PRACTITIONER'S EDGE

Medical Education for Practical Application

Advancing Diagnosis and Management of Atopic Dermatitis in Children and Adolescents

INTEGRITY CONTINUING EDUCATION

Provided by Integrity Continuing Education, Inc.
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Faculty and Affiliation

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Faculty Disclosures

Anthony J. Mancini, MD, FAAP, FAAD

Consulting Fees:
Pfizer Pharmaceuticals

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Learning Objectives

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

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Automated Mobile Coach Platform

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

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Burden of Pediatric AD

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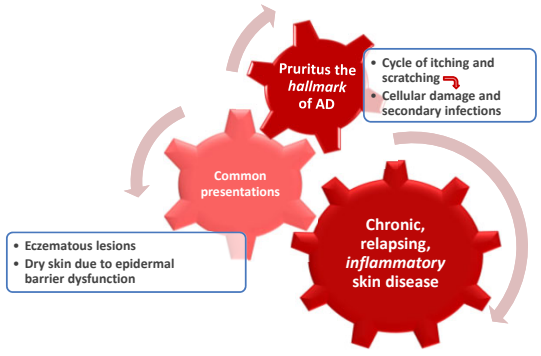
Disease Overview



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

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Prevalence of AD

- Affects 31.6 million in the US[1]
  - Most common skin disease worldwide[2]
  - Approximately 30% are children[2]
- 85% of cases present before 5 years of age[3]
- 30% of childhood cases persist into adult years[3]
- AD often the first sign of long-term disease continuum[4]
  - ~60% develop asthma or allergic rhinitis later in life
  - ~30% develop food allergies

Infant covered in wet wrap treatment
Photo courtesy of Mark Boguniewicz, MD

1. Silverberg JI. *Dermatol Clin.* 2017;35:283-289. 2. Weidinger S, Novak N. *Lancet.* 2016;387:1109-1122. 3. Boguniewicz M, et al. *Ann Allergy Asthma Immunol.* 2018;120:10-22. 4. NIH Genetics Home Reference https://ghr.nlm.nih.gov/condition/atopic-dermatitis.

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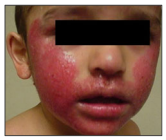
AD: Psychosocial/Health-Related Burden

Detrimental to QOL[1,2]

- Heavy psychosocial impact
  - Due to stigma, isolation, embarrassment, bullying, unpredictability of flares
- Suicidal ideation reported by ~20% with severe disease[3]
- Negative impact on academic performance



AD superinfected with toxin-secreting *S. aureus*. Photo courtesy of Mark Boguniewicz, MD

- Increased risk of cutaneous and systemic infections contribute to overuse of antibiotics[4]

QOL, quality of life.

1. Simpson EL. *J Am Acad Dermatol.* 2016;74:491-498. 2. Drucker AM. *J Invest Dermatol.* 2017;137:26-30. 3. Kimata H. *Suicide Life Threat Behav.* 2006;36:120-124. 4. Ong PY. *Immunol Allergy Clin North Am.* 2017;37:75-93.

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AD: Psychosocial/Health-Related Burden

Negative effect on sleep (mostly due to pruritus) in 47%–60% of children[1,2]

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

Heavy care/financial burden for parents, caregivers[3]

- Parents/caregivers report interrupted sleep >3x/week or more due to child's AD[4]
- Patients average 9 flares/year, each lasting ~15 days[5]
- Out-of-pocket expenses for families estimated to total ~10% of annual income[6]

HRQOL, health-related quality of life.

1. Chang Y-S, Chiang B-L. *Int J Mol Sci.* 2016;174:462. 2. Simpson EL, et al. *J Am Acad Dermatol.* 2016;74:491-498. 3. Drucker AM, et al. *J Invest Derm.* 2017;137:26-30. 4. National Eczema Association 2016 Caregiver Survey. https://nationaleczema.org/in-your-words-survey-series/. 5. Zuberbier T. *J Allergy Clin Immunol.* 2006;118:226-232. 6. Ricci G, et al. *J Pediatr Health Care.* 2006;20:311-315.

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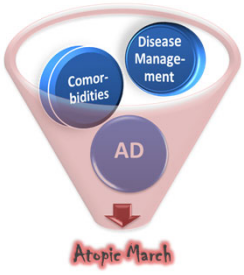
More Than Skin Deep: AD Comorbidites

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



Andersen YMF, et al. *Curr Dermatol Rep.* 2017;6:35-41. Brunner PM, et al. *J Invest Dermatol.* 2017;137:18-25.
Paller A, et al. *Am J Clin Dermatol.* 2018 Aug 30. [Epub ahead of print]

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AD Mental Health Comorbidities

- Common psychological comorbidities include[1-3]
  - Anxiety
  - Depression
  - Poor self-image
  - ADHD
  - Behavioral/conduct problems
- In GINIplus, children whose AD appeared to resolve in 1st or 2nd year of life still had emotional/behavioral difficulties by 10 years of age[4]

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

1. National Eczema Association 2016 Caregiver Survey. https://nationaleczema.org/in-your-words-survey-series/.
2. Simpson EL, et al. *J Am Acad Immunol.* 2016;74:491-498. 3. Yaghmaie P, et al. *J Allergy Clin Immunol.* 2013;131:428-433.
4. Schmitt J, et al. *J Allergy Clin Immunol.* 2010;125:404-410.

