ATOPIC DERMATITIS: ADVANCES AND UPDATES

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Pediatrics Grand Rounds, June 9th, 2021

Disclosures

- I will be discussing off-label uses of medications
- I have been on an advisory board and acted as an investigator for Regeneron
- I am co-founder of Stryke Club, a personal care brand for teens

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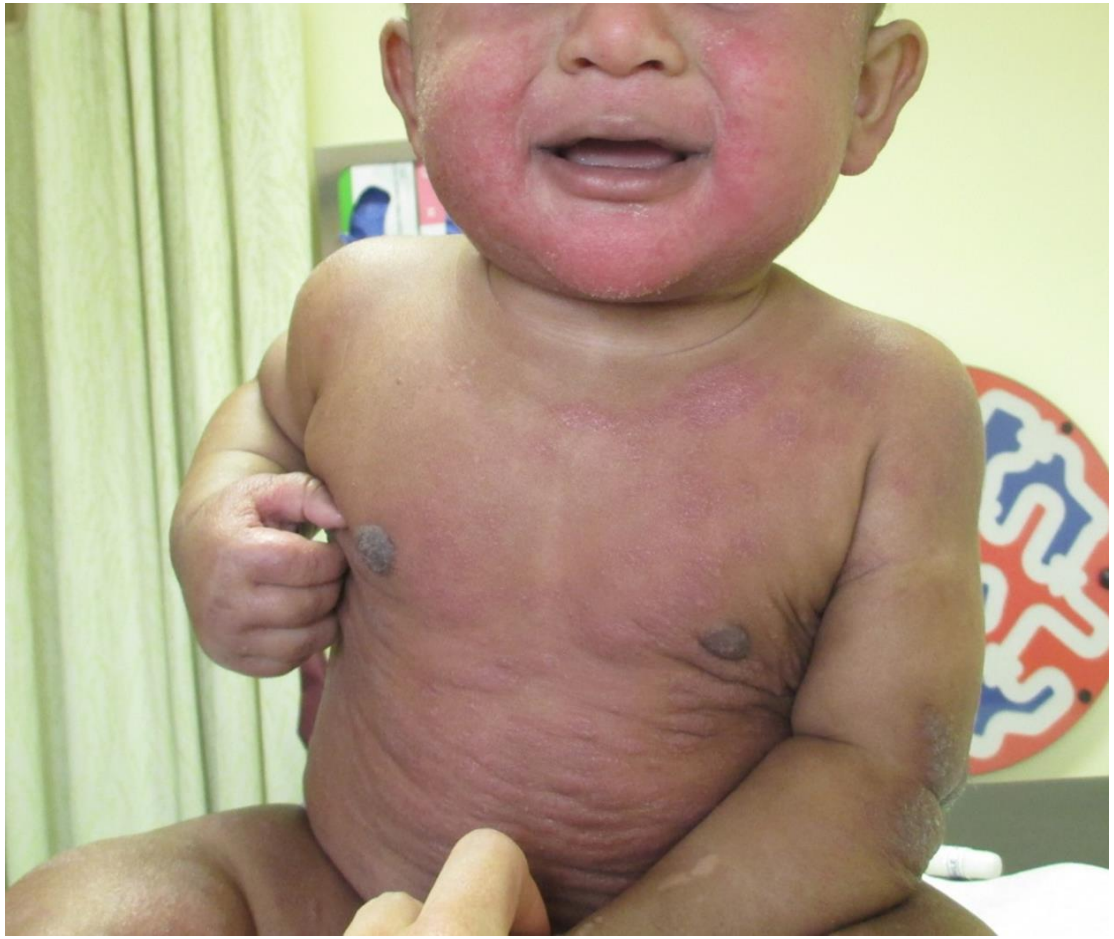
Atopic Dermatitis: ***The Challenge!***

- Time consuming
- Frequent office visits
- Steroid phobia
- Parental skepticism
- Poor compliance
- Therapeutic nihilism
- Frustration for family and health care professionals



Burden of Disease

- US spends at least >$400 million per year on the care of atopic dermatitis (similar to estimated costs for psoriasis, emphysema)
- Quality of life studies show overall QOL impact on families to *Exceed* that of asthma and *Equal* that of Type I Diabetes
- All aspects of family functioning are affected: sleep, work, interpersonal relationships

Beattie PE et al. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases**.** Br J Dermatol. 2006 Jul;155(1):145-51

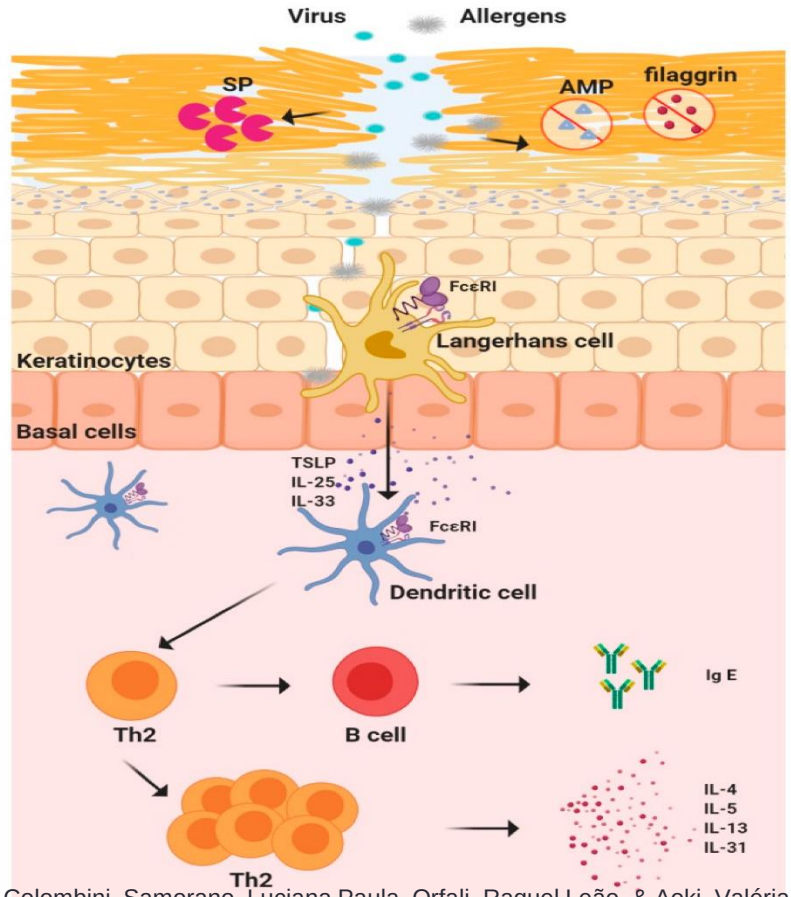
Mancini, AJ et al. The **socioeconomic impact of atopic dermatitis in the United States: a systematic review.** Pediatr Dermatol. 2008 Jan-Feb;25(1):1-6.

Atopic Dermatitis: Advances and Updates

- Atopic dermatitis is a skin barrier problem
  - Basic science review
  - Practical use of topical therapies
- Updates
  - Bathing and emollients
  - Topical calcineurin inhibitors
  - Crisaborole
- Advances: Biologic Therapies

Atopic Dermatitis: A Barrier Problem

- Pathogenesis of AD only partially understood and complex
- Defects in filaggrin compromise skin barrier and increase TEWL



Skin barrier abnormality

filaggrin
ceramides
antimicrobial peptides (AMP)
serine protease (SP) inhibitors

serine protease (SP)
tight junction (TG) disorder

Immune dysfunction

IgE levels
sensitization to allergens
Th2 cytokines
FcεRI expression
thymic stromal lymphopoietin (TSLP)

Zaniboni, Mariana Colombini, Samorano, Luciana Paula, Orfali, Raquel Leão, & Aoki, Valéria. (2016). Skin barrier in atopic dermatitis: beyond filaggrin. Anais Brasileiros de Dermatologia, 91(4), 472-478.

