Improving Diagnosis and Treatment of Atopic Dermatitis Through Collaborative Primary and Specialist Care

Learning Objectives

▪ Utilize updated criteria and guidelines to accurately diagnose AD and assess severity in individual patients
▪ Review updated guidelines and evaluate available clinical data for therapies utilized in the treatment of AD
▪ Identify the rationale for specialist referral of patients with AD and review best practices for co-management of moderate-to-severe disease with specialist physicians
▪ List documentation and prior authorization requirements to ensure access to prescribed medications for patients with AD

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Consulting Fees:
Sanofi Genzyme and Regeneron Pharmaceuticals

Burden of AD and Unmet Needs

Prevalence of AD

- Affects ~31.9 million in the US
  - 11%–20% of children
  - 7% of adults
- AD often the first sign of long-term disease continuum
  - 60% eventually develop asthma or allergic rhinitis
  - 30% develop food allergies
- 1 in 4 adults with AD report adult onset
  - 30% of childhood cases persist into adult years

References:
AD: Psychosocial/Health-Related Burden

Detrimental to QOL\(^1\)\(^\text{a}\)
- Heavy psychosocial impact
  - Due to stigma, embarrassment, isolation, unpredictability of flares
- Associated with anxiety, depression, and suicidal ideation\(^3\)
- Negative impact on academic and job-related performance

Negative effect on sleep (mostly due to pruritus)\(^4\)\(^\text{a}\)
- 87% experience itching daily
- Itching lasts ≥18 hours in ~42% of patients
- Leads to excessive daytime sleepiness, fatigue, reduced HRQOL

HRQOL, health-related quality of life; QOL, quality of life.


AD: Psychosocial/Health-Related Burden (cont.)

Infection
- Increased risk of cutaneous and systemic infections contribute to overuse of antibiotics\(^1\)

Heavy care/financial burden for parents, caregivers\(^2\)
- Interrupted sleep >3×/week or more due to AD\(^3\)
- Patients average 9 flares/year, each lasting ~15 days\(^4\)
- Out-of-pocket expenses for families estimated to total ~10% of annual income\(^5\)


More Than Skin Deep: AD Comorbidites

- Multiple comorbidities are known to be associated with AD
  - Allergic rhinitis, asthma, conjunctivitis, food allergies eosinophilic esophagitis
- Concept of “atopic march” says that for many, AD will start early and will develop into these comorbidities
- Associated nonatopic comorbidities can emerge later in life
  - Cardiometabolic, gastrointestinal-immune mediated, neuropsychiatric
Unmet Needs in AD

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


Diagnosis, Severity Assessment & Available Guidelines

Diagnostic Criteria for AD from the AAD

AD currently diagnosed based on history and clinical presentation

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

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

Differential/Exclusion Diagnoses (alternate or concomitant)
- Seborrheic dermatitis
- Contact dermatitis (allergic or irritant)
- Scales
- Immunodeficiencies
- Ichthyoses
- Psoriasis
- Photosensitivity dermatoses
- Cutaneous T-cell lymphoma
- Erythroderma of other causes

AAD, American Academy of Dermatology; IgE, immunoglobulin E.

Clinical Features in Darker Skin Types

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


Distribution Patterns Vary with Age

- Infants: Forehead, cheeks, and chin (except diaper area); extensor surfaces
- Young Children: Face, neck, antecubital/popliteal fossae, wrists, ankles
- Adolescents/Adults: Periorbital area, neck, extensor surfaces, antecubital/popliteal fossae, wrists, hands, ankles, feet


Guidelines


Guidelines for assessing and treating AD come from divergent clinical perspectives

AAAAI, American Academy of Allergy, Asthma, and Immunology; ACAAI, American College of Allergy, Asthma, and Immunology; PCPs, primary care providers.
“Yardstick” Guidelines Published in 2018*

- Developed to merge and reconcile differing recommendations from multidisciplinary specialist guidelines
- Incorporates many of the recommendations from the 4-part AAD guidelines
- Emphasis is on practical, step-by-step, “how-to” strategies to ensure clear or almost clear skin from all levels of severity

*Yardstick guidelines available as open access PDF at https://www.annallergy.org/article/S1081-1206(17)31260-7/pdf

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

Serum IgE, patch testing, and/or genetic testing should be done if necessary to rule out differential diagnoses.