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Diagnosis and Severity Assessment

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Diagnostic Criteria for AD

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

Essential (must be present)	Important (supports diagnosis)	Differential/Exclusion Diagnoses (dermatologic manifestations of alternate or concomitant diagnoses)

• 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
	• Early age of onset
	• Atopy
	• Personal and/or family history
	• IgE reactivity
	• Xerosis
		• Seborrheic dermatitis
		• Contact dermatitis (allergic or irritant)
		• Scabies
		• Immunodeficiencies
		• Ichthyoses
		• Psoriasis
		• Photosensitivity dermatoses
		• Cutaneous T-cell lymphoma
		• Erythroderma of other causes

IgE, immunoglobin E.

Boguniewicz M, et al. *Ann Allergy Asthma Immunol.* 2018;120:10-22; Eichenfield LF, et al. *J Allergy Clin Immunol.* 2017;139:S49-S57.

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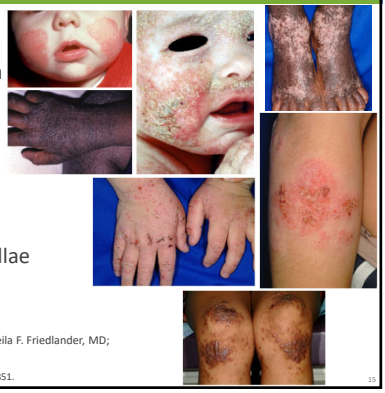
Visual Representations of Moderate-to-Severe Pediatric AD

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



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

Eichenfield LF, et al. *J Am Acad Dermatol.* 2014;70:338-351.

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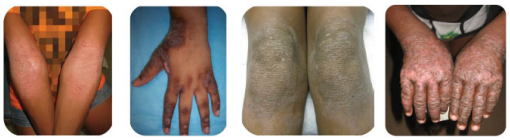
Clinical Features in Darker Skin Types

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



Siegfried EC, et al. *J Clin Med.* 2015;4:884-917.

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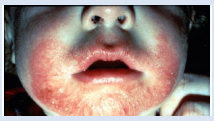
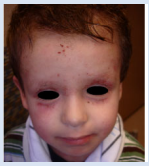
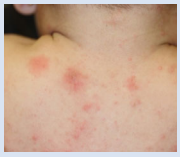
Other Diseases Can Look Like AD

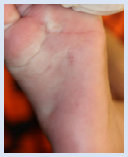
Contact Dermatitis

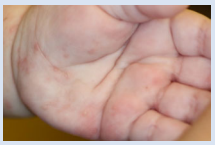




Scabies







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

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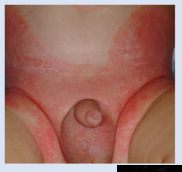
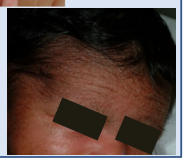
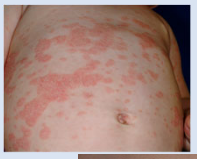
Differential Diagnosis

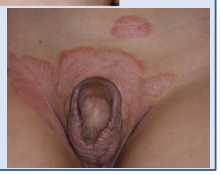
Seborrheic Dermatitis





Psoriasis





Photos courtesy of Anthony J. Mancini, MD.

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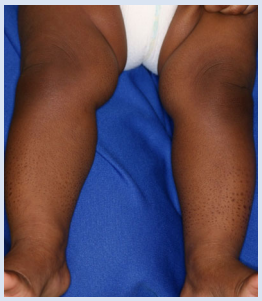
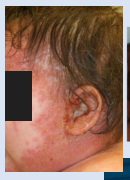
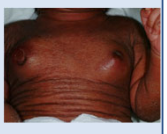
Differential Diagnosis

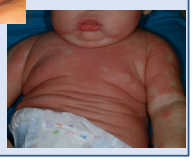
Ichthyosis vulgaris



Immunodeficiency







Photos courtesy of Anthony J. Mancini, MD.

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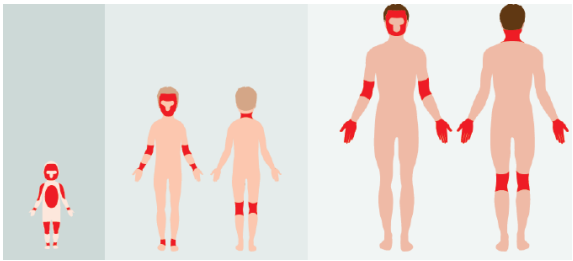
Distribution Patterns Vary with Age



Infants
Forehead, cheeks, and chin; trunk (except diaper area); extensor surfaces

Young Children
Face, neck, antecubital/popliteal fossae, wrists, ankles

Adolescents
Periorbital area, neck, extensor surfaces, antecubital/popliteal fossae, wrists, hands, ankles, feet

Simpson EL, et al. *Semin Cutan Med Surg.* 2016;35:S84-S88.

