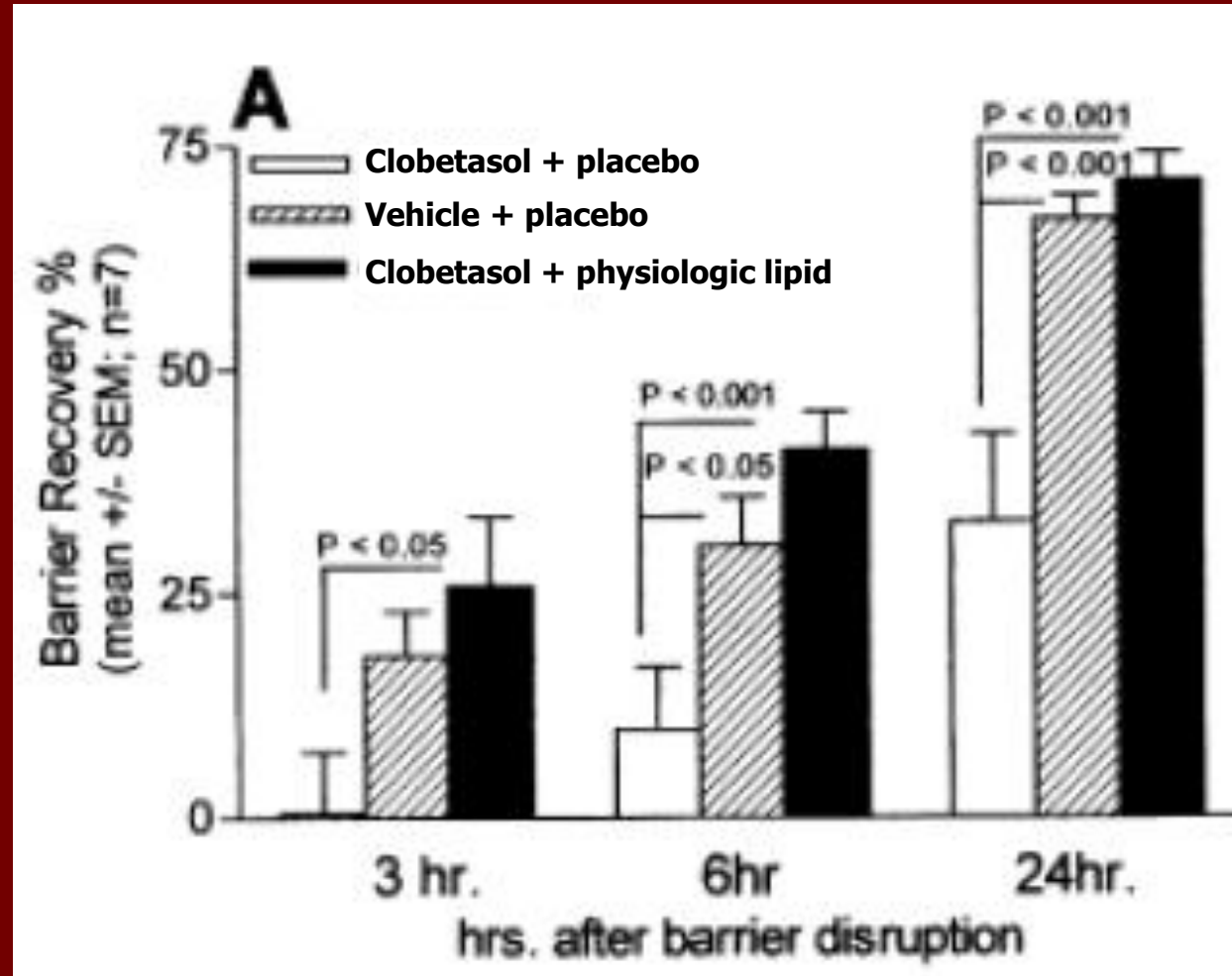
Does an Eczema Action Plan Improve Atopic Dermatitis? A Single-Site Randomized Controlled Trial

