MILD TO MODERATE ATOPIC DERMATITIS:
Pathogenesis and Therapeutic Strategies For Improved Outcomes

Saturday, April 22, 2017

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- Complete the preassessment prior to the start of the activity
- Participate in the Atopic Dermatitis presentation
- Complete the postassessment and evaluation at the conclusion of the activity
Faculty and Disclosures

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Dr Hebert has disclosed the following relationships:

Advisory Board: Anacor Pharmaceuticals, Inc; Demira; Galderma Laboratories, LP; GlaxoSmithKline; PharmaDerm; Procter & Gamble; Promius Pharma, LLC; Shionogi, Inc; Stiefel, a GSK Company; Valeant Pharmaceuticals International

Consultant: GlaxoSmithKline

Data Safety Monitoring Board: GlaxoSmithKline; Regeneron Pharmaceuticals, Inc

Speaker Honoraria: Bayer; Galderma Laboratories, LP; Intendis, Inc; Menarini Group; Novartis Pharmaceuticals; Onset Therapeutics; Pri-Med; Sinclair Pharma

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*All research funds paid to the UTHealth McGovern School of Medicine.
Faculty and Disclosures

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Maruho Co Ltd; Medimetriks Pharmaceuticals, Inc; Otsuka Pharmaceutical Co Ltd;
Pfizer Inc; Regeneron Pharmaceuticals, Inc; Sanofi Pharma; TopMD;
Valeant Pharmaceuticals

Investigator: GlaxoSmithKline; Medimetriks Pharmaceuticals, Inc; Otsuka Pharmaceutical
Co Ltd; Regeneron Pharmaceuticals, Inc
Levels of Evidence

Two types of grades are provided for any treatment recommendations made in the presentation:

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Strength of Clinical Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Used to evaluate available evidence based on the quality of study methodology and the overall focus of the study</td>
<td>• Developed based on the best available evidence</td>
</tr>
<tr>
<td>I. Good-quality patient-oriented evidence (ie, evidence measuring outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life)</td>
<td>A. Recommendation based on consistent and good-quality patient-oriented evidence</td>
</tr>
<tr>
<td>II. Limited-quality patient-oriented evidence</td>
<td>B. Recommendation based on inconsistent or limited-quality patient-oriented evidence</td>
</tr>
<tr>
<td>III. Other evidence including consensus guidelines, opinion, case studies, or disease-oriented evidence (ie, evidence measuring intermediate, physiologic, or surrogate endpoints that may or may not reflect improvements in patient outcomes)</td>
<td>C. Recommendation based on consensus, opinion, case studies, or disease-oriented evidence</td>
</tr>
</tbody>
</table>

This educational activity may contain discussion of published and/or investigational uses of therapies that are not indicated by the FDA, including roflumilast, OPA-15406, tofacitinib, SB011, and apremilast.

Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

Further, participants are encouraged to consult appropriate resources for any product or device mentioned in this program.
At the conclusion of this live activity, practitioners should be better able to:

- Summarize the role of skin barrier dysfunction and inflammatory responses in atopic dermatitis (AD) pathogenesis
- Describe the inflammatory/immunomodulating pathways in atopic dermatitis
- Evaluate the benefits and limitations of current therapies for mild to moderate atopic dermatitis
- Assess the efficacy and safety of emerging therapies and their potential role in treating atopic dermatitis
Epidemiology, Prevalence, and Pathogenesis
What’s Your Diagnosis?

- 4-month-old infant presents with erythematous scaling dermatitis of the cheeks bilaterally
- Similar-appearing lesions over the posterior neck and extensor aspects of the extremities

Photo courtesy of Adelaide A. Hebert, MD
Epidemiology in Children and Adolescents

- Affects 10%-20% of school-aged children in the US\(^1\)
- Higher prevalence in African Americans, urban residents, and children living in homes with higher education levels\(^2\)
- AD will persist into adulthood in up to 33% of children\(^1\)

Diagnostic Criteria for Atopic Dermatitis

- Pruritus (itching)
- Eczematous changes that are acute, subacute, or chronic
  - Age-specific distribution patterns
  - Intermittent course with flares and remissions

Primary Physical Findings

- Erythema
- Papules/plaques
- Excoriations
- Xerosis
- Erosions and crusting
- Lichenification
- Dyspigmentation

