The Evolving Role of Systemic Therapies in the Management of **Atopic Dermatitis:**

Key Principles in Patient Care and Education

WEDNESDAY, DECEMBER 16, 2020 | 6:00 PM – 7:15 PM CT

FACULTY | Peter Lio, MD and Jonathan I. Silverberg, MD, PhD, MPH

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This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).
This activity is supported by an educational grant from Sanofi Genzyme and Regeneron Pharmaceuticals, Inc.

The Evolving Role of Systemic Therapies in the Management of Atopic Dermatitis: Key Principles in Patient Care and Education

FACULTY

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PROGRAM OVERVIEW

This live virtual activity will review evidence-based approaches to the diagnosis and management of atopic dermatitis (AD), in addition to associated quality of life issues and adverse events associated with disease and treatment.

TARGET AUDIENCE

This activity is intended for pediatricians, dermatologists, pediatric dermatologists, primary care physicians, and other healthcare professionals involved in the management of pediatric and adolescent patients with atopic dermatitis.

LEARNING OBJECTIVES

Upon the completion of this program, attendees should be able to:

- Apply evidence-based approaches to diagnose, assess, and manage moderate-to-severe atopic dermatitis in pediatric and adolescent patients
- Assess the physical, psychosocial, and developmental impact of atopic dermatitis on patients' quality of life when selecting therapy options and evaluating therapeutic outcomes
- Recognize and manage the adverse events associated with systemic and topical therapies for the management of atopic dermatitis in pediatric and adolescent patients

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Purpose: This program would be beneficial for nurses involved in the care of pediatric and adolescent patients with atopic dermatitis. Credits: 1.25 ANCC Contact Hours.

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Jonathan I. Silverberg, MD, PhD, MPH is consultant and/or advisory board member for Abbvie, Afyx, Arena, Asana, Bluefin, Boehringer-Ingelheim, Celgene, Dermavant, Dermira, Eli Lilly, Galderma, GlaxoSmithKline, Incyte, Kiniksa, Leo, Luna, Menlo, Novartis, Pfizer, RAPT, Regeneron, Sanofi, and is on the speaker's bureau for Sanofi-Regeneron.

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The Evolving Role of Systemic Therapies in the Management of **Atopic Dermatitis**:

KEY PRINCIPLES IN PATIENT CARE AND EDUCATION

Agenda

I. Atopic Dermatitis (AD): Features and Impact

a. Features/definition of AD
b. Impact on psychosocial function/quality of life
c. Associated morbidities
d. Pathogenesis: the inflammatory loop
e. Animated theme – pathogenesis of AD

II. Evaluation and Diagnosis

a. The AD phenotype
b. Clinical diagnosis and diagnostic features
c. Classic distribution across ages
d. Phenotypic mimics
e. Other considerations: skin infections, food allergies
f. Brief Q/A

III. AD and Clinical Management

a. Disease issues vs. management issues
b. Standard treatment strategies: the 5 I's
c. Assessment of disease severity
d. Guideline based stepped therapy
e. Emollients/topicals for mild disease

IV. New and Targeted Therapy

a. Conventional systemic treatment algorithm
b. Animated theme – mechanism of action of available agents for the management of AD
c. Efficacy and safety of systemic agents (e.g., dupilumab)
d. Efficacy and safety of emerging agents (e.g., lebrikizumab, tralokinumab, JAK inhibitors)
e. Case study
f. Conclusions

V. Questions and Answer

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Disclosures

- **Peter Lio, MD** has served on the advisory board for the National Eczema Association, Modernizing Medicine, Johnson & Johnson, DermTap Inc., IntraDerm Pharmaceuticals, Regeneron, Sanofi US Services, Realm Therapeutics, Menlo Therapeutics, Syncere Skin Systems, DermVeda, GPower Inc., UCB, Altus Labs, Dermavant Sciences, Micreos Human Health B.V., Verrica Pharmaceuticals Inc., Arbonne, Yobee Care Inc., and Bodewell. Dr. Lio is a stockholder in Modernizing Medicine, LearnHealth/LearnSkin, and Medable. He has been a speaker for Pierre Fabre Dermatologie, Regeneron, Pfizer, and La Roche-Posay. He has been an investigator for La Fondation pour la Dermatite Atopique (Foundation for Atopic Dermatitis), AOBiome LLC, Regeneron, AbbVie, and National Eczema Association. He has been a consultant for Exeltis, Therplex, Odeza LLC, L'Oreal USA Inc., Franklin BioScience, AbbVie, Kiniksa Pharmaceuticals, Eli Lilly and Co., Unilever, Dermira, TopMD, Amyris Inc., Leo Pharma, and Burt's Bees.

During the course of this lecture, use of medications for both FDA-approved and non-approved indications may be discussed.

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- Jonathan Silverberg, MD, PhD, MPH, reports the following:

Relationship	Manufacturer
Consultant	Abbvie, Afyx, Arena, Asana, Bluefin, Boehringer-Ingelheim, Celgene, Dermavant, Dermira, Eli Lilly, Galderma, GlaxoSmithKline, Incyte, Kiniksa, Leo, Luna, Menlo, Novartis, Pfizer, RAPT, Regeneron, Sanofi
Speakers' Bureau	Regeneron, Sanofi
Research Funding	Galderma

During the course of this lecture, use of medications for both FDA-approved and non-approved indications may be discussed.

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Learning Objectives

- Apply evidence-based approaches to diagnose, assess, and manage moderate-to severe atopic dermatitis in pediatric and adolescent patients
- Assess the physical, psychosocial, and developmental impact of atopic dermatitis on patients' quality of life when selecting therapy options and evaluating therapeutic outcomes
- Recognize and manage the adverse events associated with systemic and topical therapies for the management of atopic dermatitis in pediatric and adolescent patients

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Features and Impact

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Features of Atopic Dermatitis (AD)

AD is a chronic, pruritic, inflammatory skin disease that typically involves:

- Childhood onset
- Familial occurrence
- Eczematous change
  - erythema
  - induration, papulation
  - excoriation
  - lichenification
- Characteristic distribution
- Intermittent flares
- Associated skin conditions (minor diagnostic criteria)
- Skin infections
- Associated morbidities

Siegfried EC, Hebert AA. *J Clin Med.* 2015;4:884-917. Ring J, et al. *J Eur Acad Dermatol Venereol.* 2012;26:1045-1060.

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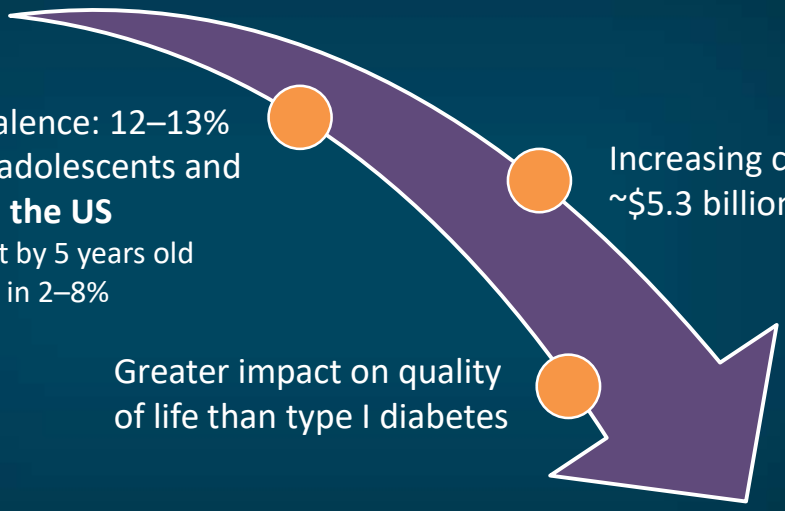
Impact of AD



Increasing prevalence: 12–13% in children and adolescents and >7% in adults in **the US**

- 85% present by 5 years old
- Adult-onset in 2–8%

Increasing costs: ~$5.3 billion/year

Greater impact on quality of life than type I diabetes

Silverberg JI. *Ann Allergy Asthma Immunol.* 2019;123:144-151. Silverberg JI, et al. *Ann Allergy Asthma Immunol.* 2018;121:340-347. Drucker AM, et al. *J Invest Dermatol.* 2017;137:26-30. Arkwright PD, et al. *J Allergy Clin Immunol Pract.* 2013;1:142-151.

