Immune mediated dermatosis: Allergic Contact Dermatitis and Atopic Dermatitis in Adults

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ALLERGIC CONTACT DERMATITIS: ADDITIONAL INSIGHTS

- **Eyelid dermatitis** (Ferrer)
  - ACD main cause (*35%*). 
  - Female: >80%. 

- **ACD from Gold in an eyelid implant involving a patient with lagophtalmos** (Tous –Romero)
  - 10 days after the insertion and resolving after the removal of the implant a few months later
  - Patch tests + to TSO (*TrueTest and 0,5 and 2% in pet*). Only 13 cases previously reported. Alternative: titanium materials.

- **Gold jewellery** common cause of ACD from cosmetics with titanium (absorbtion of gold particles: 50% clear by removing gold jewelry)
ALLERGIC CONTACT DERMATITIS FURTHER LEARNINGS

• First case reported of **Airborne CD** to acemetacin in a **pharmaceutical employee**. No evidence of cross-reactions with indomethacin

• Hand ACD to **benzoyl peroxide** in **bleached flour** in a Baker (Adelman)

• **“Slime Dermatitis”**: Persistent hand dermatitis (borax –ICD-, shaving cream, school glue, food coloring contact lens solution) due to isothiazolinones in school washable glue

• **“Potty or toilet seat dermatitis”**: “circular” (black rubber/PPD; acrylates, colophony, polyurethane (soft), quaternary ammonium in detergents)

• Parabens: elected the “Non-allergen” of the year 0.61% (widespread: 15-20% of products).
ACD IN PATIENTS WITH AD (CHEN, WU AND SILVERBERG)

- ACD and AD commonly overlap.
- ACD likely underdiagnosed in AD: eg. flexural ACD or ACD underlying flares

- Indications of patch tests in AD\(^1\) (Multidisciplinary consensus guidelines)
  - adult/adolescent onset,
  - refractory/ worsening/fast rebound,
  - atypical locations (dorsal hands and feet, face/neck),
  - prominent nummular
  - PRIOR TO INITIATE SYSTEMIC TREATMENT

- Treat active dermatitis before patch testing (risk of angry back)

- Immune-suppresants less impacting patch tests: low doses of prednisone (<10) or CyA (<2); phototherapy (except for the last 1-4 weeks) or methotrexate (little or no impact)

- Immune-suppresants more impacting patch tests: CyA >30/kg/d, Aza, MMF, prednisone >10, IM triamcinolone within last 4 weeks and UV (in the last 1-4 weeks)

- Cautious interpretation of weak reactions (could either be false positives or negative) or negative reactions in immune-suppressed patients. Late readings and/or re-testing should be considered. Not all negative are AD (criteria should be met, Silverberg)

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1. Is dupilumab effective in ACD?
2. Could ACD impair the response of AD to dupilumab?
3. Do dupilumab modulate the reactions to patch tests?
IS DUPILUMAB EFFECTIVE IN ACD?

ACD and AD share some immune-pathogenic mechanisms

- Classically ACD=Th1 and AD=Th2
- **AD**: Th1 (adults of European or Asian descent)
- **ACD**: Th2 allergens (fragrances, rubber)

  - 3 patients
  - 2 with extensive ACD due to textile and rubber allergens.
  - 1 hairdresser with severe hand occupational ACD
COULD ACD IMPAIR THE RESPONSE OF AD TO DUPILUMAB?

• **In theory No**: No differences in dupilumab response rates between AD patients with and without ACD. (A retrospective review of dupilumab for atopic dermatitis patients with allergic contact dermatitis (https://doi.org/10.1016/j.jaad.2018.12.048)

• **But....** Persistent localized (mainly facial) dermatitis in responder patients (residual underlying ACD?)
  • (potencial skewing Th2 to Th1 increasing reactions to Th1 allergens)

• recall phenomenon (H. Puerta del Mar)

DO DUPILUMAB MODULATE THE REACTIONS TO PATCH TESTS?

- Suresh (oct. 2018) **Relevant positives patch tests residual ACD** 3 pts with (Fragrances, lanolin, CS, glyceryl monothioglycolate 1%, ammonium persulfate 2.5%, PEG, neomicina, acrylate)
- Raffi (nov. 2018) **Allergen-specific patch test inhibition** reactions 11/18 pts. (3 + MI and 2 + bronopol (previously + Nickel, hp lin, *compositae* negative under dupilumab)
  - **false negatives with Th2 allergens such as fragrances and rubber** (Th2, some Th22 and smaller Th1/Th17 contribution)
  - Positive reactions with type I allergens such as nickel (innate immunity, Th1/Th17; Th22>Th2)
- **Indication of patch testing: prior to treatment with dupilumab** (preferably) or during treatment when persistent localized (mainly facial) dermatitis clinically compatible con ACD (false negative with Th2 allergens possible)

*Recall dermatitis at patch test sites in an atopic dermatitis patient treated with dupilumab (Collantes-Rodriguez et al. Contact Dermatitis. 2019;80:69–70)*
*A pragmatic approach to patch testing atopic dermatitis patients Clinical recommendations based on expert consensus opinión (Chen, Dermatitis, 2018)*
*Suresh, Murase JE. The role of expanded series patch testing in identifying causality of residual facial dermatitis following initiation of dupilumab therapy (JAAD Case Reports 2018;4:899-904)*
*Raffi et al. JAMA Derm epub 11/18*
• Erythroderma with psoriasiform changes (Stiff, e-poster) after initiation of dupilumab (initial misdiagnosis vs immune shift)

• Dupilumab – induced psoriasiform dermatitis (Novice, e-poster) (forehead rash spreading to the scalp, chest and upper arms) (disregulation of other patchways? Th1, Th17, Th22)
“ADULTS WITH AD : NOT JUST BIG KIDS” (SILVERBERG)

