What’s New in Atopic Dermatitis?

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Disclosures

- No financial disclosures relevant to this talk.
- I will discuss off-label use of medications.
Outline

- Comorbidities
- Food Allergy
- Emollients
- Bathing
- Topical Interventions
- Systemic Interventions
What’s New in Atopic Dermatitis?

- Publications from the last 3.5 years
  - 2014 – 2017
- AAD Guidelines 2014

Guidelines of care for the management of atopic dermatitis

Section 1. Diagnosis and assessment of atopic dermatitis

Section 2. Management and treatment of atopic dermatitis with topical therapies

Section 3. Management and treatment with phototherapy and systemic agents

Section 4. Prevention of disease flares and use of adjunctive therapies and approaches
Guidelines of care for the management of atopic dermatitis

Section 1. Diagnosis and assessment of atopic dermatitis

Table VI. Recommendations for the assessment of clinical associations of atopic dermatitis

Physicians should be aware of and assess for conditions associated with atopic dermatitis, such as rhinitis/rhinoconjunctivitis, asthma, food allergy, sleep disturbance, depression, and other neuropsychiatric conditions, and it is recommended that physicians discuss them with the patient as part of the treatment/management plan, when appropriate.

An integrated, multidisciplinary approach to care may be valuable and is suggested for atopic dermatitis patients who present with common associations.

Comorbidities

- Autism spectrum disorder (ASD)
- Attention deficit and hyperactivity disorder (ADHD)
- Obesity and cardiovascular disease
- Alopecia areata (AA)
- Vitiligo
- Rheumatoid arthritis (RA)
- Inflammatory bowel disease (IBD)
- Headaches
Comorbidities - ADHD

- National Health Interview Survey (NHIS) 1997 – 2013
- National Survey of Children’s Health (NSCH) 2003/4 and 2007/8
- 354,416 children (2-17y), 34,613 adults

- AD was associated with ADD/ADHD in both (adjusted OR, 95% CI)
  - Children: 1.14 (1.03 – 1.26)
  - Adults: 1.61 (1.25 – 2.06)

Comorbidities - ADHD

Higher odds in children with:
- Severe AD AND 0-3 nights of adequate sleep per week*
- AD unaccompanied by other allergic disease
- History of anemia, headaches, and obesity

Higher odds in adults with:
- Asthma, insomnia and headaches

Underweight BMI in adults is protective

Comorbidities - ADHD

Why??
- Unknown
- AD may upregulate neuroimmune factors → heightened sensitivity to stimuli, poor sleep, ADHD
- Sleep disturbance may unmask symptoms of inattention and hyperactivity
- Needs further exploration

Limitations
- +: Large sample size, highly reproducible
- -: Caregiver report of ADHD diagnosis, unable to r/o possibility of residual confounding

Comorbidities – ASD, ADHD

- Taiwan’s National Health Insurance Program 2000 – 2010
- 387,262 children with AD before age 2y

- AD before age 2 was associated with an increased hazard ratio:
  - **ASD** by 10% (HR 1.09) (0.5% vs 0.4%)
  - **ADHD** by 16% (HR 1.15) (3.7% vs 2.9%)

- Most prominent in those with earlier onset or more severe AD

Comorbidities – ASD, ADHD

Why??
- Disordered immunologic response may affect neurodevelopment
- Chronic sleep disturbance/deprivation
- Help-seeking behaviors (seeking treatment for AD → increase diagnosis)
- Shared susceptibility (? Shared etiologic process)
- Confounding factors not taken into account

Limitations
- + : large sample size, longitudinal data
- - : Lack of direct evidence re diagnosis of ASD/ADHD*

Comorbidities – Headaches

- NHIS 1997 – 2013
- 401,002 children and adolescents
- **Children with eczema had a significantly higher prevalence and odds of headaches**
  - Prevalence: 10.7% vs 5.4%
  - OR: 1.52 (95% CI, 1.45 – 1.59)
- Higher odds in children with eczema and:
  - Atopy, fatigue, sleep disturbance

