Advancements in the Diagnosis and Management of Atopic Dermatitis

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The Steering Committee members received an honorarium for their work in developing this deck.

Objectives

- Understand the pathophysiology and multifactorial nature of atopic dermatitis
- Emphasize challenges in the diagnosis of atopic dermatitis and its burden of disease
- Review management of atopic dermatitis

Presentation Overview

- Mechanism of Disease
- Diagnosis and Disease Burden of Atopic Dermatitis
- Management of Atopic Dermatitis
- Backup

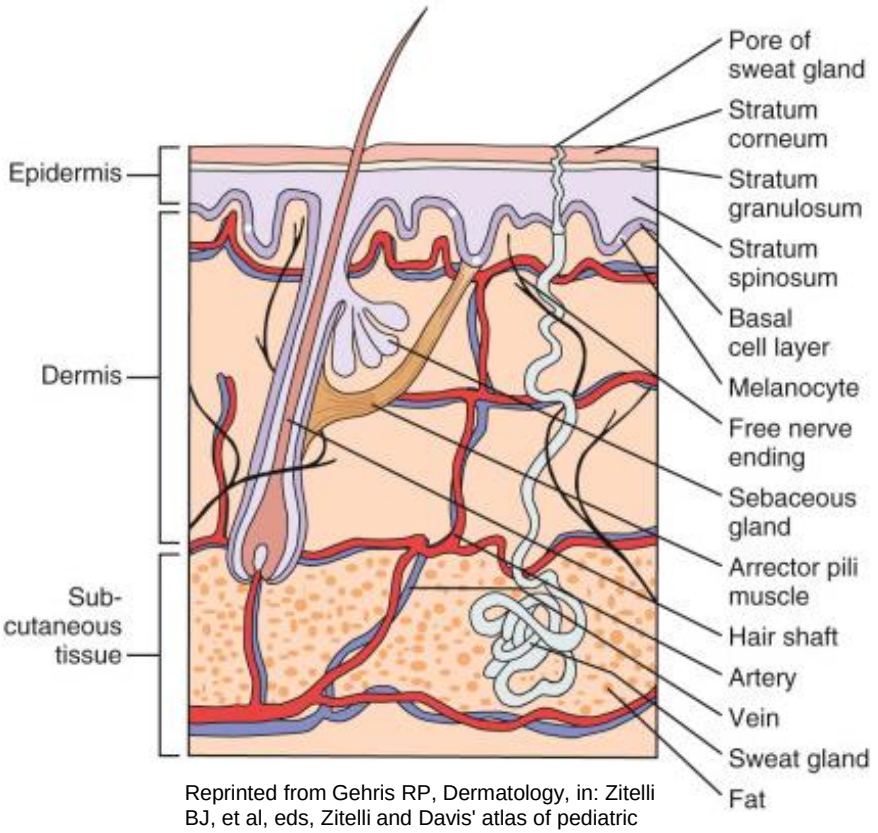
Mechanism of Disease

Normal Skin Barrier Function

The stratum corneum and lipid matrix serve as barriers to prevent loss of moisture and reduce invasion of toxins, allergens, and infectious agents[1,2*]

Role of cells[3]

- Structural cells (eg, keratinocytes)
- Immune/protection cells (eg, Langerhans cells, dermal dendritic cells, mast cells, and melanocytes)
- Sensory perception (eg, Merkel cells)



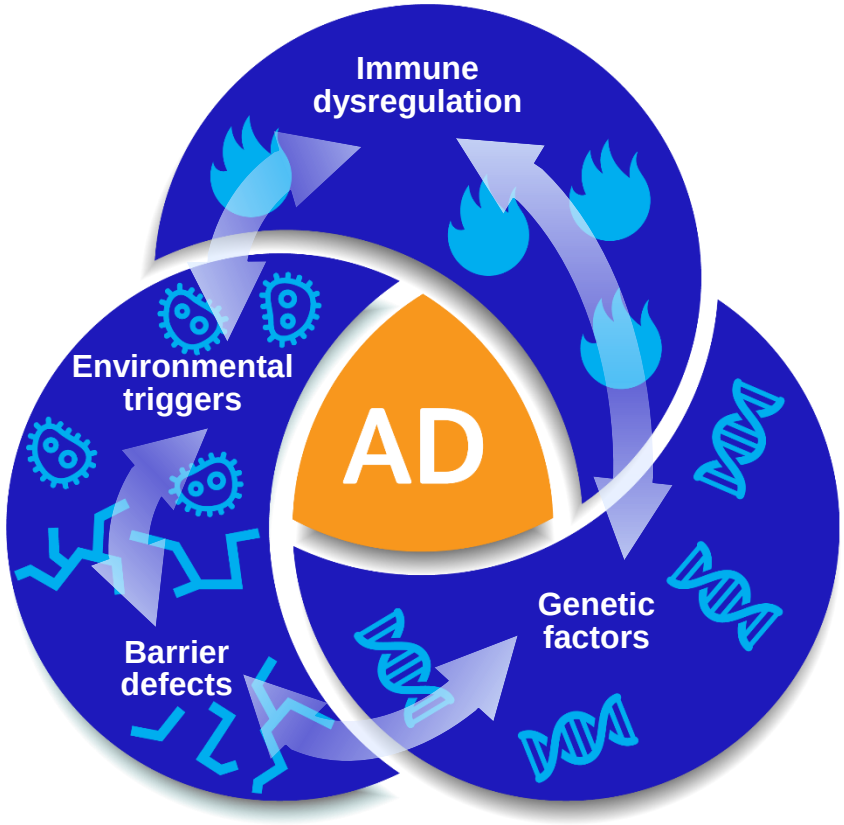
Reprinted from Gehris RP, Dermatology, in: Zitelli BJ, et al, eds, Zitelli and Davis' atlas of pediatric diagnosis, 7th ed, 2018:275-340, with permission from Elsevier.