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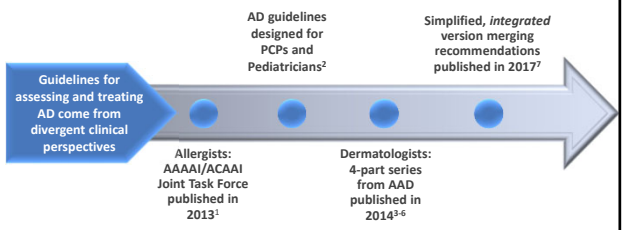
Guidelines



AAAAI, American Academy of Allergy, Asthma, and Immunology; AAD, American Academy of Dermatology; ACAAI, American College of Allergy, Asthma, and Immunology; PCPs, primary care providers.

1. Schneider L, et al. *J Allergy Clin Immunol.* 2013;131:295-299. 2. Eichenfeld LF, et al. *Pediatrics.* 2015;136:554-565.
3. Eichenfield LF, et al. *J Am Acad Dermatol.* 2014;70:338-351. 4. Eichenfeld LF, et al. *J Am Acad Dermatol.* 2014;71:116-132.
5. Sidbury R, et al. *J Am Acad Dermatol.* 2014;71:327-349. 6. Sudbury R, et al. *J Am Acad Dermatol.* 2014;71:1218-1233.
7. Eichenfeld LF, et al. *J Allergy Clin Immunol.* 2017;139:S49-S57.

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Testing Options

Testing recommendations from integrated guidelines

Do test for:	*Don't* test for:
Secondary bacterial infections with disease exacerbations	Food allergies on a routine basis
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	

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

Eichenfield LF, et al. *J Allergy Clin Immunol.* 2017;139:S49-S57.

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Severity Assessments

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

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

Boguniewicz M, et al. *Ann Allergy Asthma Immunol.* 2018;120:10-22. vIGA http://www.eczemacouncil.org/research/investigator-global-assessment-scale/.

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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

Boguniewicz M, et al. *Ann Allergy Asthma Immunol.* 2018;120:10-22. Eichenfield LF, et al. *J Allergy Clin Immunol.* 2017;139:S49-S57.

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Case Study, Part 1

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

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Case Discussion Points

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

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Case Study, Part 2

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

OTC, over-the-counter.

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Case Discussion Points

- Time to prescribe Rx topical corticosteroid?
  - If so, which one?
- What instruction will you give the parent regarding application and timing?
- What patient education would you provide to Sophia's mom?
  - Potential adverse effects
  - Risk of flares with noncompliance

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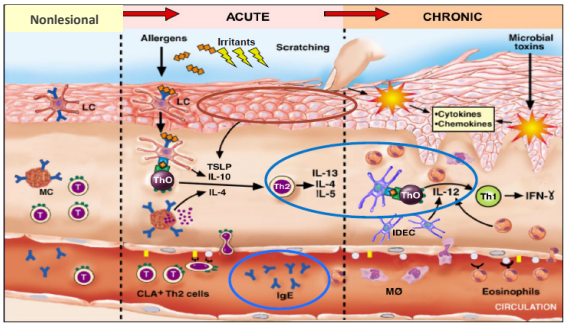
AD = Altered Epidermal Barrier + Immune Dysregulation



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

Adapted from: Boguniewicz M, et al. *Immunol Rev.* 2011;242:233-246.

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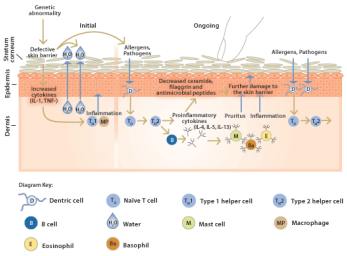
AD Pathophysiology: Filaggrin

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



Sandilands A, et al. *J Invest Dermatol.* 2006;126:1770-1775. Smith FJ, et al. *Nat Genet.* 2006;38:337-342.

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AD Pathophysiology: Barrier

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

TEWL, transepidermal water loss.

1. Kelleher MM, et al. *J Allergy Clin Immunol.* 2015;135:930-935.
2. Kelleher MM, et al. *J Allergy Clin Immunol.* 2016;137:1111-1116.

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… Then Emolliate Early?

- RCT of 124 neonates, high AD risk[1]
  - Full-body emollient Rx daily (starting 3 weeks of age) vs no emollient
  - Cumulative AD incidence at 6 months
  - Emollient arm: 50% relative risk reduction in AD
- RCT of 118 neonates, high AD risk[2]
  - Moisturizer applied daily for first 32 weeks of life
  - Cumulative AD/eczema incidence at week 32, egg white IgE
  - 32% fewer neonates with AD in emollient arm
    - No effect on allergic sensitization

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

RCT, randomized, controlled trial.

1. Simpson EL, et al. *J Allergy Clin Immunol.* 2014;134:818-823. 2. Horimukai K, et al. *J Allergy Clin Immunol.* 2014;134:824-830.

