Mild to Moderate Atopic Dermatitis: Pathogenesis and Targeted Therapies for Improved Outcomes

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Educational Objectives
By the end of this educational activity, participants should be better able to:
1. Summarize the role of skin barrier dysfunction and inflammatory responses in atopic dermatitis pathogenesis.
2. Describe the inflammation/immunomodulating pathways in atopic dermatitis.
3. Evaluate the benefits and limitations of current therapies for mild to moderate atopic dermatitis.
4. Assess the efficacy and safety of emerging therapies and their potential role in treating atopic dermatitis.

Speaker Disclosure
Dr. Hebert has disclosed that she has received grant or research support from Allergan, Amgen, Astellas, Chugai Pharma, Healthpoint, Merz Pharmaceuticals, National Institutes of Health, PPD Inc., and TopMD; she is on the advisory board for Anacor Pharmaceuticals, Galderma Laboratories, GlaxoSmithKline, PharmaDerm, Promius Pharma, Shionogi, Stiefel, and Valeant Pharmaceuticals; she is on the data safety monitoring board for Regeneron Pharmaceuticals; and she is on the speaker’s bureau for Bayer, Intendis, Menarini Group, Novartis, Onset Therapeutics, and Sinclair Pharma.

Supporter Disclosure
This CME activity is supported by an educational grant from Anacor Pharmaceuticals. It has been planned and produced by the North Carolina Academy of Family Physicians, Spire Learning, and TAFP strictly as an accredited continuing medical education activity.
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• Complete the pre-assessment using your ARS keypad at the start of the activity
• Participate in the atopic dermatology presentation
• Complete the post-assessment using your ARS keypad at the conclusion of the activity
• Complete the evaluation at the conclusion of the activity

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Disclosure Statement
Dr. Hebert has disclosed the following relationships:
Advisory Board/Honoraria: Anacor Pharmaceuticals, Inc; Galderma Laboratories, LP; GlaxoSmithKline: PharmaDerm; Promius Pharma, LLC; Shionogi USA; Stiefel; a GSK Company; Valeant Pharmaceuticals International
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Other: Grants/Research Funding: Department of Defense; Honoraria: Novartis Pharmaceuticals Corp
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Disclosure Statement
Dr. McNabb has indicated that he has no disclosures to be made.
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>
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</thead>
<tbody>
<tr>
<td>I. Good-quality patient-oriented evidence</td>
<td>Developed based on the best available evidence.</td>
</tr>
<tr>
<td>II. Limited-quality patient-oriented evidence</td>
<td>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</td>
<td>Recommendation based on consensus, opinion, case studies, or disease-oriented evidence</td>
</tr>
</tbody>
</table>

- Used to evaluate available evidence based on the quality of study methodology and the overall focus of the study
- Good-quality patient-oriented evidence (i.e., evidence measuring outcomes that matter to patients: mortality, morbidity, symptom improvement, cost reduction, and quality of life)
- Limited-quality patient-oriented evidence
- Other evidence including consensus guidelines, opinion, case studies, or disease-oriented evidence (i.e., evidence measuring intermediate, physiologic, or surrogate endpoints that may or may not reflect improvements in patient outcomes)


Off-Label Statement

The faculty intend to discuss/present information related to a non-FDA-approved or investigational use of a product/device, including the investigational use of crisaborole, roflumilast, OPA-15406, tofacitinib, SB011, dupilumab, and apremilast for the treatment of atopic dermatitis.

Participants should appraise the information presented critically and are encouraged to consult appropriate resources for any product or device mentioned in this activity.

Learning Objectives

At the conclusion of this live activity, family physicians should be able to:

- Summarize the role of skin barrier dysfunction and inflammatory responses in atopic dermatitis 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

Mild to Moderate Atopic Dermatitis:
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What's Your Diagnosis?