Comorbidities - Obesity

- Systematic review and metaanalysis
- 30 studies reviewed

- Higher odds of AD than normal weight patients:
  - Obese: 1.68 (95% CI 1.54-1.84)
  - Overweight/obese: 1.4 (95% CI 1.34-1.50)
  - Overweight: 1.27 (95% CI 1.19-1.36)

- Patients with eczema may benefit from weight loss interventions

Comorbidities - Obesity

- Overweight/obesity associated with increased prevalence and severity of AD
  - Cross-sectional nature of study precludes determination of cause

- Why??
  - Unknown
  - Obesity has been shown to alter the epidermal barrier, ↑ TEWL, dry skin
  - Obesity modified cutaneous and systemic inflammation (proinflammatory)
  - AD may predispose to a more sedentary lifestyle

Comorbidities – Vitiligo & Alopecia areata

- Systematic review and Meta-analysis
- 16 studies of vitiligo and 17 studies of alopecia areata (AA)
- Vitiligo (2 studies in pooled analysis that included control patients)
  - OR 7.82 (95% CI, 3.06 – 20.00)
  - Higher odds of AD in patients with early onset vitiligo (<12y)
- AA (3 studies in pooled analysis that included control patients)
  - OR 2.57 (95% CI 2.25 – 2.94)
  - High odds of AD in patients with alopecia totalis or universalis

Comorbidities – Vitiligo & Alopecia areata

- Cross sectional nature again precludes determination of which disorders appeared first

- Further high quality studies needed
  - Small number of studies
  - Low quality of studies

Comorbidities – RA, IBD

- Data from German National Health Insurance beneficiaries
- 655,815 aged 40 years and younger from 2005 – 2011
- **Patients with AD (n = 49,847) were at increased risk for:**
  - **Rheumatoid arthritis**: RR 1.72 (95% CI 1.25 – 2.37)
  - **Inflammatory bowel disease**
    - Crohn’s disease: RR 1.34 (95% CI, 1.11 – 1.61)
    - Ulcerative colitis: RR 1.25 (95% CI, 1.03 – 1.53)
- Increased with each physician visit and in patients receiving topical anti-inflammatory treatment for AD

Comorbidities – RA, IBD

- Why??
  - AD, IBD, RA all characterized by T-cell-mediated chronic inflammation
  - Autoreactivity in subset of patients with AD
  - Epigenetic changes secondary to prolonged systemic inflammation

Food Allergy

- **True food allergy**
  - “an adverse health event that results from stimulation of a specific immune response that occurs **reproducibly** on exposure.’’
  - “Reproducible clinical s/sx after food exposure/ingestion are necessary to diagnose food allergy”

- Food allergy **may or may not** induce eczematous dermatitis
  - Delayed reaction typically occurring 6 – 48 hours later

Food Allergy - Testing

- Positive sIgE has a poor correlation with clinical allergic responses
- Serum-specific IgE has:
  - High NPV (>95%)
  - Low specificity and PPV (40-60%)
- “Broad panel allergy testing independent of a history of a reaction to foods is NOT recommended.”

Table VI. Recommendations for other adjunctive and complementary interventions for the treatment of atopic dermatitis

- Food elimination diets based solely on the findings of food allergy test results are not recommended for the management of AD.
- If a patient has a true immunoglobulin E-mediated allergy, he or she should practice avoidance to prevent potential serious health sequelae.
- Children <5 years of age with moderate to severe AD should be considered for food allergy evaluation for milk, egg, peanut, wheat, and soy if at least 1 of the following is met: (A) persistent AD in spite of optimized treatment or (B) having a reliable history of immediate reaction after ingestion of a specific food.
**Objective**
- PPV of food antigen specific sIgE
- Trial examining safety and efficacy of pimecrolimus 1% cream
- > 1000 infants aged 3 – 18 months with mild – severe AD
- 36-month randomized double-blind phase followed by open label phase up to 33 months
- Food antigen specific serum IgE (sIgE)
  - Cow’s milk, egg white, peanut, wheat, seafood mix and soybean
  - Baseline, end of double-blind phase, end of open-label phase

Food Allergy - sIgE

- PPV for published and newly developed sIgE decision points were low
  - < 0.6 for all values tested

- sIgE levels were not clinically useful for predicting food allergy development

Food Allergy

- Incidence of food allergy in children 3 mo – 3y with mild-moderate AD
- 15.9% had at least 1 food allergy
- Peanut 6.6%
- Cow’s milk 4.3%
- Egg white 3.9%
- Seafood 0.4%
- Wheat 0.3%
- Soybean 0.4%

Food Allergy

- Peanut consumption prevents allergy!