*Bacterial, viral, and fungal.

1. Segre JA. *J Clin Invest.* 2006;116(5):1150-1158; 2. van Smeden J, et al. *Biochim Biophys Acta*. 2014;1841:295-313; 3. Nguyen AV, Soulika AM. *Int J Mol Sci.* 2019;20(8):1811. doi:10.3390/ijms20081811; 4. Gehris RP. Dermatology. In: Zitelli BJ, et al, eds. *Atlas of Pediatric Diagnosis.* 7th ed. Elsevier; 2018:275-340.

AD Is a Multifactorial, Chronic, Inflammatory, Pruritic Skin Disease[1-4]

- **Skin barrier dysfunction**
  - ↑ TEWL, allergen sensitization; altered skin microbiomes[1]
- **Genetics**
  - Familial inheritance pattern
  - ↓ filaggrin protein (↑ TEWL); skin pH alterations, and dehydration[1]
- **Immune dysregulation**
  - Type 2 inflammation (Th2 cells, eosinophils, and relevant cytokines[2])
- **Environmental factors**
  - Allergens, microorganisms, and irritants can trigger responses[3]



Nonlesional AD demonstrates epidermal and immune abnormalities, specifically abnormal proliferation and immune infiltration, compared with normal skin[4]

AD, atopic dermatitis; pH, power of hydrogen; TEWL, transepidermal water loss; Th, T helper.

1. Guttman-Yassky E, et al. *Semin Cutan Med Surg*. 2017;36(3):100-103; 2. Akdis CA, et al. [published online April 22, 2020]. *Allergy*. doi:10.1111/all.14318; 3. Boothe W, et al. *Adv Exp Med Biol*. 2017;1027:21-37; 4. Suárez-Fariñas M, et al. *J Allergy Clin Immunol*. 2011;127(4):954-964.e1-4.

Inside-Out and Outside-In Hypotheses

Inside Out

Activation of various immune pathways results in immunologic cascade, which involves chemokine production, skin barrier dysfunction, suppression of AMP, and allergic inflammation[1]

Outside In

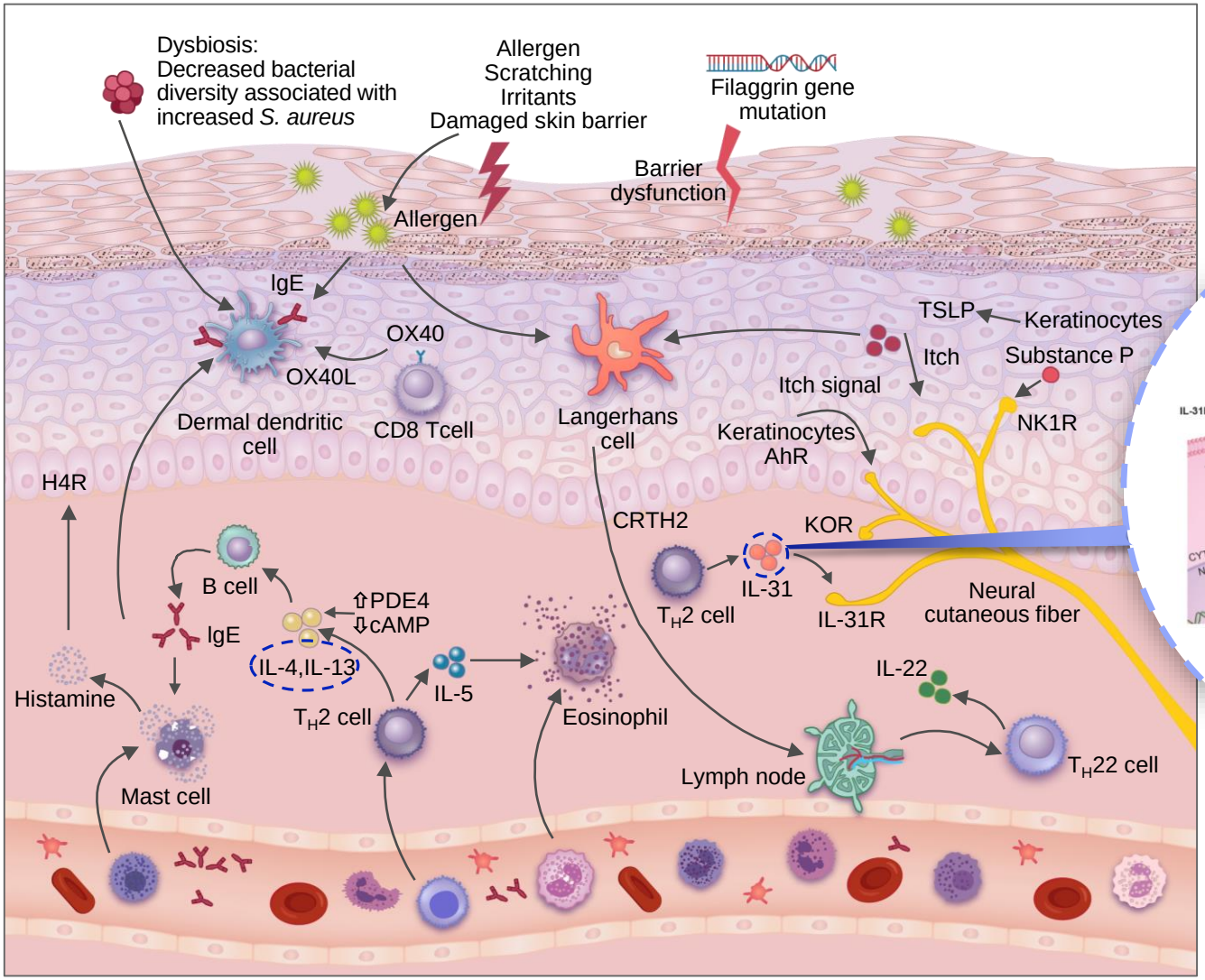
Defects in barrier dysfunction and keratinocyte differentiation allow penetration of antigens, with consequent immune sensitization and activation[1]