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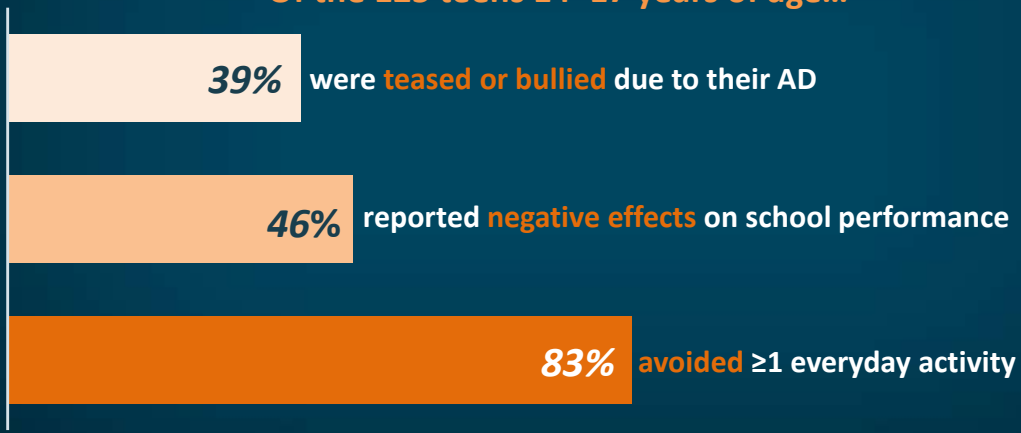
Impact of Psychosocial Function

Phone interviews in 8 countries with 2002 adolescents and adults with moderate-to-severe AD

Of the 125 teens 14–17 years of age…



39% were teased or bullied due to their AD

46% reported negative effects on school performance

83% avoided ≥1 everyday activity

Zuberbier T, et al. *J Allergy Clin Immunol.* 2006;118:226-232.

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Impact on Quality-of-Life

- Consequences of ***sleep deprivation***
  - Exhaustion
  - Mood changes
  - Impaired psychosocial functioning
- Consequences of ***social isolation***
  - School avoidance
  - Depression
- **Restricted** lifestyle choices
  - Clothing, holidays, socializing, owning pets, participating in sports

Lewis-Jones S. *Int J Clin Pract.* 2006;60:984-992.

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Associated Morbidities

Atopic	Others[1,2,6,7]
• **Allergic rhinitis** (~50% prevalence)[1]	• **Mental/behavioral health**
• **Allergic conjunctivitis**[2]	• **Skin infections**
• **Asthma** (~22–30% prevalence)[1,3,4]	• **Allergic contact dermatitis**
• **Primary eosinophilic gastrointestinal disorders**[2]	• **Immune deficiency**
• **Food allergy**[5]	• **Cataracts**

1. Whiteley J, et al. *Curr Med Res Opin.* 2016;32:1645-1651. 2. Silverberg JI. *Cutis.* 2019;104:142-143. 3. Silverberg JI, Hanifin JM. *J Allergy Clin Immunol.* 2013;132:1132-1138. 4. Wang D, Beck LA. *Am J Clin Dermatol.* 2016;17:425-443. 5. Greenhawt M. *Allergy Asthma Proc.* 2010;31:392-297. 6. Silverberg NB. *Cutis.* 2016;97:408-412. 7. De Benedetto A, et al. *J Invest Dermatol.* 2009;129:14-30.

15

Pathogenesis

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Video Presentation

We will now watch a brief animation exploring the pathophysiology of atopic dermatitis

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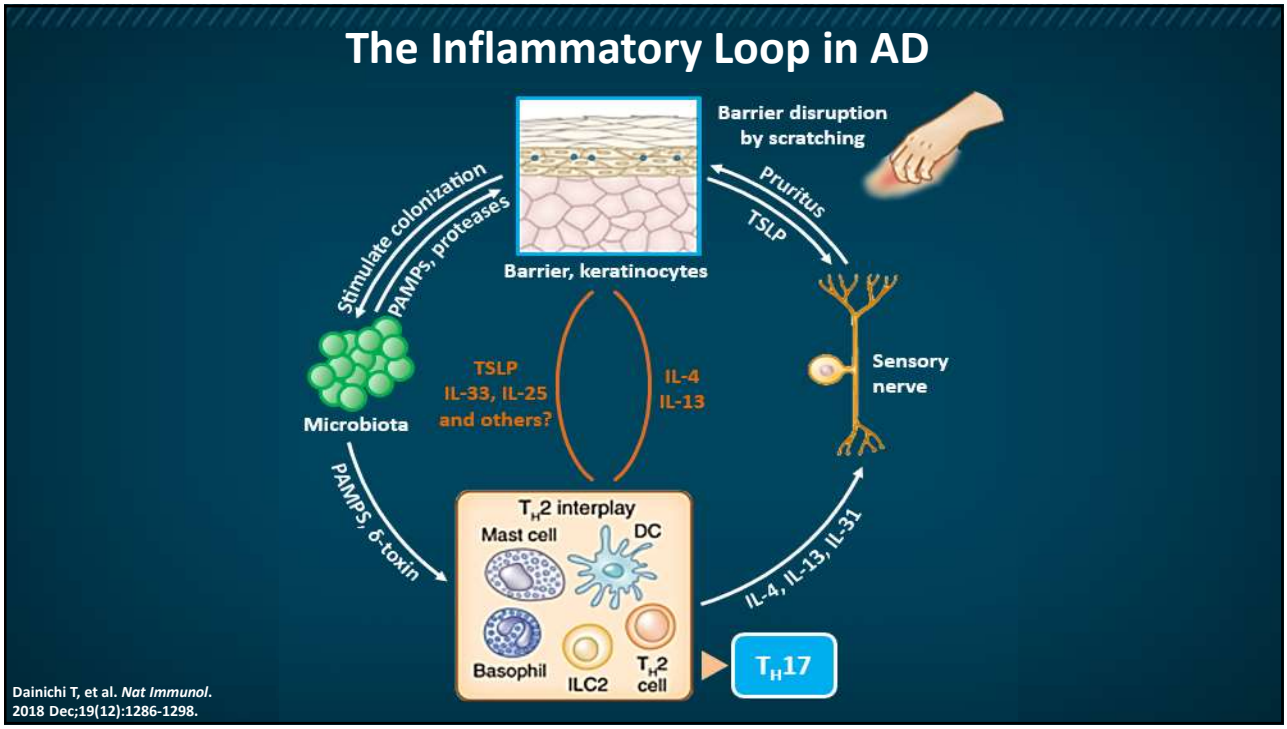

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Evaluation and Diagnosis

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Dermatitis Is a Phenotype

Characteristics

- Itch
- Skin lesions: poorly circumscribed erythema and induration with fine scale
  - Acute: edema/vesicles; quickly reversible
  - Subacute
  - Chronic: lichenification; persistent
- Histology
  - Epidermis: spongiosis, parakeratosis
  - Dermis: superficial perivascular infiltrate (lymphocytes/histiocytes > neutrophils/eosinophils)

Krafchik B. Atopic dermatitis. *Pediatric Dermatology.* 4th edition. 2011, Elsevier.

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AD Is the Most Common Chronic Eczema in Children

- **Defined diagnostic criteria**
  - Hanifin and Rajka criteria
  - UK Working Party
    - Family history of atopy, eczema, asthma, allergies
    - Early age of onset
    - Itching
- **Features**
  - Eczematous morphology
  - Distribution
  - Associated cutaneous conditions
  - Associated morbidities
  - Beware phenotypic mimics

UK = United Kingdom.

Eichenfield LF, et al. *J Am Acad Dermatol*. 2014;70:338-351. Bradby C. *Medscape*. 2019. (www.medscape.com/answers/762045-171176/what-are-the-hanifin-and-rajka-diagnostic-criteria-for-atopic-dermatitis-ad). Accessed 8/1/2020. Siegfried EC, Hebert AA. *J Clin Med*. 2015;4:884-917.

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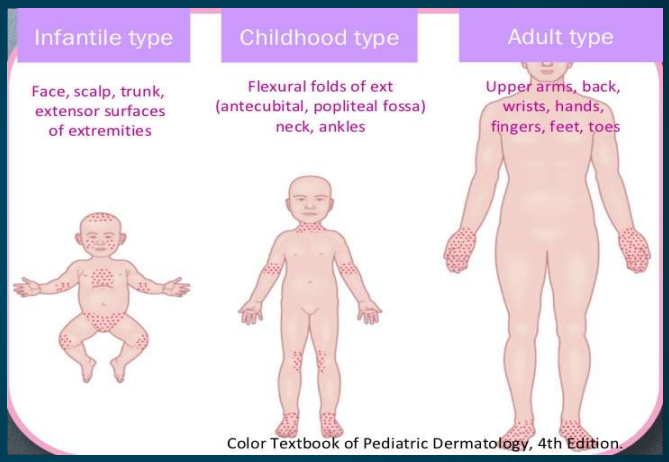
Atopic Dermatitis: Diagnosis

Clinical diagnosis

- Historical features
- Distribution and morphology of skin lesions
- Associated clinical signs



Eichenfield LF et al. *J Am Acad Dermatol.* 2014;70:338-351. Napolitano M et al. *G Ital Dermatol Venereol.* 2016;151:403-411. Kulthanan K et al. *Asian Pac J Allergy Immunol.* 2011;29:318-326.

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Atopic Dermatitis: Diagnosis Features

Features to be considered in diagnosing patients with AD

- **ESSENTIAL FEATURES**; must be present:
  - Pruritus
  - Eczema (acute, subacute, chronic):
    - Typical morphology and age-specific patterns*
    - Chronic or relapsing history

  Patterns include:
  1) facial, neck, and extensor involvement in infants and children;
  2) current or prior flexural lesions in any age group;
  3) sparing of groin and axillary regions.