A Randomized Controlled Trial of an Eczema Care Plan

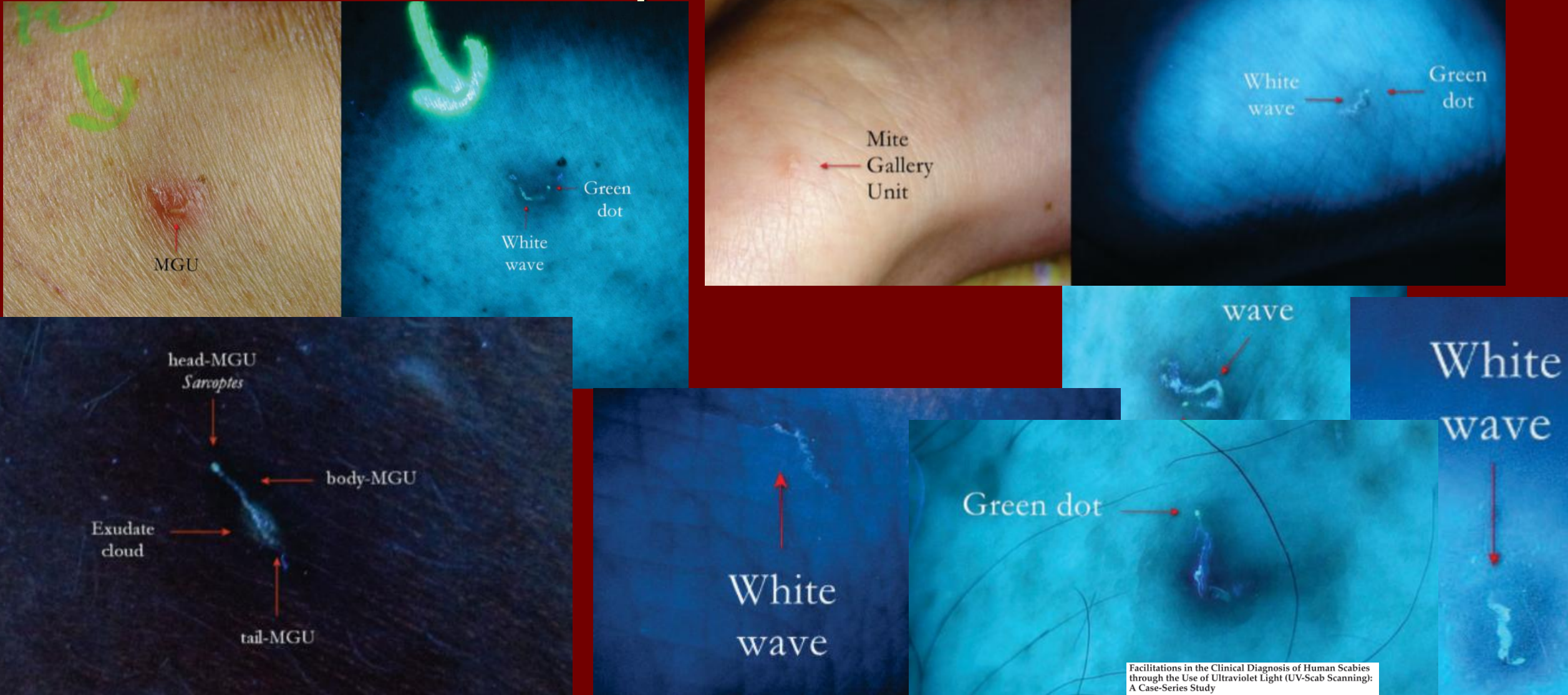
CeraVe / Clobetasol

- 50 ml clobetasol solution into 16 oz jar of CeraVe
- What is so “special” about this?
 - No allergens in vehicle
 - Makes exactly 0.005% clobetasol cream
 - Medium to high potency steroid cream in 16 oz jar
 - Ointment is a class 3
 - Most important:
 - Overcomes barrier impairment associated with short term steroid use

Physiologic Lipid Reverses Steroid Induced Barrier Impairment (3 days of clobetasol)



Use a Woods Lamp to Find Where to Scrape in Scabies



Discrepancies in Patch Testing Timing and Outcomes: A Retrospective Analysis of the Pediatric Allergic Contact Dermatitis Registry

Mykayla Sandler, BA, Eun Jae Kim, BA, Li-Chi Chen, MD MPH, JiaDe Yu, MD MS

Supplemental Table 1: Characteristics of patients in the Pediatric Allergic Contact Dermatitis Registry from 2018 to 2024, stratified by improvement of dermatitis after allergen avoidance (N=459).

	Total N=459	No Improvement	Partial Improvement	Complete Improvement	P-value
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All Comers 32% 48% 20%

AD pts only 32% 51% 17%

Supplemental Table 3. Multivariate-adjusted odds ratios and 95% confidence intervals of improvement of dermatitis after allergen avoidance among patients in the 2018-2024 Pediatric Allergic Contact Dermatitis Registry with different characteristics, stratified by allergen groups.

	Fragrances [*] (n=96)		Antimicrobial/Preservatives ^{**} (n=129)		Surfactants ^{***} (n=68)		Metals ^{****} (n=91)	
	OR (95 CI%)	P-value	OR (95 CI%)	P-value	OR (95 CI%)	P-value	OR (95 CI%)	P-value
Atopic dermatitis	0.29 (0.11-0.78)	0.015	0.44 (0.18-1.10)	0.081	0.03 (0.01-0.18)	<0.001	0.26 (0.08-0.73)	0.012



UNIVERSITY
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Rethinking Contact Dermatitis

■ 2003

An audit of the value of patch testing and its effect on quality of life

- DLQI improves by 2.2 points if a positive patch test
- DLQI improves by 3.1 points if a negative patch test
- Of those with a relevant positive patch test:
 - 4% cleared
 - 53% improved
 - 32% stayed the same
 - 11% got worse

Rethinking Contact Dermatitis

■ 2020

- DLQI improved by 5.2 points in those with positive patch test
- DLQI improved by 4.8 points in those with negative patch test

■ 2024

- Of 265 patients with a positive patch test who followed the avoidance advice, one month later:
 - 41% had gotten at least 50% better
 - 10.5% had gotten at least 90% better

What Is the Takeaway?