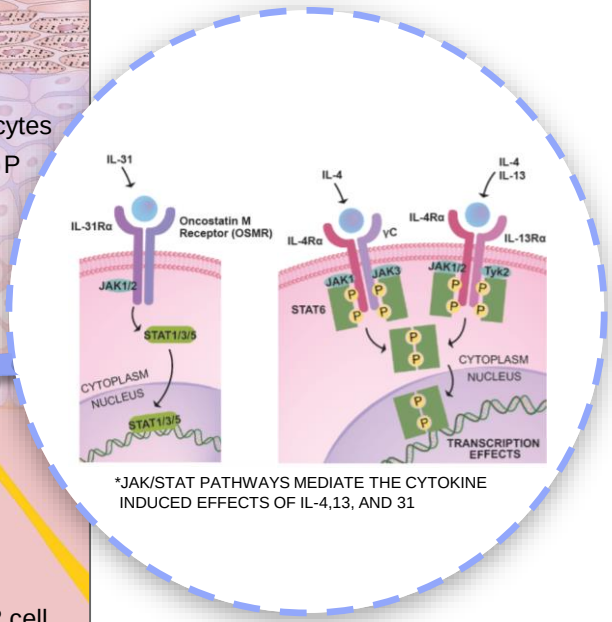
Both aberrant immune responses and skin barrier defects are believed to drive cutaneous inflammation in AD[2]

AD, atopic dermatitis; AMP, antimicrobial peptides.

1. Guttman-Yassky E, et al. *Semin Cutan Med Surg*. 2017;36(3):100-103; 2. Silverberg NB, Silverberg JI. *Cutis*. 2015;96(6):359-361.

Pathogenesis of AD Involves Abnormalities On and Below the Skin's Surface[1]





*JAK/STAT PATHWAYS MEDIATE THE CYTOKINE INDUCED EFFECTS OF IL-4,13, AND 31

Left figure: adapted by permission from Springer: *Paediatr Drugs, Nguyen HL et al. 2019;21(4):239-260.*
Above image used with permission from Dr Jonathan Silverberg.

In addition to the roles of the cytokines described here, these, and other cytokines are believed to play multiple roles in AD pathophysiology.[2]

α, alpha; AhR, aryl hydrocarbon receptor; cAMP, cyclic adenosine monophosphate; CRTH2, Chemoattractant receptor-homologous molecule expressed on Th2 cells; H4R, histamine H4 receptor; IgE, immunoglobulin E; IL, interleukin; JAK, Janus kinase; KOR, kappa-opioid receptor; NK, natural killer; PDE, phosphodiesterase; R, receptor; STAT, signal transducer and activation of transcription; TSLP, thymic stromal lymphopoietin; TYK, tyrosine kinase; γC, common gamma chain
These agents are under phase 3 development as of June 2020.
1. Nguyen HL et al. *Paediatr Drugs*. 2019;21(4):239-260. 2. Weidinger S, et al. *Nat Rev Dis Primers*. 2018;4(1):1.

Diagnosis and Disease Burden of Atopic Dermatitis

Diagnosis: American Academy of Dermatology (AAD) Guidelines[1,2*]

Essential Features

- Pruritus
- Eczema (acute, subacute, chronic)
  - Typical morphology and age-specific patterns
  - Chronic or relapsing history

Important Features

- Early age of onset
- Atopy
  - Personal and/or family history
  - IgE reactivity
  - Xerosis

