

#AAD2019

Highlights
AEDV

IN 77TH AAD CONGRESS

1-5 MARCH 2019

★ WASHINGTON ★

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**Immune mediated dermatosis:
Allergic Contact Dermatitis
and Atopic Dermatitis in Adults
Dra. María Antonia Pastor-Nieto**

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ALLERGIC CONTACT DERMATITIS: ADDITIONAL INSIGHTS

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- **Eyelid dermatitis** (Ferrer)
 - Retrospective study **9970 pts in 38 años** (1980-2018): **10%** of the tested patients. **ACD main cause (35%)**. **Female: >80%**. **Monosensitization**. To: fragrances, BP, isothiazolinones, PPDA, nickel, CS, neomicin. Main source: cosmetics.
- **ACD from Gold in an eyelid implant involving a patient with lagophthalmos** (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** (absorbption of gold particles: 50% clear by removing gold jewelry)

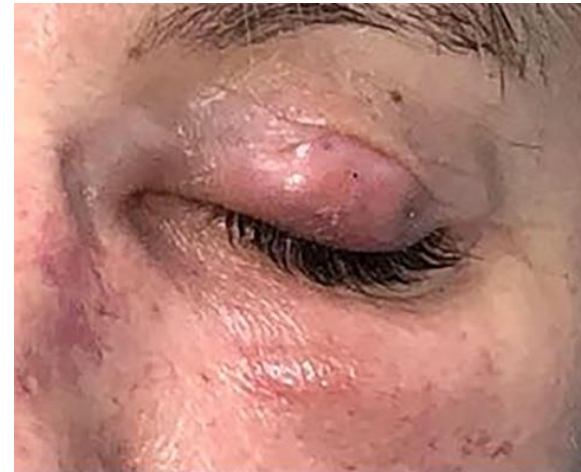


Fig. 1



ALLERGIC CONTACT DERMATITIS FURTHER LEARNINGS

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- First case reported of **Airborne CD** to **acetaminophen** 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).



Figure 1. Clinical presentation. Erythematous patches in the eyelids, nasolabial folds and chin.



Figure 2. Clinical presentation. Papules on an erythematous base in the neck, frontal upper trunk



Figure 3. Patch tests for the different compounds of the capsules were positive only for acetaminophen.



Figure 4. Patch tests with different concentrations of acetaminophen (0.1%, 1%, 10% and 30%) show positive results for every concentration tested.

ACD IN PATIENTS WITH AD (CHEN, WU AND SILVERBERG)

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- **ACD and AD commonly overlap.**
- **ACD likely underdiagnosed in AD:** eg. flexural ACD or ACD underlying flares
- **Indications of patch tests in AD¹**
(Multidisciplinary **consensus guidelines**)
 - **adult/adolescent onset,**
 - **refractory/** worsening/fast rebound,
 - **atypical** locations (dorsal hands and feet, face/neck),
 - prominent **nummular**
 - **PRIOR TO INICIATE SYSTEMIC TREATMENT**
- **Treat active dermatitis before patch testing** (risk of angry back)
- **Immune-suppressants 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-suppressants 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)

¹A Pragmatic Approach to Patch Testing Atopic Dermatitis Patients: Clinical Recommendations Based on Expert Consensus Opinion *DERMATITIS*, Vol 27 i No 4 j July/August, 2016

DUPILUMAB, ACD AND AT

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)**

- Goldminz AM, Scheinman PL. A case series of **dupilumab-treated allergic contact dermatitis patients**. *Dermatol Ther*. 2018 Nov;31(6) Epub 2018 Sep 24.
- 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?

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- **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?

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- 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-Rodríguez et al. Contact Dermatitis. 2019;80:69–70)

A pragmatic approach to patch testing atopic dermatitis patients Clinical recommendations based on expert consensus opinion (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

PSORIASIFORM CHANGES AFTER DUPILUMAB INITIATION

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- **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)



•Figure 2: pink to erythematous patches to thin plaques on the forehead extending into the scalp with fine white flaky scale



“ADULTS WITH AD : NOT JUST BIG KIDS” (SILVERBERG)

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- **Prevalent** (<20%: asymptomatic 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
- Kirchof (2018) document consensus to address the topic of adult onset AD

THE PRESENT



- **Consensus-based European guidelines** for treatment of atopic eczema (atopic dermatitis) in adults and children: part I (JEADV **2018**, 32, 657–682)
- Severe in adults: includes **Dupilumab and alitretinoin oral**
- **Atopic dermatitis yardstick practical recommendations** for an evolving therapeutic landscape Boguniewicz M et al. Ann Allergy Asthma Immunol **2018**.
- Moderate. Topical crisaborole 2%
- Severe: includes dupilumab

includes a discussion of upcoming topical therapies such as topical selective PDE-4 inh (crisaborole) and topical (JAK) inh (tofacitinib). However, neither crisaborole nor tofacitinib is currently licensed in Europe and no recommendations are made for their use

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

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- **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 diffence 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**
Roseomona mucosa (2018)

Systemic

- **Topical LXR Agonist/VTP38543** (Czarnowicki T....Gu`mnan-Yassky E . *Ann Allergy Asthma Immunol.* 2018;120(6):631-640). 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