Atopic Dermatitis: A Barrier Problem

- Barrier dysfunction leads to:
  - Increased colonization with staph aureus
  - Increased penetration of antigens/allergens
  - Increased risk over time for allergic rhinitis, asthma and food allergies
  - Shift from Th1 ➡ Th2 immune response:
    - immune dysregulation

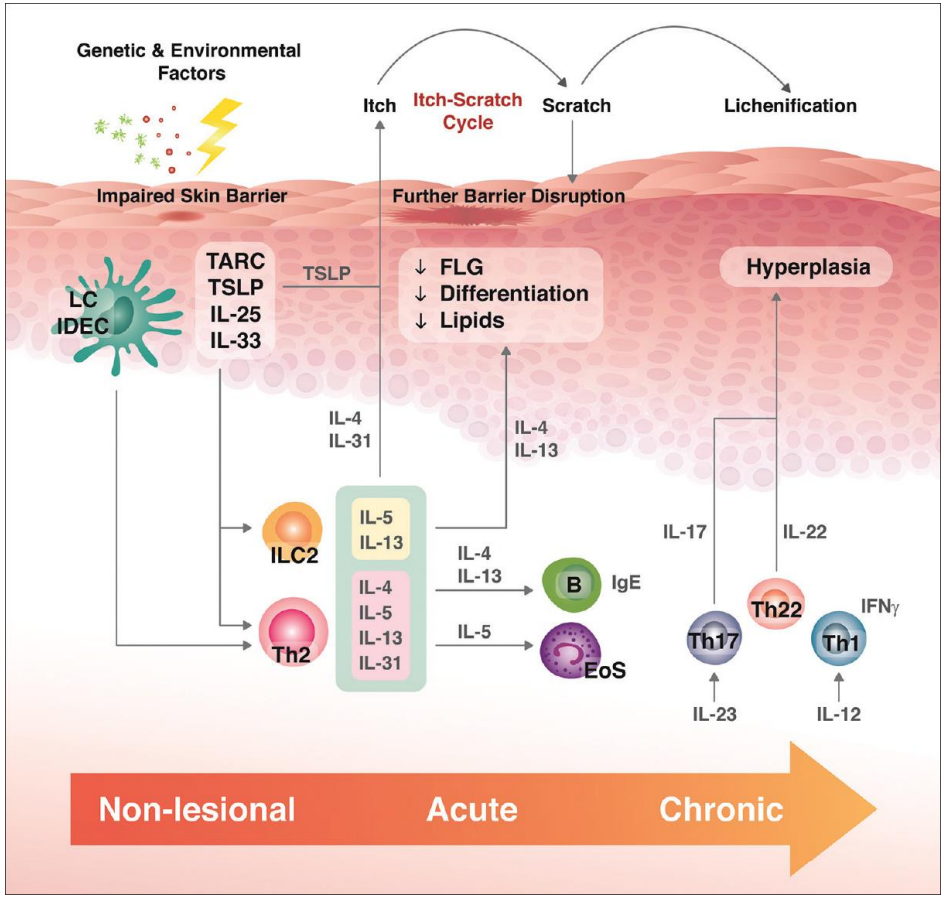
Atopic Disease: Pathogenesis and Relationships

- Atopic individuals typically present with 1 or more interconnected disorders:
  - atopic dermatitis (AD)
  - asthma
  - allergic rhinitis
  - food allergy
  - hymenoptera allergy
  - eosinophilic esophagitis

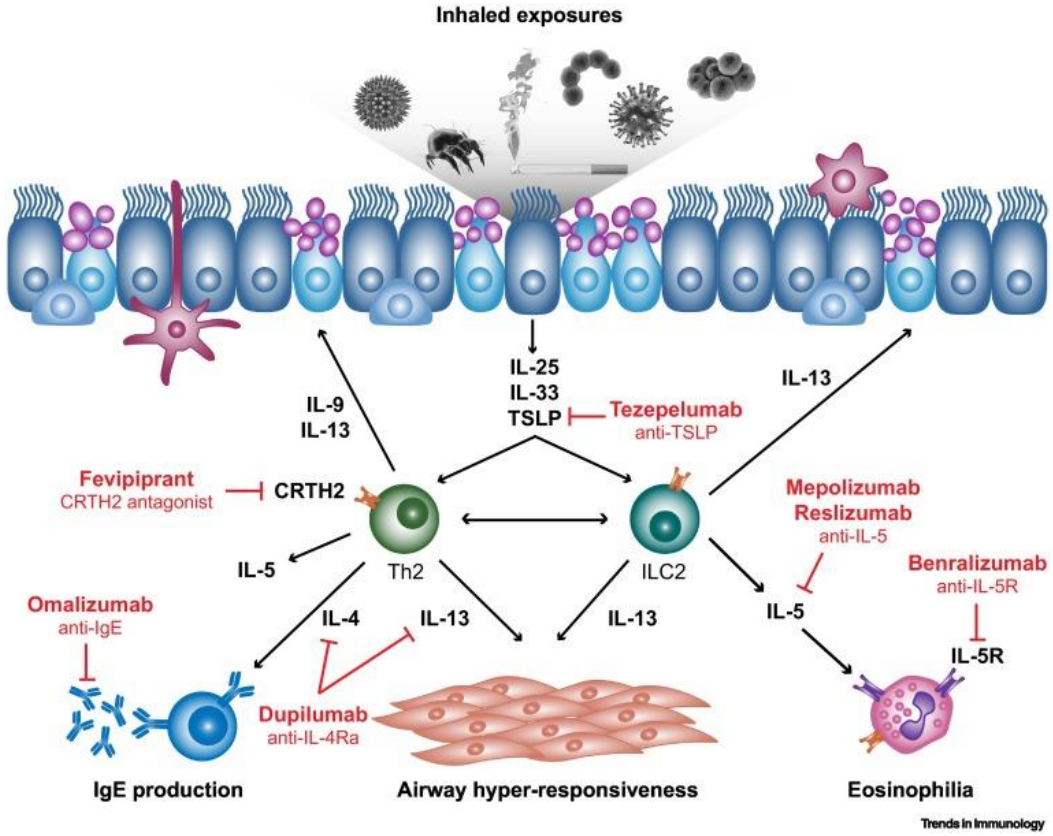
Impaired skin barrier leads to increased exposure to airborne and food allergens which drive the Th2 disease response

Atopic Dermatitis, Asthma and Epicutaneous Sensitization

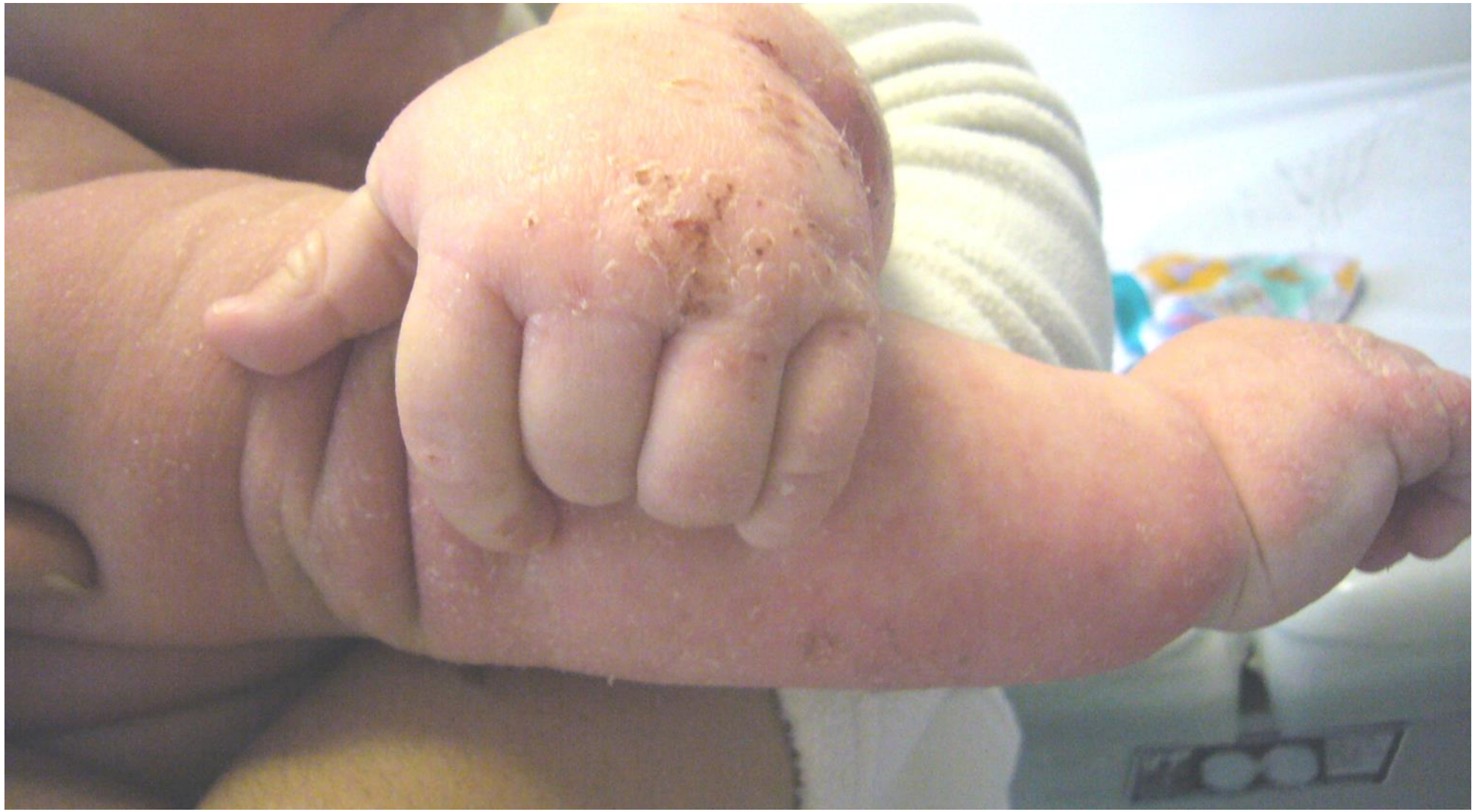
Epithelial barrier dysfunction (Filaggrin LOF) + cutaneous exposures = aeroallergen sensitization



Respiratory epithelium and aeroallergen exposures



What to Do?