Photos courtesy of Lawrence F. Eichenfield, MD

Distribution of Atopic Dermatitis Varies With Age

Infants
*Face, trunk (except diaper area), extensor extremities*

Children
*Flexors (wrists, ankles, antecubital/popliteal fossae)*

Adolescents
*Flexors, neck, wrists, hands, ankles*

Photos courtesy of Lawrence F. Eichenfield, MD, and Adelaide A. Hebert, MD

Clinical Presentation in Children

- More than 7 million healthcare provider visits per year for AD\(^1\)
- Approximately 67\% of children have mild disease that can be managed by a primary care provider\(^2\)
- Specialist referral is required in moderate (20\%) and severe (2\%) cases\(^3\)

Mild Atopic Dermatitis

Photo courtesy of Adelaide A. Hebert, MD
Moderate Atopic Dermatitis

Photo courtesy of Anthony J. Mancini, MD
Severe Atopic Dermatitis

Photo courtesy of Lawrence F. Eichenfield, MD
Features in Darker Skin Types

Follicular accentuation
Pityriasis alba
Erythema (hard to see due to pigmentation)
Marked lichenification

Photos courtesy of Lawrence F. Eichenfield, MD, and Adelaide A. Hebert, MD
Differential Diagnosis of Atopic Dermatitis: Common Disorders

- Seborrheic dermatitis
- Scabies
- Impetigo
- Contact dermatitis (allergic and irritant)
- Psoriasis
- Ichthyosis vulgaris
- Tinea corporis
- Keratosis pilaris
Scabies

Photo courtesy of Adelaide A. Hebert, MD
Impetigo

Photo courtesy of Lawrence F. Eichenfield, MD
Metabolic/nutritional/genetic disorders

- Acrodermatitis enteropathica
- Zinc deficiency (prematurity; breast milk deficient in zinc; cystic fibrosis)
- Other nutritional deficiencies (biotin, essential fatty acids)
- Netherton syndrome
- Phenylketonuria
- Omenn syndrome
- Prolidase deficiency
- Gluten sensitivity-related dermatitides
- Hurler syndrome
Differential Diagnosis of Atopic Dermatitis: Rare Disorders in Infancy and Childhood

**Immune disorders**
- Hyperimmunoglobulin E syndrome
- Severe combined immunodeficiency disorder
- Wiskott-Aldrich syndrome
- Agammaglobulinemia
- Ataxia-telangiectasia
- Neonatal lupus erythematosus

**Proliferative disorders**
- Langerhans cell histiocytosis
Differential Diagnosis of Atopic Dermatitis: Rare Disorders in Adolescents and Adults

- Cutaneous T-cell lymphoma (Mycosis fungoides or Sézary syndrome)
- HIV-associated dermatoses
- Dermatomyositis
- Graft-versus-host disease
- Lupus erythematosus
- Pemphigus foliaceus
- Drug eruptions
Complex, heterogeneous pathogenesis

• Skin barrier dysfunction
  – Filaggrin mutations
  – Diminished ceramides

• Inflammation

• Pruritus/scratching

• Microbial colonization

• Allergy
Colonization by *Staphylococcus aureus*

- Worsens disease status
- Renders disease harder to control
- Patients do not have to be infected to be adversely impacted by *S. aureus*
- Skin that is colonized has a true trigger for disease flares


Immunopathogenesis of Atopic Dermatitis

Pathogenesis of Atopic Dermatitis

Burden of Disease

• Quality of Life
  – An average of 9 flares per year, each lasting 15 days¹
  – Poor quality of sleep²
    • Sleep disturbances ~7.3 nights per flare¹
    • Increased co-sleeping (up to 30% in one study)³
    • Polysomnography showing high number of arousals in AD children, independent of scratching⁴
  – Itching⁵
    • 87% experience itching daily
    • Itching lasts ≥ 18 hours in 41.5% of patients

Impact of Comorbidities

- Asthma
- Allergic rhinitis
- Food allergy
- Contact dermatitis
- Emerging comorbidities
  - Obesity
  - Hypertension

Available Therapies and Management Strategies
Case 2: Therapy Recommendations

- Apply mild to moderate potency topical steroids twice daily (A,I) for 1-2 weeks, several days beyond clearing for flare control
- Emollients 2 to 3 times per day (A,I)
- Sedating antihistamines can be considered if sleep is disturbed….BUT…skin-directed therapy should be emphasized!