- **IMPORTANT FEATURES**; seen in most cases, adding support to the diagnosis:
  - Early age of onset
  - Atopy
    - Personal and/or family history
    - IgE reactivity
  - Xerosis

- **ASSOCIATED FEATURES** ; these clinical associations help to suggest the diagnosis of AD but are too non-specific to be used for defining or detecting AD for research and epidemiologic studies:
  - Atypical vascular responses (e.g., facial pallor, white dermographism, delayed blanch response)
  - Keratosis pilaris / pityriasis alba / hyperlinear palms / ichthyosis
  - Ocular / periorbital changes
  - Other regional findings (e.g., perioral changes / periauricular lesions)
  - Perifollicular accentuation / lichenification / prurigo lesions

- **EXCLUSIONARY CONDITIONS;** it should be noted that a diagnosis of AD depends on excluding conditions such as:
  - scabies
  - seborrheic dermatitis
  - contact dermatitis (irritant or allergic)
  - ichthyoses
  - cutaneous T-cell lymphoma
  - psoriasis
  - photosensitivity dermatoses
  - immune deficiency diseases
  - erythroderma of other causes

Eichenfield LF et al. *J Am Acad Dermatol.* 2003;49:1088-1095. Eichenfield LF et al. *J Am Acad Dermatol.* 2014;70:338-351.

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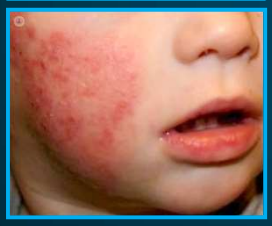
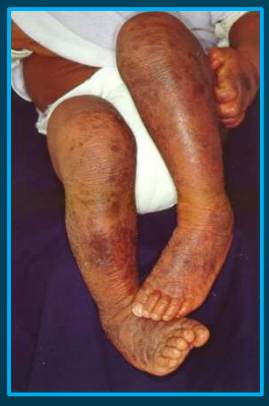
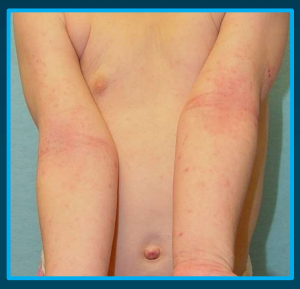
Classic AD Distribution Changes with Age

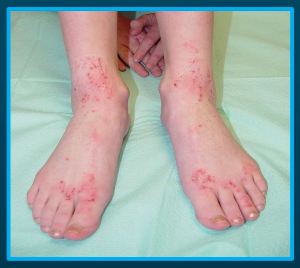
Infants: face, extensor extremities

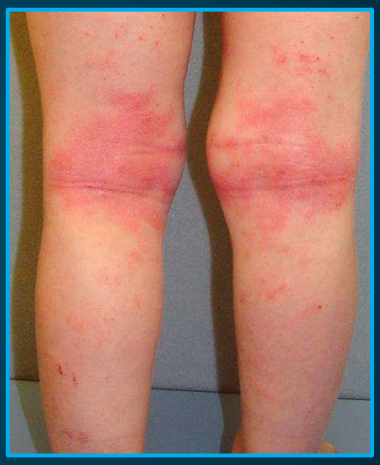
Children: wrists, ankles, antecubital and popliteal fossae











AD across lifespan (https://atopicdermatitis.net/across-lifespan/). Accessed 8/1/2020.

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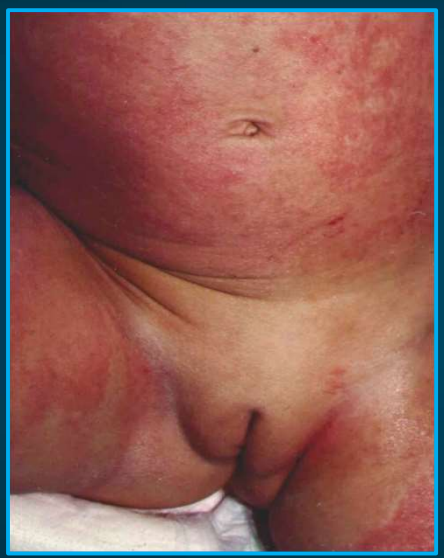
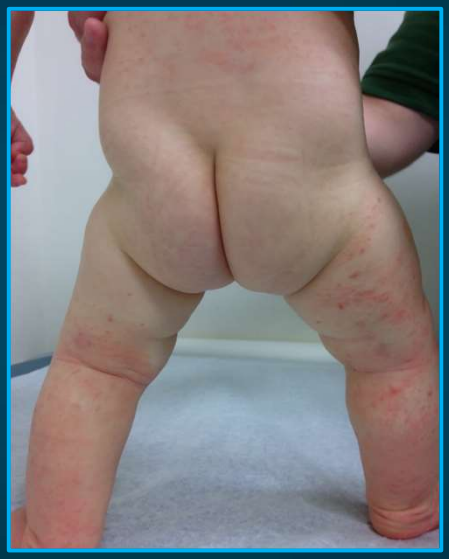
Diaper-Area Sparing: a Diaper and Therapeutic Feature





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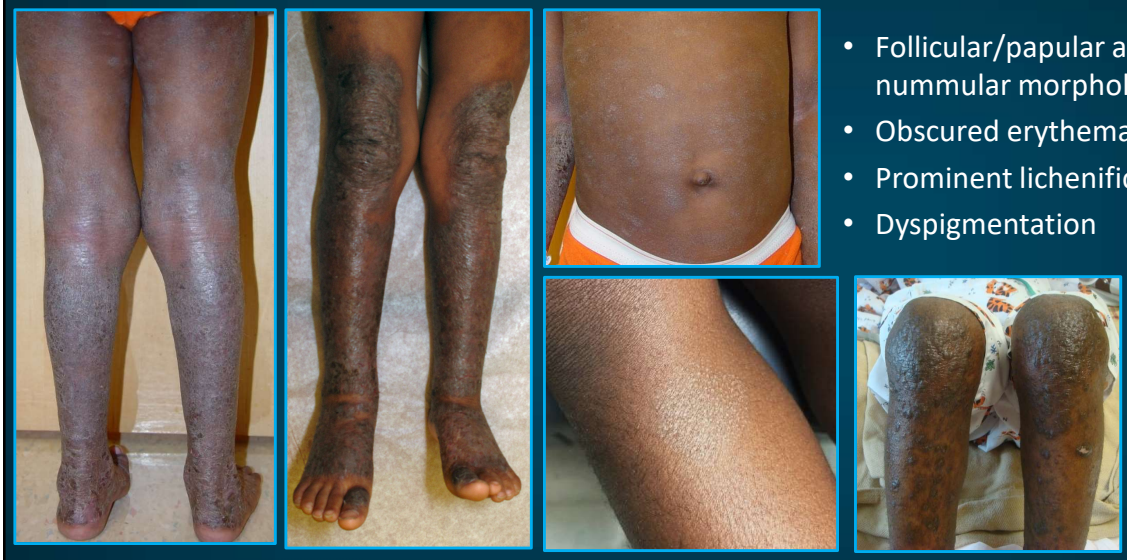
More Common Features in Skin of Color



- Follicular/papular and nummular morphology
- Obscured erythema
- Prominent lichenification
- Dyspigmentation

Boguniewicz M, et al. *J Allergy Clin Immunol Pract.* 2017;5:1519-1531. Poladian K, et al. *Cutis.* 2019;104:164-168. Siegfried EC, Hebert AA. *J Clin Med.* 2015;4:884-917.

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Phenotypic Mimics

Otherwise healthy

- **Pityriasis alba**
- **Keratosis pilaris**
- **Ichthyosis vulgaris**
- Lichen simplex chronicus
- Contact dermatitis
- Psoriasiform overlap
- Seborrheic dermatitis
- Tinea
- Scabies

Unhealthy

- Immune deficiencies
- Nutritional deficiencies
- Cutaneous T-cell lymphoma (CTCL)
- Genodermatoses

Siegfried EC, Hebert AA. *J Clin Med.* 2015;4:884-917. Wine SJ, Steinberg S. *Can Fam Physician.* 1972;18:65-66. Purohit MP. Lichen simplex chronicus. *DoveMed.* 2018 (www.dovemed.com/diseases-conditions/lichen-simplex-chronicus/). Fields D. *NEWS Medical.* 2019 (www.news-medical.net/health/Types-of-Genodermatoses.aspx). All URLs accessed 8/1/2020.

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Recognizing Skin Infections

- Requires a high index of suspicion
- History, family history, and clinical findings are supportive
- Laboratory confirmation (variable sensitivity)
  - Fungal: skin and scalp reservoir swab + pulled hairs, nail clippings
  - HSV: skin scraping on ice for PCR, viral culture; serology
  - Coxsackie: nasal swab for PCR
  - Strep: skin and throat reservoir swab for culture (*Staph aureus* is a colonizer)
  - Skin biopsy
- Cutaneous HSV and group A Streptococcal coinfection can occur
- Impact: avoid unnecessary treatment, prevent complications

Goodyear H. *Paediatr Child Health.* 2015;25:72-77. Lyons JJ, et al. *Immunol Allergy Clin North Am.* 2015;35:161-183.