Atopic Dermatitis: Intensive Topical Therapies

- Intensive topical therapies address all symptoms of the disease together

Itch
Dry skin
Inflammation
Infection/colonization

- A combination of skin barrier repair, anti-inflammatory, antimicrobial measures
- Wet wrap therapy is extremely effective
- Most children do extremely well, improving without need for systemic therapies

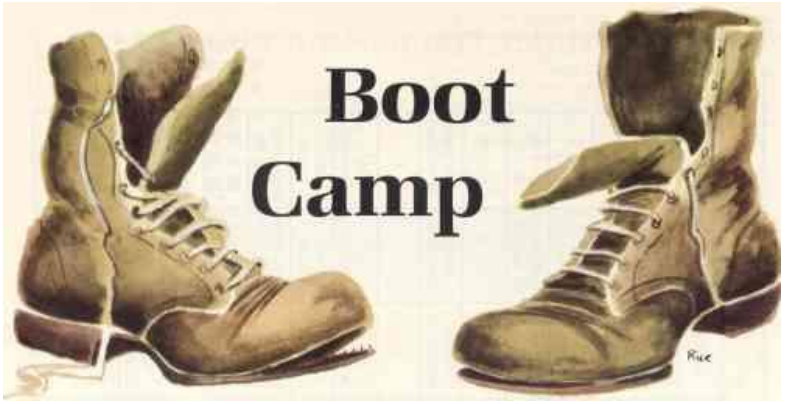
Intensive Topical Therapy: Wet Dressings

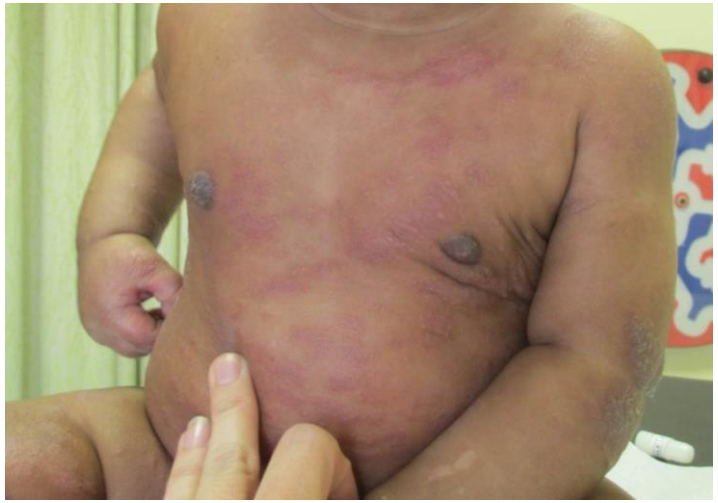
- Retrospective study from Mayo clinic on wet dressings and topical corticosteroid for rapid control of AD:
  - 218 patients over 30 years
  - 45% had 75-100% improvement
  - 83% of patients had >50%improvement
  - No adverse events reported
  - Many patients also received oral antibiotics

Dabade TS, Davis, D et al. Wet dressing therapy in conjunction with topical corticosteroids is effective for rapid control of severe pediatric atopic dermatitis: Experience with 218 patients over 30 years at Mayo Clinic. JAAD. 2012 Jul;67(1):100-6..

Intensive Topical Therapy: *Eczema 'Boot Camp'*

- 2 week intensive plan
- Optimize topical therapy
    1) Bleach Baths
    2) Topical Steroids
    3) Emollients
    4) Wet Pajamas
- **<u>Patient education, detailed instructions</u>**
- Use of adjunctive antihistamines
- If necessary, oral antibiotics



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dermatologist recommended
100% pure petroleum jelly
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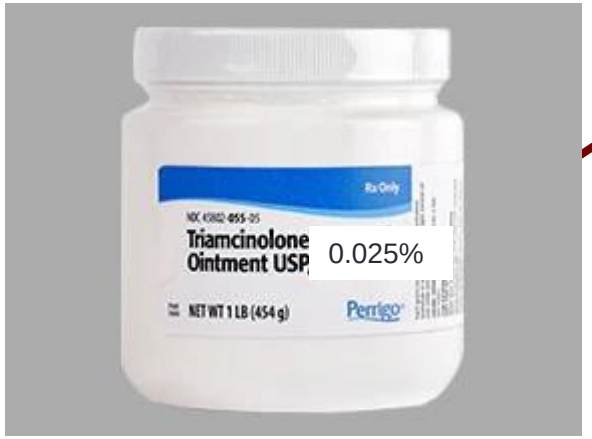
Rx Only
Triamcinolone
Ointment USP
0.025%
NET WT 1 LB (454 g)
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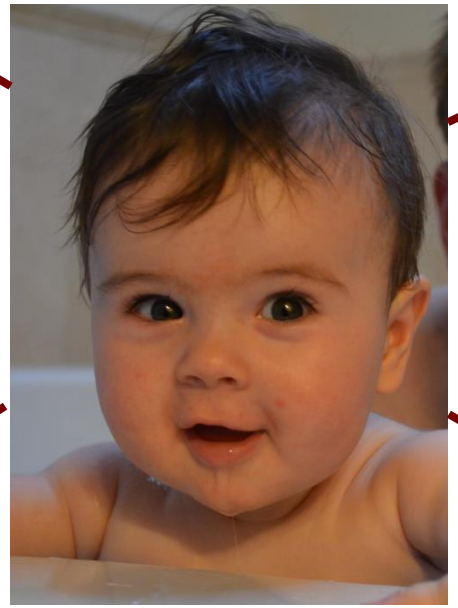


Intensive Topical Therapy: *Eczema 'Boot Camp'*

- Take a 10-minute dilute bleach **bath** in lukewarm water nightly for two weeks
- After bathing, **pat skin** dry. Within 3 minutes, apply the following topical anti-inflammatory medications:

  To rashes on the **body**, apply Triamcinolone 0.025% oint twice daily as needed.

  To rashes on the **face**, apply Hydrocortisone 2.5% oint twice daily as needed.

Intensive Topical Therapy: *Eczema 'Boot Camp'*

- Follow with a thick moisturizer like Vaseline or Aquaphor ointment. Use this **moisturizer on top** of the medications twice a day, even if no bath is taken. Avoid lotions.
- At night, follow with **wet wraps** (see instructions***)
- *For skin **infection**, take _____x day for ___ days*
- *For itching **at night**, take _____30 min before bedtime*

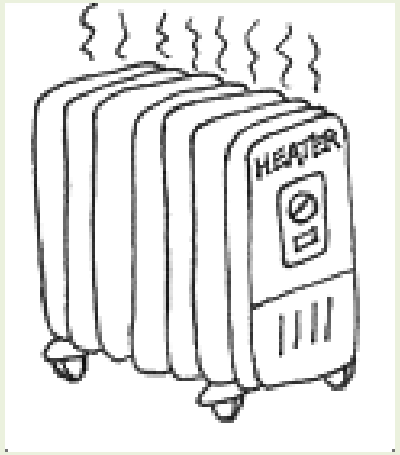
Intensive Topical Therapy: Wet Wraps

1. Take one pair of pajamas or a onesie and soak it in warm water.

2. Wring out the onesie or pajamas until they are only slightly damp.

3. Put the damp onesie or pajamas on your child. Then put the dry onesie or pajamas on top of the wet onesie/pajamas.

4. Make sure the child's room is warm enough before your child goes to sleep.



Advocacy: Wet Wrap Therapy Supplies

- Generous support from the Groves Foundation's allows us to provide much needed supplies for patients
- Wet wrap therapy supplies:
  - Emollients, cotton pajama wraps, bleach, measuring cups and spoons
- We have found this enhances compliance and outcomes

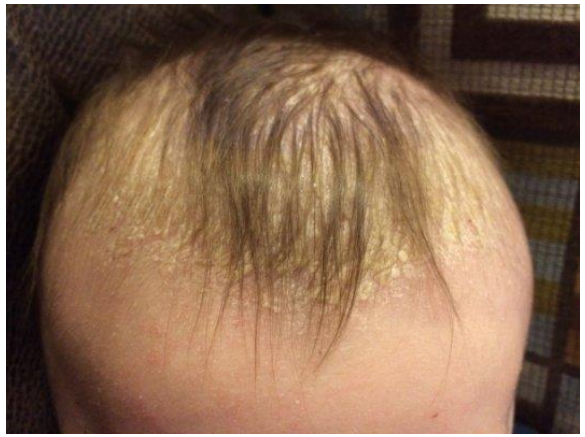
Can Atopic Dermatitis Be Predicted?

- Atopic dermatitis is very common, 12.5% of children in the US are affected
- Family history is the most significant risk factor
  - Risk increases 5 fold if both parents are affected
  - Filaggrin mutations thought to be the reason for this (autosomal dominant inheritance)
- Are there other factors that can help us identify at-risk infants earlier
  - Do interventions (such as early emollient application) help prevent disease?