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PRACTITIONER'S EDGE

Treatment Approaches

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"Yardstick" Guidelines Published in 2018

- Developed to reconcile differing recommendations from multidisciplinary guidelines
- Emphasis is on practical, step-by-step, "how-to" strategies to ensure clear or almost-clear skin from all levels of severity

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

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Treatment Goals

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

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Topical Treatments for Mild Disease

Corticosteroids
- TCs usually the first line of treatment to reduce local inflammation
- Can cause skin atrophy and thinning if used inappropriately (eg, chronic use of high-potency TCs)
- No consensus regarding optimal dosing or frequency

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

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

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

Ahmed A, et al. *Br J Dermatol.* 2018;178:659-662. Boguniewicz M, et al. *Ann Allergy Asthma Immunol.* 2018:120:10-22. Paller AS, et al. *J Allergy Clin Immunol.* 2017;140:633-643.

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TCS: Available Potencies

Class	Drug	Vehicle	Strength (%)
Superpotent (1)	Augmented betamethasone dipropionate	O	0.05
	Clobetasol propionate	C F O	0.05
	Diflorasone diacetate	O	0.05
	Halobetasol propionate	C O	0.05
Potent (2)	Amcinonide	C L O	0.1
	Augmented betamethasone dipropionate	C	0.05
	Betamethasone dipropionate	C F O S	0.05
	Desoximetasone	C O	0.25
	Desoximetasone	G	0.05
	Diflorasone diacetate	C	0.05
	Fluocinonide	C G O S	0.05
	Halcinonide	C O	0.1
	Mometasone furoate	O	0.1
	Triamcinolone acetonide	C O	0.5
Mid-Strength (3 – 4)	Betamethasone valerate	C F L O	0.1
	Clocortolone pivalate	C	0.1
	Desoximetasone	C	0.05
	Fluocinolone acetonide	C O	0.025
	Flurandrenolide	C O	0.05
	Fluticasone propionate	C	0.05
	Fluticasone propionate	O	0.005
	Mometasone furoate	C	0.1
	Triamcinolone acetonide	C O	0.1
Lower Mid-Strength (5)	Hydrocortisone butyrate	C O S	0.1
	Hydrocortisone probutate	C	0.1
	Hydrocortisone valerate	C O	0.2
	Prednicarbate	C	0.1
Mild (6)	Alclometasone dipropionate	C O	0.05
	Desonide	C G F O	0.05
	Fluocinolone acetonide	C S Oi	0.01
Least Potent (7)	Hydrocortisone	C L O S	0.25, 0.5, 1
	Hydrocortisone acetate	C O	0.5 - 1

C, cream; F, foam; G, gel; L, lotion; Oi, Oil; O, ointment; S, solution.

Adapted from: Eichenfield LF, et al. *J Am Acad Dermatol.* 2014;71:116-132.

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TCIs

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

Currently Available TCIs		
TCI	**Vehicle**	**Indications**
Pimecrolimus (1%)	cream	Mild-to-moderate AD (2 years and older)
Tacrolimus (0.03% and 0.1%)	ointment	Moderate-to-severe AD (2 years and older: 0.03%; 15 years and older: 0.1%)

Eichenfield LF, et al. *J Am Acad Dermatol.* 2014;71:116-132. Stein SL, et al. *JAMA.* 2016;315:1510-1511.

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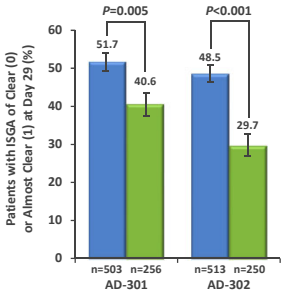
PDE4 Inhibition

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



Paller AS, et al. *J Am Acad Dermatol.* 2016;75:494-503.

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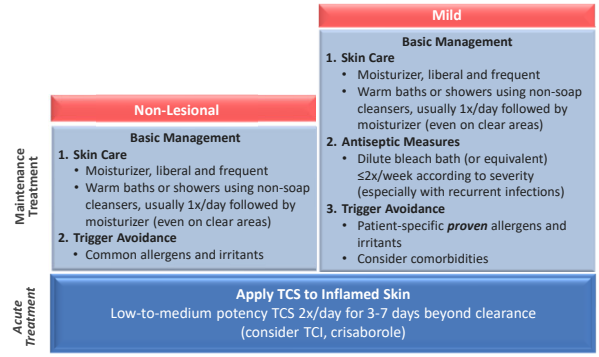
Step-Care Management: Mild AD



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

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Treatments for Moderate-to-Severe Disease

Systemic Immunosuppression	Phototherapy	Biologics
• Cyclosporine • Methotrexate • Mycophenolate mofetil • Azathioprine • Corticosteroids **Limitations:** • All but corticosteroids are off-label for AD • Not usable for long-term maintenance because of multiple systemic adverse events	• Primarily narrow-band UVB **Limitations:** • Available only for patients ≥12 years • Access/convenience (few phototherapy centers) • Cost and travel time often not covered by insurance • Very low risk for cutaneous malignancies and cataracts	• Dupilumab, only targeted biologic approved for moderate-to-severe AD **Limitations:** • Currently approved only for patients ≥18 years • Subcutaneous injection • Too new to be included in guidelines • No data for optimal ways to step down or discontinue after clear skin is achieved

UVB, ultraviolet B.