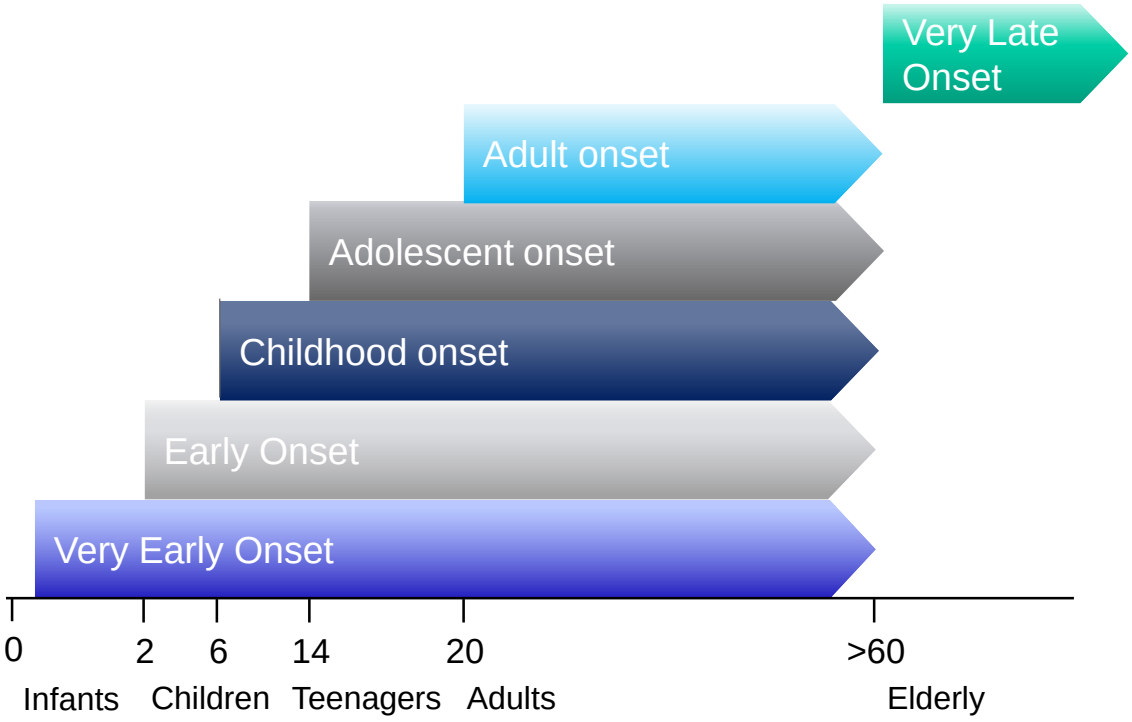
Associated Features

- Atypical vascular responses
- Keratosis pilaris/pityriasis alba/hyperlinear palms/ichthyosis
- Ocular/periorbital changes
- Other regional findings
- Perifollicular accentuation/lichenification/ prurigo lesions

IgE, immunoglobulin E.
*Exclusionary conditions include scabies, seborrheic dermatitis, irritant or allergic contact dermatitis, ichthyoses, cutaneous T-cell lymphoma, psoriasis, photosensitivity dermatoses, immune deficiency diseases, erythroderma, or other causes.[1]
1. Eichenfield L, et al. *J Am Acad Dermatol.* 2003;49(6):1088-1095. 2. Eichenfield L, et al. *J Am Acad Dermatol*. 2014;70(2):338-351.

Variations by Age of Onset

Age of Onset and the Natural History of AD[1]*



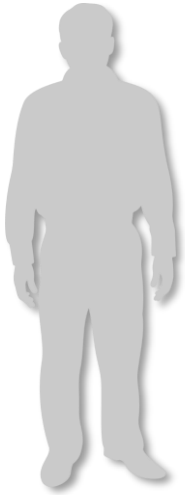
- Studies have identified at least 6 different types of onset of AD[1]
  - Very early (3 months-2 years)
  - Early (2-6 years)
  - Childhood (6-14 years)
  - Adolescent (14-18 years)
  - Adult (20-60 years)
  - Very late (>60 years)

Phenotypic differences have been observed across studies for adult- versus childhood-onset AD[2]

*Without remission.
AD, atopic dermatitis.
1. Bieber T, et al. *J Allergy Clin Immunol.* 2017;139(4S):S58-S64; 2. Lee HH, et al. *J Am Acad Dermatol.* 2019;80(6):1526-1532.e7.

Atopic Dermatitis (AD): Adult and Pediatric Epidemiology

Approximately 40% of pediatric patients have recurrent symptoms into adulthood[1]



Pediatric[1]

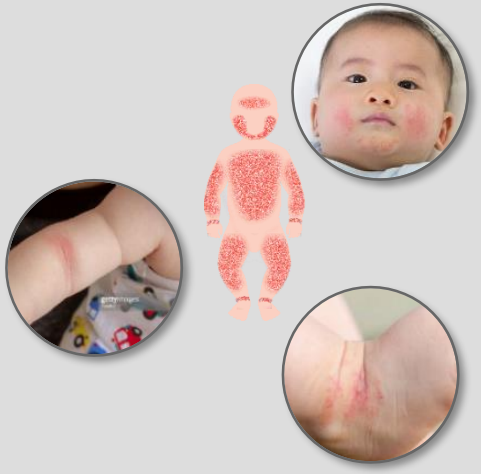
- Approximately 45% of patients develop early-onset AD during the first 6 months of life
- 85% of patients develop AD before the age of 5 years

Adult[2]

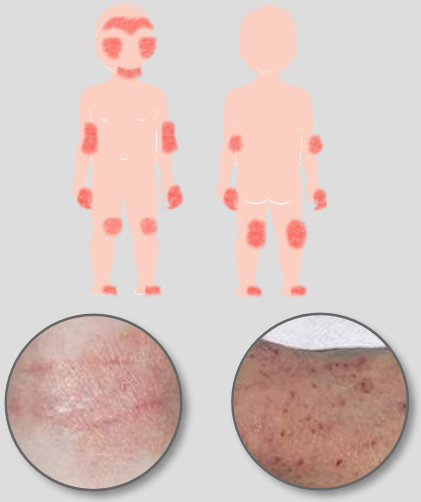
- The prevalence of AD in adults is approximately 7%
- One in four adults with AD report adult onset of their disease

1. McAleer MA, et al. Atopic dermatitis. In: Bolognia JL, et al, eds. *Dermatology*. 4th ed. Elsevier; 2018:208-227; 2. Vakharia PP, Silverberg J. *Am J Clin Dermatol*. 2019;20(6):771-779.

