Advancing Diagnosis and Management of Atopic Dermatitis in Children and Adolescents

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Faculty Disclosures

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Consulting Fees:
Pfizer Pharmaceuticals

Learning Objectives

- Review updated guidelines to accurately diagnose atopic dermatitis (AD) and make treatment decisions based on severity for children and adolescents
- Evaluate recent clinical evidence on the utility of approved and emerging biologic agents that treat moderate-to-severe AD
- Describe effectiveness of shared decision making in pediatric conditions and using action plan components for managing AD
Automated Mobile Coach Platform

- Mobile Coach follow-up platform reinforces education following primary activity.
- Mobile Coach utilizes an intelligent chatbot to deliver responsive text message conversations to participants.
- Following enrollment, participants will receive 1-3 text messages a week for a period of 8 weeks.
- Text messages are sent at varied times during the day and consist of informational reminders, mechanisms for goal setting in the next week, and interactive questions.
- To participate, please add your cell number at the end of the evaluation form under Additional Education OR Text “Hi Addie” to (539) 210-3167
- You may opt out at anytime.

Burden of Pediatric AD

Disease Overview

- Chronic, relapsing, inflammatory skin disease
- Cycle of itching and scratching
- Cellular damage and secondary infections
- Eczematous lesions
- Dry skin due to epidermal barrier dysfunction

Prevalence of AD

- Affects 31.6 million in the US
  - Most common skin disease worldwide
  - Approximately 30% are children
- 85% of cases present before 5 years of age
- 30% of childhood cases persist into adult years
- AD often the first sign of long-term disease continuum
  - ~60% develop asthma or allergic rhinitis later in life
  - ~30% develop food allergies

References:

Photo courtesy of Mark Boguniewicz, MD
AD: Psychosocial/Health-Related Burden

Detrimental to QOL1,2

- Heavy psychosocial impact
  - Due to stigma, isolation, embarrassment, bullying, unpredictability of flares
  - Suicidal ideation reported by ~20% with severe disease3
- Negative impact on academic performance
- Increased risk of cutaneous and systemic infections contribute to overuse of antibiotics1


AD: Psychosocial/Health-Related Burden

Negative effect on sleep (mostly due to pruritus) in 47%-60% of children1,2

- 87% experience itching daily
- Itching lasts >18 hours in ~42% of patients
- Leads to excessive daytime sleepiness, fatigue, anxiety, depression, reduced HRQOL

Heavy care/financial burden for parents, caregivers3

- Parents/caregivers report interrupted sleep >3x/week or more due to child’s AD4
- Patients average 9 flares/year, each lasting ~15 days5
- Out-of-pocket expenses for families estimated to total ~10% of annual income6

HRQOL, health-related quality of life.


More Than Skin Deep: AD Comorbidities

- Referred to as “atopic march,” comorbidities recognized as components of AD disease continuum usually begin early in life
- Systemic immune activation underlying AD correlates with common noncutaneous comorbidities
  - Allergic rhinitis, asthma, conjunctivitis, food allergies, eosinophilic esophagitis
- Without aggressive early treatment, nonatopic comorbidities can emerge later in life
  - Cardiometabolic, gastrointestinal-immune mediated, neuropsychiatric disorders


AD Mental Health Comorbidities

- Common psychological comorbidities include1-3
  - Anxiety
  - Depression
  - Poor self-image
  - ADHD
  - Behavioral/conduct problems
- In GINIplus, children whose AD appeared to resolve in 1st or 2nd year of life still had emotional/behavioral difficulties by 10 years of age4

ADHD, attention deficit hyperactivity disorder; GINIplus, German Infant Nutrition Intervention plus.