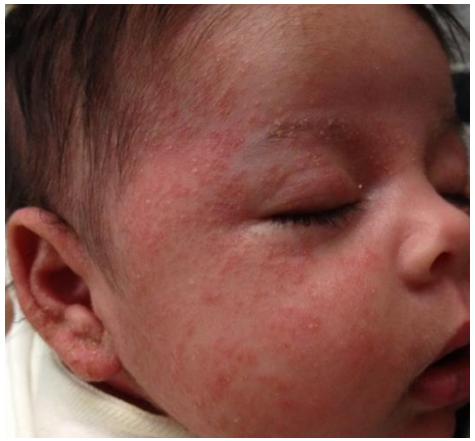
Early Signs of Atopic Dermatitis: Infant Predictors?

- Neonates may exhibit early signs of skin barrier dysfunction
- This may manifest in different clinical presentations

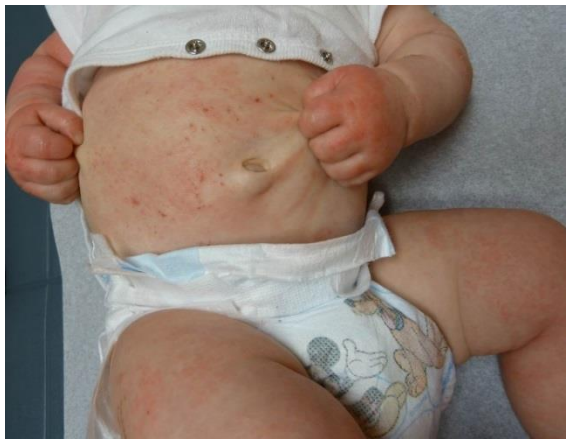
Cradle Cap/ Seb Derm



Infantile Acne/ Cephalic Pustulosis



Early Onset = Severe Disease



Can Atopic Dermatitis Be Predicted?

- We retrospectively reviewed 455 infants 0-3 months of age for infant predictors of AD and evaluated their risk for AD development:
  - Infantile acne/cephalic pustulosis
  - Seborrheic dermatitis
  - Early AD diagnosis

	Infant Predictor		Acne <= 3 months		Seb derm		Early AD	
	Yes	No	Yes	No	Yes	No	Yes	No
AD								
Yes	88 (58)	42 (14)	14 (36)	64 (24)	36 (51)	96 (26)	63 (79)	69 (19)
No	65 (42)	248 (86)	25 (64)	200 (76)	35 (49)	278 (74)	17 (21)	296 (81)
OR (95% CI)	7.99 (5.06-12.64)		1.75 (0.86-3.57)		2.98 (1.77-5.01)		15.90 (8.76-28.86)	
P-value†	<.0001		0.1233		<.0001		<.0001	

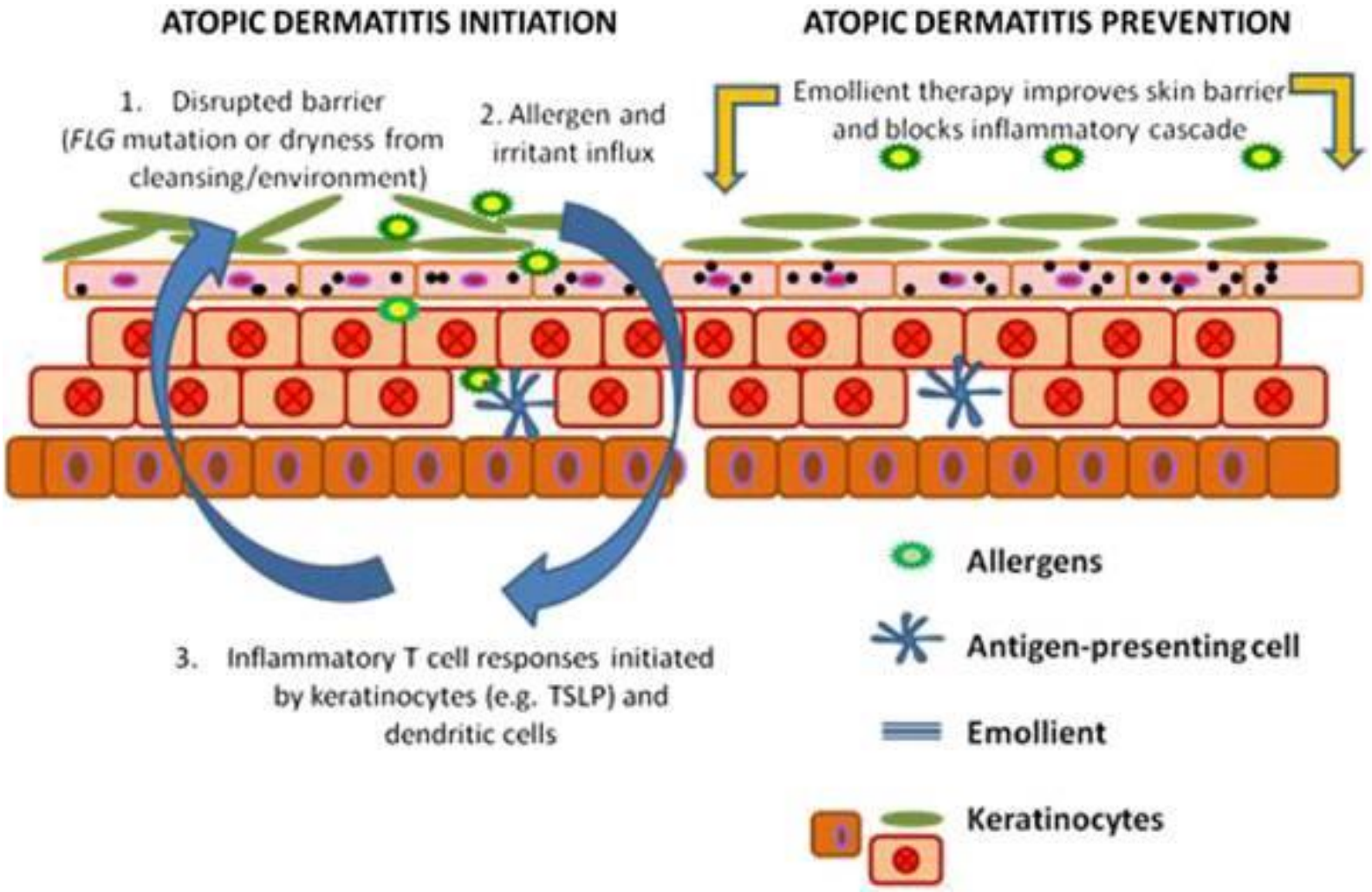
Dodds, M, Maguiness, SM. Infant Predictors of Atopic Dermatitis. Submitted for publication

Can Atopic Dermatitis be Prevented by Regular Application of an Emollient?

- Two recent RCTs demonstrate application of emollient at least once daily in infancy can reduce the risk of developing atopic dermatitis
- At risk infants were treated with either petrolatum, a bland emollient, or an oil starting in the neonatal period

Simpson E, et al. Emollient enahncement of the skin barrier from birth offers effective atopic dermatitis prevention. J Allergy Clin Immunol. 2014 Oct;134(4):818-23

AD Prevention: Barrier Replacement



Simpson E, et al. Emollient enahncement of the skin barrier from birth offers effective atopic dermatitis prevention. J Allergy Clin Immunol. 2014 Oct;134(4):818-23

Can Atopic Dermatitis be Prevented?

- Relative risk reduction was up to 50% at age 6 months compared to no emollient
- In one of the studies 43% of the control group vs 22% of the emollient group developed AD

There were no emollient related adverse events

Practice Changing – but is there more to this story?

Simpson E, et al. Emollient enahncement of the skin barrier from birth offers effective atopic dermatitis prevention. J Allergy Clin Immunol. 2014 Oct;134(4):818-23

BEEP Study:
Barrier Enhancement and Emollient Protection Study

- Large study of barrier enhancement done in the UK
- 1394 infants randomized to emollient vs no emollient
- Discussion of best bathing practices
- Two emollients utilized: *Doublebase Gel* and *Diprobase Cream*

- **Doublebase Gel Ingredients**:Isopropyl myristate (15% w/w) and liquid paraffin (15% w/w), glycerol, carbomer, sorbitan laurate, triethanolamine, phenoxyethanol and purified water.
- **Diprobase Cream Ingredients**: White Soft Paraffin, Cetostearyl Alcohol, Liquid Paraffin, Macrogol Cetostearyl Ether, Chlorocresol, Sodium Dihydrogen Phosphate, Sodium Hydroxide, Phosphoric Acid and Purified Water

BEEP Study

- By age 2 the BEEP study found no difference in the incidence of atopic dermatitis in either group treated with these emollients (23% vs 25%)
- There was a slight risk for increased skin infection in the emollient treated group (1%)

Study Limitations:

- Infant bathing practices varied in the study and were not standardized
- Liquid soaps also were not standardized
- Application of the emollient was once daily head to toe and after bathing
- No petrolatum based emollient was used

Chalmers JR, Haines RH, Bradshaw LE, Montgomery AA, Thomas KS, Brown SJ, Ridd MJ, Lawton S, Simpson EL, Cork MJ, Sach TH. Daily emollient during infancy for prevention of eczema: the BEEP randomised controlled trial. The Lancet. 2020 Mar 21;395(10228):962-72.