*Against use of systemic antihistamines: sedating C, III, and nonsedating A, II.
Maintenance Therapies for Atopic Dermatitis

- **Skin care**
  - Liberal and frequent application of moisturizers
  - Warm baths/showers (<5 min) using nonsoap cleansers or mild soaps
- **Antiseptic measures**
  - Dilute bleach baths
- **Trigger avoidance**

Management of Acute Flares

- Avoid trigger factors
- Restore barrier integrity
- Control itching
- Treat infection/control colonization

Barrier Defect
Gently cleanse twice a day

Use mild, nonsoap cleansers (syndets)
  - Eg, CeraVe®, Cetaphil®, Equate®, etc

Use an effective moisturizer every day after cleansing
Water: Irritant or Treatment?

• **Water irritates skin IF:**
  – Skin is frequently wet, without immediate application of effective moisturizer
  – Moisture evaporates, causing skin barrier to become dry, irritated

• **Water hydrates skin IF:**
  – Effective moisturizer is applied and hydration is retained, keeping skin barrier intact and flexible
Importance of Barrier Integrity
Topical Corticosteroids (TCS): Benefits and Limitations

Benefits:
• Highly effective at treating inflammation
• Rapid onset of action
• Multiple potency and delivery vehicles
  – Varied potency frequently required per patient

Limitations:
• Product-specific age limits (although often used off-label)
• Potential for local and systemic side effects (but rare when used appropriately):
  – Local: striae, telangiectasias, skin atrophy, dyspigmentation, periorificial dermatitis, acne rosacea
  – Systemic: HPA axis suppression
  – Periorbital administration: cataracts, glaucoma

HPA, hypothalamic-pituitary-adrenal.
### Table V. Relative potencies of topical corticosteroids

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Dosage form(s)</th>
<th>Strength (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Very high potency</td>
<td>Augmented betamethasone dipropionate</td>
<td>Ointment</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Clobetasol propionate</td>
<td>Cream, foam, ointment</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Diflorasone diacetate</td>
<td>Ointment</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Halobetasol propionate</td>
<td>Cream, ointment</td>
<td>0.05</td>
</tr>
<tr>
<td>II. High potency</td>
<td>Aminiconde</td>
<td>Cream, lotion, ointment</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>Augmented betamethasone dipropionate</td>
<td>Cream</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Betamethasone dipropionate</td>
<td>Cream, foam, ointment, solution</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Desoximetasone</td>
<td>Cream, ointment</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>Desoximetasone</td>
<td>Gel</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Diflorasone diacetate</td>
<td>Cream</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Flucinonide</td>
<td>Cream, gel, ointment, solution</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Halcinonide</td>
<td>Cream, ointment</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>Mometasone furoate</td>
<td>Ointment</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>Triamcinolone acetonide</td>
<td>Cream, ointment</td>
<td>0.5</td>
</tr>
<tr>
<td>III-IV. Medium potency</td>
<td>Betamethasone valerate</td>
<td>Cream, foam, lotion, ointment</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>Clocortolone pivalate</td>
<td>Cream</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>Desoximetasone</td>
<td>Cream</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Fluocinolone acetonide</td>
<td>Cream, ointment</td>
<td>0.025</td>
</tr>
<tr>
<td></td>
<td>Flurandrenolide</td>
<td>Cream, ointment</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Fluticasone propionate</td>
<td>Cream</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Fluticasone propionate</td>
<td>Ointment</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>Mometasone furoate</td>
<td>Cream</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>Triamcinolone acetonide</td>
<td>Cream, ointment</td>
<td>0.1</td>
</tr>
<tr>
<td>V. Lower-medium potency</td>
<td>Hydrocortisone butyrate</td>
<td>Cream, ointment, solution</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone probutate</td>
<td>Cream</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone valerate</td>
<td>Cream, ointment</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>Prednicarbate</td>
<td>Cream</td>
<td>0.1</td>
</tr>
<tr>
<td>VI. Low potency</td>
<td>Alclometasone dipropionate</td>
<td>Cream, ointment</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Desonide</td>
<td>Cream, gel, foam, ointment</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Fluocinolone acetonide</td>
<td>Cream, solution</td>
<td>0.01</td>
</tr>
<tr>
<td>VII. Lowest potency</td>
<td>Dexamethasone</td>
<td>Cream</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone</td>
<td>Cream, lotion, ointment, solution</td>
<td>0.25, 0.5, 1</td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone acetate</td>
<td>Cream, ointment</td>
<td>0.5-1</td>
</tr>
</tbody>
</table>