AD, attention deficit hyperactivity disorder; GINIplus, German Infant Nutrition Intervention plus.
Diagnosis and Severity Assessment

Diagnosis and Severity Assessment

Diagnostic Criteria for AD

- AD is currently diagnosed based on history and clinical presentation
  - Personal or family history of atopy is a risk factor
  - Biomarkers not specific enough to confirm diagnosis or assess severity

Diagnostic Criteria for AD

Essential (must be present)
- Pruritus
- Eczema (acute, subacute, chronic)
- Morphology: typical or atypical?
- Age-specific patterns:
  - Infants and children: facial, neck, extensor involvement
  - Any age: current or previous flexural lesions, sparing of groin and axillary regions
- History: chronic or relapsing

Diagnostic Criteria for AD

Important (supports diagnosis)
- Early age of onset
- Atopy
- Personal and/or family history
- IgE reactivity
- Xerosis

Diagnostic Criteria for AD

Differential/Exclusion Diagnoses (dermatologic manifestations of alternate or concurrent diagnoses)
- Seborrheic dermatitis
- Contact dermatitis (allergic or irritant)
- Scabies
- Immunodeficiencies
- Ichthyoses
- Porokeratosis
- Photosensitivity dermatoses
- Cutaneous T-cell lymphoma
- Erythroderma of other causes

Diagnostic Criteria for AD

Visual Representations of Moderate-to-Severe Pediatric AD

- Xerosis
- Ill-defined erythema
- Papules, plaques
- Erosions, excoriations
- Oozing, crusting
- Lichenification
- Generally spares axillae and groin

Visual Representations of Moderate-to-Severe Pediatric AD

Clinical Features in Darker Skin Types

- Erythema may be difficult to see
- Follicular accentuation
- Hypopigmentation
- Grayish-white skin discoloration ("ashy skin")

Clinical Features in Darker Skin Types

Photos courtesy of: Mark Boguniewicz, MD; Sheila F. Friedlander, MD; Anthony J. Mancini, MD

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13 14 15 16
Other Diseases Can Look Like AD

Contact Dermatitis

Scabies

Photos courtesy of Sheila F. Friedlander, MD and Anthony J. Mancini, MD.

Differential Diagnosis

Seborrheic Dermatitis

Psoriasis

Photos courtesy of Anthony J. Mancini, MD.

Differential Diagnosis

Ichthyosis vulgaris

Immunodeficiency

Photos courtesy of Anthony J. Mancini, MD.

Distribution Patterns Vary with Age

Infants

Forehead, cheeks, and chin

Young Children

Forehead, cheeks, and chin

Adolescents

Periorbital area, neck, extensor surfaces, extensor surfaces of fingers and toes, wrists, hands, ankles, feet

Guidelines

Allergists: AAAI/ACAAI Joint Task Force published in 2013

Dermatologists: 4-part series from AAD published in 2014

Simplified, integrated version merging recommendations published in 2017


AD guidelines designed for PCPs and Pediatricians

AD guidelines designed for PCPs and Pediatricians

Testing Options

Testing recommendations from integrated guidelines

Do test for:

- Secondary bacterial infections with disease exacerbations
- Food allergies for patients <5 years with refractory AD despite optimal treatment and/or clinical history of allergic reaction to certain foods
- Contact dermatitis for refractory AD despite optimal treatment, especially if involving the face and/or feet

Don’t test for:

- Food allergies on a routine basis

Simplified, integrated version merging recommendations published in 2017

Severity Assessments

- Accurate assessment of disease severity important for optimal treatment
- Validated clinical scoring systems are not recommended by guidelines for general clinical use
- Disease categorized into “mild,” “moderate,” and “severe” based on clinician assessment
  - IGA and ISGA scores that rank lesion severity from 0 (clear) to 4 (severe) are most often used
  - Validated IGA score (vIGA-AD) recently introduced by International Eczema Council

Severity Scoring in Clinical Practice

- Guidelines recommend clinicians ask patients or their parents/caregivers general questions about itch, sleep, impact of disease on daily life, and disease persistence
  - Incorporate available patient-friendly scales only when practical
### Case Study, Part 1

- 2-year-old girl, Sophia, presents with rash on cheeks and chest
- Mother says Sophia scratches frequently
- Patient formerly slept through the night but now wakes up at least twice a night
- How would you diagnose and assess this patient?