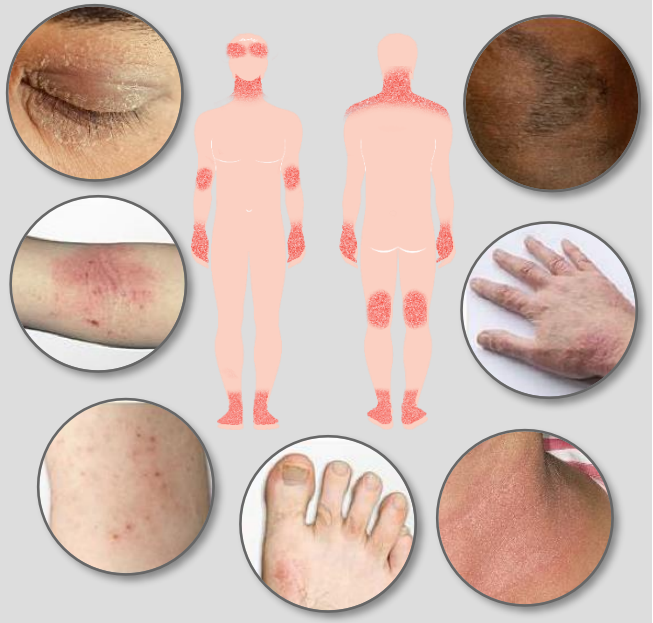
AD Clinical Phenotype: The Age-Related Clinical Picture



INFANTS:
Lesions often initially appearing as edematous papules and papulovesicles on the cheeks; lesions become drier with oozing and crusting and most commonly appear on forehead, cheeks, neck, elbows, and knees[1]



CHILDREN:
Lesions often confined to flexures of elbows and knees as well as wrists and ankles; lesions may become lichenified with excoriations, papules, and nodules[2]



ADULTS:
Lesions present at head, neck, shoulders, flexures, wrists, and ankles; AD is more likely to have an extensive and erythrodermic aspect in patients with a longstanding natural history of AD[3,4]

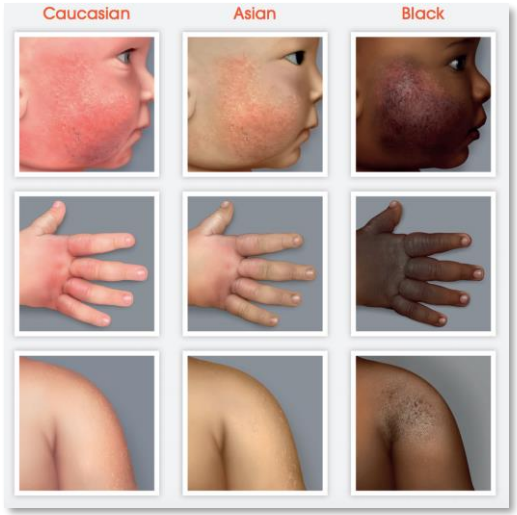
AD may present differently in infants, children, and adults[5]

AD, atopic dermatitis.

1. McAleer MA, et al. Atopic dermatitis. In: Bolognia JL, et al, eds. *Dermatology.* 4th ed. Elsevier; 2018:208-227; 2. Thomsen SF. *ISRN Allergy*. 2014:354250. doi:10.1155/2014/354250;
3. Weidinger S, Novak N. *Lancet.* 2016;387(10023):1109-1122; 4. Bieber T, et al. *J Allergy Clin Immunol*. 2017;139(4S):S58-S64; 5. Ahn C, Huang W. *Ad Exp Med Bio*l. 2017;1027:39-46.

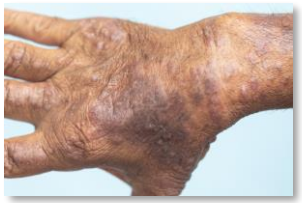
Assessing AD in Different Skin Types

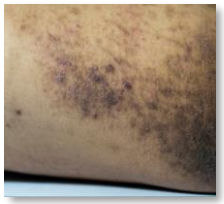
Patients with SOC may have a unique pattern of AD presentation, which can pose a challenge in the diagnosis and severity assessment of AD[1,2]

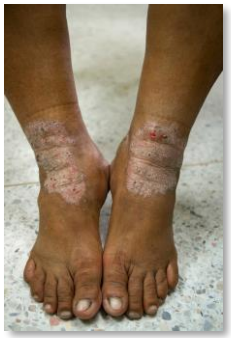


© Eczema Foundation
Please note that these are not actual patient images.

- Erythema may be less pronounced and may appear violaceous[1]
- May develop close-set, small, pruritic follicular papules[2]
- Lichenoid lesions are more common[1,3]
- Extensor involvement may be present[1]
- There is a greater risk of post-inflammatory hyper/hypopigmentation[1]







Images used under license from Shutterstock.com.

Understanding the unique characteristics of AD in patients with SOC can lead to better disease management[4]