- Don't think of a patch test like a DIF for immunobullous disease
 - i.e. don't think of it as diagnostic
- Think of comprehensive patch testing like an ANA
 - Pretty good at ruling out contact dermatitis if negative
 - Highly non-specific when positive and needs to be correlated with overall clinical picture
- The only way to diagnose contact dermatitis is via seeing people get better when they avoid something
 - Patch testing helps you figure out what to tell them to avoid

What Is the Even More Boiled Down Take Home Message?

- We've been overdiagnosing contact dermatitis
- We've been overusing patch testing
 - The patch testers need to provide outcome data to justify it
 - It is insanely expensive for patients, the most morbidity of any test we do and actually kind of dangerous (via driving to appts)
- In my experience most cases of true ACD are obvious
 - Gloves, nickel, objects, etc
 - Might go empiric avoidance or straight to patch testing
 - When it isn't obviously ACD, assume it's AD and treat
 - Only consider patch testing if AD treatment doesn't work

Maybe Contact Dermatitis Isn't Common?

- Definitely not saying that
 - Saying that relevant positive patch tests cannot be used as a proxy for how common contact dermatitis
 - It is definitely still common, but just not as common as we've thought as a cause of non-specific dermatitis
- You should still think about it frequently in specific types of dermatitis
 - Face, hand, earlobe, with a history that relates it something
 - Non-specific dermatitis when it fails AD therapy

The impact of the menstrual cycle on exacerbations of atopic dermatitis: a systematic review

Nickel contact allergy and menstrual cycle

- Rashes that appear in synch with the menstrual cycle are most likely either atopic dermatitis or systemic nickel dermatitis
 - Autoimmune Progesterone Dermatitis is EXTREMELY rare

The Diagnosis You're Missing Most Often

- Evidence is clear and undeniable
 - Numerous randomized, double blind challenges to nickel ingestion
 - Amounts that are typical in normal US diet regularly cause flares in nickel allergic patients and never cause them in non-nickel allergic patients
 - Improvement in rash that correlates with decrease in blood/urine nickel
- Best estimate is that **at least** 1% of the general population gets symptoms from nickel ingestion
 - Psoriasis is 2%
 - How many cases of nickel SCD have you diagnosed compared to how much psoriasis you diagnose?

Table 2. Estimated doses of ED₅₀ and lower responses with 95% confidence limits

Ni doses (mg)	Studies 12 and 19		Studies 5, 6, 7, 11 and 13		Studies 4 and 14	
	Estimate	95% limits	Estimate	95% limits	Estimate	95% limits
ED ₅₀	1.27	0.77–172	2.00	1.47–2.35	3.06	2.15–4.30
ED ₂₅	0.83	0.37–1.19	1.32	0.68–1.69	2.01	1.13–2.74
ED ₁₀	0.55	0.17–0.86	0.87	0.31–1.26	1.33	0.53–1.94
ED ₅	0.41	0.10–0.70	0.65	0.18–1.04	1.00	0.31–1.57
ED ₂	0.29	0.05–0.54	0.45	0.09–0.81	0.70	0.16–1.21
ED ₁	0.22	0.03–0.45	0.35	0.05–0.67	0.53	0.09–1.00

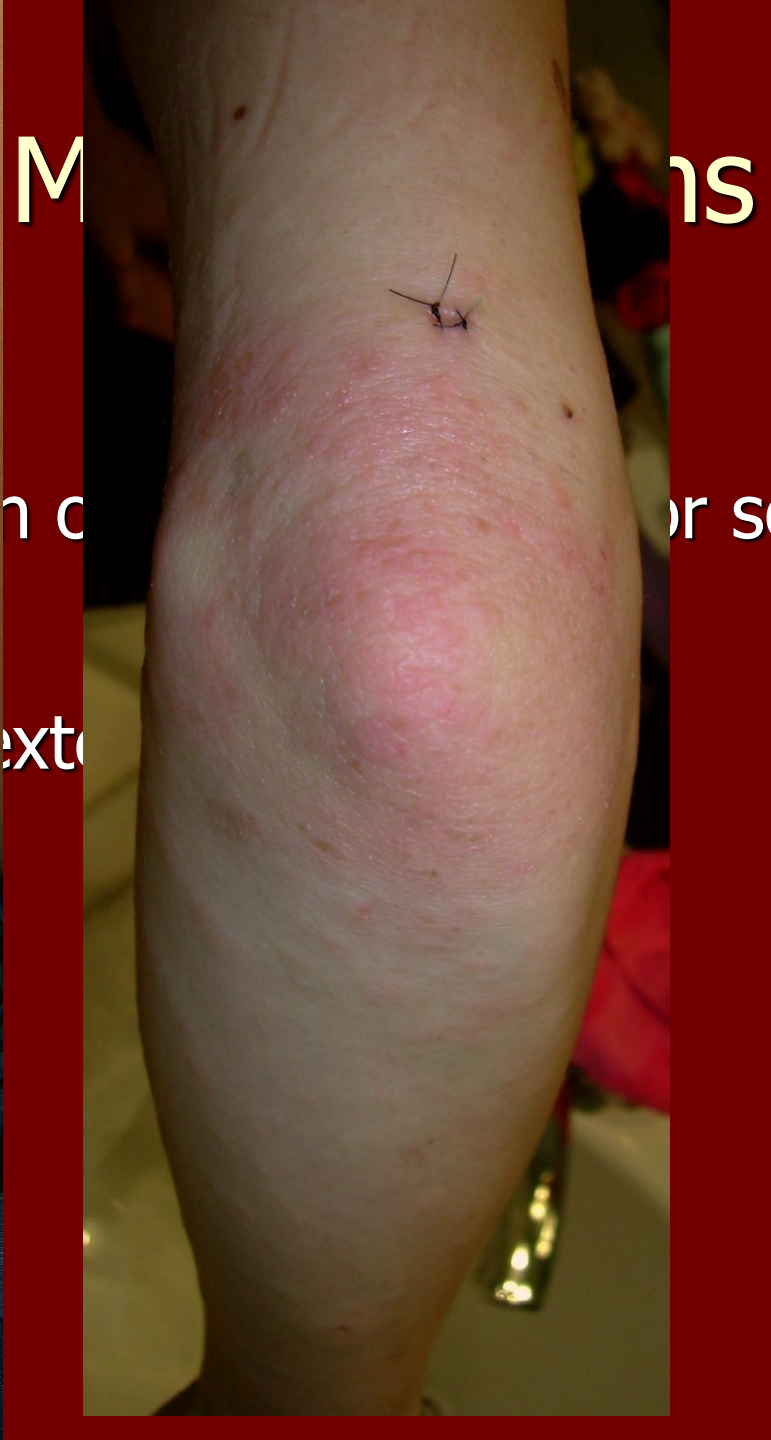
- Estimated dose of nickel that is 'easy' to get in a healthy diet is 1 mg.
- Based on *multiple* RDBPC dose escalation trials, about 10% of nickel allergic patients will respond to 1 mg
- Since at least 15% of the US population is nickel allergic, we know that 1-2% of the population is getting nickel SCD