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Topical Corticosteroids

- Low potency: hydrocortisone 1%-2.5% or desonide 0.05%
- Mid potency: triamcinolone 0.1%
- High potency: fluocinonide 0.05%

Topical Calcineurin Inhibitors (TCI) Benefits

- Extensive clinical trials experience
- Steroid-sparing
- Good efficacy for mild, moderate, and severe AD
- Used for acute and maintenance therapies
- Little systemic absorption
- Can be applied to face (including periorbital regions), extremities, and genital area

Available TCIs

<table>
<thead>
<tr>
<th>TCI</th>
<th>Vehicle</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pimecrolimus</td>
<td>Cream</td>
<td>Approved for mild to moderate AD (2 years and older)</td>
</tr>
<tr>
<td>(1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Ointment</td>
<td>Approved for moderate to severe AD (0.03%: 2 years and older; 0.1%: 15 years and older)</td>
</tr>
<tr>
<td>(0.03% and 0.1%)</td>
<td></td>
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</tr>
</tbody>
</table>

• Both TCIs were shown to be more effective than vehicle in short-term (3-12 weeks) and long-term studies (up to 12 months) in adults and children with active disease
  – Decline in Eczema Area and Severity Index (EASI) score
  – Decrease in percent body surface involved
  – Reduction in patient evaluated symptoms and signs of disease

TCI Limitations and Potential Adverse Events

- Not indicated for use in children <2 years of age
- Not indicated for long-term continuous therapy
- Second-line agents
- Limited range of vehicles available vs TCSs
- Stinging and burning in a small subset of patients
- FDA-mandated black box warning and medication guide
- The only time in FDA history that a black box was given for potential risk

Phosphodiesterase Type 4 (PDE4)

- Elevated in patients with AD compared with control patients\(^1\)
- Reduces intracellular cyclic adenosine monophosphate (cAMP) and suppresses protein kinase A, leading to increased levels of proinflammatory cytokines\(^1\)
- Topical and oral PDE4 inhibitors currently under clinical investigation

Crisaborole Topical Ointment

- A nonsteroidal, boron-based PDE4 inhibitor
- Approved for mild to moderate AD in adults and children ≥2 years in December 2016
- Reduces inflammation and itching
- Maintains skin barrier
# Crisaborole Topical Ointment

<table>
<thead>
<tr>
<th></th>
<th>AD-301 (Crisaborole/Vehicle) N = 503/256</th>
<th>AD-302 (Crisaborole/Vehicle) N = 513/250</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Efficacy Endpoint</strong></td>
<td>32.8%/25.4% (P = .038)</td>
<td>31.4%/18.0% (P &lt; .001)</td>
</tr>
<tr>
<td>• Percentage of patients who</td>
<td></td>
<td></td>
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<tr>
<td>achieved success in ISGA (defined as score of 0 [clear] or 1 [almost clear] with a minimum 2-grade improvement) at Day 29</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Secondary Efficacy Endpoint</strong></td>
<td>51.7%/40.6% (P = .005)</td>
<td>48.5%/29.7% (P &lt; .001)</td>
</tr>
<tr>
<td>• Percentage of patients achieving ISGA clear (0) or almost clear (1) at Day 29</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

50% of patients treated with crisaborole achieved improvement in pruritus by 1.37 days (compared with 1.73 days for the vehicle group, P = .001)

ISGA, Investigator’s Static Global Assessment.
1. Paller AS, et al. Presented at: Fall Clinical Dermatology Conference; October 1-4, 2015; Las Vegas, NV.
2. Hebert AA, et al. Presented at: Fall Clinical Dermatology Conference; October 1-4, 2015; Las Vegas, NV,
Crisaborole 48-Week Safety Study

- Open-label study (after Phase 3), 517 patients
- Disease severity assessed every 4 weeks using ISGA scale
- Patients received 4-week cycles of crisaborole as needed
- Safety measures: local tolerability, adverse events, serious adverse events, clinical laboratory results, vital signs, physical examinations

Crisaborole Safety Profile

• Favorable safety profile over 48-week study
  – Treatment-related TEAEs in ≥1% of patients:
    AD (3.1%), application site pain (2.3%), application site infection (1.2%)¹
  – TEAEs in at least 5% of patients: AD (11.2%), upper respiratory tract infection (10.3%), nasopharyngitis (7.7%), cough (6.8%), and pyrexia (5.6%)¹
  – Limited systemic exposure²
  – No atrophy, telangiectasia, hypopigmentation