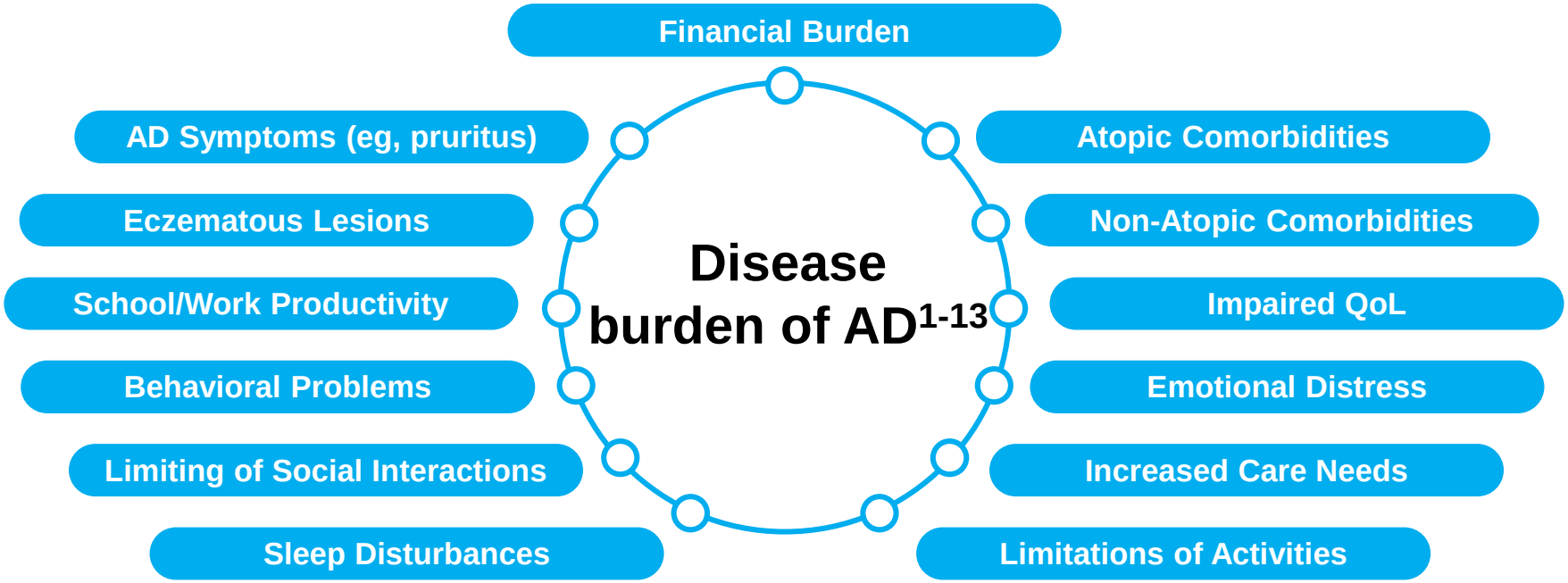
AD, atopic dermatitis; SOC, skin of color.
1.Kaufman BP, et al. *Exp Dermatol.* 2018;27(4):340-357; 2. Silverberg NB. *Clin Dermatol.* 2017;35(4):354-359; 3. Leung DY. *J Allergy Clin Immunol.* 2015;136(5):1265-1267;
4. Vachiramon V, et al. *Pediatr Dermatol.* 2012;29(4):395-402.

Scoring Systems for Clinician Assessment of AD: Disease Severity

Scoring System	Description	Severity Rating
Consider for Use in Clinical Practice*		
Patient-Oriented SCORAD (PO-SCORAD)[1†]	Adaptation of SCORAD for patients that assess extent of affected areas, severity of dry skin outside affected areas, symptom intensity of affected areas, severity of itching, and sleep disturbance	Mild <25, moderate >25 to <50, severe >50
Patient-Oriented Eczema Measure (POEM)[1†‡]	7 symptoms scored over past week (how many days has your skin been itchy, red, bleeding, weeping or oozing clear fluid, cracked, flaking, felt dry or rough because of your eczema)[†]	Clear or almost clear 0–2, mild 3–7, moderate 8–16, severe 17–24, very severe 25–28
Investigator Global Assessment (IGA)[1]	FDA categorization of AD severity based on investigator's subjective assessment of a representative lesion according to erythema, induration or papulation, and/or oozing or crusting	0 = clear to 4 = severe
Often Used in Clinical Trials		
Peak Pruritus Numerical Rating Scale (NRS)[2]	Single self-reported item designed to measure peak pruritus, or "worst" itch over previous 24 hours	0 = "no itch" to 10 = "worst itch imaginable"
Eczema Area and Severity Index (EASI)[1]	2 components: (1) area score recorded for 4 regions; (2) severity score for each region calculated based on scratching, lichenification, intensity of redness, thickness or swelling	Mild 1.1–7, moderate 7.1–21, severe 21.1–50, very severe 50.1–72

AD, atopic dermatitis; FDA, Food and Drug Administration; HOME, Harmonising Outcome Measures for Eczema.
*BSA is also assessed in clinical practice; however, there are no defined severity assessments for this parameter.
† Assessed as a patient-reported outcome measure.
‡Recommended by HOME organization.
1. Boguniewicz M, et al. *Ann Allergy Asthma Immunol*. 2018;120(1):10-22.e2; 2. Yosipovitch G, et al. *Br J Dermatol*. 2019;181(4):761-769.

AD Disease Burden



AD has an impact on adult and pediatric patients and their caregivers

AD, atopic dermatitis; QoL, quality of life.

1. Weidinger S, Novak N. *Lancet.* 2016;387(10023):1109-1122; 2. Nutten SA. *Nutr Metab*. 2015;66(suppl 1):8-16; 3. Simpson E. *Curr Dermatol Rep.* 2012;1(1):29-38; 4. Zuberbier T, et al. *J Allergy Clin Immunol*. 2006;118(1):226-232; 5. Drucker AM, et al. *J Invest Dermatol*. 2017;137(1):26-30; 6. Lewis-Jones S. *Int J Clin Pract*. 2006;60(8):984-992; 7. Strom MA, et al. *Br J Dermatol*. 2016;175(5):920-929; 8. Moore K, et al. *Br J Dermatol*. 2006;154(3):514-518; 9. Ramirez FD, et al. *JAMA Dermatol*. 2019;155(5):556-563; 10. Chung J, Simpson EL. *Ann Allergy Asthma Immunol*. 2019;122(4):360-366; 11. Eckert L, et al. *J Am Acad Dermatol*. 2017;77(2):274-279.e3; 12. Silverberg JI, et al. *Ann Allergy Asthma Immunol*. 2018;121(3):340-347; 13. Simpson EL, et al.*JAMA Dermatol*. 2018;154(8):903-912.