Pathophysiology

- In patients with systemic reactions to ingested nickel, the following events occur
 - Blood monocyte, B-cell and T-cell counts drop as they migrate into gut mucosa
 - IL-5 levels rise significantly, IL-6 and IL-10 levels rise less
 - Duodenal biopsies show dramatic infiltration of CD45RO+ cells
 - Nickel content of sweat and urine rises

Clinical Manifest







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Management Approach

■ Low Nickel Diet

- In most recent study, worked in about 80% of people with chronic dermatitis and a positive patch test to nickel
 - Chronic urticarial lesions
 - Adult onset atopic dermatitis
 - Generalized pruritus
 - Scattered non-specific dermatitis

Low Nickel Diet

- First truly user friendly low nickel diet came “online” this year

www.thelownickeldiet.com

- Cookbook with general information and very specific meal plans
 - Takes into account general tenets of healthy eating
 - Written by dietitian who has severe dietary nickel sensitivity and got herself better
 - Now a 3rd year medical student!

Do Supplements Help?

- Taking 1000 mg of vitamin C with each meal MAY help
 - I haven't been impressed
- Taking 40 mg of Disodium EDTA with each meal helps A LOT

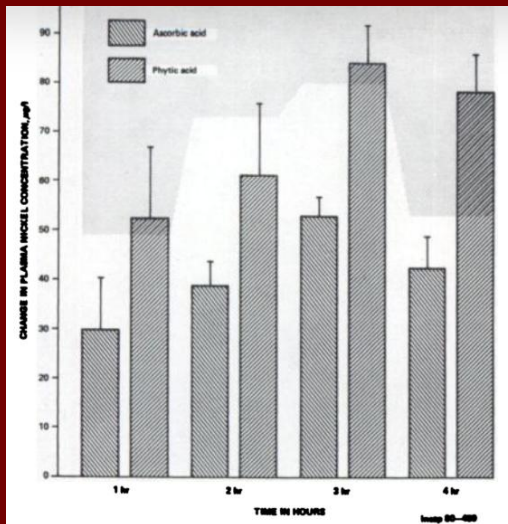


Fig. 6 Change in plasma nickel concentration (means $\pm$ SE) at 4 hourly intervals following ingestion of 22.4 mg of $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ (5 mg of elemental nickel) with 1 g of ascorbic acid or 112 mg of phytic acid. The lower border of the shaded area represents the mean of the changes in plasma nickel level after ingestion of 5 mg of nickel in water. Each bar represents the mean of five subjects.

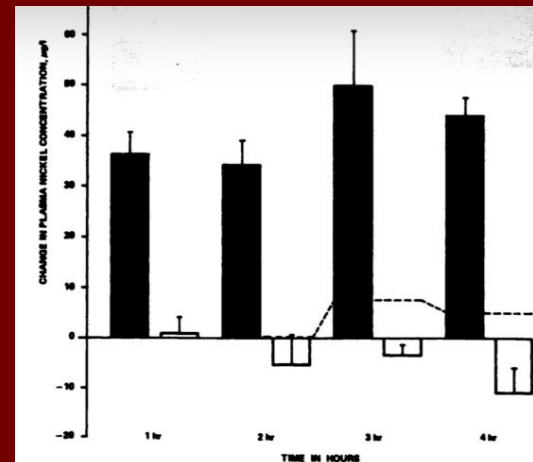


Fig. 7 Change in plasma nickel concentration (means $\pm$ SE) at 4 hourly intervals following ingestion of 22.4 mg of $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ (5 mg of elemental nickel) with 40 mg of NaFeEDTA or 40 mg of $\text{Na}_2\text{EDTA} \cdot 2\text{H}_2\text{O}$ in 100 ml of water. The lower border of the shaded area represents the mean of the changes in plasma nickel level after ingestion of 5 mg of nickel in water. The dotted line represents the mean of the changes in fasting plasma nickel level. Each experiment represents the mean of five subjects.