### Case Discussion Points

- Which tests should/shouldn’t be done?
- Questions to ask about patient’s personal and family history
- Severity assessment questions to ask
- Questions about disease impact on quality of life for everyone in the family
- What would you prescribe?

### Case Study, Part 2

- Recommendation was made to Sophia’s mother to avoid triggers and apply topical OTC anti-inflammatory medication as needed
- Mother returns with Sophia 6 weeks later expressing dissatisfaction with treatment
- How would you manage this patient further?

### Case Discussion Points

- Time to prescribe Rx topical corticosteroid?
  - If so, which one?
- What instruction will you give the parent regarding application and timing?
- What patient education would you provide to Sophia’s mom?
  - Potential adverse effects
  - Risk of flares with noncompliance
AD = Altered Epidermal Barrier + Immune Dysregulation

CLA, cutaneous lymphocyte-associated; IDEC, inflammatory dendritic epidermal cells; IFN, interferon; IL, Interleukin; LC, Langerhans cells; MC, mast cell; MØ, macrophage; TSLP, thymic stromal lymphopoietin.


Nonlesional AD Pathophysiology: Filaggrin

- Epidermal protein binds keratin fibers
- Functions
  - Contributes to barrier function
  - Releases free amino acids water retention (NMF)
- 2006: FLG mutations associated with early-onset AD, more persistent AD, ichthyosis vulgaris


AD Pathophysiology: Barrier

- Barrier dysfunction – predictive of future AD¹
  - 1,903 infants, TEWL measured day 2, and 2/6 months
  - AD scored at 6 and 12 months
    - AD (6 months): 18.7%; AD (12 months): 15.5%
    - TEWL at 2 days → highly predictive of AD at 12 months
    - TEWL at 2 months → also strongly predictive of AD
- Similar study²
  - TEWL at 2 days → predictive of food allergy at 2 years
  - Transcutaneous allergen sensitization?

TEWL, transepidermal water loss.

... Then Emolliate Early?

- RCT of 124 neonates, high AD risk³
  - Full-body emollient Rx daily (starting 3 weeks of age) vs no emollient
  - Cumulative AD incidence at 6 months
  - Emollient arm: 50% relative risk reduction in AD
- RCT of 118 neonates, high AD risk³
  - Moisturizer applied daily for first 32 weeks of life
  - Cumulative AD/eczema incidence at week 32, egg white IgE
  - 32% fewer neonates with AD in emollient arm
  - No effect on allergic sensitization

Emollient should be applied after topical medications

Address barrier dysfunction in all AD patients: good skin care (daily short bath or shower, application of emollient/barrier repair product after) may even play a role in prevention. Emollient should be applied after topical medications.

RCT, randomized, controlled trial.
Treatment Approaches

“Yardstick” Guidelines Published in 2018
- Developed to reconcile differing recommendations from multidisciplinary guidelines
- Emphasis is on practical, step-by-step, “how-to” strategies to ensure clear or almost-clear skin from all levels of severity


Treatment Goals
- Restore barrier integrity
- Control skin inflammation and itch
- Decrease xerosis
- Treat secondary infection
- Recognize and prevent triggers
- Reduce frequency of flares
- Improve and maintain QOL

Topical Treatments for Mild Disease

Corticosteroids
- TCs usually the first line of treatment to reduce local inflammation
- Can cause skin atrophy and thinning if used inappropriately (eg., chronic use of high-potency TC)
- Not consensus regarding optimal dosing or frequency

Calcineurin Inhibitors
- TCIs: tacrolimus and pimecrolimus
- Nonsteroidal
- Approved in 2000–2001
- Inhibit calcineurin-dependent T-cell activation
- No risk of skin atrophy
- Use may be impeded by black-box warning about increased risk for malignancy, despite lack of evidence to date

PDE4 Inhibitor
- Crisaborole
- Nonsteroidal
- FDA approved in 2016, first new treatment approved for AD in >15 years
- Inhibits cAMP levels
- No data yet on long-term use

CAMP, cyclic adenosine monophosphate; FDA, Food and Drug Administration; PDE4, phosphodiesterase 4; TC, topical corticosteroid; TCI, topical calcineurin inhibitors.