Food Allergy

- EAT Study
- Early introduction of allergenic foods in infants
- High drop out rate
- Did not find a difference in early introduction group and control group
- Brings up several questions
  - When is the age to introduce?
  - What is the dose to introduce at?
- Likely okay to introduce food earlier than AAPs "exclusive breastfeeding x 6 months, but need more data"
Food Allergy

- Recommendations on early peanut introduction for your eczema patients …
Food Allergy - Summary

- Discuss role of food allergy with your patients
- Identify symptoms of true food allergy
- Encourage early feeding, but refer severe eczema to allergist prior to first feed
Prevention/Treatment

MOVING ON...
Table II. Recommendations for nonpharmacologic interventions for the treatment of atopic dermatitis

The application of moisturizers should be an integral part of the treatment of patients with AD as there is strong evidence that their use can reduce disease severity and the need for pharmacologic intervention.

Bathing is suggested for patients with AD as part of treatment and maintenance; however, there is no standard for the frequency or duration of bathing appropriate for those with AD.

Moisturizers should be applied soon after bathing to improve skin hydration in patients with AD.

Limited use of nonsoap cleansers (that are neutral to low pH, hypoallergenic, and fragrance free) is recommended.

For the treatment of patients with AD, the addition of oils, emollients, and most other additives to bath water and the use of acidic spring water cannot be recommended at this time, because of insufficient evidence.

Use of wet-wrap therapy with or without a topical corticosteroid can be recommended for patients with moderate to severe AD to decrease disease severity and water loss during flares.
Topical Treatment

- Apply bland emollient BID–QID
- Avoid complex topicals
- Use adequate quantities of medication
Emollients

- RCT of 124 neonates in US and UK at high risk for AD
- Intervention
  - Full body emollient starting with in 3 weeks of birth
- Control
  - No emollients

Emollients

- Statistically significant protective effect with daily emollient on the cumulative incidence of AD
  - relative risk reduction of 50%
- Emollient therapy from birth: feasible, safe, and effective approach for AD prevention.

Emollients

- Similar study in Japan
Emollients

- Coconut oil
Bathing

- Dilute bleach baths
- Dilute bleach baths; twice weekly to daily baths have become standard maintenance care after studies showed reduced AD severity at 1 and 3 months (Paller) [Huang 2009 Pediatrics, Huang 2011 Arch Derm; Wong J Dermatol; Wong J Dermatol 2013] [Hon J Derm Treat: over 4 weeks, bleach no diff than water baths]
- already knew these were effective but recent studies also show
  - Effect on skin barrier vs water [Shi]
- Tx with TCS is enough to normalize the cutaneous skin microbiota [Gonzalez]
- Evidence that bleach baths have direct anti-inflamm effect
Melatonin

- Randomized, double-blind, placebo-controlled crossover study of 48 children (1 – 18y)
- Physician diagnosed AD involving at least 5% BSA
- Melatonin 3 mg/day or placebo x 4 weeks then 2 week washout and crossover to the alternate treatment x 4 weeks
- Primary outcome: drop in SCORAD
- Secondary outcome: other sleep variables*

Melatonin

- Decrease in SCORAD by 9.1 compared with placebo
- Sleep-onset latency shortened by 21.4 minutes
- Improvement in SCORAD did not correlate significantly with change in sleep onset latency
- Other sleep variables did not differ significantly
  - Sleep efficiency, wake in sleep, total sleep time, mobility in sleep, etc.
- No adverse events reported
- Effects may be due to effects on sleep and/or immunomodulatory or antioxidative properties