Supplements?

- However, Disodium EDTA can be fatal due to hypocalcemia
 - The reports I have been able to find involved large doses given intravenously (3000 mg/dose)
 - Unclear if oral administration at any dose could cause this
 - However, I remain cautious and emphasize to patients that they should not take any more than my instructions indicate
 - The dose recommended is approximately 40 mg/dose, the amount shown to effectively eliminate nickel absorption, which is almost 100 fold lower than doses shown to be toxic IV
 - No need to monitor Ca, Mg, Zn

The testing showed that nickel triggers an immune reaction in your body. It is possible that nickel in the things you eat and drink is triggering an immune reaction that is leading to the rashes and itching and could be leading to other types of inflammation in your body, such as fatigue, arthritis, headaches, abdominal pain, etc.

The only way to find out if nickel is the culprit is to get away from it for two months and see if your body recovers. It is almost impossible to stay away from nickel by avoiding particular foods, as the amount of nickel in plants is determined by the soil and fertilizer. So, instead we are going to have you use a dietary supplement that will bind to nickel before it can be absorbed into your body.

Nickel can also be in water naturally or from being released into the water from metal storage tanks, pipes or plumbing fixtures.

Nickel in water does not cause any problems from bathing or swimming in the water.

You should do the following:

1. Get the Disodium EDTA and follow these instructions:
 1. Put ¼ teaspoon of the powder into 16 oz of water.
 2. Every time you eat, take 2-3 sips of the EDTA water (about 2 tablespoons, but it just has to be close – no need to measure it out), while you are eating. Taking it immediately before or after you eat is also ok, but best if you can take the sips in the middle of eating, so that it is mixed in with the food while it is in your stomach (the nickel doesn't get absorbed into your body until after the food leaves your stomach).
 3. It should take about 2-3 days to go through the 16 oz bottle of water.
 4. Most people find that they need to do this consistently for a couple of months, then they can stop and just use it on and off – starting it if their symptoms start back up and stopping when they feel back to normal.
 5. You MUST also do your best to follow the low nickel diet found at www.thelownickeldiet.com
 1. We recommend using the supplement for at least the first two months, as it is the most reliable way to avoid nickel getting into your system, but if it helps, then some people are able to stop the supplement and manage the issue by watching their diets, other people do better using the supplement long term.
 6. If it hasn't helped after doing both the diet and the supplement for two months it means that addressing nickel in your diet isn't the answer and you can stop doing it.
2. You should only drink distilled or purified water. Do not drink tap water or spring water. Bottled drinks (like soda) should be fine.
3. If you take a vitamin or any supplements, take them with the EDTA water instead of regular water.

Cross-elicitation responses to 2-methoxymethyl-p-phenylenediamine in p-phenylenediamine-allergic individuals: Results from open use testing and diagnostic patch testing.

2-methoxymethyl-para-phenylenediamine containing hair dye as a less allergenic alternative for para-phenylenediamine allergic individuals

- Recommend Wella Koleston Perfect Me+ for patients allergic to hair dye who want a salon brand
- Clairol Natural Instincts for a drugstore brand

“Desktop Dermatitis”: A Case Series of 7 Patients with Forearm Contact Dermatitis from Frequent Surface Cleaning

- Can be irritant or allergic contact dermatitis
- Can recommend wiping surfaces down with water when get to work or after cleaning at home
- Think of just like toilet seat dermatitis in kids



Formaldehyde in Clothing

- 1 in 20 cotton items releases detectable formaldehyde, including sheets and pillowcases.
 - 1 in 5 for men's dress shirts.
- No way to know which items.
- Do formaldehyde allergic patients with widespread dermatitis need to replace everything they have that is cotton?

Formaldehyde in Clothing

- Even if they do, they can't
- So what to do instead?
 - Add ½ cup of non-fat powdered milk with the detergent when doing laundry
 - Supposedly the casein in the milk binds to and removes the formaldehyde
 - It slowly reaccumulates, so do it every time they do laundry

**Nonfat Dry Milk Helps
Prevent Formaldehyde
Dermatitis**

Residual Washing Detergent in Cotton Clothes: A Factor of Winter Deterioration of Dry Skin in Atopic Dermatitis

Household laundry detergents disrupt barrier integrity and induce inflammation in mouse and human skin

- Related to water hardness, water temperature, and water volume.
- If retained detergent, gets released by warm, acidic sweat from skin and causes dermatitis
- Options:
 - Do a double rinse
 - Add ½ cup of vinegar to the rinse cycle
 - Use low irritancy laundry detergent

Does Sulfate Free Matter?