TEAE, treatment-emergent adverse event.
Dupilumab

- Approved March 2017
- Injectable biologic therapy
- Blocks cytokines IL-4 and IL-3
- Indicated for adults with moderate to severe AD

Controlling the Itch

- Frequent moisturization to reduce dryness
- Apply low- to mid-potency TCSs to control inflammation
- Antihistamines are not effective at alleviating itching
  - Sedating antihistamines can be used to improve sleep

Antihistamines in Atopic Dermatitis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Vehicle</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pramoxine</td>
<td>C, L</td>
<td>Topical anesthetic – blocks nerve conduction and impulses by inhibiting depolarization of neurons</td>
</tr>
<tr>
<td>Diphenhydramine*</td>
<td>Oral</td>
<td>Sedating antihistamine</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>Oral</td>
<td>Sedating antihistamine</td>
</tr>
<tr>
<td>Doxepin</td>
<td>Oral, L</td>
<td>Sedating antihistamine</td>
</tr>
<tr>
<td>Cetirizine*</td>
<td>Oral</td>
<td>Non-sedating antihistamine</td>
</tr>
</tbody>
</table>

C, cream; L, lotion.
*Available over the counter.
Dilute Bleach Baths

• Mechanism of action still unclear
  – Anti-inflammatory actions or suppression of *S. aureus* overgrowth?\(^1\)

• Preparation: \(\frac{1}{8}-\frac{1}{2}\) cup of bleach per standard bathtub, at least 2 times per week\(^2\)

• Supporting evidence: see references 1-3

Case 3

Photo courtesy of Adelaide A. Hebert, MD
Case 3

Photo courtesy of Adelaide A. Hebert, MD
Case 3: Therapy Recommendations

Initial therapy

- Disease control
  - Face: low-potency TCS or TCI (A,I)
  - Body: mid-potency TCS, with or without wet wraps (A,I)
- Emollients 2-3 times per day (A,I)
- Antihistamines if necessary/desired*
- Dilute bleach baths if skin is red and crusted (B,II)

After-flare control

- Intermittent treatment with TCS, TCI (A,I)

*Against use of systemic antihistamines: sedating C, III, and nonsedating A, II.
Patient and Caregiver Education

- 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 if skin “appears” healthy
- Appearance of AD changes with age
Specialty Referral

• Early referral in the case of severe, persistent disease
• Otherwise, refer if the patient is not responding to conservative measures and standard treatment modalities
• For food allergy evaluation for milk, egg, peanut, wheat, and soy if at least 1 of the following conditions is met:
  – Persistent AD in spite of optimized management and topical therapy
  – Reliable history of immediate reaction after ingestion of a specific food
Eczema Herpeticum

Photo courtesy of Adelaide A. Hebert, MD
Eczema Herpeticum

Photo courtesy of Adelaide A. Hebert, MD
Emerging Therapies for Atopic Dermatitis
Other Emerging Treatments for Atopic Dermatitis

• Topical therapies
  – PDE4 inhibitors (eg, roflumilast,\textsuperscript{1} OPA-15406\textsuperscript{2})
  – Janus kinase inhibitors: tofacitinib ointment\textsuperscript{3}
    • Phase 2 trial results (2% ointment, BID)
      – EASI score for tofacitinib -87.7\% (compared with -29.9\% with vehicle, \(P<0.001\))
      – Significant improvements in EASI, PGA, and BSA by week 1, pruritus by day 2 with tofacitinib
      – More AEs were observed for vehicle (55.9\%) vs tofacitinib (31.4\%)
      – No patients treated with tofacitinib discontinued treatment due to AEs
      – No SAEs were reported in either group
      – Fewer TEAEs reported for tofacitinib (5.7\%) vs vehicle (11.8\%)
  – Calcineurin inhibitor: SB011\textsuperscript{4}

EASI, Eczema Area and Severity Index; PGA, Physician’s Global Assessment; BSA, Body Surface Area; AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Other Emerging Treatments for Atopic Dermatitis

- Systemic therapies
  - Apremilast: an oral PDE4 inhibitor\(^1\)
- Other new agents on the horizon that look promising

1. ClinicalTrials.gov Identifier: NCT02087943.
Clinical Pearls

• Do not undertreat the disease
• Stress the importance of moisturization in disease control to patients/parents
• Control infection/colonization
• Oral steroids are very rarely indicated in the treatment of AD
Questions
Thank You

Please complete the **postassessment and evaluation** located in your meeting handout.