AD Comorbidities

Atopic Disease[1]	• **History of allergic rhinitis** is common and patients are at increased risk for **developing asthma** • **Food allergies** have been reported with high prevalence and may be more severe
Sleep Disturbance[2]	• **More frequent sleep disturbances** have been observed in patients with moderate-to-severe AD than patients with mild AD
Mental Health[3]	• **Depression and suicidal ideation** may be more likely in adults and children with AD
Infection[4-6]	• **Higher risk of skin infections** (eg, impetigo, cellulitis, MRSA) was associated with AD in pediatric and adult patients • **Urinary tract infections, strep throat, and ear infections** may occur more frequently • **Viral infections** (EC, EH, eczema vaccinatum, molluscum contagiosum) may occur more frequently

Other[7,8]	• **Emerging data suggests**
	  • AD patients have moderately **increased risk of non-fatal cardiovascular** outcomes
	  • Patients with moderate-to-severe AD may be **at increased risk for osteoporosis**, particularly older adults

AD, atopic dermatitis; EC, eczema coxsackium; EH, eczema herpeticum; MRSA, methicillin-resistant *Staphylococcus aureus*.

1. Silverberg JI, et al. *Pediatr Allergy Immunol*. 2013;24(5):476-486; 2. Simpson EL, et al. *JAMA Dermatol.* 2018;154(8):903-912; 3. Patel KR, et al. *J Am Acad Dermatol*. 2019;80(2):402-410; 4. Serrano L, et al. *J Am Acad Dermatol*. 2019;80(4):904-912; 5. Sun D, Ong PY. *Immunol Allergy Clin North Am*. 2017;37(1):75-93; 6. Thomsen SF. *ISRN Allergy.* 2014:354250; 7. Silverwood RJ, et al. *BMJ*. 2018;361:k1786. doi:10.1136/bmj.k1786; 8. Shaheen MS, et al. *J Am Acad Dermatol.* 2019;80(2):550-551.

Management of Atopic Dermatitis

Goals of Treatment[1-7]

Treatment Goals

1. Reduce the number and severity of flares
2. Reduce pruritus
3. Maintain normal activities of daily living
4. Maximize disease-free periods
5. Prevent infectious complications
6. Avoid/minimize side effects of treatment
7. Achieve clear skin rapidly and induce long-term remission
8. Avoid pigmentary changes
9. Improve sleep and mental health

1. Schneider L, et al. *J Allergy Clin Immunol.* 2013;131(2):295-299.e27; 2. Lyons JJ, et al. *Immunol Allergy Clin North Am.* 2015;35(1):161-183; 3. Tang TS, et al. *J Allergy Clin Immunol*. 2014;133(6):1615-1625.e1; 4. Boguniewicz M, et al. *Ann Allergy Asthma Immunol.* 2018;120 (1):10-22.e2; 5. Brar KK, et al. *J Allergy Clin Immunol Pract.* 2019;7(1):1-16; 6. Silverberg JI. F1000Res. 2018;7:303; 7. Davis EC, et al. *J Clin Aesthet Dermatol*. 2010;3(7):20-31.

General Approach to the Management of AD

Nonpharmacologic[1]

- Moisturizers
- Bathing practices
- Wet-wrap therapy
- Phototherapy

Pharmacologic[2]

- Topical corticosteroids
- Topical calcineurin inhibitors
- Topical PDE4 inhibitor
- Systemic immunosuppressants*
- Monoclonal antibody IL-4/IL-13 inhibitor

AD, atopic dermatitis; IL, interleukin; PDE, phosphodiesterase.
*Not all systemic immunosuppressants are approved in the United States.
1. Eichenfield LF, et al. *J Am Acad Dermatol*. 2014;71(1):116-132; 2. Boguniewicz M, et al. *Ann Allergy Asthma Immunol.* 2018;120(1):10-22.e2.

Guidelines, Updates, and Clinical Reports[1-4]

Expert Opinions	Year Published	Target Audience	Organization
Atopic Dermatitis: A Practice Parameter Update 2012	2013	Allergists	AAAAI/ACAAI Joint Task Force
Guidelines of Care for the Management of Atopic Dermatitis	2014	Dermatologists	AAD
Clinical Report: Atopic Dermatitis: Skin-Directed Management	2014	Pediatricians	AAP
Atopic Dermatitis Yardstick	2018	Allergists Dermatologists Pediatricians	ACAAI

AAAAI, American Academy of Allergy, Asthma & Immunology; AAD, American Academy of Dermatology; AAP, American Academy of Pediatrics; ACAAI, American College of Allergy, Asthma & Immunology

1. Eichenfield LF, et al. *J Am Acad Dermatol*. 2014;71(1):116-132; 2. Schneider L, et al. *J Allergy Clin Immunol*. 2013;131(2):295-299.e27; 3. Tollefson MM, Bruckner AL. *Pediatrics.* 2014;134(6):e1735-e1744; 4. Boguniewicz M, et al. *Ann Allergy Asthma Immunol*. 2018;120(1):10-22.e2.