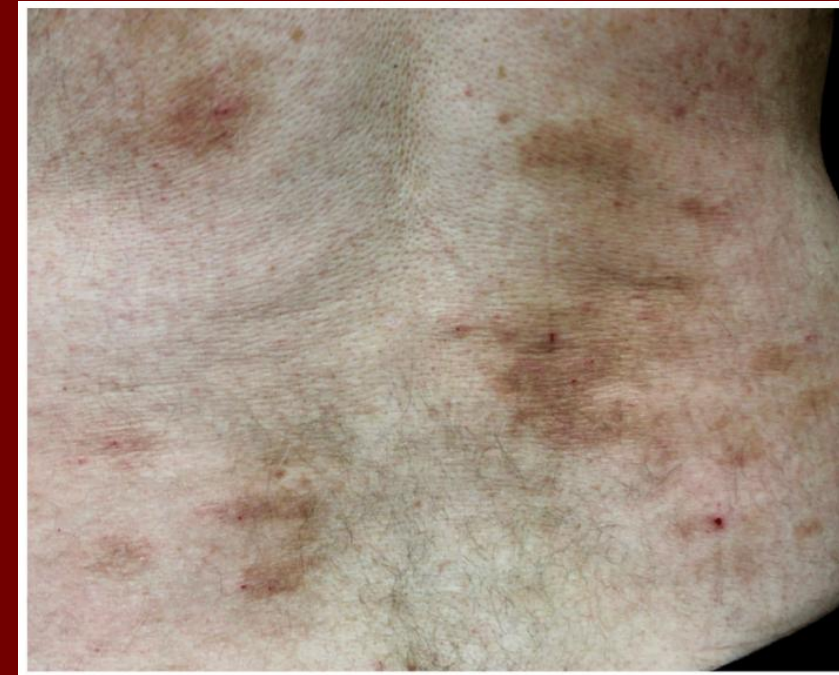
- Sulfates, no.
- Persulfates, yes.
- Historically thought that primary exposure was in hair bleach
 - We were wrong. REALLY, REALLY WRONG
- About 2% of patch tested patients will test positively
 - They are usually male
 - They usually have a widespread, non-specific rash
 - They usually own a hot tub



North American Contact Dermatitis
Group Patch Test Results:
2019–2020

Allergy to Persulfates

- Used as shock treatment in hot tubs and pools
 - Doesn't matter if chlorine, bromine, UV, copper, etc used to "disinfect"
 - Shock treatment keeps the water clear from organic materials like skin oils, skin cells, dirt, etc.
- My experience:
 - Hot tubs and "commercial" swimming pools are the primary problems



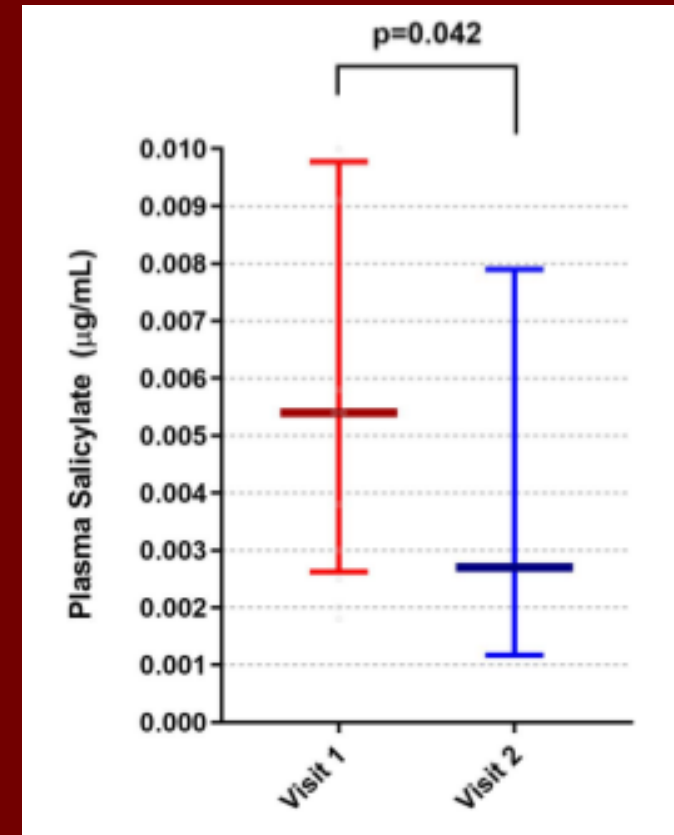
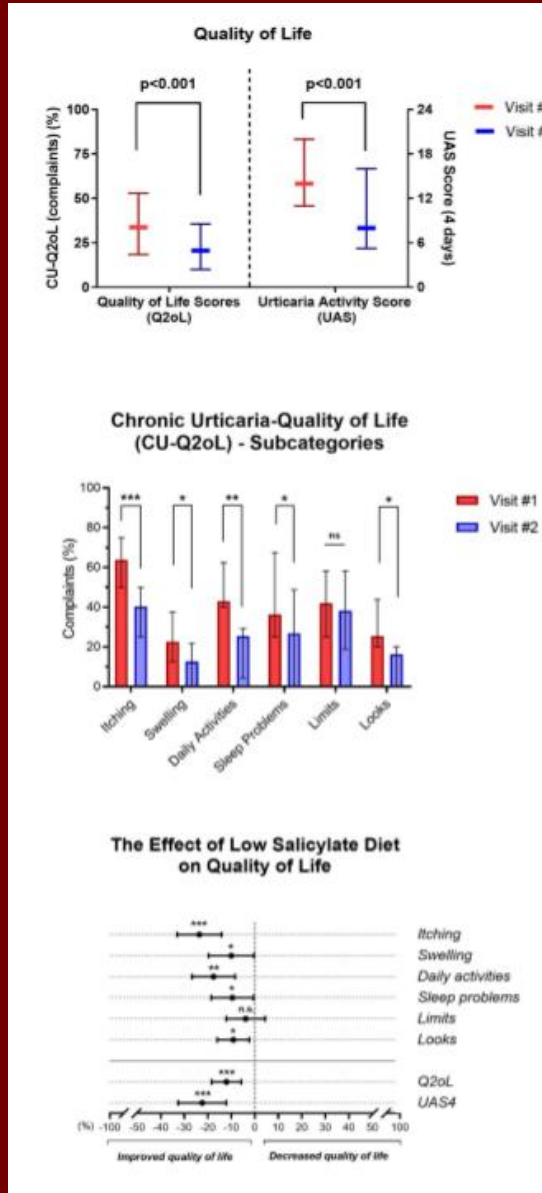
Persulphates allergic contact dermatitis from spa: A new aetiology of nummular contact dermatitis