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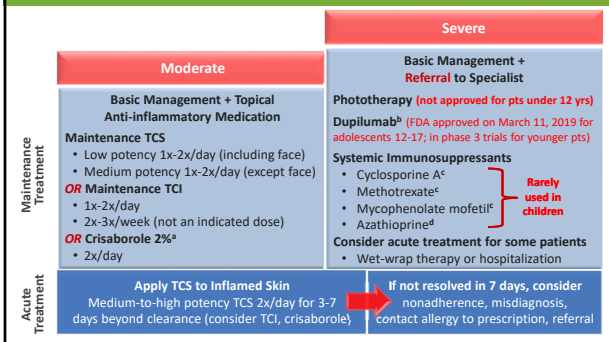
Step-Care Management: Moderate-to-Severe AD



[a]Indicated for patients at least 2 years old; [b]Indicated for patients at least 12 years old; [c]Not approved by FDA to treat AD; [d]Not recommended for long-term maintenance.

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

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Oral Antihistamines in AD

Some Currently Available Oral Antihistamines	
Agent	**Properties**
Diphenhydramine*	Sedating
Hydroxyzine	Sedating
Doxepin	Sedating
Cetirizine*	Non-sedating

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

*Available OTC

Sidbury R, et al. *J Am Acad Dermatol.* 2014;71:116-132.

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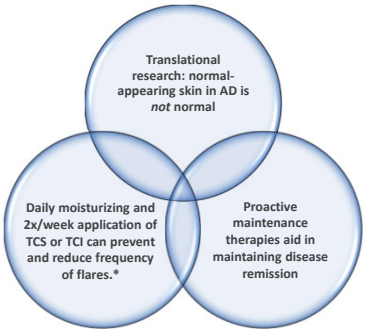
Antiflare Maintenance Therapy



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

Eichenfield LF, et al. *J Am Acad Dermatol.* 2014;71:116-132. Stein SL, et al. *JAMA.* 2016;315:1510-1511.

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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

"Misdiagnosis of atopic dermatitis is a concern … it can contribute to making the disease worse."[2]
~Dirk M. Elson, MD
Past President, AAD
2013–2014

1. Li AW, et al. *JAMA Dermatol.* 2017;153:1036-1042. 2. Simpson EL, *J Am Acad Dermatol.* 2016;74:491-498.

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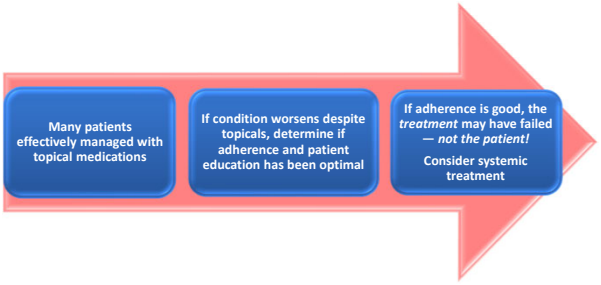
When to Use Systemic Treatment



Simpson EL, et al. *J Am Acad Dermatol.* 2017;4:623-633.

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PRACTITIONER'S EDGE

Biologic Therapy

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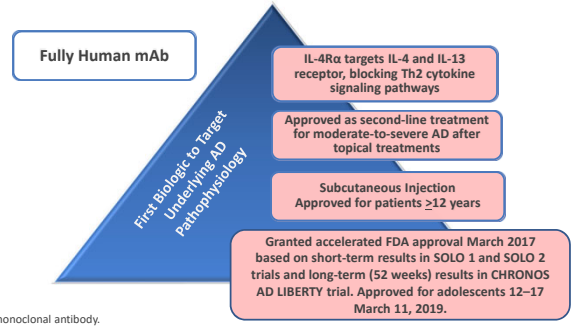
One Approved Biologic Agent: Dupilumab



mAb, monoclonal antibody.

Boguniewicz M, et al. *Ann Allergy Asthma Immunol.* 2018:120:10-22. Dupilumab (Dupixent®) PI 03/2019.

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Dupilumab Phase 3 Clinical Trials

Safety and efficacy demonstrated in 3 placebo-controlled clinical trials

SOLO 1, SOLO 2	LIBERTY AD CHRONOS
Evaluated dupilumab as monotherapy for 16 weeks	Evaluated dupilumab in combination with TCS for 52 weeks

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

Blauvelt A, et al. *Lancet.* 2017;389:2287-2303. Simpson EL, et al. *N Engl J Med.* 2016;375:2335-2348.