Pimecrolimus

- Pimecrolimus – talked early on about allergic march, there is a study about whether pimecrolimus limits the atopic march (interesting question esp in light of these emollient studies which show decrease incidence of AD with emollients, so what if you actually use something anti-inflammatory?? – cut to the punch line, it didn’t work 😞, but, on the upside, pimecrolimus was safe/well tolerated! ;)
- TCI Black Box warning
- 2016 Systematic review of published trials [Siegfried]: No lymphoma for TCIs
- Pimecrolimus [Margolis 2015], [Sigurgeirsson 2015]
- Cochrane database review 2015 showed “no evidence was found to support the possible increased risk of malignancies]
- Slightly increased risk of lymphoma in pt with AD [Legendre 2015]
AD and lymphoma

- Systematic literature search and separate meta-analysis on case control and cohort studies
- Of 3979 articles, 24 met inclusion criteria
- Slightly increased risk of lymphoma in AD patients
- Severity of AD is a significant risk factor
  - Role of topical steroids and topical calcineurin inhibitors unlikely to be significant

Crisaborole

- Exciting new topical option, esp for the steroid phobic families
- Boron based phosphodiesterase type 4 inhibitor (PDE4i)
  - PDE4 is expressed in immune cells and keratinocytes
  - Inhibition of PDE4 elevates intracellular cAMP levels, results in modulation of inflammatory mediators
- Boron may improve penetration
- No to minimal blood levels after topical application incl in children and adolescents (Paller) [Tom][Zane]
- No clinically imp safety signals
- FDA approved in Dec 2016 for mild to mod AD in pt age 2 and up
- Paller et al Phase 3 trial RPCDB Crisaborole oint v vehicle 2-18y
  - Primary endpoint: Clear/almost clear 30 vs 10%
  - Secondary endpoint: Improvement in pruritus 58% v 42% at day 8; 63 v 53% at day 29.
- Adverse effects: Application site pain 45% v 6%; staph infxn 1% v 5%
- In terms of efficacy, probably closest to pimecrolimus (? Low potency topical steroid)
Tofacitinib

- JAK (Janus associated kinase inhibitor), unlike AA, stopping inflammation in the epidermis may be beneficial
- RPCDB trial of tofacitinib ointment (Phase 2a)
  - 69 adults with AD, BID application
  - EASI score change: 81.7% vs 29.9%
  - PGA clear or almost clear: 71.4% vs 20.6%
- Barriers: cost, accessibility, unclear monitoring needs

- In terms of oral tofacitinib, there’s a case report [Levy], but efficacy and risk:benefit ratio still needs clarification in AD (Simpsons comment)
Dupilumab

- Injectable biologic targeting IL4/13 (imp mediators of Th2 inflammation)
- Also studied in asthma, sinusitis, nasal polyposis
- Phase 3: SOLO-1 (671 patients), SOLO-2 (708 patients)
- Primary outcome: Clear or almost clear AND 2 point improvement on IGA
  - 300 mg SQ weekly: 36%, 37%
  - 300 mg SQ every other week: 36%, 38%
  - Placebo: 8%, 10%
  - P < 0.001
- At least 75% reduction in EASI score significant better in both treatment groups
- Secondary outcomes: itch, EASI, QoL, depression/anxiety scores
- Adverse reactions: injection site reactions, conjunctivitis, nasopharyngitis (common but matches placebo), HSV infections of the skin, no medication related serious adverse events
Apremilast

- Systemic phosphodiesterase inhibitor (PO)
- Not yet approved for AD, currently used for moderate to severe plaque psoriasis, PsA
- No literature other than case reports
- May be useful in:
  - AD-psoriasis overlap
  - Palmoplantar involvement
- Advantages: No blood draws
- Adverse effects: GI, mood are biggest concerns
Ustekinumab

- There were some promising case reports, but two controlled trials showed negative results [Guttman-Yassky and the one from Japan]
- Focus on what’s out an available, but lots of things cooking
Nemolizumab

- IL31 has been implicated in the induction of pruritus, the major symptom of AD
- Significant reductions in itch with modest reduction in inflammation
- AE profile unclear, with more exacerbations and peripheral edema in treatment group
- Will itch blockade be enough to treat AD
Anti-Itch

- CT327 (NGF)
- Tradipitant

Addendum Guidelines for prevention of peanut allergy in US. JACI 2017

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