TCS: Available Potencies

<table>
<thead>
<tr>
<th>TCIs</th>
<th>Vehicle</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pimecrolimus (1%) cream</td>
<td>Mild-to-moderate AD (2 years and older)</td>
<td></td>
</tr>
<tr>
<td>Tacrolimus (0.03% and 0.1%) ointment</td>
<td>Moderate-to-severe AD (2 years and older: 0.03%; 15 years and older: 0.1%)</td>
<td></td>
</tr>
</tbody>
</table>

Can be applied to face, extremities, and genital area
Little systemic absorption
Stinging/burning at application site most frequently cited adverse event
Not indicated for:
- Children <2 years of age
- Long-term, continuous treatment
Sun protection should be used as a precaution

Currently Available TCIs

PDE4 Inhibition

- PDE4 a key regulator of inflammatory cytokines
- Crisaborole 2% ointment, only PDE4 inhibitor approved for AD
  - Approved for mild-to-moderate AD in adults and children ≥2 years
- Efficacy proven in 2 phase 3 studies (N=1,522 patients ≥2 years old) with mild-to-moderate AD randomized 2:1 to crisaborole or placebo
- Primary endpoint: IGA score of clear (0) or almost clear (1) by day 29 with ≥2 grades improvement from baseline

Step-Care Management: Mild AD

Apply TCS to Inflamed Skin
Low to medium potency TCS 2x/day for 3-7 days beyond clearance (consider TCI, crisaborole)


Sun protection should be used as a precaution


PDE4 Inhibition

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Step-Care Management: Mild AD

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Treatments for Moderate-to-Severe Disease

Systemic Immunosuppression
- Cyclosporine
- Methotrexate
- Mycophenolate mofetil
- Azathioprine
- Corticosteroids

Limitations:
- All but corticosteroids are off-label for AD
- Not usable for long-term maintenance because of multiple systemic adverse events

Phototherapy
- Primarily narrow-band UVB

Limitations:
- Available only for patients ≥12 years
- Access/convenience (few phototherapy centers)
- Cost and travel time often not covered by insurance
- Very low risk for cutaneous malignancies and cataracts

Biologics
- Dupilumab, only targeted biologic approved for moderate-to-severe AD

Limitations:
- Currently approved only for patients ≥18 years
- Subcutaneous injection
- Too new to be included in guidelines
- No data for optimal ways to step down or discontinue after clear skin is achieved

**Oral Antihistamines in AD**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine*</td>
<td>Sedating</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>Sedating</td>
</tr>
<tr>
<td>Doxepin</td>
<td>Sedating</td>
</tr>
<tr>
<td>Cetirizine*</td>
<td>Non-sedating</td>
</tr>
</tbody>
</table>

- Although there is some controversy, many patients use these, especially for sleep
- Hydroxyzine most commonly used (by pediatric dermatologists) sedating antihistamine at bedtime

*Available OTC


Antiflare Maintenance Therapy

Translational research: normal-appearing skin in AD is not normal

Daily moisturizing and 2x/week application of TCS or TCI can prevent and reduce frequency of flares.*

Proactive maintenance therapies aid in maintaining disease remission

*This would be considered off-label treatment in the US.

Causes for Treatment Failure

- Poor understanding of disease
  - Clinicians, caregivers, patients unaware AD is systemic, inflammatory disorder
- Poor adherence/incorrect medication use
  - TCS phobia affects up to 80% of patients and caregivers¹
- Exacerbating factors/environmental triggers
- Secondary infection
  - Bacterial, viral, dermatophyte
- Hypersensitivity reactions to treatments
- Incorrect diagnosis

¹Misdiagnosis of atopic dermatitis is a concern ... it can contribute to making the disease worse."²