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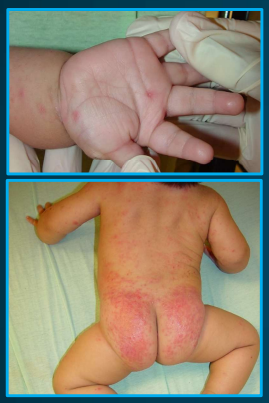
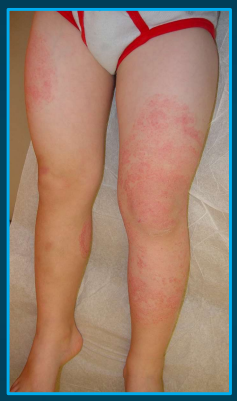
Common Skin Infections in AD

Scabies



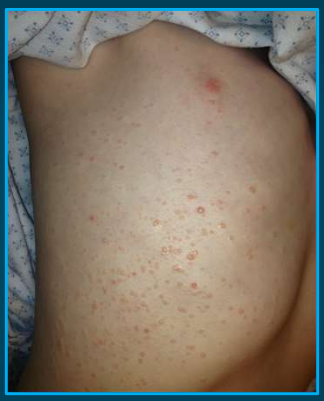
Webspace and palmoplantar lesions

Tinea



Scaly plaques with border accentuation

Molluscum



Pearly dome-shaped papules with central umbilication

Herpes simplex

Grouped vesicles and punched-out erosions

Paul D, Papier A. *J Fam Pract.* 2020;69:10-17. Bhagavatula M, Powell C. *Paediatr Child Health.* 2011;21:132-136. Siegfried EC, Hebert AA. *J Clin Med.* 2015;4:884-917.

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Atopic Dermatitis and Food Allergies

- Many families feel that this is a "root cause"
- Good data that excluding foods in unselected patients offers no benefit
- This also suggests that non-allergic mechanisms probably play little or no role

Gelmetti C. *J Eur Acad Dermatol Venereol*. 2000;14:439–40. Bath-Hextall F, et al. *Allergy*. 2009;64:258–64.

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AD and Food Allergy

- The ***prevalence*** of food allergy is higher in children with moderate-to-severe AD (~30%)
- The ***role*** of food allergens in the pathogenesis of AD is unclear
- The association between AD and food allergy is complex and is a common source of conflicting therapeutic recommendations

Diagnosis	Clinical signs and symptoms	Most common, relevant food allergens in atopic children
Clinically confirmed signs and symptoms after food exposure PLUS Laboratory evidence of sensitization (Diagnostic criteria not well established)	Range from transient/self limited to anaphylaxis Life-threatening reactions are rare Risk not predicted by initial presentation, laboratory parameters, or increasing clinical concern	Cow's milk Egg Wheat Soy Tree nut/peanut

Boyce JA, et al. *J Allergy Clin Immunol.* 2010;126:S1-S58. Heratizadeh A, et al. *Curr Allergy Asthma Rep.* 2011;11:284-291. Mehta H, et al. *Curr Opin Allergy Clin Immunol.* 2013;13:275-279. Akuete K, et al. *Ann Allergy Asthma Immunol.* 2017;119:339-348.e1. National Institute of Allergy and Infectious Diseases (NIAID). Guidelines for diagnosis and management of food allergy in US. 2011 (www.niaid.nih.gov/sites/default/files/faguidelinespatient.pdf). Schneider Chafen JJ, et al. *JAMA.* 2010;303:1848-1856. Järvinen KM, et al. *J Allergy Clin Immunol.* 2009;124:1267-1272.

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Questions So Far?

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Management

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Disease Issues

- AD is a *chronic disease* with episodic flares
- There is **no cure;** the goal of treatment is to maintain control
- Early and consistent disease control may minimize long-term atopy risk

Johns Hopkins Medicine. Eczema. (https://www.hopkinsmedicine.org/health/conditions-and-diseases/eczema). Accessed August 26, 2020. Tollefson MM, Bruckner AL. *Pediatrics.* 2014;134:e1735-e1744.

35

Management Issues

Variables impacting treatment choice

- Patient preference and ability
- Safety and efficacy
- Cost and access
- Comorbidities

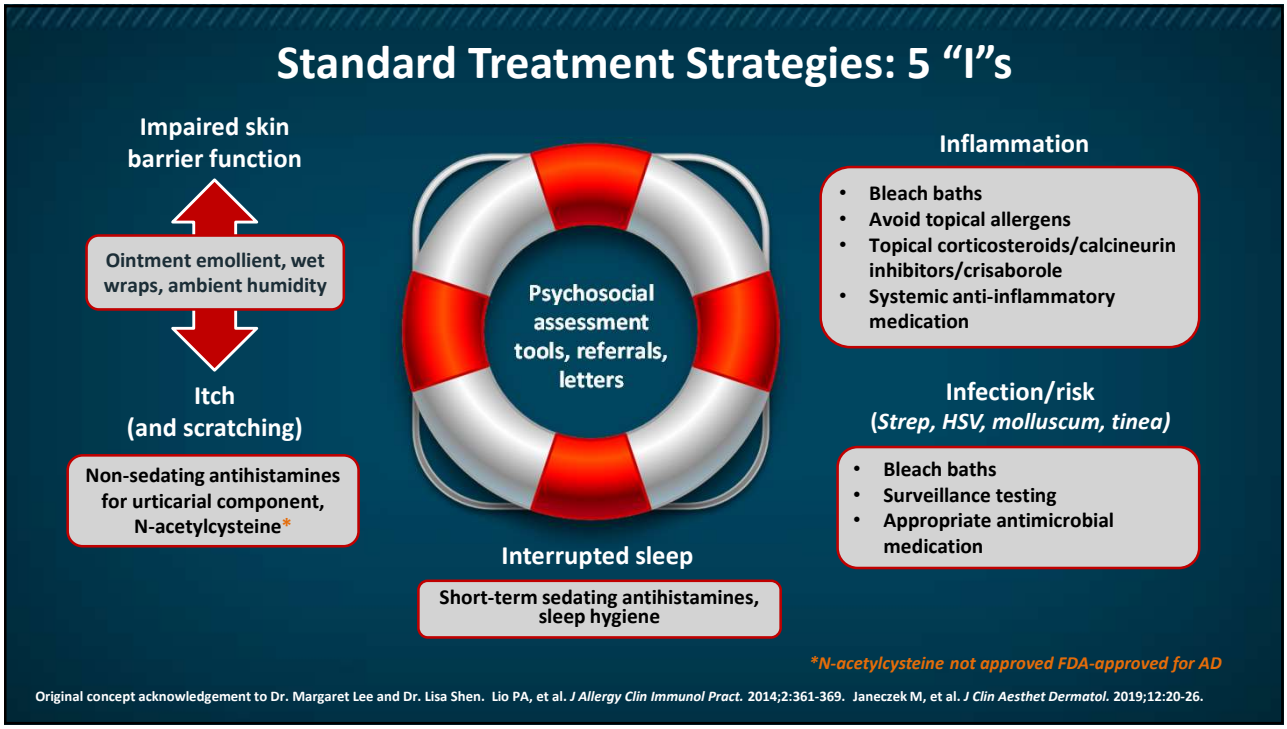
Therapeutic goals

- To reduce symptoms, prevent exacerbations and minimize therapeutic risks
- Prolonged remission and infrequent flares
  - Improved adherence through affordable, easy-to-use and effective regimen
  - Resultant improved quality of life, including restful sleep and undisturbed activities of daily living

Retzler J, et al. *Qual Life Res.* 2019;28:2373-2381. Tollefson MM, Bruckner AL. *Pediatrics.* 2014;134:e1735-e1744. Weston WL, Howe W. Treatment of atopic dermatitis. 2020 (https://www.uptodate.com/contents/treatment-of-atopic-dermatitis-eczema). Accessed August 26, 2020. Avena-Woods C. *AJMC.* 2017 (https://www.ajmc.com/view/overview-of-atopic-dermatitis-article). Accessed August 26, 2020.

36

Standard Treatment Strategies: 5 "I"s



*N-acetylcysteine not approved FDA-approved for AD

Original concept acknowledgement to Dr. Margaret Lee and Dr. Lisa Shen. Lio PA, et al. *J Allergy Clin Immunol Pract.* 2014;2:361-369. Janeczek M, et al. *J Clin Aesthet Dermatol.* 2019;12:20-26.