Severity Assessments

- Accurate assessment of disease severity important for optimal treatment
- Validated clinical scoring systems 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

IGA, Investigator Global Assessment; ISGA, Investigator Static Global Assessment.

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 1, Part 1: Joshua
Etiology/Pathophysiology and Treatment Approaches

AD Etiology: Altered Epidermal Barrier + Immune Dysregulation

- Pruritus: hallmark of AD
- Chronic inflammatory skin disease

Common presentations:
- Eczematous lesions
- Dry skin due to epidermal barrier dysfunction
- Cycle of itching and scratching
- Cellular damage and secondary infections


AD = Altered Epidermal Barrier + Immune Dysregulation

**Treatment Goals**

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

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**Step-Care Management: Mild AD**

**Mild Management**

1. **Basic Management**
   - **Skin Care**
     - Moisturizer, liberal and frequent
     - Warm baths or showers using non-soap cleansers, usually 1×/day followed by moisturizer (even on clear areas)

2. **Trigger Avoidance**
   - Common allergens and irritants
   - Consider comorbidities
   - Apply TCS to Inflamed Skin
     - Low-to-medium potency TCS 2×/day for 3–7 days beyond clearance
     - Consider TCI, crisaborole

**Non-Lesional Management**

1. **Basic Management**
   - **Skin Care**
     - Moisturizer, liberal and frequent
     - Warm baths or showers using non-soap cleansers, usually 1×/day followed by moisturizer (even on clear areas)

2. **Trigger Avoidance**
   - Common allergens and irritants

**Apply TCS to Inflamed Skin**

(TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.)

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**OTC for Mild AD or Maintenance**

- Daily moisturizing can reduce incidence of flare and overall disease severity
  
- Topical OTC hydrocortisone can temporarily relieve pruritus and inflammation due to mild AD
  
  - Professional medical attention should be sought if symptoms worsen or last >7 days
  
  - Not to be used on children <2 years
  
  - OTC treatments should not contain ingredients known to be AD irritants
    - eg, soaps, detergents, perfumes

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Case Study 1, Part 2: Joshua

- Josh’s physician prescribed a medium-potency TCS
  - Triamcinolone 0.1% ointment 2×/day
- Patient returns 3 weeks later reporting dissatisfaction
  - Says itching has gotten worse
  - Lesions have enlarged and are redder
  - Also says he doesn’t like ointments
- What is your next step in the management of Josh?

Topical Treatments for Mild Disease

<table>
<thead>
<tr>
<th>Corticosteroids</th>
<th>Calcineurin Inhibitors</th>
<th>PDE4 Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>• TCS usually the first line of treatment to reduce local inflammation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Can cause skin atrophy and thinning if used inappropriately (eg, chronic use of high-potency TCS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• No consensus regarding optimal dosing or frequency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• TCA: tacrolimus and pimecrolimus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Nonsteroidal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Approved in 2000–2001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Inhibit calcineurin-dependent T-cell activation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• No risk for skin atrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Use may be impeded by black-box warning about increased risk for malignancy, despite little evidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cisapride</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Nonsteroidal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• FDA approved in 2016</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Inhibits cAMP levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• No data yet on long-term use</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Although any of these classes can be used as initial therapy after diagnosis, many insurance companies require step-wise management with TCS first.

cAMP, cyclic adenosine monophosphate; TCA, Food and Drug Administration; PDE4, phosphodiesterase 4.


TCIs

- Can be applied to face, extremities, and genital area
- Stinging/burning at application site most frequent 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

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

Note: Despite black-box warnings for TCIs, postmarketing registry studies have shown virtually no risk for malignancy.
**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=1522 patients >2 years) with mild-to-moderate AD randomized 2:1 to crisaborole or placebo
- In both studies, crisaborole shown to be more effective than placebo at achieving clear or almost-clear skin
- Stinging/burning at application site most frequent adverse event


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**When to Use Systemic Treatment**

- Many patients effectively managed with topical medications
- If condition warrants 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

**Step-Care Management: Moderate-to-Severe AD**

- **Moderate**
  - Basic Management + Topical Anti-inflammatory Medication
    - Maintenance TCS
      - Low potency 1-2 x/day (including face)
      - Medium potency 1-2 x/day (except face)
    - OR Maintenance TCI
      - 2-3 x/day
    - OR Crisaborole 2%*
      - 2 x/day