- **Prevalent** (<20%: assymptomatic past 20 years) Nationally representative cohort form (USA): adults 7.2% and children 12%. (Chiesa, J Invest Dermatol 2019)

- **Adult-onset AD unique subset** with specific epidemiology, genetics, pathogenesis, comorbidities, clinical phenotypes, course and treatment approaches (Silverberg)

- **Indication of patch tests**

- **Low Outpatient healthcare utilization**: visits decrease with age (chronic with flares< chronic<acute)

- FLG null mutations not-associated with adult onset (analogous ACD or healthy controls)

- Flexural: less common in adult onset AD

- **Burden of skin pain** (Vakharia) 42% (past week); 13% (severe or very severe); 16% skin pain was part of their itch (reminiscent of neuropathic) : Independent symptom

- Kirchhof (2018) document consensus to address the topic of adult onset AD
THE PRESENT


- Severe in adults: includes Dupilumab and alitretinoin oral


- Moderate. Topical crisaborole 2%
- Severe: includes dupilumab

Crisaborole ointment was approved by the U.S. FDA for the treatment of AD in December 2016, and dupilumab approved for AD in adults in 2017 (currently the only systemic approved for adults with moderate-to-severe AD) They were therefore not incorporated in the earlier guidelines.
“AD EMERGES AS A SYSTEMIC DISEASE” (GUTTMAN): CO-MORBIDITIES

- **high level of systemic immune activation** emphasizing the **need for systemic treatments** for moderate-to-severe cases (Guttman)

- **Sleep disturbances**: 44% (biggest Qol impact); 3 times more insomnia than general population, parasomnias; daytime sleepiness; conduct disturbances

- **Anxiety, depression**: Many adults with severe symptoms not being diagnosed by a healthcare provider: screening and referral! **Suicidability** 66% saw a physician the previous month. Improvement with disease control (Silverberg, )

- **33% suicidal attempt** (Sandu JK, JAMA Dermatology, 2019)

- **Systemic infections** (endocarditis, meningitis, encephalitis, bone, joint, sepsis, ear, throat, urinary tract)

- **Cardiovascular co-morbidities**
  - (Cohort studies): myocardial infarction, stroke, ischemic stroke, angina, heart failure
  - obesity , DM , high blood pressure
  - high blood pressure and heart disease (indirect effects of moderate or severe AD)
  - NO increased mortality rates in AD with congestive heart failure
  - Increased hospital complications in AD with DM
  - Effect of elderly status on complications
RATIONAL FOR USING BLEACH BATHS

Yes:

• European guidelines (1918) Adding antiseptics such as sodium hypochlorite to the bathwater may be useful for the treatment of AE (1b, A).

• E-poster: 1 study in vitro 0.0005% reduces serin protease in cultured keratynocytes (essential homeostasis barrier)”

No (Silverberg):

• “Studies comparing with water baths: only 2 found greater reductions, 1 found less and 1 no differences. No differences of S. aureus colonization or infection

• 1 study in vitro published this week
  • 3 different strains of S aureus and 2 strains of S epidermidis
  • No antimicrobial properties of 0-0.01% bleach (bactericidal effects were only observed at cytotoxic concentrations 0.03% )
  • No difference by strain, type of bleach, log-phase vs stationary phase growth Petri dish vs pig skin culture
MEDICATIONS FOR THE FUTURE??

**Topical**

- **Topical delgocitinib (pan-JAK inh):** efficacious and safe:
  - **moderate-to-severe AD** (phase III randomized double blind vehicle controlled study in *Japanese adults*)
  - in **chronic hand eczema** (worm) (multicenter randomized double blind phase IIa proof-of-concept study:
    - **Success in 45.7%** (vs. 14.9% vehicle) (PGA)

- **Topical ruxolitinib (JAK1/JAK2 inh)** Phase 2 adults bid superior to triamcinolone;
  - Significant **reduction in itch NRS** within 36 h of 1.5% vs. Vehicle. High performance for a topical drug with no safety concerns

- **Tapinarof cream** (AhR modulating agent TAMA)
  - improves epidermal barrier phase 2a (Paller) Nasopharyngitis, folliculitis and AD (8, 7 and 6%) Mean reduction in the mean TSS and BSA

- **Difamilast OPA-15406 MM36** other topical PDE4 inh Phase 2 maximal use in pediatr

- **Bacteriotherapy**

- **Microbiome transplant therapies** *Roseomon a mucosa* (2018)

**Systemic**

  - Barrier-based approach modulating terminal differentiation and lipid measures: no significant effects on clinical efficacy, or immune abnormalities

- **ILV-094/anti-IL-22 in AD A monotherapy study** (Guttman-Yassky E el. JAAD January 2018)
  - High baseline expression of IL-22 predicts improvement; worsening when low baseline IL-22

- **Tralokinumab (anti IL-13)** phase 2b: *Staph aureus negativization* 61% pts, treated with 300 mg vs. 23.5% placebo and reduction of AD-serum biomarkers (IgE, periostin, CCL17)

- **Lebrikizumab : IL-13** Phase 2 (no conjunctivitis)

- **Tezepelumab TSLP** Phase 2 a 113 pts no safety signals

- **Nemolizumab IL-31** Phase 2 (Anti itch)

- **ANB020 IL-33** Phase 2

- **MOR106 IL-17C** Phase 1 25 pts (EASI 50 in 83% 4 weeks)

**Oral**

- **ZPL 3893787** H4R antagonist phase 2 a

- **Baricitinib JA JAK1/2** phase 2 and parallel phase 3 monotherapy

- **Upadacitinib** JAK-1 specific inh

- **Abrocitinib** JAK1 inh phase 2