How Often Should Patients with AD Bathe?

- Patients may be counseled to limit bathing as there exists some thought that frequent bathing ‘dries the skin out’
  - This might be true if detergent based cleansers, harsh soaps or bubble baths are used
  - This might be true if no emollient is applied after the bath

- A recent randomized cross over study examined the frequency of bathing on the severity of atopic dermatitis
  - 63 patients were randomized to 2x week bathing or 2 x day bathing with vanicream cleanser
  - Emollient was standardized to bid application, Vanicream
  - 58% of the bathing group achieved a 30% reduction in the SCORAD vs 15% of the dry group

Cardona ID, Kempe EE, Lary C, Ginder JH, Jain N. Frequent Versus Infrequent Bathing in Pediatric Atopic Dermatitis: A Randomized Clinical Trial. J Allergy Clin Immunol Pract. 2020 Mar;8(3):1014-1021

Bathing and Emollients: Best Practices?

- More frequent bathing is recommended **if** followed by an emollient
- Liquid gentle cleansers are safe to use
- Application of a bland cream or ointment based emollient reduces TEWL
- Paraffin based emollient application as an eczema prevention
  - Plain Petrolatum or Safflower oil based

Blume-Peytavi U, Cork MJ, Faergemann J, Szczapa J, Vanaclocha F, Gelmetti C. Bathing and cleansing in newborns from day 1 to first year of life: recommendations from a European round table meeting. J Eur Acad Dermatol Venereol. 2009 Jul;23(7):751-9. doi: 10.1111/j.1468-3083.2009.03140.x. PMID: 19646134.

Atopic Dermatitis: Topical (Skin Directed) Treatments

- Topical steroids continue to be the mainstay of treatment
- Wet wraps and dilute bleach baths remain integral to care
- Topical calcineurin inhibitors
  - Helpful adjunct for sensitive areas or as a steroid sparing agent (proactive treatment)
- Crisaborole
  - FDA approved non-steroidal ointment

Topical Therapy Updates

- What about the Black Box warning on calcineurin inhibitors?
- How does crisaborole work?

Atopic Dermatitis: Topical Calcineurin Inhibitors

- Topical calcineurin inhibitors are safe and effective steroid sparing agents
- Effective in adjunctive topical management of AD
- What about the black box warning on potential for hematologic malignancies?

In 2005, the Pediatric **Advisory** Committee of the US **FDA** implemented a '**black box**' **warning** for **tacrolimus** ointment and pimecrolimus cream due to the lack of long-term safety data and the potential risk of the development of malignancies.

Atopic Dermatitis: Topical Calcineurin Inhibitors

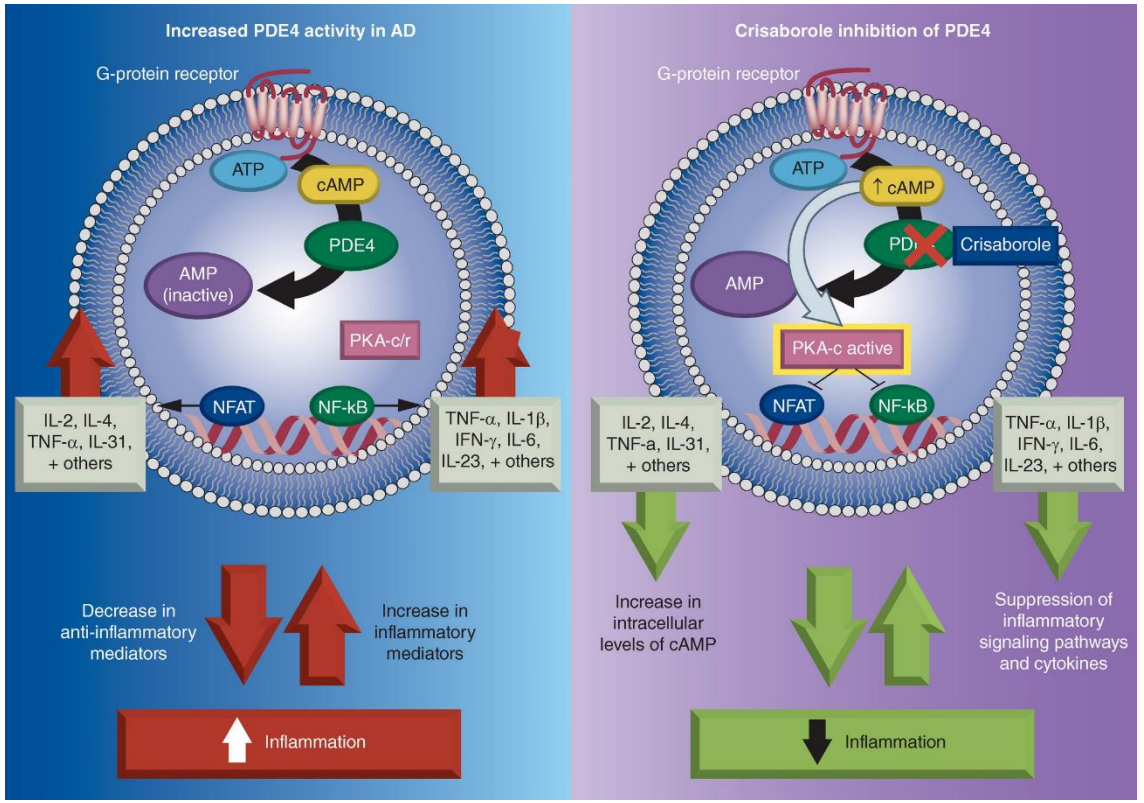
- Multiple studies have demonstrated TCIs do not pose a risk factor for malignancy
- 2020 landmark international study with >44,000 person –years did not show increased risk for cancer in children with AD treated with topical calcineurin inhibitors
- Another recent study in patients with vitiligo treated with phototherapy demonstrated similar results of no long term lymphoma or skin cancer risk

Topical calcirnJu, Hyun Jeong, et al. "The long-term risk of lymphoma and skin cancer did not increase after topical calcineurin inhibitor use and phototherapy in a cohort of 25,694 patients with vitiligo." *Journal of the American Academy of Dermatology* (2021).

Amy S. Paller, et al. No evidence of increased cancer incidence in children using topical tacrolimus for atopic dermatitis,Journal of the American Academy of Dermatology,Volume 83, Issue 2,

Atopic Dermatitis: What About Crisaborole?

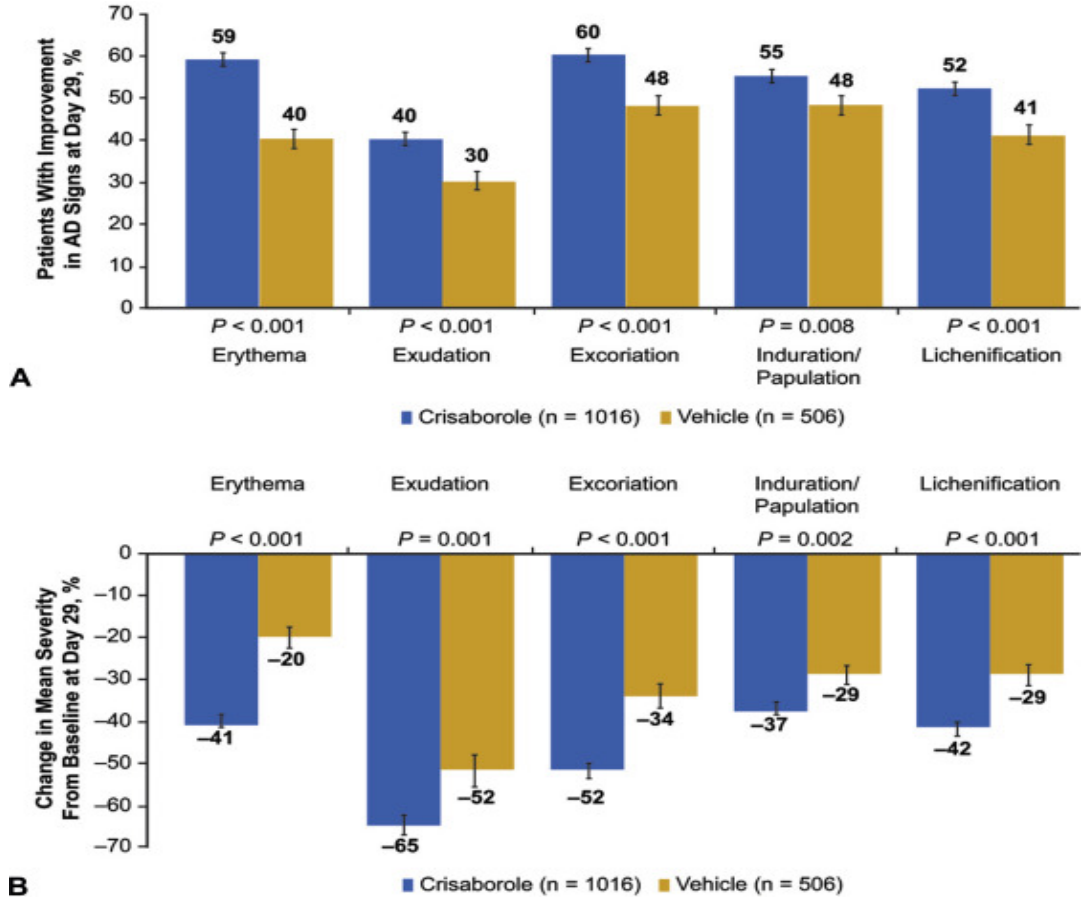
- Crisaborole (Eucrisa)
- Topical PDE4 inhibitor which ultimately reduces inflammation via the NF-kB pathway
- Ointment preparation, 2%
- FDA approved for use in AD for infants 3 months and over
- Safe, non-steroidal option