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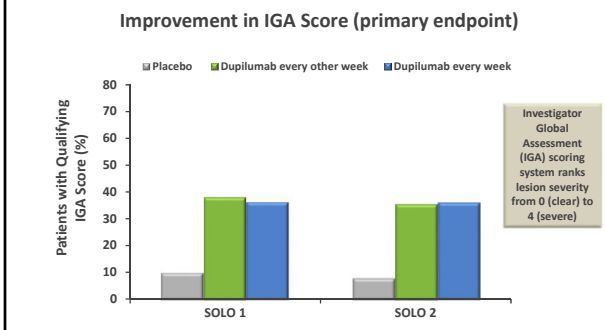
Efficacy in Global Assessment



Adapted from: Simpson EL, et al. *N Engl J Med.* 2016;375:2335-2348.

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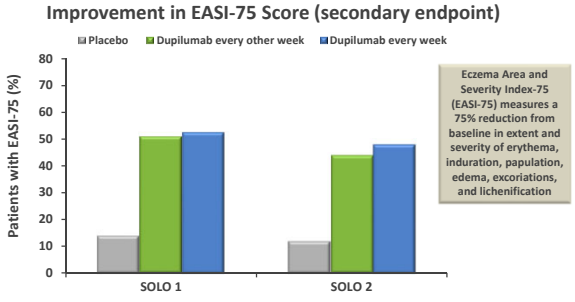
Efficacy in Reducing Disease Severity



Adapted from: Simpson EL, et al. *N Engl J Med.* 2016;375:2335-2348.

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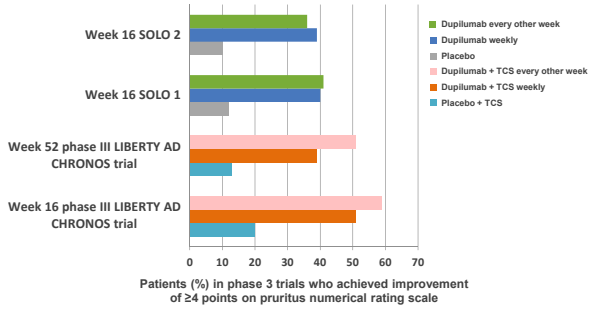
Efficacy in Pruritus



Adapted from: Awosika O, et al. *Clin Cosmet Investig Dermatol.* 2018;11:41-49.

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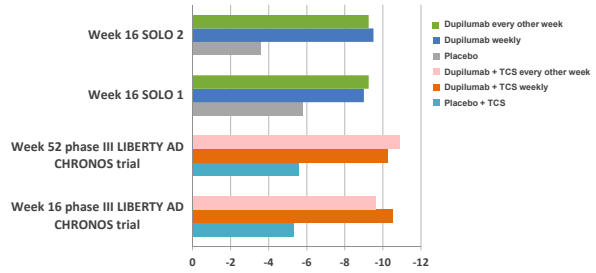
Efficacy in QOL Improvements



Patients in phase 3 trials who demonstrated improvements in QOL (eg, sleep, anxiety, depression) as indicated by least squares[a] mean change in dermatology life quality index (DLQI) score

[a]Least squares incorporate percent change over time, primary analysis, and sensitivity analysis.

Adapted from: Awosika O, et al. *Clin Cosmet Investig Dermatol.* 2018;11:41-49.

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Dupilumab: Trial Findings in Safety

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

Simpson EL, et al. *N Engl J Med.* 2016;375:2335-2348.

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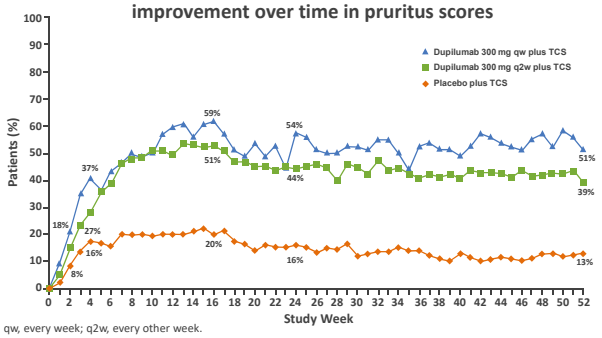
Long-term Efficacy

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



qw, every week; q2w, every other week.

Adapted from: Blauvelt A, et al. *Lancet.* 2017;389:2287-2303.

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Phase 3 Trial of Dupilumab in Adolescents

- First ever biologic trial for AD in ages 12–17 years (NCT03054428)
  - 251 patients with moderate-to-severe disease not controlled by topicals randomized to dosing every 4 weeks (Q4W), biweekly (Q2W), or placebo
  - Coprimary endpoints EASI-75 response and IGA score of 0 (clear) or 1 (almost clear)
  - Secondary endpoints improvement in pruritus NRS and CDLQI
- Preliminary phase 3 results presented September 2018 at EADV showed statistically significant improvement in skin, pruritus, and QOL by week 16
  - Priority review application submitted to FDA in November for approval in adolescents; approval granted March 11, 2019

CDLQI, Children's Dermatology Life Quality Index; EADV, European Academy of Dermatology and Venereology; NRS, numerical rating scale.

Clinicaltrials.gov. NCT03054428. https://clinicaltrials.gov/ct2/show/NCT03054428. Updated August 2, 2018. Accessed 10/4/2018; Simpson EL, et al. EADV abstract D3T01.1L. Presented September 15, 2018.