- **Severe**
  - Basic Management + Referral to Specialist
    - Phototherapy (not approved for pts under 12 yrs)
    - Dupilumab† (FDA approved on March 11, 2019 for adolescents 12-17; in phase 3 trials for younger pts)
    - Systemic Immunosuppressants
      - Cyclosporine A‡
      - Methotrexate‡
      - Mycophenolate mofetil‡
      - Azathioprine §

*Consider acute treatment for some patients
- Wet-wrap therapy or hospitalization
- Apply TCS to Inflamed Skin
  - Medium-to-high potency TCS 2-5 x/day for 3-7 days beyond clearance (consider TCI, crisaborole)

If not resolved in 7 days, consider nonadherence, misdiagnosis, contact allergy to prescription, referral

*Indicated for patients at least 2 years old. †Indicated for patients at least 12 years old. ‡Not approved by FDA to treat AD. §Not recommended for long-term maintenance.


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**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

**Efficacy in Pruritus**

- Week 16 SOLO 2
- Week 16 SOL 1
- Week 52 phase 3 LIBERTY AD CHRONOS trial
- Week 16 phase 3 LIBERTY AD CHRONOS trial

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

Q2W, every 2 weeks; QW, every week; TCS, topical corticosteroid.


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Notes:
- mAb, monoclonal antibody.
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- mAb, monoclonal antibody.
- Q2W, every 2 weeks; QW, every week; TCS, topical corticosteroid.
**Phase 3 Trial of Dupilumab in Adolescents**

- **First biologic study of AD in ages 12–17 years (NCT03054428)**
  - 251 patients with moderate-to-severe disease not controlled by topicals randomized to dosing every 4 weeks, every 2 weeks, 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

**References**

Effectiveness in QOL Improvements

- *Least squares incorporate percent change over time, primary analysis, and sensitivity analysis.
  - CDLQI, Children’s Dermatology Life Quality Index.
  - EASI, Eczema Area and Severity Index.

Presented September 15, 2018.


CDLQI, Children’s Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EADV, European Academy of Dermatology and Venereology; NRS, numerical rating scale.


P,'%n
- *Efficacy in QOL Improvements*
  - *First biologic study of AD in ages 12–22 years (mean change in DLQI score 16)*
  - Preliminary phase 3 results presented September 2018 at EADV showed statistically significant improvement in skin, QOL by week 16
  - Priority review application submitted to FDA in November for approval in adolescents; approval granted March 11, 2019

**Long-Term Efficacy**

- CHRONOS AD LIBERTY trial: Patients (%) showing sustained improvement over time in pruritus scores with dupilumab plus TCS

Phase 3 Dupilumab Trial in Adolescents: Results

Patients Achieving Trial Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Dupilumab 300 mg Q4W</th>
<th>Dupilumab 200/300 Q2W</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGA</td>
<td>37.9</td>
<td>24.4</td>
<td>17.9</td>
</tr>
<tr>
<td>EASI-75</td>
<td>38.1</td>
<td>41.3</td>
<td>45.5</td>
</tr>
<tr>
<td>Pruritus NRS</td>
<td>46.5</td>
<td>47.9</td>
<td>29.9</td>
</tr>
</tbody>
</table>

Q2W, every 2 weeks; Q4W, every 4 weeks.


Phase 3 Dupilumab Trial in Adolescents: Safety

Most Common Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Dupilumab 300 mg Q4W</th>
<th>Dupilumab 200/300 Q2W</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin Infections</td>
<td>13</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>11</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Injection-Site Reactions</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>


Ongoing/Recruiting Clinical Trials of Dupilumab in Children

<table>
<thead>
<tr>
<th>Trial Name* / Number</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>≥6 mos to &lt;18 yrs</td>
<td>3</td>
<td>October 2023</td>
</tr>
<tr>
<td>NCT03345914</td>
<td>Efficacy and safety of dupilumab with TCS</td>
<td>≥6 mos to &lt;12 yrs</td>
<td>3</td>
<td>April 2019</td>
</tr>
<tr>
<td>LIBERTY AD PRESCCHOOL/ NCT03346434</td>
<td>Safety, PK, &amp; efficacy of dupilumab in severe AD</td>
<td>≥6 mos to &lt;6 yrs</td>
<td>2/3</td>
<td>April 2022</td>
</tr>
</tbody>
</table>

*If applicable.
†Enrolling by invitation.
PK, pharmacokinetics.