- A 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

US Prevalence of Atopic Dermatitis

- More than 50 million people suffer from allergic diseases
- Lifetime prevalence of AD is 10% - 20% in children and 1% - 3% in adults
- Prevalence of AD has been increasing in industrialized countries
- Children with MILD AD have a 55% chance of having it as an adult
- Children with MODERATE to SEVERE AD have a 77% - 91% chance of having it as an adult
- There are 7 million healthcare provider visits per year for contact dermatitis and other eczemas, including AD

Atopic Dermatitis: Criteria of the American Academy of Dermatology

- Pruritus (itching)
- Eczematous changes that are acute, subacute, or chronic
  - Typical and age-specific patterns:
    - Facial, neck, and extensor involvement in infants and children
    - Current or prior flexural lesions in adults/any age
    - Sparing of groin and axillary regions
    - Chronic or relapsing course


Differential Diagnosis

- Scabies
- Seborrheic dermatitis
- Contact dermatitis (irritant or allergic)
- Ichthyoses
- Cutaneous T-cell lymphoma
- Psoriasis
- Photosensitivity dermatoses
- Immune deficiency disease
- Erythroderma of other causes


Pathogenesis

Complex, heterogeneous pathogenesis:
- Skin barrier dysfunction
  - Diminished ceramides
- Allergy/immunology
- Pruritus


Atopic Dermatitis: Features in Fitzpatrick Skin Types IV-V

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

Burden of Disease

- Quality of Life
  - An average of 9 flares per year, each lasting 15 days
  - Sleep disturbances ~7.3 nights per flare
  - 86% of patients avoid ≥1 type of everyday activity
- Socioeconomic elements
  - 2.5 lost days of school or work per year
- Psychosocial elements
  - 55% of patients worry about their next flare
  - 62%-65% of caregivers worry about their child’s next flare


Interplay Between Barrier, Allergy/Immunology, Pruritus

Environment

Barrier disruption

Contact dermatitis

Allergy: sensitization

Development of AD

Environment

Barrier disruption

High UV

Allergic march

High UV

Interplay among the barrier, allergy, and pruritus as a trinity. Pages 3-11. Copyright (2016), with permission from Elsevier.
Case 1

Patient photos not available for handout.

Management of Acute Flares

- Restore barrier integrity
- Recognize trigger factors
- Control itching
- Reverse infection

Case 1: Therapy Recommendations

- Emollients 2 to 3 times per day A, I
- Low-potency topical steroids A, I
- Oral antihistamines if necessary*

Management of Acute Flares

- Restore barrier integrity
- Recognize trigger factors
- Control itching
- Reverse infection

Barrier Defect
Repairing Barrier Integrity
Requires Fundamental Skin Care

- Gently cleanse BID
- Use mild, nonsoap cleansers (syndets)
  - E.g., 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:
  - After skin is wet, effective moisturizer is applied within 3 minutes
  - Hydration is retained, keeping skin barrier intact, flexible

Importance of Barrier Integrity

Ceramide-Containing Moisturizers

- Adds to the skin “what is missing”
- Restores the barrier
- Gives patients and parents a sense of control of the disease

Available Ceramide-Containing Moisturizers*

- CeraVe® cream or lotion
- Cetaphil RestoraDerm®
- Aveeno® Eczema Therapy

Topical Corticosteroids (TCS): Benefits and Limitations

Benefits:

- Highly effective
- Rapid onset of action
- Multiple potency and delivery vehicles
  - Varied potency frequently required per patient

Limitations:

- Product-specific age limits
- Limited to use on small surface areas
- Short-term duration of administration due to side effects
  - Systemic: HPA axis suppression, growth delay, decreased bone mineral density
  - Local: striae, telangiectasias, skin atrophy, dyspigmentation, perioral dermatitis, acne rosacea, periorbital administration can potentially lead to cataracts, glaucoma

Topical Steroids

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

<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>Doxepin</td>
<td>L</td>
<td>Potent antihistamine</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</td>
<td>Sedating antihistamine</td>
</tr>
<tr>
<td>Cetirizine*</td>
<td>Oral</td>
<td>Sedating antihistamine</td>
</tr>
</tbody>
</table>

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

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Case 2

Patient photos not available for handout.

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Case 2: Therapy Recommendations

- Emollients 2 to 3 times per day A, I
- Low- to mid-potency topical steroids to control flares A, I
- Calcineurin inhibitors to maintain control A, I
- Antihistamines if necessary*
- Diluted bleach baths if skin is red and crusted B, II

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

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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 large body surface areas, face, and genital area

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Available TCIs

<table>
<thead>
<tr>
<th>TCI</th>
<th>Vehicle</th>
<th>Indications</th>
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<tbody>
<tr>
<td>Pimecrolimus (1%)</td>
<td>Cream</td>
<td>Approved for mild to moderate AD</td>
</tr>
<tr>
<td>Tacrolimus (0.03% and 0.1%)</td>
<td>Ointment</td>
<td>Approved for moderate to severe AD</td>
</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 EASI score
- Decrease in percent body surface involved
- Reduction in patient evaluated symptoms and signs of disease