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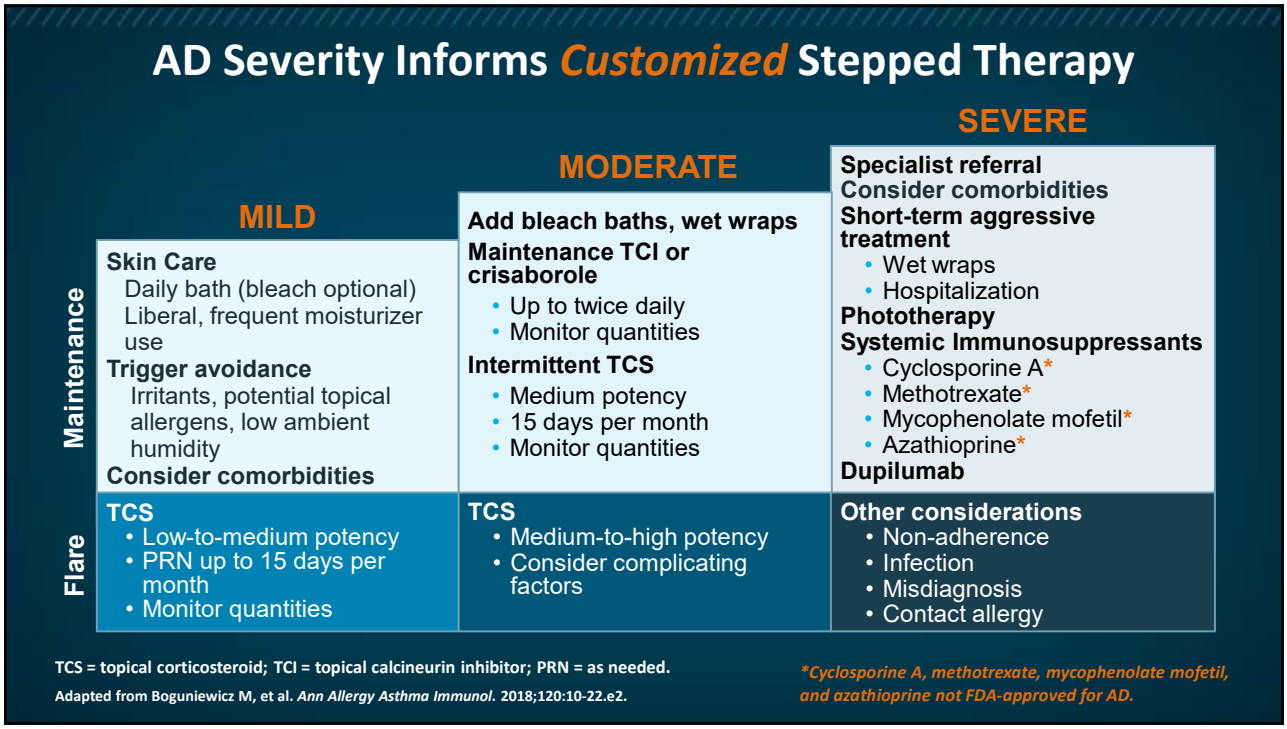
Assessment of Disease Severity

- Validated AD-specific severity scales
  - **SCORAD** (**SCOR**ing **A**topic **D**ermatitis index): includes extent, sleep, and itch
  - **EASI**—**E**czema **A**rea and **S**everity **I**ndex: includes extent
  - **IGA**—**I**nvestigator's **G**lobal **A**ssessment: simple 0–5 point scale
- Modified forms used in clinical trials
- SCORAD and EASI are too cumbersome for clinical practice
- IGA is simple, useful, and may be required for insurance authorization

Siegfried EC, et al. *Pediatr Dermatol.* 2018;35:303-322. Chopra R, et al. *Br J Dermatol.* 2017;177:1316-1321. Brunk D. *Dermatol News.* 2020 (www.mdedge.com/dermatology/article/220713/atopic-dermatitis/expert-discusses-her-approach-using-systemic-agents). Accessed 8/1/2020. Silverberg JI, et al. *Br J Dermatol.* 2019;181:80-87.

38

AD Severity Informs *Customized* Stepped Therapy



TCS = topical corticosteroid; TCI = topical calcineurin inhibitor; PRN = as needed.

Adapted from Boguniewicz M, et al. *Ann Allergy Asthma Immunol.* 2018;120:10-22.e2.

**Cyclosporine A, methotrexate, mycophenolate mofetil, and azathioprine not FDA-approved for AD.*

39

Atopic Dermatitis: Current Treatment Options

Considerations for Treatment

- Majority of patients with mild AD can expect to obtain clinical improvement and disease control with use of emollients, conventional topical therapies (TCS and/or TCI), and environmental and/or occupational modifications, when necessary.1
- These interventions may not be sufficient for patients with moderate-to-severe or difficult-to-control disease.

Sidbury R et al. *J Am Acad Dermatol.* 2014;71:327-349. Wollenberg A et al. *J Eur Acad Dermatol Venereol.* 2016;30:729-747. Saeki H et al. *J Dermatol.* 2016;43:1117-1145.

40

Emollient Options

- Affordability
- Tactile acceptance
- Low allergenicity
- Options
  - Non-allergenic: plain petroleum jelly, plain mineral oil (beware tocopherol), Vanicream™ Moisturizing Ointment (formerly Vaniply™ Ointment)
  - Physiologic lipids (eg, CeraVe®, EpiCeram®); equimolar ratio of ceramides, cholesterol, fatty acids for benefit
  - pH <5 (A-Mantle™)
  - Colloidal oatmeal (Aveeno®)
  - Prescription skin-barrier devices (Hylatopic ®, Mimyx ®, Atopiclair ®)
- Wet wraps

Elias PM, et al. *Skin Pharmacol Physiol.* 2019;32:1-7. Dhandha MM, Siegfried EC. *Skin.* 2017;1:48-51 (www.jofskin.org/index.php/skin/article/download/4/pdf). URLs accessed 8/1/2020. Cincinnati Childrens. (https://www.cincinnatichildrens.org/health/e/eczema). Accessed August 25, 2020.

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Safe and Effective Use of Topical Medications in Children

How much, how often, how to monitor?

**Refer to individual medication PI for approved indications and guidelines for treatment*

Medication	Quantity	Frequency	Possible Safety Monitoring	Prescribing Guideline
Corticosteroids*	15–60 gm/mo (based on age/body site/potency)	15 days/mo	AM cortisol	Potency and age group specific
Calcineurin inhibitors*	100–200 gm/mo; Supplied in 30–100 gm tubes	BID	Tacrolimus peak	≥2 years
PDE-4 inhibitors*	100–200 gm/mo; Supplied in 60–100 gm tubes	BID	—	≥3 months

mo = month(s); BID = twice daily; AM = morning; PDE-4 = phosphodiesterase-4.

See individual PIs for prescribing information. Carr WW. *Paediatr Drugs.* 2013;15:303-310. Eichenfield LF, et al. *J Am Acad Dermatol.* 2014;71:116-132. Schwartz RA. Pediatric atopic dermatitis medication. 2020 (https://emedicine.medscape.com/article/911574-medication). Accessed 8/4/2020. Pharmacist's Letter. (http://snapaprn.org/docs/SNAP%20Comparison%20of%20Topical%20Steroids.pdf). Accessed August 25, 2020. National Eczema Society. https://eczema.org/wp-content/uploads/Topical-steroids-Sep-19-1.pdf). Accessed August 25, 2020.

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Adherence

- The ***most important contributory factor*** to successful treatment
- Barriers
  - Time constraints
  - Unclear or difficult-to-follow instructions
  - Medication phobia
  - Cost/access
- Confirming medication use will inform therapeutic response

Strategies for Improvement

- **Consistent messaging across providers**
- **Frequent follow-up visits**
- **Patient/parent education**
- **Giving specific skin care instructions**
- **Prescribing adequate quantities**
- **Monitoring of medication use**
- **Electronic reminders, eg, email, text messages**
- **Experience positive outcomes**

Bass AM, et al. *J Clin Med.* 2015;4:231-242. Snyder A, et al. *Cutis.* 2015;96:397-401. Ellis RM, et al. *Pediatr Dermatol.* 2011;28:242-244. Smith SD, et al. *Med J Aust.* 2013;199:467-469. Shi VY, et al. *JAMA Dermatol.* 2013;149:481-483. Pena-Robichaux V, et al. *Dermatol Res Pract.* 2010;2010. Pérez-Jover V, et al. *J Med Internet Res.* 2019;21:e12505.

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Optimizing Long-Term Control

Address only intermittent flares

Prescription antibiotics, potent TCS, and prednisone

Yields alternating roller-coaster improvement and flares

Practice daily skin care

Use adequate amounts of topical medication

Recognize and avoid triggers

Maintains control

Wollenberg A, et al. *J Eur Acad Dermatol Venereol.* 2016;30:729-747. Torrelo A, et al. *Actas Dermosifiliogr.* 2013;104:409-417. Thaci D, et al. *J Eur Acad Dermatol Venereol.* 2010;24:1040-1046. Sidbury R, et al. *J Am Acad Dermatol.* 2014;71:1218-1233.