Pharmacologic Therapies for Mild-to-Moderate Atopic Dermatitis

TCSs[1]

- Decrease acute and chronic symptoms of AD and relieve itch
- Use for active inflammation and relapses; mid/high potency for flare-ups; lowest effective potency for maintenance
- Can be used intermittently and proactively as maintenance therapy (1-2 times/wk) on areas that commonly flare

TCIs[1-3]

- Available agents have varied indications based on AD severity
- Relieve inflammatory signs and symptoms
- Can be used intermittently and proactively as maintenance therapy (2-3 times/wk) on areas that commonly flare

PDE4 Inhibitor[4]

- Topical nonsteroidal PDE4 inhibitor for mild to moderate AD in patients aged ≥3 months and older
- Used twice daily to affected areas

AD, atopic dermatitis; PDE, phosphodiesterase; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

1. Eichenfield LF, et al. *J Am Acad Dermatol*. 2014;71(1):116-132; 2. Elidel [package insert]. Bridgewater, NJ. Valeant Pharmaceuticals North America LLC; 2017; 3. Protopic [product monograph]. Parsippany, NJ: LEO Pharma Inc; 2016; 4. EUCRISA® (crisaborole) Full Prescribing Information. April 2020.

Pharmacologic Therapies for Moderate-to-Severe Atopic Dermatitis

TCSs[1]

- Decrease acute and chronic symptoms of AD and relieve itch
- Use for active inflammation and relapses; mid/high potency for flare-ups; lowest effective potency for maintenance
- Can be used intermittently and proactively as maintenance therapy (1-2 times/wk) on areas that commonly flare

TCIs[1-3]

- Available agents have varied indications based on AD severity
- Relieve inflammatory signs and symptoms
- Can be used intermittently and proactively as maintenance therapy (2-3 times/wk) on areas that commonly flare

Monoclonal Antibody[4]

- Injectable monoclonal antibody IL-4/IL-13 inhibitor for moderate-to-severe AD in adult and pediatric patients

Systemic Immunosuppressants[5*]

- Systemic immunosuppressants for symptoms not controlled by topical treatments

AD, atopic dermatitis; IL, interleukin; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.
*Used off-label for treatment of AD in the US.
1. Eichenfield LF, et al. *J Am Acad Dermatol*. 2014;71(1):116-132; 2. Elidel [package insert]. Bridgewater, NJ. Valeant Pharmaceuticals North America LLC; 2017; 3. Protopic [product monograph]. Parsippany, NJ: LEO Pharma Inc; 2016; 4. Dupixent [prescribing information]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2020. 5. Sidbury R, et al. *J Am Acad Dermatol*. 2014;71(2):327-349.

Backup

Scoring Systems for Clinician Assessment of AD: QOL Scales

Consider for Use in Clinical Practice

Scoring System	Description	Severity Rating
Dermatology Life Quality Index (DLQI)	10-item questionnaire that inquires about skin symptoms, feelings of embarrassment, and how skin disease has affected day-to-day activities, working, and social life	Each question on DLQI is scored from 0 to 3, with a maximum score of 30 and high scores representing worse QoL
Children's Dermatology Life Quality Index (CDLQI)	10 questions designed for children ages 4 through 16 that encompass different aspects of a child's life that could be affected by their skin disease. The instrument includes physical symptoms, such as itching and sleep loss, as well as psychosocial questions regarding friendships, bullying, school performance, sports participation, and enjoyment of vacation	The questions are graded from 0–3, with a possible maximum score of 30, with higher scores representing worse QoL
Infants' Dermatitis Quality of Life Index (IDQOL)	10 questions regarding an infant or young child's difficulties with mood, sleep, bathing, dressing, play, mealtimes, other family activities, and treatment	Each question is graded from 0–3, with a maximum total score of 30
The Dermatitis Family Impact (DFI)	10 questions related to housework, food preparation and feeding, sleep, family leisure activity, shopping, expenditure, fatigue, emotional distress, and relationships	Each question is graded from 0–3, with a maximum possible score of 30

Rehal B, et al. *PLoS ONE*. 2011;6(4):e17520. doi:10.1371/journal.pone.0017520.

Scoring Systems for Clinician Assessment of AD: QOL Scales (cont'd)

Often Used in Clinical Trials

Scoring System	Description	Severity Rating
Parent's Index of Quality of Life in Atopic Dermatitis (PIQoL-AD)[1]	28 questions designed to assess the QOL of parents with children aged 8 years or younger	Scores range from 0 to 28, with a high score indicating poor QoL
Eczema Disability Index (EDI)[2]	15 questions categorized under 5 headings including daily activity, work or school, personal relationships, leisure, and treatment	Each question is answered on a 1-7 linear analogue scale, representing grades from "not at all" to "very much"
Skindex[3]	Skindex-29: 29-question version of Skindex that measures frequency of experience based on symptoms, emotions, and functions Skindex-16: 16-question version of Skindex that measures bother of experience based on symptoms, emotions, and functions	All responses are transformed to a linear scale of 100, varying from 0 (no effect) to 100 (effect experienced all the time)
Short Form 36 (SF-36)[4]	36 questions assessing 8 domains of health status, including physical functioning, usual physical role activities, bodily pain, general health prescriptions, vitality, social functioning, usual emotional role activities, and mental health	All scores are standardized on a scale of 0-100, with higher scores indicating a better QoL
Hospital Anxiety and Depression Scale (HADs)[5]	14 questions designed to assess anxiety and depression symptoms in patients (7 questions in each subscale)	Each question is rated on a 4-point (0-3) scale, giving maximum scores of 21 for anxiety and 21 for depression

1. McKenna SP, et al. *Qual Life Res*. 2005;14(1):231-241; 2. Salek MS, et al. *Br J Dermatol*. 1993;129(4):422-430; 3. Chren MM. *Dermatol Clin*. 2012;30(2):231-236, xiii; 4. Maksimović N, et al. *J Dermatol.* 2012;39(1):42-47; 5. Snaith RP. *Health Qual Life Outcomes*. 2003;1:29. doi:10.1186/1477-7525-1-29.