Source: ClinicalTrials.gov in late October 2018 using advanced search filters for Child (birth–17); recruiting; enrolling by invitation; active, not recruiting; phase 2, and phase 3.
Considerations in Prescribing Dupilumab

- Cost and coverage important considerations
- Method of administration
  - Subcutaneous injection may be difficult for some
- Increased risk of infection
- Documentation required by insurance
  - Preauthorization almost always required
- Impact of disease on QOL

Biologics and Payers

- Insurance companies will require prior authorization for immunomodulators or biologics
  - Forms and requirements for each company are different
- For insurance to cover, clinicians must document
  - Diagnosis of AD (not just "eczema")
  - Condition severity
  - Prior treatments and failures
    - Specify the type of failure: eg, inadequate response to medium or high-potency TCS, suboptimal improvement, failure to achieve long-term control, unacceptable adverse events
- 2 pharmacoeconomic studies demonstrated cost efficacy of dupilumab in patients with moderate or severe disease

Emerging Biologics and Small-Molecule Agents Being Studied in Adolescents and Adults

<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 2,094 adults and adolescents with moderate-to-severe AD</td>
</tr>
</tbody>
</table>

JAK, Janus kinase inhibitor; SC, subcutaneous.

Nemolizumab in Atopic Dermatitis

- An antibody against interleukin-31 receptor A
- Phase 2 trial reduced pruritus in moderate-to-severe atopic dermatitis
- There is a role of interleukin-31 in the pathophysiology of atopic dermatitis

Case Study 2, Part 1: Amanda
Considerations in Co-management of AD

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 caregivers\(^1\)
- Exacerbating factors/environmental triggers
- Secondary infection
  - Bacterial, viral, dermatophyte
- Hypersensitivity reactions to treatments
- Incorrect diagnosis


Who Should Be Referred to Specialists?

Stepping up from Moderate to Severe AD:
If patient is still symptomatic\(^*\) despite optimal therapy and conservative management, options include the following\(^†\)

- Phototherapy\(^‡\)
- Dupilumab\(^§\)
- Systemic immunosuppressants\(\|^\(\|^\)

\(^*\) Poorly or inadequately controlled signs and symptoms of AD. \(^†\) Before stepping up therapy, patient should be assessed for nonadherence, comorbidities, other factors that could mitigate against treatment response.

\(^‡\) Patient should be willing and able to commit to phototherapy’s cost and understand its limited access.

\(^§\) Indicated for patients ≥18 years with moderate-to-severe AD.

\(\|^\) Most are not approved by FDA to treat AD.

Multidisciplinary Collaboration

- Patients with moderate-to-severe AD are good candidates for multidisciplinary management
  - Incorporating biologic, behavioral, psychological, and nutritional aspects of disease management
- AD specialist expert is most likely to be a dermatologist or allergist
  - PCPs (family physicians as well as NPs or PAs) and pediatricians refer to and work with the specialists to develop treatment plan
  - Other experts include psychologists, nurses, and dietitians

NPs, nurse practitioners, PAs, physician assistants.

Collaborative Decision Making

Expertise
- Healthcare Provider (pediatrician, nurse, NP, PA, other clinicians)
  - Diagnosis
  - Treatment options
  - Potential benefits
  - Potential AEs
  - Treatment expectations

Patient/Caregiver
  - Values
  - Lifestyle preferences (may include schedule, socioeconomic factors)
  - Previous experience

Shared Decision


Shared Decision Making (cont.)

- An integral, patient-centered component of therapeutic education
  - Involves asking open-ended questions to assess patient’s/caregiver’s level of knowledge
  - Works best in chronic diseases for which there is no one “best” treatment
  - Recognizes importance of patient’s/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 (eg, ointments vs creams), texture/thickness, smell
  - Costs are important to patients/caregivers; offering options of different expense levels is helpful

Summary
- AD an inflammatory disease involving immune dysregulation and epidermal barrier breakdown
- Disease negatively affects QOL of children and adults, as well as their family members
- Diagnosis based on clinical presentation
- AD associated with multiple comorbidities — even later in life
- Severity assessments are necessary to determine treatment

Summary
- 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!