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New and Targeted Therapy

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Video Presentation

We will now watch a brief animation describing the mechanisms of action of approved and emerging therapies in AD

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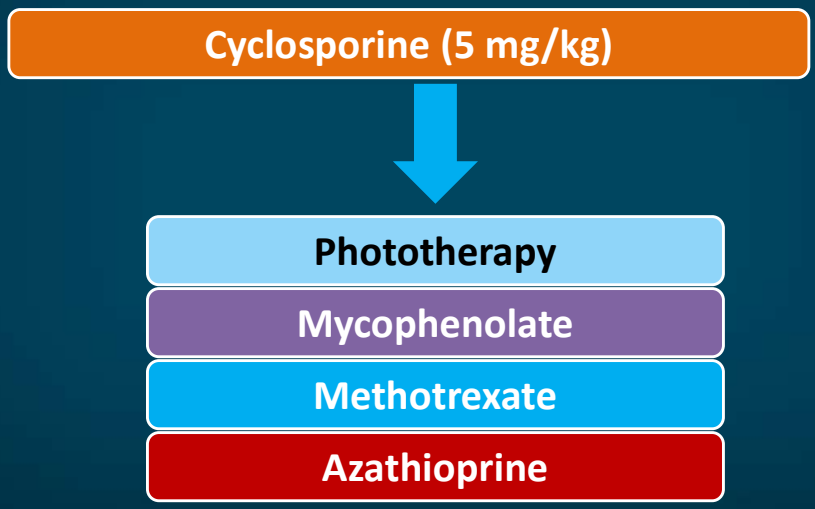
Conventional Systemic Treatment Algorithm



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Discontinuation Rates of Immunosuppressives

	CsA (N = 356) (at 6-year follow-up)[1]	AZA (N = 94) (at 3-year follow-up)[2]	MTX (N = 89) (at 2-year follow-up)[3]	EC-MPS (N = 84) (at 3-year follow-up)[2]
Adverse Event	22%	36%	25%	14%
Inefficacy	16%	19%	15%	38%
Controlled AD	26%	11%	6%	11%
Other Reasons	11%	6%	7%	4%

CsA = cyclosporine A; AZA = azathioprine; MTX = methotrexate; EC-MPS = enteric-coated mycophenolate sodium.

1. van der Schaft J, et al. *Br J Dermatol.* 2015;172(6):1621-1627. 2. van der Schaft J, et al. *Br J Dermatol.* 2016;175(1):199-202. 3. Politiek K, et al. *Br J Dermatol.* 2016;174(1):201-203.

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Dupilumab

- A human monoclonal antibody against IL-4 receptor alpha
- Inhibits signaling of IL-4 and IL-13
- FDA-approved for moderate-to-severe AD in adults in March 2017, for ≥12 years in 2019, and for ≥6 years in 2020
- Also FDA-approved for moderate-to-severe eosinophilic asthma (≥12 years) and for add-on maintenance therapy for CRSwNP (adults)
- Subcutaneous (SC) injection every 2 weeks

CRSwNP = chronic rhinosinusitis with nasal polyposis.

Dupilumab (Dupixent®) PI 2020 (https://www.regeneron.com/sites/default/files/Dupixent_FPI.pdf). Press release 5.26.20 (https://www.prnewswire.com/news-releases/fda-approves-dupixent-dupilumab-as-first-biologic-medicine-for-children-aged-6-to-11-years-with-moderate-to-severe-atopic-dermatitis-301065273.html).

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Dupilumab: Clinical Trials in Pediatric Patients

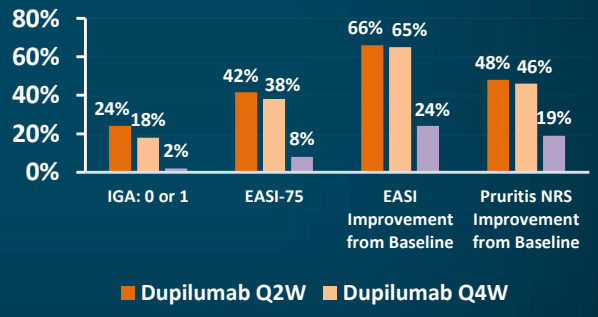
Completed Pediatric Trials

Phase 3 Trial (May 2018)[1]
- 16-week trial in 251 patients aged 12 to 17 yrs
- Dupilumab 200 or 300 mg every 2 weeks (Q2W)
- Dupilumab 300 mg every 4 weeks (Q4W)
- Placebo

Phase 2 Trial (March 2017)[2]
- 12-week trial of 78 patients aged 6-17 yrs who failed prior therapy
- 63% to 76% improvement in Eczema Area and Severity Index (EASI) from baseline
- 31% to 42% improvement in itch from baseline

Additional Trials
- Case series (6 patients; 7-15 yrs): efficacy/safety over 8.5 months[3]
- Phase 3 trial (6 mo-17 yrs): Enrolling
- Phase 2 and 3 (6 mo-6 yrs): Enrolling

Dupilumab vs Placebo: Clinical Endpoints



All *P*<.001 vs placebo; NRS = Numeric Rating Scale

Dupilumab is FDA-approved for moderate-to-severe AD in patients ages 12 yrs and older.

1. Press Release 9.15.2018 (https://newsroom.regeneron.com/news-releases/news-release-details/positive-phase-3-trial-dupixentr-dupilumab-adolescents). 2. MDedge Pediatrics (https://www.mdedge.com/pediatrics/article/133798/atopic-dermatitis/dupilumab-improved-eczema-scores-children-open-label). 3. Treister AD, et al. *Pediatr Dermatol.* 2019;36(1):85-88.

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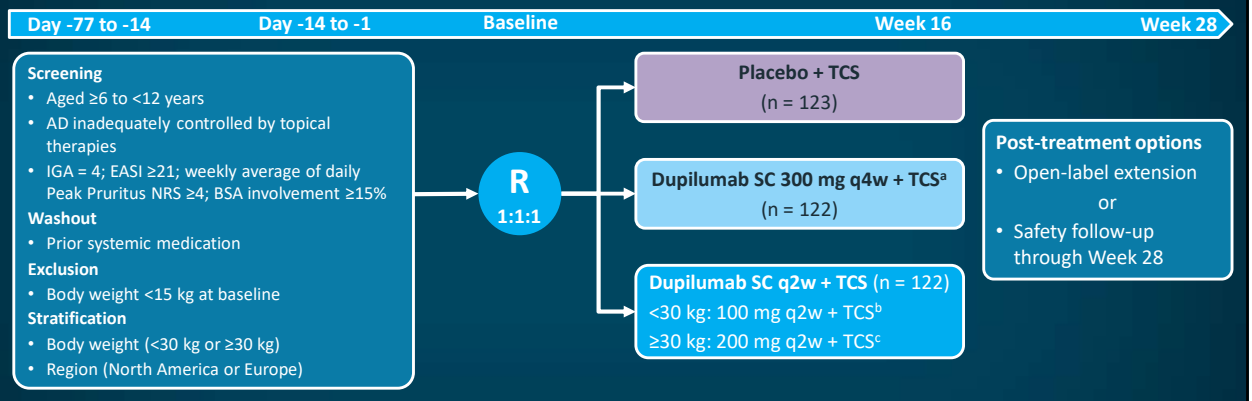
Dupilumab Adolescent Data

- 12-17-year-olds with moderate-to-severe AD, 1:1:1 placebo, 300 mg SC every 4 wks or 200 mg/300 mg SC every 2 wks
- For most endpoints, patients with the every 2 weeks regimen was superior to patients with the every 4 weeks regimen
- Safety profile was acceptable: Conjunctivitis and injection-site reactions were higher vs placebo, but AD exacerbation and non-herpetic skin infections were lower vs placebo
- Both placebo-corrected efficacy and safety of dupilumab in adolescents were similar to those in adults

Simpson EL, et al. *JAMA Dermatol*. 2020;156:44-56.

52

Dupilumab Ages 6 to 12 Years



[a]600 mg loading dose; [b]200 mg loading dose; [c]400 mg loading dose.
BSA = body surface area; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; NRS = Numerical Rating Scale; R = randomization; SC = subcutaneous; TCS = topical corticosteroids .
Paller AS, et al. Revolutionizing Atopic Dermatitis (RAD) Conference 2020. Poster 215.

