What to do when patch testing is negative?

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I have no disclosures.
What to do when patch testing is negative

- Is patch testing really negative?
  - False negative
- The patches really are negative
  - What now?
- Is there another diagnosis?
  - Differential diagnosis
- Polling of experts
- Current literature
- Therapeutic options
- Recent study
Patch testing is the gold standard for diagnosing allergic contact dermatitis.
* Metals
  * nickel, cobalt, gold
* Preservatives
  * Benzalkonium chloride, MCI, thimerosal, formaldehyde releasers, CAPB
* Sunscreens
  * benzophenone
* Medicaments
  * antibiotics, B-blockers
* Nail Products
  * acrylates, tolysalide
* Rubber
  * sponges applicators
* Fragrances
Sometimes patch testing is negative....
Sometimes the diagnosis is not ACD....
Treatment resistant chronic dermatitis sent for patch testing

Patient frustrated
  - Decreased quality of life
    - Sleep deprived
    - Social issues
    - Work concerns

Physician frustrated

Prolonged process

Challenging diagnostic/management and therapeutic issues

Multifactorial
Patients referred for expanded patch testing
- Often billed as the answer to the problem
- Evaluate and consider differential diagnoses
- Consider benefit/timing of patch testing
- Set expectations
Differential Diagnosis considerations

- Allergic contact dermatitis
- Irritant contact dermatitis
- Psoriasis
- Atopic dermatitis
- Cutaneous T cell lymphoma
- Drug reaction
- Myeloproliferative disease
- Dermatomyositis
- Immunobullous disease
- Scabies
- Tinea
Challenge of patch testing

- Often have diffuse disease
- Often on systemic medications
- Challenging
  - Calm the skin down in order to perform patch testing
• Common problem
• Often multifactorial
• Half of patients will have relevant positive patch tests
• Allergen is often in one of prescribed creams

Common Allergens in Generalized Dermatitis

- Balsam of Peru
- Quaternium-15
- Formaldehyde
- Fragrance Mix
- Methyldibromoglutaronitrile/phenoxethanol
- Propylene glycol
- Diazolidinyl urea
- 2-bromo-2-nitropropane-1,3-diol
- Tixocortol-21-pivalate
- DMDM hydantoin
- Cocamidopropyl betaine
- Ethylene urea melamine formaldehyde
- Amidoamine
- Budesonide

What to do when patch testing is negative?
Negative patch test results
Considerations…..

* no allergy exists
* did not test to correct allergen
  * expanded allergen series
* improper testing technique
  * no delayed reading
  * immunosuppressants on board
TRUE Test

- Thin-layer Rapid Use Epicutaneous Test
- introduced in 1995
- 35 allergens and 1 control
- increased ease of use
- limited (static) number of allergens
Standard Allergen Testing

- Any standard tray may be inefficient
- Beyond TRUE Test - non FDA approved
- Limitations
- Increased allergens, better yield
- Doesn’t account for patient specifics
  - Occupational
  - Personal exposures
  - Hobbies
  - Environmental issues
Are there really no allergen/s
  * If only TRUE Test consider more extensive testing
  * 25-33 % of allergens missed with TRUE Test only
  * 25 % of patients had at least one relevant non-NACDG allergen
Revisit History
Look for other allergen sources

- Ask the questions again
- Consider other possible contacts
  - spouse/significant other
  - child
  - pet
  - someone individual is caring for
- Other sources of allergens
  - Occupation - Site visit
  - Hobbies
  - Infrequent exposures
Still concerned about ACD

- “Elimination Diet”
- Use Test
- Repeat open application test
  - Apply product to localized body site
  - 1-2 times daily for 7-10 days
  - Observe for localized dermatitis
Considerations when patch testing is negative

✓ Expanded patch testing needs to be performed.
Negative patch test results
Considerations…….

* Was patch testing performed correctly?
  * Allergens active and stored properly
  * Good application/adherence
  * 48 hour occlusion
  * Was a second delayed reading performed?
  * Any immunosuppressives on board?
  * Any recent sunburn or topical steroids?
Two readings necessary
- 27% of dermatologists do 1 reading
- could miss 1/3 of reactions
- helps differentiate irritant from allergic
Possible Delayed Reactors

- disperse blue dyes
- bacitracin
- gold
- corticosteroids
- p-phenylenediamine
- cocamidopropyl betaine
Considerations when patch testing is negative

- Expanded patch testing needs to be performed.
- Two readings must be performed.
Improper Testing
Other Considerations