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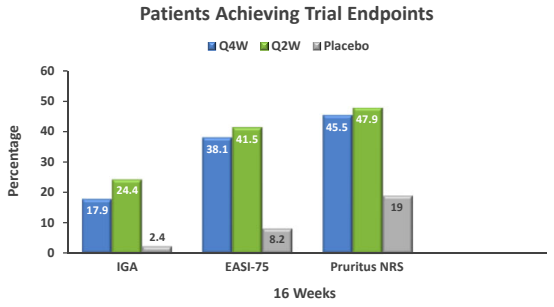
Phase 3 Dupilumab Trial in Adolescents: Results



Simpson EL, et al. EADV abstract D3T01.1L. Presented September 15, 2018.

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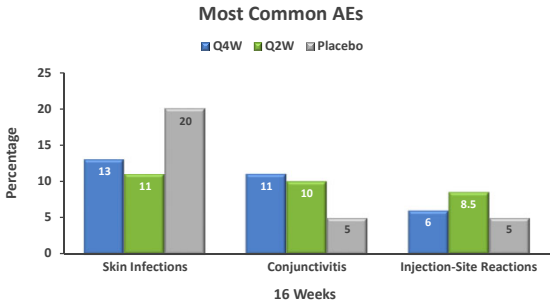
Phase 3 Dupilumab Trial in Adolescents: Safety



Simpson EL, et al. EADV abstract D3T01.1L. Presented September 15, 2018.

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Ongoing/Recruiting Clinical Trials of Dupilumab in Children

Trial Name*/ Number	Focus	# Pts/Ages	Phase	Estimated Completion
NCT02612454†	Long-term safety	765 ≥6 mos to <18 yrs	3	October 2023
NCT03345914	Efficacy and safety of dupilumab with TCS	240 ≥6 mos to <12 yrs	3	April 2019
LIBERTY AD PRESCHOOL / NCT03346434	Safety, PK, and efficacy of dupilumab in severe AD	280 ≥6 mos to <6 yrs	2/3	April 2022

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

PK, pharmacokinetics.

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Considerations in Prescribing Dupilumab

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

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

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Emerging Biologics and Small-Molecule Agents Being Studied in Adolescents

Agents	Inhibitor Class	Trial Phase	Route	# Children in Trials
Tralokinumab	IL-13	3	SC	1 ongoing/recruiting trial involving 294 adults and adolescents with moderate-to-severe AD
Upadacitinib	JAK 1	3	oral	4 ongoing/recruiting trials involving 2,694 adults and adolescents with moderate-to-severe AD

JAK, janus kinase inhibitor; SC, subcutaneous.

Source: ClinicalTrials.gov October 2018, using filters for "atopic dermatitis eczema," "phase 3," "phase 2," and "child (birth–17).

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PRACTITIONER'S EDGE

Considerations in AD Management

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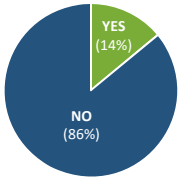
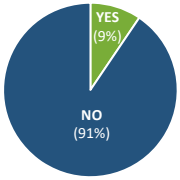
Improving Patient Satisfaction

Results from National Eczema Association's "In Your Words" patient satisfaction survey (N=192) in 2016

Treatment Satisfaction:
Overall, are you satisfied with the treatment of AD?



Physician Satisfaction:
Overall, do you think doctors know how to treat AD?



National Eczema Association 2016 Caregiver Survey. https://nationaleczema.org/in-your-words-surveyseries/.

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Improving Patient Satisfaction *(cont.)*

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

National Eczema Association 2016 Caregiver Survey. https://nationaleczema.org/in-your-words-surveyseries/.

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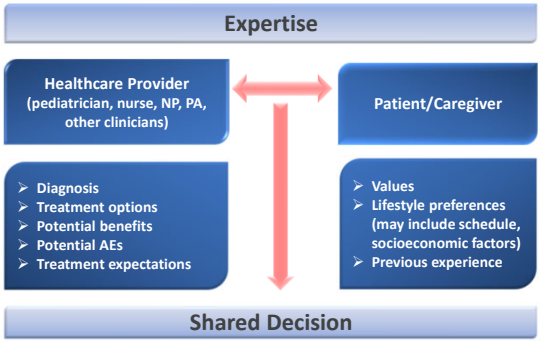
Shared Decision Making



Adapted from: Blaiss MS, et al. *Ann Allergy Asthma Immunol*. 2018 Aug 31. [Epub ahead of print]

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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

Blaiss MS, et al. *Ann Allergy Asthma Immunol*. 2018 Aug 31. [Epub ahead of print]. Felix K, et al. *J Dermatol Treat*. 2018;17:1-18.
LeBovidge J, et al. *Semin Cutan Med Surg*. 2017;36:131-136.

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Important Patient Education Points

Eichenfield LF, et al. *Pediatrics*. 2015;136:554-565.