Allergy to Persulfates

- Ask people with widespread dermatitis if they have a hot tub
 - If yes, stay out of it for 2 months and see if they get better
 - If they do, get back in and see if they flare
 - If they “can’t stay out of it” have them drain it and refill it every time they want to shock it

Dietary Recommendations for CSU Patients

- We know salicylates (ibuprofen, naproxen, aspirin) make urticaria worse.
- There are many foods (plants) that contain significant levels of salicylates.
- Open label trial of patients on antihistamines and/or omalizumab who were not adequately controlled



Effect of low salicylate diet and blood salicylate level on the symptom control of chronic spontaneous urticaria

Demodex Therapy

- Ivermectin 1 mg / 10 lbs x 1, repeat in a week
- Metronidazole 250 mg po tid x 14 days, first dose at same time as first dose of ivermectin
- Maintenance topical therapy with metronidazole and ivermectin

Evaluation of the efficacy of oral ivermectin in comparison with ivermectin-metronidazole combined therapy in the treatment of ocular and skin lesions of *Demodex folliculorum*

International Journal of Infectious Diseases 17 (2013) e343–e347

Efficacy of Azithromycin in Treatment of Acne Vulgaris: A Mini Review

Efficacy of oral azithromycin versus oral doxycycline in treating moderate acne vulgaris and their effects on patients' quality of life

- Many studies
 - Generally show equivalent or better than doxy 100 mg qd
 - In my opinion, azith has a better safety profile than doxycycline or minocycline
 - Much less concern about resistance
 - Bugs we care about (Staph) are already resistant
 - Two regimens make most sense to me
 - 500 mg po qd x 3 days per week
 - 500 mg po qd x 4 days, then 500 mg po qd once a week

Patient survey reports association between compression stocking use adherence and stasis dermatitis flare frequency

Saniya Shaikh, D.O., Payal M. Patel, M.D., Eric S. Ambrecht, PhD., M. Yadira Hurley, M.D.

- 1 in 4 wear them, at best
- Main issues are getting them on and comfort
- USE LOWER STRENGTH
 - 15-20 mmHg
 - Amazon, like \$3/pair
- Great for AD and psoriasis below the knee

Patient use of compression stockings:	
Almost daily	26
2-3 times per week	11
3-5 times per week	21
Not at all	42
Number of times reason cited for non-compliance with recommended treatment:	
Inability to put on the compression stockings	31
Discomfort (too tight)	25
Unclear how the treatment will help	13
Cost	12

Acne Keloidalis Nuchae

- Generic 1% diclofenac gel
 - OTC, costs about \$10
 - BID x 3 months, then QD
 - Worth trying in:
 - PFB
 - Dissecting Cellulitis
 - HS



Sebaceous Hyperplasia

- Curable.
- Permanently?
- Isotretinoin 40 mg po qd x 2 months
- I don't check any labs
 - These are adults – if their baseline triglyceride is 400, they already know it
 - That is the only lab finding that would prevent me from giving this