- Poor occlusion
  - Hairy back
  - Sweat prevents proper adherence
- Patch testing with active dermatitis
- Steroids - decrease elicitation of contact hypersensitivity
- Other immunosuppressives
- Sunburn - decreases Langerhans cells
Patients with positive patch test
Retested on prednisone of differing doses
Higher doses resulted in suppression of reactions
Prednisone and Patch Testing

- **Prednisone 40 mg/day**
  - 25% complete suppression
  - 66% diminished response
  - 8% no effect

- **Prednisone 30 mg/day**
  - 22% complete suppression
  - 33% diminished response
  - 44% no effect

- **Prednisone 20 mg/day**
  - 94% maintained reaction
24 nickel allergic patients
- Tested on and off prednisone 20 mg/day
- Decreased number of positive reactions
- Decrease in intensity of reactions
**Sunburn and patch testing**

* Local effect of acute low-dose UVB impairs induction of contact hypersensitivity

* Broad spectrum sunscreens protect against UV induced suppression of contact hypersensitivity

Immunosuppressants and patch testing


- Not a contraindication to patch testing
- Test at lowest possible dose
- ++ or +++ most reliable
- Lose weak relevant reactions
Can still elicit positive patch test
- Azathioprine
- Cyclosporin
- Infliximab
- Adalimumab
- Etanercept
- Methotrexate
- Mycophenolate mofetil
- Tacrolimus

Did not test off immunosuppressives
Unclear effect of suppressing ACD
Patch testing and immunomodulators: expert opinion

- Topical steroids
- UV
- Oral prednisone
- Time off oral prednisone
- IM prednisone 40 mg
- Methotrexate
- TNF inhibitors
- Azathioprine
- Cyclosporine
- Mycophenolate mofetil

- Avoid for 3-7 days
- Avoid for 1 week
- Test on 10 mg if necessary
- Avoid for 3-5 days
- Wait 4 weeks after injection
- Little to no effect
- Little to no effect
- Dose-dependent inhibition
- Dose-dependent inhibition
- Dose-dependent inhibition
Considerations when patch testing is negative

- Expanded patch testing was performed.
- Delayed reading was done.
- Testing was performed correctly.
Good news
* No known allergen/s identified
* No need to avoid products

Bad news
* No diagnosis made
* No clear path to resolution
* Additional testing
When patch testing is negative...

- Paucity of literature
- Much of this will be anecdotal
- Informal polling of colleagues
- Need for research
- Formal survey of ACDS conducted
- Other studies in progress
What to call Patch test negative dermatitis??

- Endogenous eczema
- Unclassified eczema
- Widespread eczema
- Nonspecific endogenous eczema
- Nonspecific endogenous dermatitis
- Constitutional eczema
- Idiopathic eczema
- Undefined eczema
When Patch Testing is Negative
Expert comments

- “delve into weaker reactions and take them seriously”
- “education is often the game changer for patients who have seen 6 derms and 2 allergists”
- “multifactorial approach”
- “Eczema is a phenotype, not a diagnosis- manifesting from various elements- genetic, immunologic, environmental, behavioral”
- “as a patch test referral center you end up with a collection of chronic dermatitis patients”
Clinical scenario

- Dermatitis - inflammatory response of the skin
  - Clinical
    - itching, redness, scaling, vesicles, papules
  - Histopath
    - epidermal spongiosis with acanthosis and lymphohistiocytic infiltrate
Differential Diagnosis considerations

- Allergic contact dermatitis
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- Tinea
Rule out other causes

- Patch test – negative
- Biopsy
  - not typically helpful- spongiosis
  - Done to rule out other conditions- CTCL/immunobullous
- Labs to consider
  - CBC with diff
  - Complete metabolic panel
  - Age appropriate screening
  - TSH
  - IgE
  - SPEP
  - Sezary count
  - ANA
  - Dust mite
Revisit the patient history

- Past medical history
- Family history
- Work exposure
- Pathology
- Laboratory results
- Symptoms
Avoid irritants - elimination diet

Control itch

Good skin care
  * Emollient creams
  * Mild soaps
  * Short, lukewarm showers

Get rid of loofas
  * Source of bacteria

Education helpful
**Patient education**

Arch Derm Venereol 91:12-17, 2011.

- Effect of education on quality of life and severity of disease
- Information provided in clinical setting
- Empowers patients and care givers
- 10 studies 2000-2008
  - (8 AD and 2 AD and psoriasis)
- 5 demonstrated improvement in quality of life
- 3 (of 6) demonstrated improvement in severity of disease
Patch test negative dermatitis: Few Studies in the literature

* Unclassified endogenous eczema.
  * *Contact Dermatitis* 41: 18-21, 1999.