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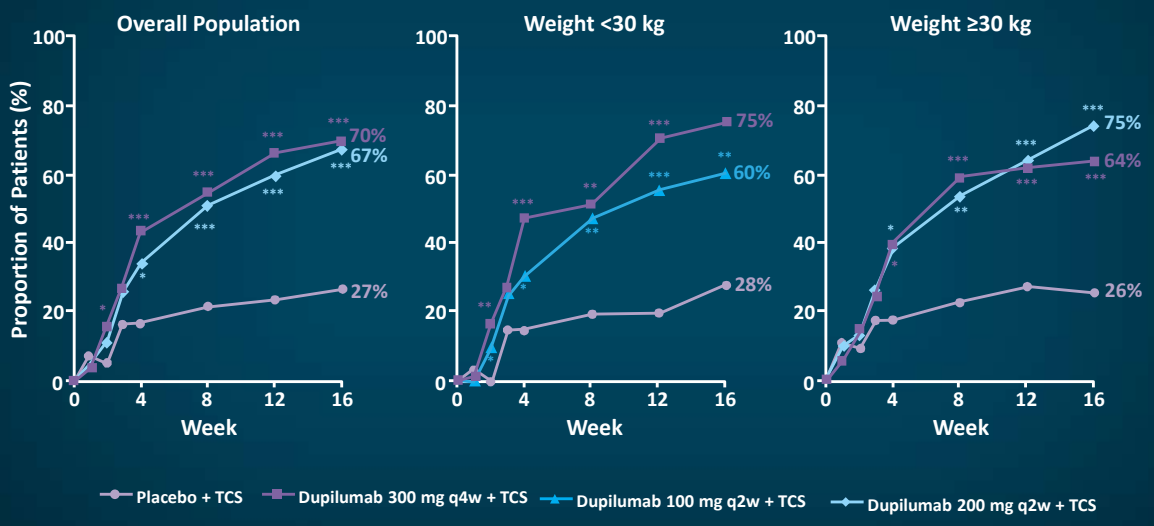
Proportions of Patients Achieving EASI-75



Paller AS, et al. Revolutionizing Atopic Dermatitis (RAD) 2020 Conference. Poster 215.

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Dupilumab

- It appears much safer than conventional immunosuppressants, but other potential considerations include:
  - Conjunctivitis in up to 10% of patients
  - Injection site reaction/systemic reactions
  - Cost may be a factor
  - Injection

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Pipeline: Selected Agents

Drug	Target
TOPICAL	
Delgocitinib	JAK1, JAK2, JAK3, TYK2
E6005	PDE4
OPA-15406	PDE4
Ruxolitinub	JAK1 and JAK2
Tapinarof	AHR ligand
ORAL	
Abrocitinib	JAK1
ASN002	JAK
Baricitinib	JAK1 and JAK2
Upadacitinib	JAK1
SYSTEMIC INJECTION	
Lebrikizumab	IL-13
Nemolizumab	IL-31
Tralokinumab	IL-13

JAK = Janus kinase; TYK2 = tyrosine kinase 2; PDE4 = phosphodiesterace-4; AHR = aryl hydrocarbon receptor; IL = interleukin.

National Eczema Association (https://nationaleczema.org/research/ eczema-treatment-research). Accessed September 19, 2019. Vakharia PP, Silverberg JI. *Lancet Child Adolesc Health*. 2019;3(5):343-353.

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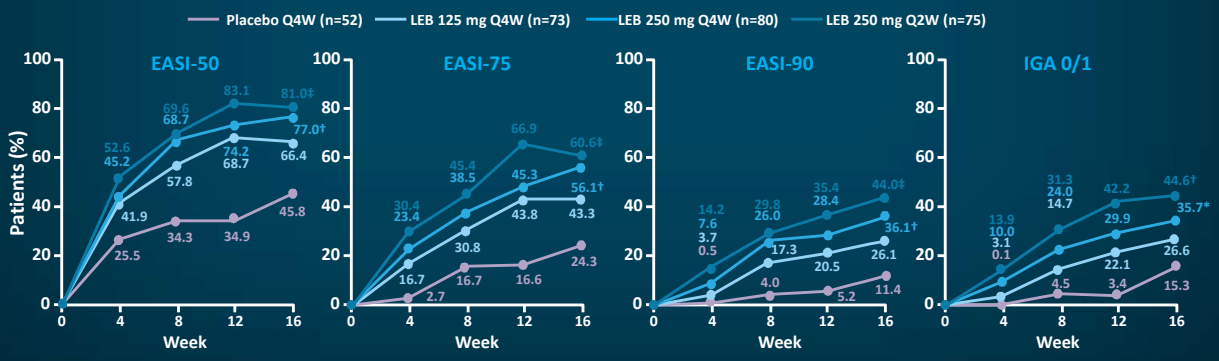
Emerging Agent: Lebrikizumab (anti-IL-13)

- A phase 2, randomized, monotherapy trial in 280 adults with moderate-to-severe AD inadequately controlled with TCS
- At week 12, significantly more patients achieved EASI 50/75/90 with lebrikizumab 250 mg every 2 weeks or every 4 weeks vs placebo



Guttman-Yassky E, et al. *JAMA Dermatol*. 2020:156:411-20.

57

Emerging Agent: Tralokinumab (anti-IL-13)

Study	Treatment	IGA 0/1 response at Wk 16	EASI-75 Response at Wk 16
ECZTRA 1[1]	Tralokinumab	16%	25%
	Placebo	7%	13%
	Placebo-adjusted Response	**9%**	**12%**
ECZTRA 2[1]	Tralokinumab	22%	33%
	Placebo	11%	11%
	Placebo-adjusted Response	**11%**	**22%**
ECZTRA 3[2]	Tralokinumab	39%	56%
	Placebo	26%	36%
	Placebo-adjusted Response	**13%**	**20%**

- ECZTRA 1/2: 51-60% maintained response over 52 wks
- ECZTRA 3: 78-93% maintained response over 32 wks

1. Wollenberg A, et al. *Br J Dermatol.* 2020;Sep 30. doi: 10.1111/bjd.19574. 2. Silverberg J, et al. *Br J Dermatol.* 2020 Sep 30. doi: 10.1111/bjd.19573.

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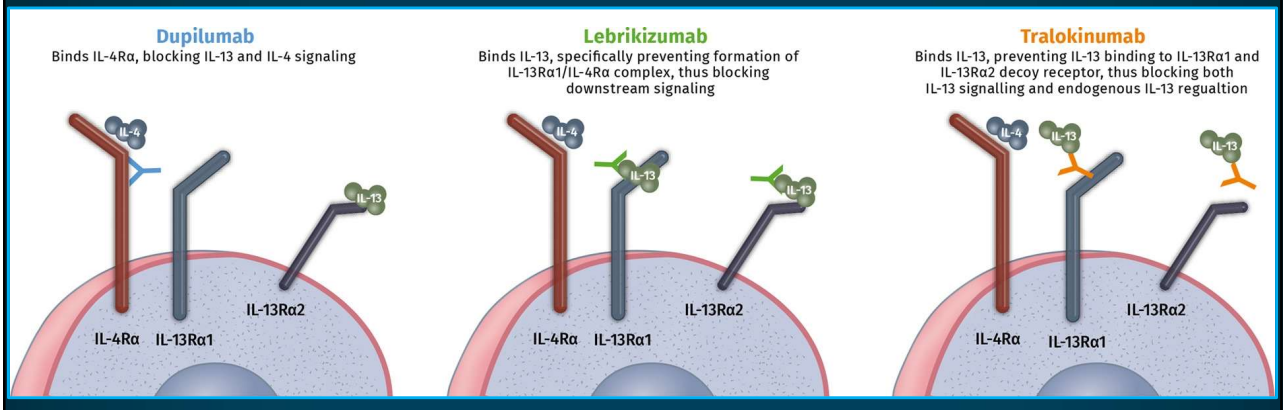
Not Identical Mechanisms



Lebrikizumab does not prevent binding to Ra2 → no increased levels of IL-13

Tralokinumab prevents the binding to Ra2 → thus increased total IL-13 levels

What does this mean?

We don't know!

Moyle M, et al. *Exp Dermatol.* 2019;28(7):756-768.

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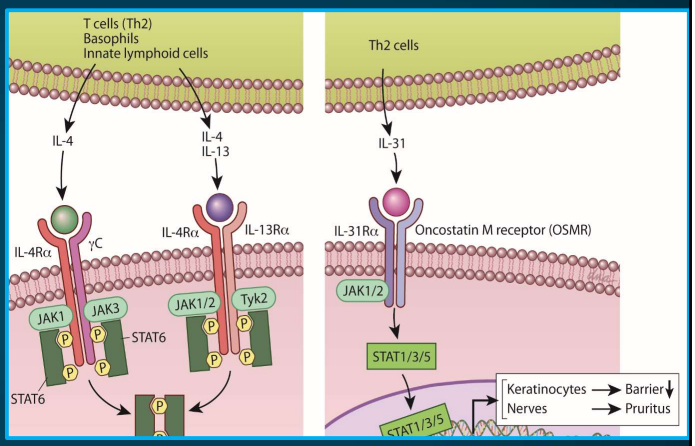
Janus Associated Kinase

- The JAK-STAT pathway is a conserved master regulator of immunity and myeloproliferation
- JAK inhibitors are used to treat several hematologic and inflammatory diseases
- Small molecules (including JAK inhibitors) show improvement in AD disease scores, patient-reported outcomes, and quality of life



Cotter DG, et al. *J Am Acad Dermatol*. 2018;78(1):S53-S62. Mobasher P, et al. *J Dermatolog Treat*. 2019;30:550-557. Paller AS, et al. *J Allergy Clin Immunol*. 2017;140:633-643.