Crisaborole: Efficacy

- Modest benefit over vehicle in one controlled clinical trial
  - More crisaborole-treated patients achieved success in ISGA score at day 29 than vehicle*-treated patients (32.8% vs 25.4%)
- Use limited by cost ($140/60g) stinging/burning, not as effective as calcineurin inhibitors or mild topical steroids

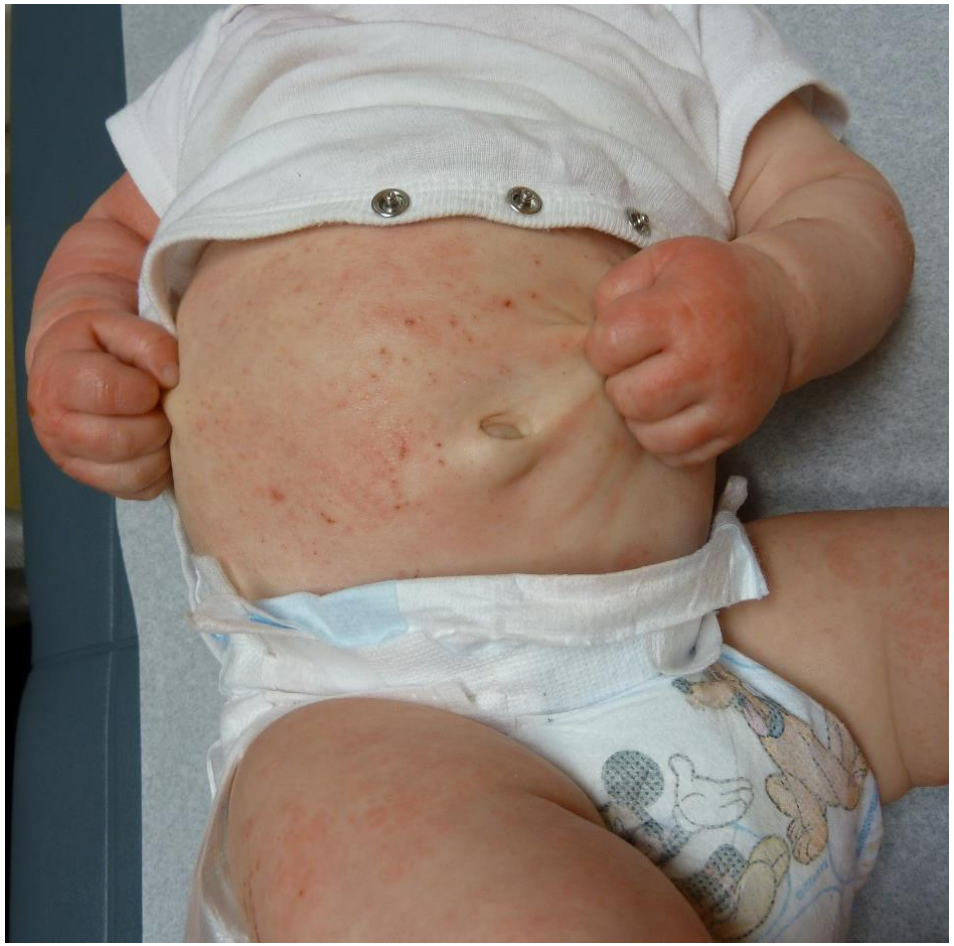
*vehicle not specified, proprietary



Paller A. et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults, Journal of the American Academy of Dermatology,Volume 75, Issue 3,

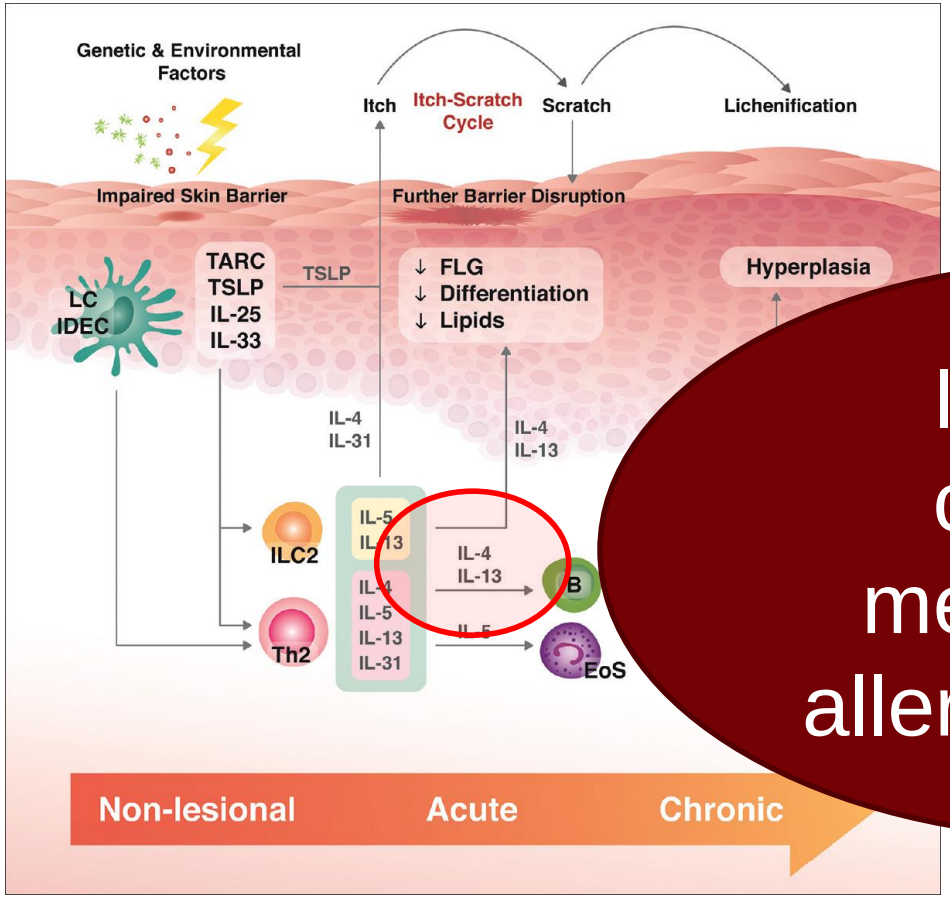
Atopic Dermatitis Advances: An Exciting New Era

- Dupilumab: mAb against IL-4,-13
  - Th2 cytokines important in all atopic disease
- First targeted systemic therapy for AD
- Also indicated for pediatric asthma (12+) and nasal polyposis (18+)



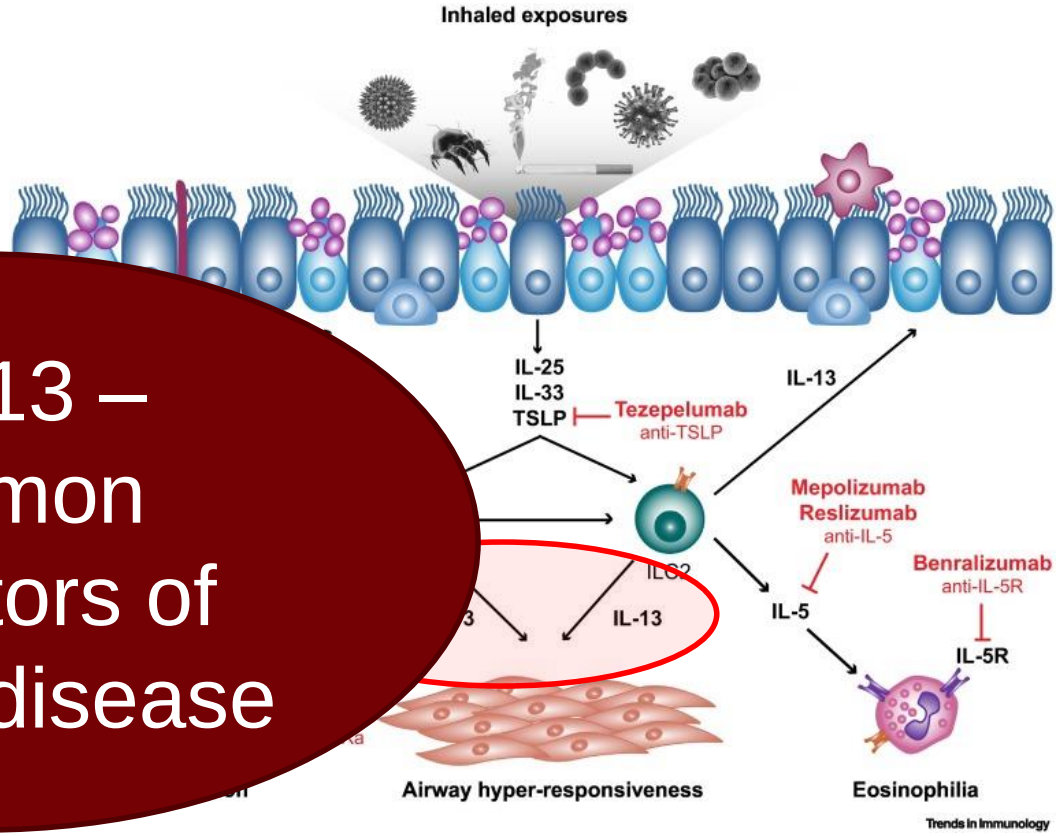
Epicutaneous Sensitization: A first Step in the Atopic March