* A clinical and patch test study of adult widespread eczema
  * *Contact Dermatitis* 47: 341-344, 2002.

* Prognosis of unclassified eczema.
  * *Archives of Dermatology* 2008 144:160-164, 2008.

* The value of patch testing patients with a scattered generalized distribution of dermatitis…

* Generalized Dermatitis in Clinical Practice
  * Springer
Unclassified Endogenous Eczema
CD 41:18-21, 1999.

- 8% of patch test population - 583
- Patch test negative
- Intractable eczema referred for patch testing
- Further studies performed
45 patients – 34 agreed to further studies
  * 48% male, 62% female
* Average age 50
* Average duration 35.7 months
* 12/34 elevated IgE >100 IU/ml
* Path
  * 24/26 chronic subacute dermatitis
  * 2/26 urticarial dermatitis
Unclassified Endogenous Eczema
CD 41:18-21, 1999.

- Outcomes: two year follow up
- 2/3 improved or resolved
  - 25% totally resolved
  - 22% greatly improved
  - 16% improved
    - 63% improve
- 29% stayed the same
- 10% worse
- 80% of those with high IgE improved
Scattered Generalized Distribution of Dermatitis


- NACDG study
- Difficult diagnosis and therapeutic challenge
- 14.9% of those referred
  - > 3 body sites
  - men more likely
  - history of atopic dermatitis more common
Scattered Generalized Distribution of Dermatitis


* 49% with at least one relevant positive allergen
  * Patch testing is beneficial
  * 16% had at least one non-NACDG allergen
  * Most common allergen sources
    * Personal care products 56%
    * Topical medicaments 13%
    * Clothing 8%
    * Jewelry 6%

* 51% no relevant patch test
* 51% with no relevant patch tests

* Diagnosis
  * Other dermatitis 20.4%
    LSC, spongiotic
  * Atopic dermatitis 15.8%
  * Other dermatosis 15.2%
    Nonspongiotic CTD, LP
  * Nummular dermatosis 3.4%
  * Psoriasis 3.3%
  * Irritant 3.1%
Clinical and patch test study of adult widespread eczema


* 108 Widespread eczema
* Men more common
* Older population compared to controls 47.6 years
* ACD 26.9%
* ACD suspected 39.8%
* Unclassified 31.5%
* “Not rare in dermatology practice”
* “Few systemic studies reported”
655 patients

- 43.7% allergic contact dermatitis
- 32.1% unclassified eczema
- 21.9% other forms of eczema
- 2.3% atopic dermatitis

Outcomes 1 year

- 15% clearance of unclassified eczema
- 36% improved

“Not uncommon, should be recognized and further studied”
9% of patients in CD clinic diagnosed with AD >20
- Diagnosis- PMH or FH of atopy
- Elevated IgE >100 IU/ml
- + prick test
Women: 65% > men: 38%
Sites
- Generalized
- Hands
- Face
First Line Therapy
- NBUVB
- Mycophenolate
- Methotrexate
- Cyclosporin to clear or rescue
  - Low dose cyclosporin or mycophenolate for maintenance
- Azathioprine - with caution
  - Side effects
  - Secondary cancers
Skin hydration
* Topical anti-inflammatory
* Anti-pruritic
* Anti-infectious
* Phototherapy
* Systemic therapy
Patch Test Negative Eczema

* Treatment options
  * Emollients
  * Steroids
    * Topical - soak and smear
    * Systemic - rescue
  * Topical calcineurin inhibitors
  * Ultraviolet light
    * UVA1
    * NBUVB
  * Methotrexate
  * Mycophenolate mofetil
  * Cyclosporin
  * Azathioprine
  * Other
Treatment options - side effects

- Steroids
  - Topical
    - atrophy, striae, telangiectasia, acneiform eruptions
  - Systemic
    - cardiac, GI, bone density, adrenal suppression
- Ultraviolet light
  - skin cancer, availability
- Methotrexate
  - liver toxicity
- Mycophenolate mofetil
  - Immunosuppression, registry
- Cyclosporin
  - Nephrotoxicity, hypertension, immunosuppression
- Azathioprine
  - Cytopenia, secondary cancers
Moisturizers should be integral part of AD treatment
- Reduces disease severity
- Decreases need for pharmacologic treatment
- Lessens symptoms: decrease, itch, erythema, fissures
- Apply soon after bathing to improve skin hydration
- Choice is patient dependent (cheap, free of allergens)
28 patients referred for refractory chronic dermatitis