When to Use Systemic Treatment

- Many patients effectively managed with topical medications
- If condition worsens despite topicals, determine if adherence and patient education has been optimal
- If adherence is good, the treatment may have failed — not the patient!
- Consider systemic treatment

One Approved Biologic Agent: Dupilumab

- Fully Human mAb
- IL-4Ra targets IL-4 and IL-13 receptor, blocking Th2 cytokine signaling pathways
- Approved as second-line treatment for moderate-to-severe AD after topical treatments
- Subcutaneous injection
- Approved for patients ≥12 years

Granted accelerated FDA approval March 2017 based on short-term results in SOLO 1 and SOLO 2 trials and long-term (52 weeks) results in CHRONOS AD LIBERTY trial. Approved for adolescents 12–17 March 11, 2019.

References:
Dupilumab Phase 3 Clinical Trials

Safety and efficacy demonstrated in 3 placebo-controlled clinical trials

**SOLO 1, SOLO 2**
Evaluated dupilumab as monotherapy for 16 weeks

**LIBERTY AD CHRONOS**
Evaluated dupilumab in combination with TCS for 52 weeks

Total of 2,119 adults with moderate-to-severe AD


### Efficacy in Global Assessment

**Improvement in IGA Score (primary endpoint)**

- Placebo
- Dupilumab every other week
- Dupilumab every week


### Efficacy in Reducing Disease Severity

**Improvement in EASI-75 Score (secondary endpoint)**

- Placebo
- Dupilumab every other week
- Dupilumab every week


Eczema Area and Severity Index-75 (EASI-75) measures a 75% reduction from baseline in extent and severity of erythema, induration, papulation, edema, excoriations, and lichenification.

### Efficacy in Pruritus

Patients (%) in phase 3 trials who achieved improvement of ≥4 points on pruritus numerical rating scale

Efficacy in QOL Improvements

- Patients in phase 3 trials who demonstrated improvements in QOL (e.g., sleep, anxiety, depression) as indicated by least squares mean change in dermatology life quality index (DLQI) score.


- Least squares incorporate percent change over time, primary analysis, and sensitivity analysis.

Long-term Efficacy

- CHRONOS Study: Patients (%) showing sustained improvement over time in pruritus scores.


Dupilumab: Trial Findings in Safety

- Dupilumab found to be highly tolerable in both SOLO 1 and SOLO 2:
  - Only serious AE (SAE) was exacerbation of AD, reported in 2 patients in SOLO 1 and 1 patient in SOLO 2.
    - Same SAE experienced by patients taking placebo: 3 in SOLO 1, 5 in SOLO 2.
  - Other AEs included infections: ~35% in both trials vs ~30% for those taking placebo.
  - Injection-site reactions also common: 13%-19% for those injecting the drug weekly vs 6% for placebo.


Phase 3 Trial of Dupilumab in Adolescents

- First ever biologic trial for AD in ages 12-17 years (NCT03054428):
  - 251 patients with moderate-to-severe disease not controlled by topicals randomized to dosing every 4 weeks (Q4W), biweekly (Q2W), or placebo.
  - Coprimary endpoints EASI-75 response and IGA score of 0 (clear) or 1 (almost clear).
  - Secondary endpoints improvement in pruritus NRS and CDLQI.

- Preliminary phase 3 results presented September 2018 at EADV showed statistically significant improvement in skin, pruritus, and QOL by week 16.
  - Priority review application submitted to FDA in November for approval in adolescents; approval granted March 11, 2019.