60

JAK Inhibitors: Systemic

- **Abrocitinib**
  - Received breakthrough therapy designation in February 2018
  - Positive topline results from phase 3 trial in patients ≥ 12 years of age with severe disease
    - By Week 12, % of patients who met each co-primary efficacy endpoint and each key secondary endpoint with either dose, 100 mg or 200 mg, was significantly higher than placebo
- **Baricitinib**
  - In a phase 2 trial more subjects achieved an EASI-50 score on 4 mg dose every day than placebo
    - All patients were using TCS for 1 mo prior to initiation
    - Side effects included lymphopenia, neutropenia, AD exacerbation, and headache with no serious adverse events
  - Multiple phase 3 trials for adults are evaluating safety and efficacy and use as monotherapy
- **Upadacitinib**
  - Received breakthrough therapy designation in January 2018
  - Phase 2b trial revealed that 30 mg dose was superior to placebo in EASI score improvement and pruritus reduction
  - Phase 3 trials underway

Ruzicka T, et al. *N Engl J Med*. 2017;376:826-835. Guttman-Yassky E, et al. *J Am Acad Dermatol*. 2019;80:913-921. BioSpace.com (https://www.biospace.com/article/pfizer-s-abrocitinib-hits-primary-endpoints-in-atopic-dermatitis-trial). Accessed November 19, 2020.

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JAK Inhibitors: Topical

- **Delgocitinib**
  - Dose ranging (0.25-3% ointment) twice daily vs vehicle vs tacrolimus 0.1% x 4 weeks
  - All doses > vehicle in EASI (73% vs 12% in 3% group)
  - Tacrolimus = 62% reduction
  - No serious adverse events
- **Ruxolitinub**
  - Phase 2 randomized, dose-ranging, vehicle- and active-controlled study to evaluate safety and efficacy in adult patients
    - 1.5% twice daily group > vehicle in EASI (71.6% improvement at 4 weeks) and noninferior to triamcinolone cream 0.1%
  - Phase 1 study in children ages 2-7 and two phase 3 studies in patients ≥12 (TruE-AD1 and TruE-AD2) are underway

Nakagawa H, et al. *Br J Dermatol*. 2018;178(2):428-432. Bissonnette R. *Br J Dermatol*. 2018;178(2):321.

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Topical AHR Receptor Ligand

- Tapinarof
  - Activates epidermal aryl hydrocarbon receptors
  - Improves barrier function and ceramide production
  - Coal tar may work through a similar mechanism
  - Randomized, vehicle-controlled, double-blind phase 2b dose-finding study in adolescents and adults with moderate to severe AD
    - IGA 0 or 1 with ≥2-point reduction
    - 1% BID vs vehicle 53% vs 24%
    - Itch reduction at 1 week
    - AE: Stinging/burning

Peppers J, et al. *J Am Acad Dermatol.* 2019;80(1):89-98.

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Case Study

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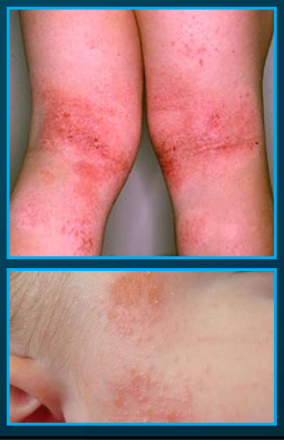
Case Study

A 3-year-old child comes to your clinic after several months of experiencing an itchy rash on the neck, face, upper back, antecubital fossae, upper and lower legs with predilection for popliteal fossae. Treatments tried so far include essential oils without improvement.

The next best step in treatment would be:

A) Emollient barrier cream
B) Topical therapy, emollient, and gentle skin care
C) Oral corticosteroids
D) Systemic therapy
E) Referral for allergy testing



Photos: National Eczema Association

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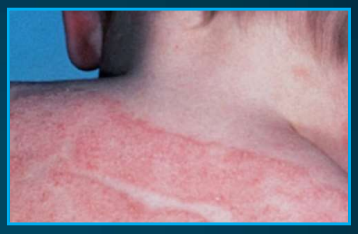
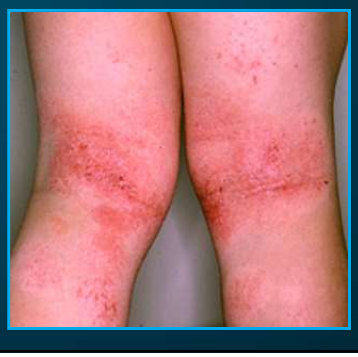
Atopic Dermatitis

- Gentle skin care—avoid irritants (fragrance, etc.)
- Emollient to replace defective barrier—twice a day
- Topical therapy: topical corticosteroids, topical calcineurin inhibitors, etc.
- ± bleach baths, topical antibiotics
- Oral corticosteroids can lead to AD flares upon treatment withdrawal.





Photos: National Eczema Association

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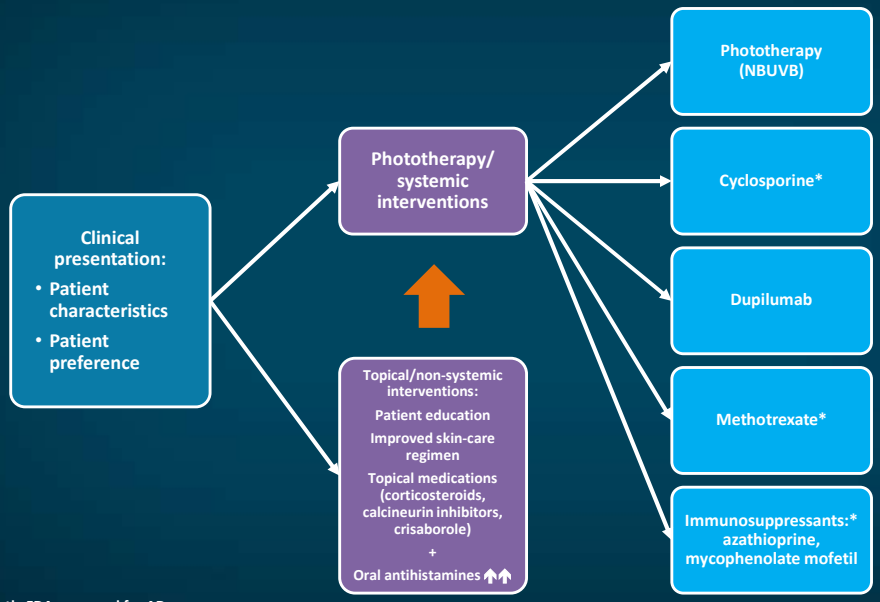
Management and Treatment Decisions



*Not currently FDA approved for AD

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Conclusions

- AD is a chronic disease with significant impact on quality of life
- **A pro**active approach is more effective than **re**active treatment
- Proactive treatment is stepwise and based on severity
- Management can be ***difficult*** and potentially complicated by conflicting messages from different care-team members (clinicians and family)
- **Adherence** is **key** to successful therapy
- Evolving biomarkers and targeted treatments promise to revolutionize treatment

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Thank You!

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Responsive Website

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Online Poster Portal

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Atopic Dermatitis Overview

Resource	Address
Du Toit G, et al. Food Allergy: Update on Prevention and Tolerance. *J Allergy Clin Immunol.* 2018;141:30-40.	https://www.jacionline.org/article/S0091-6749(17)31815-8/fulltext
Drucker AM, et al. The Burden of Atopic Dermatitis: Summary of a Report for the National Eczema Association. *J Invest Dermatol.* 2017;137:26-30.	https://www.jidonline.org/article/S0022-202X(16)32120-0/fulltext
Frischmeyer-Guerrerio PA, et al. IgE Testing Can Predict Food Allergy Status in Patients With Moderate to Severe Atopic Dermatitis. *Ann Allergy Asthma Immunol.* 2019;122:393-400.e2.	https://www.annallergy.org/article/S1081-1206(19)30001-8/fulltext
Gaudinski MR, Milner JD. Atopic Dermatitis and Allergic Urticaria: Cutaneous Manifestations of Immunodeficiency. *Immunol Allergy Clin North Am.* 2017;37:1-10.	https://www.sciencedirect.com/science/article/abs/pii/S0889856116300790
Guttman-Yassky E, et al. Systemic Immune Mechanisms in Atopic Dermatitis and Psoriasis With Implications for Treatment. *Exp Dermatol.* 2018;27:409-417.	https://onlinelibrary.wiley.com/doi/full/10.1111/exd.13336
Kantor R, Silverberg JI. Environmental Risk Factors and Their Role in the Management of Atopic Dermatitis. *Expert Rev Clin Immunol.* 2017;13:15-26.	https://www.tandfonline.com/doi/full/10.1080/1744666X.2016.1212660
Kim K. Influences of Environmental Chemicals on Atopic Dermatitis. *Toxicol Res.* 2015;31:89-96.	http://koreascience.or.kr/article/JAKO201520448048501.page
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American Academy of Pediatrics	https://www.aap.org/en-us/Pages/Default.aspx
Asthma and Allergy Foundation of America	http://www.aafa.org/page/eczema.aspx
International Eczema Council	https://www.eczemacouncil.org/
National Eczema Association	https://nationaleczema.org/
National Eczema Society	http://www.eczema.org/atopic-eczema