* 20 minutes plain water soak
* followed by mid strength topical steroid
* Continue for up to 2 weeks

**Outcomes**

* 17 complete response
* 9 90-100% improvement
* 1 80% improvement
* 1 75% improvement
Steroid sparing anti-inflammatory agent

19 studies (10 tacrolimus, 9 pimecrolimus)

Pimecrolimus
- Effective in mild atopic dermatitis
- Value in long term maintenance/steroid sparing effect
- Daily application for 6 months- fewer AD flares, less CS
- Equivalent to mildly potent CS

Tacrolimus
- More effective than mild topical CS
- Helpful in moderate to severe eczema
- First line instead of CS

Calcineurin inhibitors

Review of literature

Limited evidence

9 trials

- 3 UVA1 faster and more efficacious in acute AD
- NBUVB superior in treatment of chronic AD
Methotrexate

- Antimetabolite
- Oral weekly
- Low cost
- Slow onset
- Well tolerated: GI, LFTs, pulmonary
- Lasting effect 3 months out
- FDA approved: oncologic diseases and inflammatory diseases
- Off label for Atopic dermatitis
No randomized controlled trials prior to 2011

- MTX 10 mg (22.5)
- Azathioprine 1.5 mg/kg/day (2.5)
- 12 weeks
- Decrease in SCORAD
  * Methotrexate 42%
  * Azathioprine 39%

- More side effects with azathioprine - lymphopenia and infection
Cyclosporin

- Originally used for graft antirejection
- Off label use for atopic dermatitis
- Rapid onset
- Quick relapse
- Side effects: nephrotoxicity, hypertension, drug interactions
Double blinded placebo controlled
46 patients, 23 active, 23 placebo
5mg/kg/day for 6 weeks
Total body severity improved 55%
Extent of disease improved by 40%
9/14 who completed improved 75%
3/14 cleared completely
55 atopic dermatitis

- Cyclosporin 5mg/kg/day for 6 weeks
- Randomized to low dose 3mg/kg/day or mycophenolate
- 30 weeks
- 1st 6 weeks, SCORADs all significantly improved

Follow up:
- mycophenolate maintained greater disease control
Azathioprine

- Purine analog
- FDA approved: rheumatoid arthritis, transplant rejection
- Dosing based on TMPT levels
- No concurrent phototherapy due to risk of skin cancer
- Side effects: GI, leukopenia, increase LFTs, cancers
Azathioprine

- Double blinded randomized placebo controlled crossover
- 37 adults with atopic dermatitis
- Atopic scoring decreased to 26% vs control 3%
- Improved sleep, pruritus
- Effective but not always well tolerated
- Severe nausea and vomiting, leukopenia, elevated LFTs
Mycophenolate mofetil

- FDA approved: organ transplant rejection prophylaxis
- Off label for atopic dermatitis
- Variable effect in treatment of atopic dermatitis
- Well tolerated
- Open label study- 34 weeks
- 16 patients of 3+ month duration
- Mycophenolate mofetil 1 - 2g/day
- 12/16 improved patient global assessment
- 14/16 improved by investigator global assessment
  - 3 cleared
  - 6 almost cleared
- Well tolerated
Endogenous Eczema

Other treatment considerations

- Education
- Bleach baths
- Antibiotics
- Dust mite avoidance
- Antihistamines
- Leukotriene receptor antagonists
- Humanized monoclonal antibodies to IgE
* 90% are colonized with staph
* Yeast colonization with malassezia also common
* Treatment considerations
  * Topical/oral antibiotics
    * Decrease inflammation
    * Treat active infection
  * Oral antifungals
* Decreases colonization with staph
* 1/4 - 1/2 cup of common liquid bleach (6%) into bath water.
* Mix the bleach in the water
* Creates a solution of diluted bleach (about 0.005%)
* Repeat 2-3 times a week
No strong clinical evidence

Some recommend
- allergen-impermeable bedding covers
- High filtration vacuum cleaner
* Evidence lacking in the literature
* Insufficient evidence to recommend
* Short term sedating antihistamines may help aid sleep
* Many dermatologists use them
Elevated IgE

- Increased in AD 43-82%
- Normal IgE does not exclude Atopic dermatitis
- IgE generally not elevated in non-atopic dermatosis
Increased IgE-bearing Langerhans cells
Increased leukotrienes produced by proinflammatory cells
Monteleukast


- cysteiny1 leukotriene receptor antagonist
- FDA Approved for asthma
- Oral medications dosed daily
- Side effects- well tolerated
  - GI disturbances
  - Insomnia
  - Hypersensitivity
  - Hallucinations
Monteleukast