### Phase 3 Dupilumab Trial in Adolescents: Results

**Patients Achieving Trial Endpoints**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Q4W</th>
<th>Q2W</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGA 16W</td>
<td>12%</td>
<td>24%</td>
<td>3%</td>
</tr>
<tr>
<td>EASI-75</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Pruritus NRS 16W</td>
<td>28%</td>
<td>12%</td>
<td>19%</td>
</tr>
</tbody>
</table>

**Phase 3 Dupilumab Trial in Adolescents: Safety**

**Most Common AEs**

<table>
<thead>
<tr>
<th>AE</th>
<th>Q4W</th>
<th>Q2W</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin Infections</td>
<td>13%</td>
<td>11%</td>
<td>8.5%</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>20%</td>
<td>11%</td>
<td>10%</td>
</tr>
<tr>
<td>Injection-Site Reactions</td>
<td>6%</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>

### Ongoing/Recruiting Clinical Trials of Dupilumab in Children

<table>
<thead>
<tr>
<th>Trial Name Type</th>
<th>Focus</th>
<th># Pts/Ages</th>
<th>Phase</th>
<th>Estimated Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02612454†</td>
<td>Long-term safety</td>
<td>765</td>
<td>3</td>
<td>October 2023</td>
</tr>
<tr>
<td>NCT03345914</td>
<td>Efficacy and safety of dupilumab with TCS</td>
<td>240</td>
<td>3</td>
<td>April 2019</td>
</tr>
<tr>
<td>LIBERTY AD PRESCHOOL / NCT0346434</td>
<td>Safety, PK, and efficacy of dupilumab in severe AD</td>
<td>280</td>
<td>2/3</td>
<td>April 2022</td>
</tr>
</tbody>
</table>

*If applicable; Enrolling by invitation. †Enrolling by invitation.

**Considerations in Prescribing Dupilumab**

- Cost and coverage important considerations
- Method of administration (subcutaneous may be particularly difficult for children)
- For insurance to cover, clinicians must document
  - Diagnosis of AD (not just “eczema”)
  - Condition severity
  - Prior treatments and failures
    - Specify the type of failure
      - inadequate response to medium or high-potency TCS, suboptimal improvement, failure to achieve long-term control, unacceptable adverse events
      - Impact of disease on QOL

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Emerging Biologics and Small-Molecule Agents Being Studied in Adolescents

<table>
<thead>
<tr>
<th>Agents</th>
<th>Inhibitor Class</th>
<th>Trial Phase</th>
<th>Route</th>
<th># Children in Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tralokinumab</td>
<td>IL-13</td>
<td>3</td>
<td>SC</td>
<td>1 ongoing/recruiting trial involving 294 adults and adolescents with moderate-to-severe AD</td>
</tr>
<tr>
<td>Upadacitinib</td>
<td>JAK 1</td>
<td>3</td>
<td>oral</td>
<td>4 ongoing/recruiting trials involving 2,089 adults and adolescents with moderate-to-severe AD</td>
</tr>
</tbody>
</table>

JAK, Janus kinase inhibitor; SC, subcutaneous.


Considerations in AD Management

Improving Patient Satisfaction

Results from National Eczema Association’s “In Your Words” patient satisfaction survey (N=192) in 2016

Treatment Satisfaction:
- Overall, are you satisfied with the treatment of AD?
  
  YES (14%)
  NO (86%)

Physician Satisfaction:
- Overall, do you think doctors know how to treat AD?
  
  YES (96%)
  NO (91%)

Improving Patient Satisfaction (cont.)

- Participant recommendations from “In Your Words” survey to improve satisfaction
  - Pay attention to the mental health/QOL impact of AD
  - Demonstrate understanding that AD is more than just a skin condition
  - Treat root cause, not just symptoms
  - Convey an attitude of caring about the patient
  - Don’t rely too heavily on corticosteroids
  - Quickly recognize when patients should be referred for more advanced treatments

**Shared Decision Making**

- **Expertise**
  - Healthcare Provider (pediatrician, nurse, NP, PA, other clinicians)
  - Patient/Caregiver

- **Shared Decision**
  - Diagnosis
  - Treatment options
  - Potential benefits
  - Potential AEs
  - Treatment expectations
  - Values
  - Lifestyle preferences (may include schedule, socioeconomic factors)
  - Previous experience


**Shared Decision Making (cont.)**

- An integral, patient-centered component of therapeutic education
  - Involves asking open-ended questions to assess patient/caregiver’s level of knowledge
  - Works best in chronic diseases for which there is no one “best” treatment
  - Recognizes importance of patient/caregiver’s preferences
  - Transfers information/skills from clinician to patient/caregiver
  - The best way to individualize/personalize treatment
  - Improves outcomes and QOL