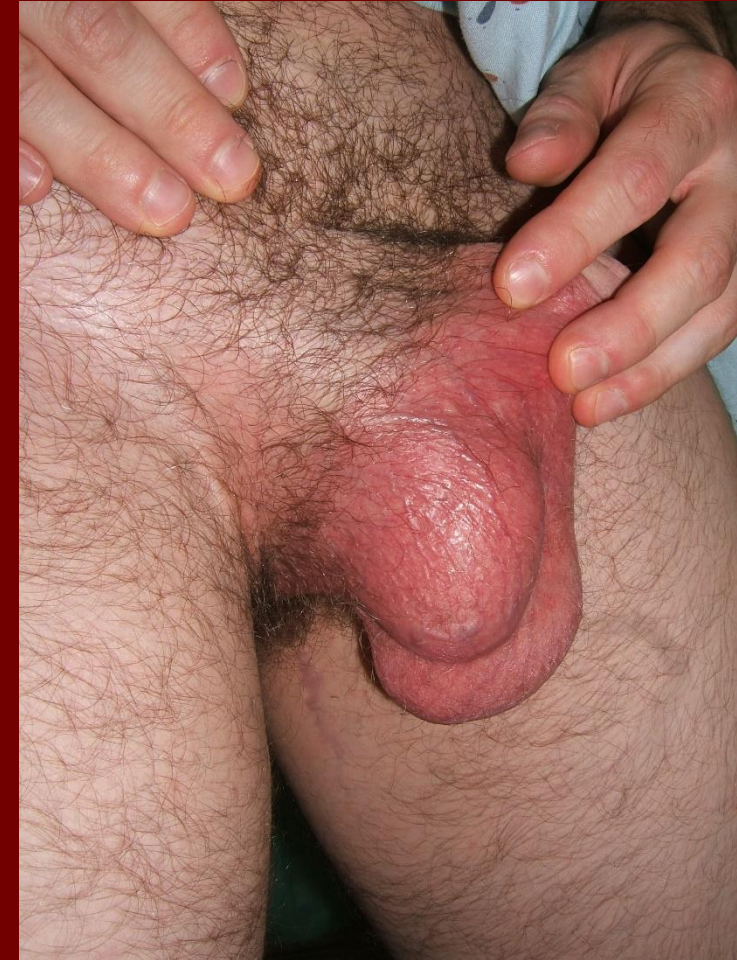
**Sebaceous hyperplasia: systemic treatment
with isotretinoin***

<http://dx.doi.org/10.1590/abd1806-4841.20153192>

Combined carvedilol and gabapentin treatment induces a rapid response in red scrotum syndrome

Rapid improvement of burning scrotum syndrome with indomethacin

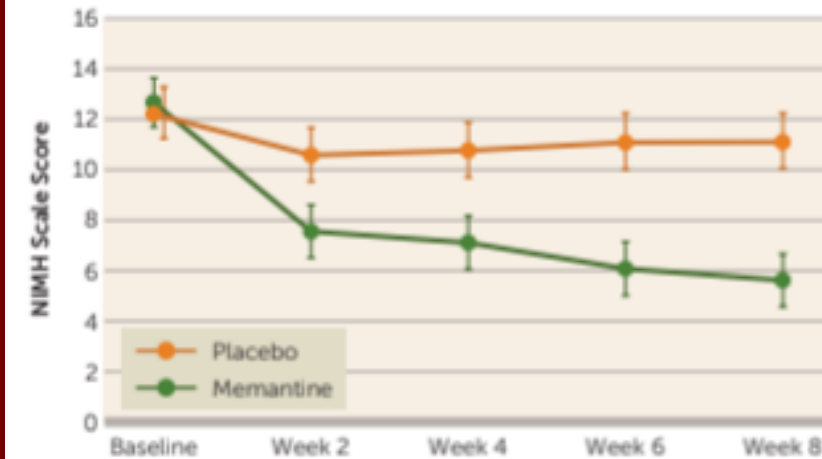
- Carvedilol orally has been the most effective treatment I've found for red scrotum syndrome
 - I start 3.125 mg bid and titrate up to symptom control
 - Have seen some bradycardia, but no hypotension or fatigue
- Indomethacin has also helped as short term rescue when carvedilol not adequate
 - Max dose is 50 mg tid – taper as quickly as possible
- Have had success with topical diclofenac and topical timolol as well



Double-Blind Placebo-Controlled Study of Memantine in Trichotillomania and Skin-Picking Disorder

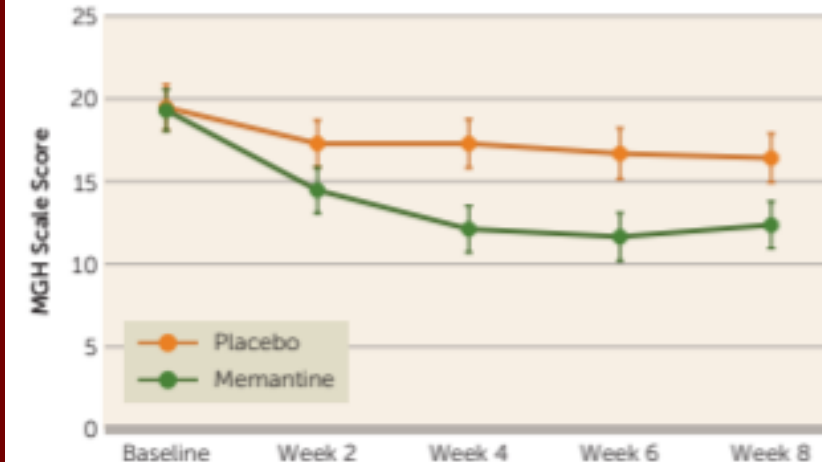
- Very safe Alzheimer's drug
 - 10 mg/d x 2 weeks, then
 - 20 mg/d long term
- 60% much or very much approved in memantine group, only 8% in placebo group

FIGURE 2. Change in NIMH scale score over time with memantine and placebo^a



^a Statistically significant differences between groups emerged at week 4 and continued through week 8. NIMH scale=NIMH Trichotillomania Symptom Severity Scale, modified to include skin picking.

FIGURE 3. Change in MGH self-report scale total score over time with memantine and placebo^a



^a Statistically significant differences between groups emerged at week 4 and continued through week 8. MGH scale=Massachusetts General Hospital Hairpulling Scale, modified to include skin picking.

Thank You.