* Use in Eczema- off-label
  * Inconclusive results
    * Improved sleep
    * Improved dermatitis
    * Improved itch
    * Decreased eosinophil count
    * Decreased disease severity
Omalizumab


- DNA derived recombinant humanized monoclonal antibody specific for Fc-binding domain of IgE
- FDA approved for asthma/chronic idiopathic urticaria
- Dosage based on body weight and pretreatment IgE levels
- Subcutaneous every 2-4 weeks
- Side effects - well tolerated
  - Anaphylaxis, heart disease, headaches, injection site reactions
  - Dizziness, upper respiratory and viral infections
* Omalizumab
  * Off-label uses
    * AD, allergic rhinitis, food allergies
    * Failure and successes with treatment in severe atopic dermatitis
Survey of ACDS Members:
Generalized Dermatitis Management

* 26 question survey
* Survey Monkey
* Distributed to ACDS members
* 123/718 responded
62% work at patch test center
94% test beyond the standard tray
91% perform two patch test reads
50:50 male:female ration
55% patch test over 100 patients/year
Q10 What percentage of your patch test patients are patch test negative at their final read?

Answered: 119   Skipped: 4
What to call patch test negative dermatitis?

- Generalized dermatitis 38%
- Adult onset atopic dermatitis 18%
- Undefined eczema 13%
- Other Dermatosis- Derm NOS 10%
- Endogenous eczema 8%
If a patient with dermatitis is taking systemic immunosuppressants that cannot be discontinued, on which of the following medicines will you patch test a patient?

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine</td>
<td>64.10%</td>
<td>35.90%</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>46.15%</td>
<td>53.85%</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>81.20%</td>
<td>18.80%</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>62.39%</td>
<td>37.61%</td>
</tr>
<tr>
<td>Prednisone 10mg/day</td>
<td>84.62%</td>
<td>15.38%</td>
</tr>
<tr>
<td>Prednisone 20 mg/day</td>
<td>27.35%</td>
<td>72.65%</td>
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<tr>
<td>Prednisone 30mg/day</td>
<td>7.69%</td>
<td>92.31%</td>
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<tr>
<td>TNF-alpha inhibitors</td>
<td>79.49%</td>
<td>20.51%</td>
</tr>
</tbody>
</table>
Next steps after negative PT

- Revisit history 97%
- Good skin care education 94%
- Skin biopsy 84%
  - Helpful <25%
- Lab work 74%
- Treat without further testing 65%
Lab tests ordered if PT negative

- CBC/diff: 86%
- Liver panel: 75%
- Renal function: 74%
- TSH: 50%
- IgE: 42%
- ESR: 40%
- SPEP: 35%
- Dust Mite: 12%
How often do you biopsy PT negative patients?

- Do not biopsy: 27%
- Biopsy but not useful: 5%
- Biopsy < 25% useful: 45%
- Biopsy 26-50% useful: 13%
- Biopsy 51-75% useful: 4%
- Biopsy 75-100% useful: 6%
Treatment options- topical
(select all that apply)

* Topicals
  * Corticosteroids 88%
  * Soak and smear 46%
  * Calcineurin inhibitors 42%
### Treatment options - Phototherapy

- Narrowband UVB: 72%
- UVB: 6%
- PUVA: 5%
- Do not use: 17%
Q19 If all treatments are options (assuming no reason to not use a particular drug) and you have decided to prescribe systemic medications to a patch test negative patient with generalized dermatitis, then which medication(s) do you use? Please list from 1 being most often used to 7 being least often used.

Answered: 113  Skipped: 10
What medications do you use most commonly?

- Prednisone 48%
- Methotrexate 23%
- Cyclosporin 8.85%
- Mycophenolate 8.85%
Use of antihistamines

- 15% often helpful
- 74% sometimes helpful

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyzine</td>
<td>91%</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>85%</td>
</tr>
<tr>
<td>Doxepin</td>
<td>79%</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>65%</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>61%</td>
</tr>
<tr>
<td>Loratadine</td>
<td>55%</td>
</tr>
</tbody>
</table>
Does food allergy play a role?

- No 69%
- Yes 31%

- 63% sometimes refer to allergy
- 25% never refer to allergy
When patch testing is negative..

- Make sure patch testing is really negative
  - Thorough history to make allergen selection
  - Expanded testing
  - Proper technique
- Consider other diagnosis
  - Biopsy and labs as needed
- Review basics of skin care
- Form a treatment plan
• Thank you?
• Questions?
• cmowad@geisinger.edu