Epithelial barrier dysfunction (Filaggrin LOF) + cutaneous exposures = aeroallergen sensitization



IL 4,13 – common mediators of allergic disease

Respiratory epithelium and aeroallergen exposures



Dupilumab: Targeted Therapy for Adult AD

- Lancet study, June 2017 ➡ FDA approval
  - 310 patients treated with DP + CS weekly
  - 106 patients treated with DP + CS q2 week
  - 315 patients treated with placebo + CS
- **64-69% of patients achieved EASI 75, compared to 23% of placebo
  - Every other week injections as effective as weekly
  - No concerning lab abnormalities

Beck, Lisa A., et al. "Dupilumab treatment in adults with moderate-to-severe atopic dermatitis." *New England Journal of Medicine* 371.2 (2014): 130-139.
Blauvelt A et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial**.** Lancet. 2017 Jun 10;389(10086):2287-230

Dupilumab: Safety Profile

- Lab monitoring not required
- Side effect profile when compared to placebo include:
  - Injection site reaction
  - Ocular symptoms - Conjunctivitis
  - Headache
  - Nasopharyngitis
  - HSV

Melinda J. Gooderham, H. Chih-ho Hong, Panteha Eshtiaghi, Kim A. Papp, Dupilumab: A review of its use in the treatment of atopic dermatitis, Journal of the American Academy of Dermatology, Volume 78, Issue 3, Supplement 1,2018,

Dupilumab: Targeted Therapy for Pediatric AD

- FDA Approved for ages 6+ March 2020
  - *69% of children treated achieved an EASI 75 compared to 27% placebo (p<0.001)*
  - *REGN AD-1539 pediatric trial for children 6 months to 6 years of age ongoing*
- **Other systemic medications used off-label for childhood AD include <u>cyclosporine, methotrexate, mycophenolate mofetil</u>**
  - **All are immunosuppressive with concern for ADRs and require close lab monitoring**

Dupilumab in children: Weight Based Dosing

DOSAGE AND ADMINISTRATION

Administer by subcutaneous injection. (2)

Atopic Dermatitis

Adults

- The recommended dose is an initial dose of 600 mg (two 300 mg injections in different injection sites), followed by 300 mg given every other week (Q2W). (2.1)

Pediatric Patients

Body Weight	Initial Dose	Subsequent Doses[a]
15 to less than 30 kg	600 mg (two 300 mg injections)	300 mg Q4W
30 to less than 60 kg	400 mg (two 200 mg injections)	200 mg Q2W
60 kg or more	600 mg (two 300 mg injections)	300 mg Q2W

[a] Q2W – every other week; Q4W – every 4 weeks

Treister, A. D., & Lio, P. A. (2018). Long-term off-label dupilumab in pediatric atopic dermatitis: A case series. *Pediatric dermatology*.

Siefgried EC, Igelman S, Jaworsk JC, Antaya RJ, et al. Use of dupilimab in **pediatric** atopic dermatitis: Access, dosing, and implications for managing severe atopic dermatitis. Pediatr Dermatol. 2019 Jan;36(1):172-176

Dupilumab in children: Limitations

- Optimal dosing in children under 6 not yet established, trials ongoing
- We are regularly using this off-label with success in younger patients
- Pediatric dermatologists gaining experience with use in younger children
  - Consideration re: vaccination status; the recommendation is to avoid live vaccines
- Lack of long term data -
  - Concern for unanticipated long term complications

Dupilumab in children: Limitations

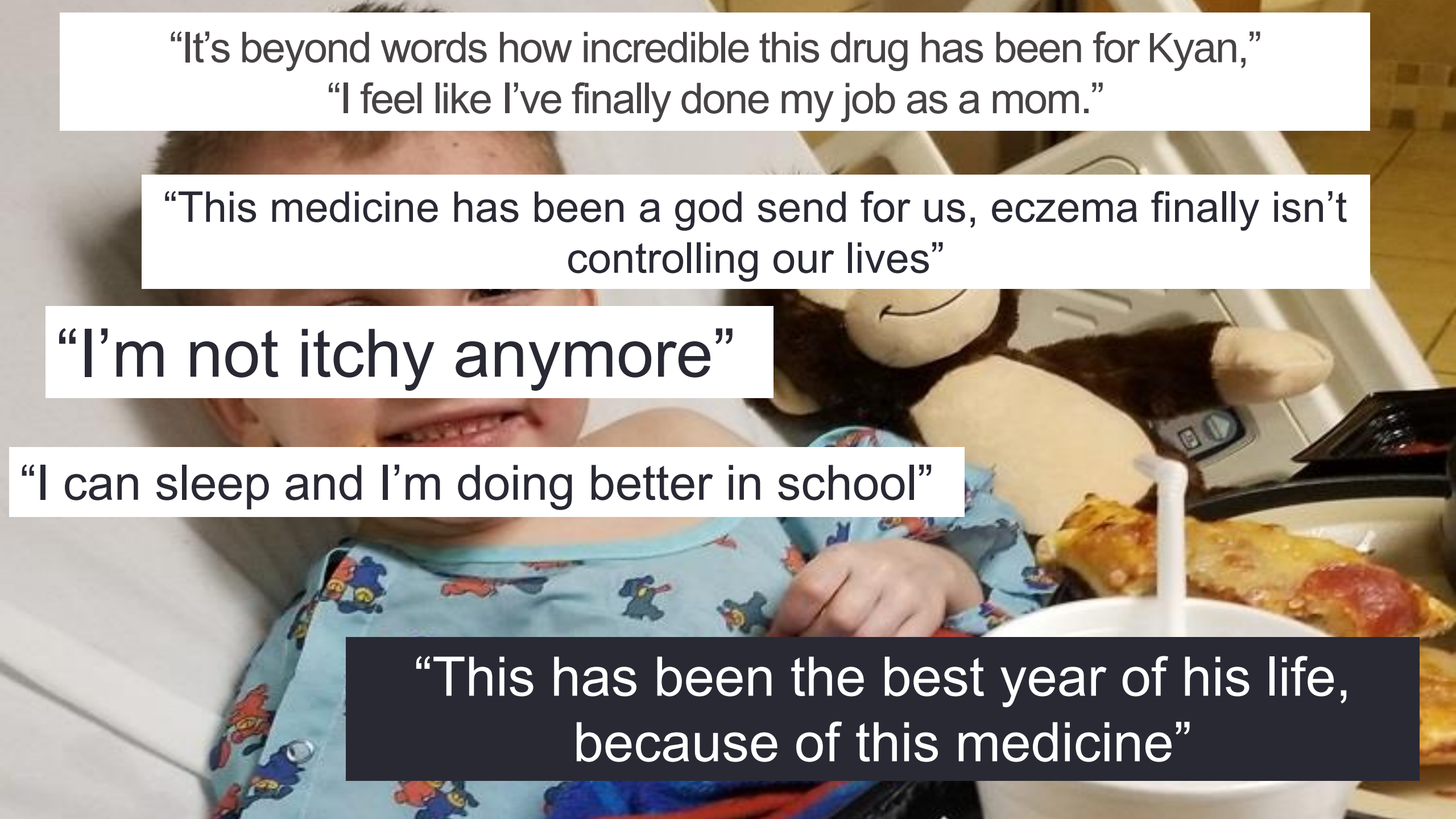
- Access/Insurance Approval → Patient Advocacy
  - Insurance companies are often asking for patients in the approved age range to try and fail other non-approved immunosuppressive therapies and/or other topicals/phototherapy with less evidence for benefit.
- Our team at the U of M follows > 100 patients <18 on Dupilumab
- Side effects rare, injection site pain, conjunctivitis most common

Dupilumab: Use in Immunosuppressed Populations

- There are several case reports of successful use of dupilumab in the setting of adults on immunosuppression post solid organ transplant
- Our team has treated three adolescent organ transplant patients with severe AD with dupilumab with excellent results
- Evolving range of diseases may benefit from IL 4,13 inhibition
  - Hyper IGE syndrome
  - DOCK 8 deficiency
  - Mast Cell Activation Syndrome