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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
Colonization of Staphylococcus aureus

- Worsens disease status
- Renders disease harder to control

Staphylococcal Colonization

- 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

Diluted Bleach Bath

- Mechanism of action still unclear
  - Anti-inflammatory actions or suppression of S. aureus overgrowth?
- Preparation: ½ cup of bleach per standard bath tub, at least 2 times per week
- Supporting evidence: see references 1-3

Referral to a Dermatologist

- Early referral in the case of severe disease
- Otherwise, refer if the patient is not responding to conservative measures and standard treatment modalities
- Provide the consulting dermatologist with a concise referral letter, a copy of the treatment record, and pretreatment photographs (if available)

Eczema Herpeticum

Patient photos not available for handout.

Emerging Therapies for Atopic Dermatitis
Phosphodiesterase Type 4 (PDE4)

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


Crisaborole Topical Ointment

- A nonsteroidal, boron-based PDE4 inhibitor
- Submitted NDA for treatment of mild to moderate AD in adults and children ≥2 years in January 2016
- Favorable safety profile over 48-week study:
  - Treatment-related TEAEs in ≥1% of patients: atopic dermatitis (3.1%), application site pain (2.3%), application site infection (1.2%)1
  - TEAEs in at least 5% of patients: atopic dermatitis (11.2%), upper respiratory tract infection (10.3%), nasopharyngitis (7.7%), cough (6.8%), and pyrexia (5.6%)1
  - Limited systemic exposure2


Crisaborole Topical Ointment (Cont’d)

<table>
<thead>
<tr>
<th></th>
<th>AD-301 (Crisaborole/Vehicle)</th>
<th>AD-302 (Crisaborole/Vehicle)</th>
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<tbody>
<tr>
<td>Primary Efficacy Endpoint1</td>
<td>32.6%/25.4% (P=0.038)</td>
<td>31.4%/19.8% (P=0.001)</td>
</tr>
<tr>
<td>Secondary Efficacy Endpoint1</td>
<td>51.7%/40.6% (P=0.005)</td>
<td>48.5%/29.7% (P=0.001)</td>
</tr>
</tbody>
</table>

50% of patients treated with crisaborole achieved improvement in pruritus by 1.37 days (compared to 1.70 days for the vehicle group, P=0.001)2

ISGA, Investigator’s Static Global Assessment.

Other Emerging Treatments for Atopic Dermatitis

- Topical therapies
  - PDE4 inhibitors (e.g., roflumilast,1 OPA-154062)
  - Janus kinase inhibitors: tofacitinib ointment3
  - Calcineurin inhibitor: SB0114
- Systemic therapies
  - Dupilumab: injectable biologic therapy, blocks cytokines IL-4 and IL-135
  - Apremilast: an oral PDE4 inhibitor6
- Other new agents on the horizon that look promising

5. ClinicalTrials.gov identifier: NCT02575689.

Thank you

Please complete the evaluation for this session.
The following medications were discussed in this presentation. The table below lists the generic and trade name(s) of these medications.

<table>
<thead>
<tr>
<th>Generic Name</th>
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<tbody>
<tr>
<td>Apremilast</td>
<td>Otezla</td>
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<tr>
<td>Cetirizine</td>
<td>Zyrtec</td>
</tr>
<tr>
<td>Crisaborole</td>
<td>None</td>
</tr>
<tr>
<td>Desonide</td>
<td>Desonate, Desowen, Verdeso</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Benadryl</td>
</tr>
<tr>
<td>Doxepin</td>
<td>Zonalon</td>
</tr>
<tr>
<td>Fluocinonide</td>
<td>Lidex, Vanos</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>Vistaril</td>
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<tr>
<td>Pimecrolimus</td>
<td>Elidel</td>
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<tr>
<td>Pramoxine/Hydrocortisone</td>
<td>Epifoam, Pramosone</td>
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<tr>
<td>Roflumilast</td>
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<tr>
<td>Tacrolimus</td>
<td>Protopic</td>
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<tr>
<td>Tofacitinib</td>
<td>Xeljanz</td>
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<tr>
<td>Triamcinolone</td>
<td>Triderm</td>
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