- Empowering patients to select among treatment options helps to ensure adherence
  - Patients often have strong preferences in topicals based on vehicle (e.g., ointments vs creams), texture/thickness, smell
  - Costs are important to patients/caregivers; offering options of different expense levels is helpful


**Important Patient Education Points**

- Written treatment plan increases likelihood of adherence
- Moisturize frequently throughout the day
- Topical medications do not take the place of moisturizers
- Continue maintenance therapies even when skin appears healthy
- AD treatments will not work if they aren’t used!


**Treatment Adherence**

- Nonadherence pervasive in AD, especially for long-term treatment
  - Reasons
    - Frustration with medication efficacy
    - Medication inconvenient/dosing too frequent
    - Fear of AEs
    - Financial burden
    - Patient/caregivers don’t understand disease
    - Forgetfulness
    - Distaste/dislike of healthcare provider
    - Dislike of medication delivery vehicle

Proven Strategies to Improve Adherence

- Written eczema “action plans”
- Nurse-led eczema workshops
- Extra office visit at 1 week
- 2-hour education workshop
- Multidisciplinary patient education
- Discussing patients’ fears about treatment
- Asking patients to choose preferred treatment vehicle (especially with topicals)

Summary

- AD is an inflammatory disease involving immune dysregulation and epidermal barrier breakdown
- Disease negatively affects QOL of children and parents/caregivers
- Diagnosis based on clinical presentation
- AD leads to multiple comorbidities — even later in life
- Severity assessments are necessary to determine treatment
- Multiple treatments available depending on disease severity
- Systemic immunosuppression not suitable for long-term maintenance and none approved in children
- Dupilumab the only biologic thus far available
  - Trials show long-term efficacy
  - Recent phase 3 trial in adolescents yielded positive results

Thank You!

Back Up Slides
Unmet Needs in AD

Effective treatments that relieve symptoms and improve long-term outcomes
Effective strategies to ensure/encourage medication adherence
Reliable biomarkers to guide treatment selection
Clear, up-to-date, consensus-based guidelines

Epidermal Barrier Breakdown: A Vicious Cycle

Cytokines:
- IL-4, IL-13
- IL-31

Inflammatory Cascade

Simplified Step-Care Management

Refractory, Severe AD
Moderate-to-Severe AD
Mild-to-Moderate AD
Dry Skin Only

Step 1: Basic treatment: skin hydration, emollients, avoiding irritants, identifying and addressing specific triggers
Step 2: Low-to-mid potency TCS and/or TCI
Step 3: Mid-to-high potency TCS and/or TCI or crisaborole
Step 4: Systemic therapy or UV therapy

Limitations of Therapies for Moderate-to-Severe AD in Pediatric Population

- **Phototherapy:** Not approved for children under 12 years; very few data on efficacy in children
- **Systemic immunosuppression:** Generally avoided in children
  - Gastrointestinal and hepatic AEs common as well as infections and bone marrow suppression, among others
- **Systemic corticosteroids:** Unacceptable AEs
  - Can be used for short courses in some cases, however, no agreement about optimal dose and duration of “short course”
- **Biologics:** Dupilumab only currently available biologic
  - Strong safety and efficacy in adults and adolescents (data for adolescents presented at EADV Congress in September 2018)
  - Not yet approved for patients under 18 years

*Over the age of 2 years.
TCS, topical corticosteroid; TCI, topical calcineurin inhibitor.

†As of October 2018. EADV, European Academy of Dermatology and Venereology.
Identifying Treatment Failure

- No validated biomarkers to assess treatment response
- No standard definition for treatment failure

Definitions Proposed by Expert Panel in 2017

- Inadequate clinical improvement
- No relief from impairment (particularly in QOL)
- Lack of stable, long-term control (flares continue)
- Unacceptable AEs leading to treatment discontinuation