Dupilumab in a Patient with DOCK8 Deficiency

- 8 year old male
- History of severe AD with erythroderma and recurrent skin infection
  - Numerous hospitalizations for wet wrap treatment and systemic antibiotics
- Multiple food allergies
- IGE 25,000
- Heterozygous mutation in DOCK8

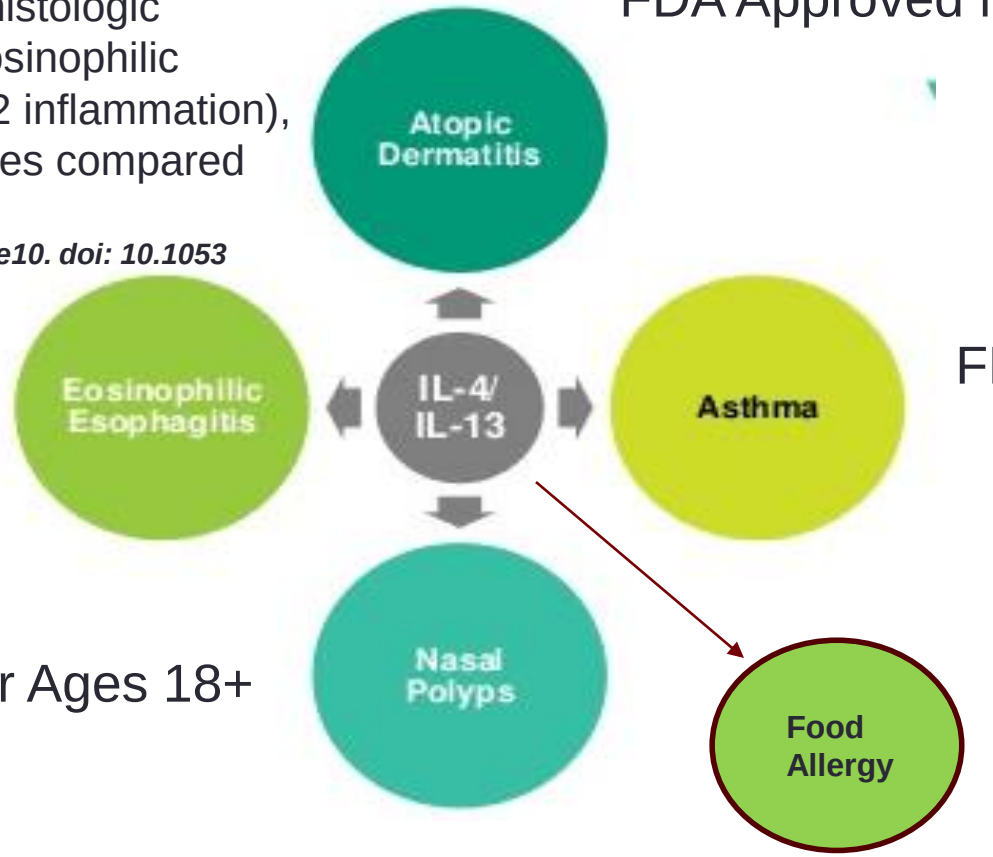

“It’s beyond words how incredible this drug has been for Kyan,”
“I feel like I’ve finally done my job as a mom.”
“This medicine has been a god send for us, eczema finally isn’t controlling our lives”
“I’m not itchy anymore”
“I can sleep and I’m doing better in school”
“This has been the best year of his life, because of this medicine”

Dupilumab: A New Paradigm for Allergic Diseases

In a phase 2 trial of patients with active EoE, dupilumab reduced dysphagia, histologic features of disease (including eosinophilic infiltration and a marker of type 2 inflammation), and abnormal endoscopic features compared with placebo

Gastroenterology. 2020 Jan;158(1):111-122.e10. doi: 10.1053

FDA Approved for Ages 6+



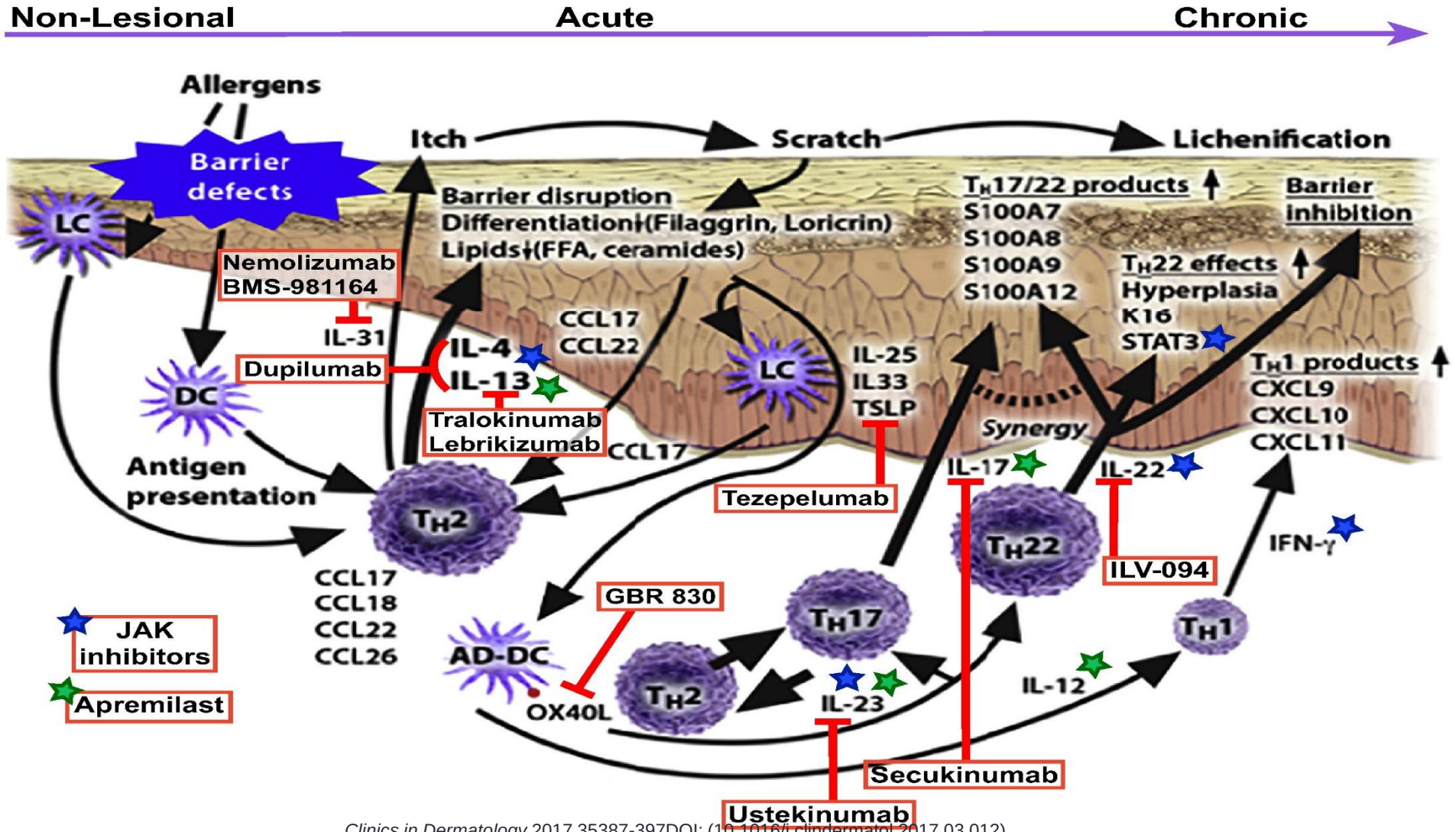
FDA Approved for Ages 12+

FDA Approved for Ages 18+

Ongoing clinical trial to evaluate the effect of Dupilumab on change in clinical eliciting dose (i.e. lowest dose causing an allergic reaction) in subjects with peanut, hazelnut, walnut, cow's milk, hen's egg and/or soybean allergy

NCT04462055

Biologic Therapies for AD: The Pipeline



Clinics in Dermatology 2017 35387-397DOI: (10.1016/j.clindermatol.2017.03.012)

Summary and Take Home Points

- Atopic dermatitis is a disorder of the skin barrier
- Mutations in filaggrin predispose to atopic diseases
- IL 4,13 are important mediators of Th2 (atopic) inflammation

- Frequent bathing and regular emollient application have benefit in AD
- Topical calcineurin inhibitors are a safe alternative to topical steroids and not associated with increased risk for malignancy over time

- Targeted biologic therapies, such as Dupilumab, are emerging as the future of management for all atopic diseases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The Society for Pediatric Dermatology (SPD) is the only national organization in the United States specifically dedicated to the field of Pediatric Dermatology.
The Society's objective is to promote, develop, and advance education, research, and care of skin disease in all pediatric age groups. The organization holds meetings twice a year to educate physicians about advances in pediatric dermatology, help them support children with dermatological diseases, and improve their care.

Thank you!


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