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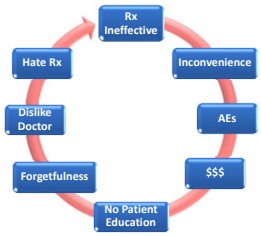
Treatment Adherence

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



Boguniewicz M, et al. *Ann Allergy Asthma Immunol*. 2018;120:10-22. Eichenfield LF, et al. *J Allergy Clin Immunol*. 2017;139:S49-S57.
Patel N, Feldman SR. *Adv Exp Med Biol*. 2017;1027:139-159.

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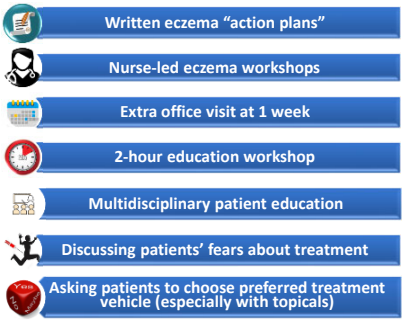
Proven Strategies to Improve Adherence



Bass AM, et al. *J Clin Med.* 2015;4:231-242. Borok J. *Dermatology News.* June 27, 2017. Patel NU, et al. *Am J Clin Dermatol.* 2017;18:323-332. Snyder, et al. *Cutis.* 2015;96:397-401.

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Summary

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

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PRACTITIONER'S EDGE

Thank You!

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PRACTITIONER'S EDGE

Back Up Slides

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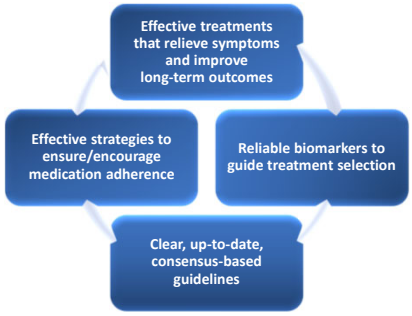
Unmet Needs in AD



Leung DYM. *J Allergy Clin Immunol.* 2017;139(4S):S47-S48. Patel N, Feldman SR. *Adv Exp Med Biol.* 2017;1027:139-159.
Silverberg JI. *Allergy Asthma Proc.* 2017;38:243-249.

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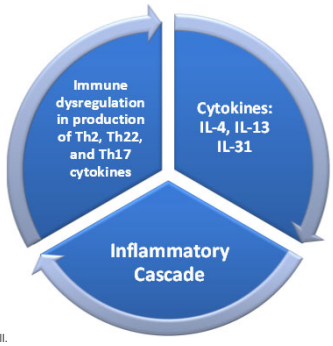
Epidermal Barrier Breakdown: A Vicious Cycle



IL, interleukin; Th, T-helper cell.

Boguniewicz M, et al. *Ann Allergy Asthma Immunol.* 2018:120:10-22. Cork MJ, et al. *J Allergy Clin Immunol.* 2006;118:3-21.
Irvine AD, et al. *N Engl J Med.* 2011;365:1315-1327.

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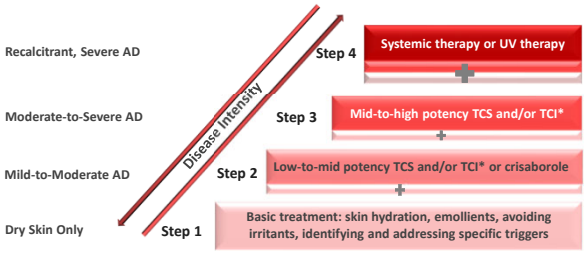
Simplified Step-Care Management



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

Adapted from: Boguniewicz M, et al. *Ann Allergy Asthma Immunol.* 2018:120:10-22 **and** Akdis CA, et al. *J Allergy Clin Immunol.* 2006;118:152-169.

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

- **Phototherapy:** Not approved for children under 12 years; very few data on efficacy in children
- **Systemic immunosuppression:** Generally avoided in children
  - Gastrointestinal and hepatic AEs common as well as infections and bone marrow suppression, among others
- **Systemic corticosteroids:** Unacceptable AEs
  - Can be used for short courses in ***some cases***, however, no agreement about optimal dose and duration of "short course"
- **Biologics:** Dupilumab only currently available biologic[1]
  - Strong safety and efficacy in adults and adolescents (data for adolescents presented at EADV Congress in September 2018)
  - Not yet approved for patients under 18 years

AEs, adverse events; EADV, European Academy of Dermatology and Venereology.

1. As of October 2018. 2. Simpson EL, et al. EADV abstract D3T01.1L. Presented September 15, 2018.

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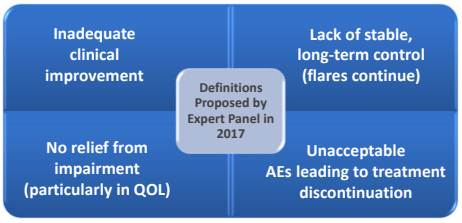
Identifying Treatment Failure

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



Boguniewicz M, et al. *J Allergy Clin Immunol Pract*. 2017;5:1519-1531. Spergel JM. UpToDate. Last Updated: August 15, 2018.

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