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In Atopic Dermatitis, Looks Can Be Deceiving

During a Science and Innovation Theater presentation at the 2016 Academy of Managed Care Pharmacy annual meeting in San Francisco, California (April 19-22, 2016), Jonathan Silverberg, MD, PhD, MPH, assistant professor of dermatology at Northwestern University Feinberg School of Medicine, uncovered the burdens of atopic dermatitis (AD); communicated the current science, which demonstrates the underlying inflammation in AD; highlighted the association between inflammation and T helper type 2 cell (Th2)-driven immune dysregulation; and described how optimal management can reset expectations of disease control.

This conference presentation and supplement were sponsored by Regeneron Pharmaceuticals, Inc, and Sanofi US.

BURDEN OF AD

AD is a common, chronic, inflammatory skin disease.¹ It is associated with immune dysregulation and skin barrier dysfunction.²

Prevalence and Age of Onset

AD affects millions in the United States and it is one of the most common dermatoses.^{3,4} The number of individuals affected has been increasing in industrialized countries.⁴ Up to 10% of adults have eczema, and an estimated 3.2%, or 7 to 8 million US adults, have AD.^{3,5} It is estimated that 1.6 million adults who have been diagnosed and treated for moderate-to-severe disease remain uncontrolled.⁶⁻⁸ Up to 25% of children experience AD, and it is the top diagnosis at dermatologist visits in children 4 years and younger.^{9,10}

However, AD is not just a pediatric disease.² The onset of symptoms spans all ages (Figure 1¹¹).^{2,11} AD may be a persistent, life-long disease. The Pediatric Eczema Elective Registry follow-up examined the natural history of children with mild-to-moderate AD (N = 7157).¹² Figure 2¹² demonstrates the proportion of individuals with at least 5 years of follow-up at a given age who ever reported a 6-month symptom-free and medication-free period (N = 2416). It was not until 20 years of age that 50% of patients experienced at least one 6-month symptom-free interval.¹²

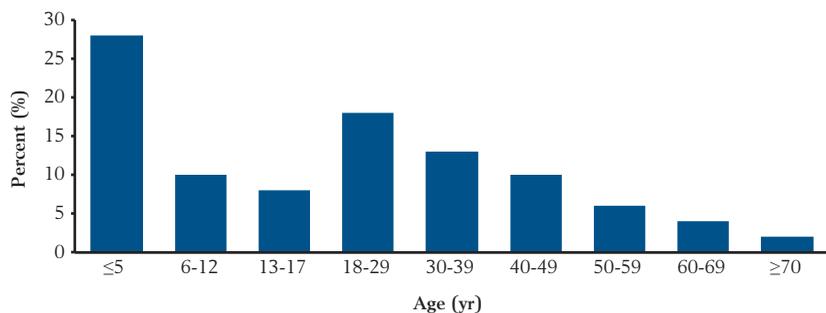
Signs and Symptoms of AD

Patient-reported signs and symptoms of AD can occur on a daily basis. Baseline data for 380 adults with moderate-to-severe AD recruited into a randomized treatment study showed that 91% experienced dry or rough skin 5 to 7 days per week. A total of 78% reported flaking skin, 67% had cracking skin, 51% experienced bleeding, and 34% reported oozing at least 5 days per week (Figure 3¹³).¹³

The presentation of AD differs in its acute, subacute, and chronic forms. Acute and subacute lesions are intensely pruritic and are characterized by erythema, papulovesicles, excoriations, and serous exudate. Chronic lesions are characterized by lichenification, papules, plaques, and excoriations. Patients with moderate-to-severe AD can experience acute and chronic lesion simultaneously.¹⁴



Figure 1. Age of Onset of Symptoms in Individuals With AD (N = 6931) Among Surveyed US Households (N = 42,249)¹¹



AD indicates atopic dermatitis.

In addition to causing dermatologic lesions, patients with AD are susceptible to skin infections and colonization with *Staphylococcus aureus*. In a study of 687 patients with AD, *Staphylococcus aureus* colonization rates of 74% and 38% were reported in acute (n = 97 of 131) and chronic lesions (n = 211 of 556), respectively, versus 3% from the skin of patients with urticaria (n = 8 of 247).¹⁵ Other studies have

shown that AD causes exaggerated clinical manifestations of viral infections and an increased susceptibility to dermatophyte fungal infections.¹⁶

Effects of Symptoms on Daily Life

In patients with moderate-to-severe AD, itch is the most common and persistent burden. Eighty-six percent of patients enrolled in one study reported the daily presence of itch, and more than one-third (41.5%) reported itching at least 18 hours per day.¹³ In another study, approximately 40% of participants who completed an internet-based questionnaire had more than 10 episodes of itch per day, and 35% had experienced itching for over 20 years.¹⁷ In a separate study, more than 50% of participants who completed an internet-based questionnaire reported pain sensation associated with itch.¹⁸

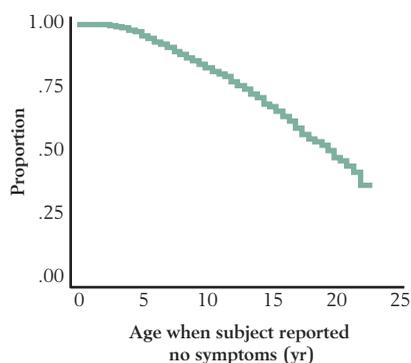
Sleep disruption is also a problem for patients with moderate-to-severe AD. Nearly 9 of 10 patients with moderate-to-severe AD report disrupted sleep at least 1 night a week and slightly more than half have their sleep disrupted at least 5 nights a week.¹³ Sleep disruptions are often doubled in patients with eczema than in those with no disease. In a 2012 US population-based survey (N = 34,613) conducted by the National Health Interview Study, individuals with eczema were more likely than those with no disease to experience fatigue (adjusted OR 2.23; 95%

CI, 1.93-2.58), daytime sleepiness (OR 2.04; 95% CI, 1.75-2.38), insomnia overall (OR 1.83; 95% CI, 1.59-2.12), insomnia and fatigue (OR 2.74; 95% CI, 2.28-3.29), and insomnia and daytime sleepiness (OR 2.47; 95% CI, 2.04-2.99) (all significant [$P < .0001$]).¹⁹

AD occurs in relapsing and remitting cycles.²⁰ In the International Study of Life with Atopic Eczema (ISOLATE), patients (>13 years) and caregivers (of children 2-13 years) underwent in-depth telephone interviews. The study included a minimum of 150 patients recruited from 8 countries; all patients had moderate-to-severe AD. The 1371 patients with moderate AD reported an average of 8.3 episodes of exacerbated symptoms per year, totaling 113 symptomatic days per year and 33 nights of sleep disruption per year (calculated by multiplying the number of flares per year by the number of nights sleep was affected during a flare). For the 631 patients with severe AD, exacerbated symptoms occurred nearly once per month, an average of 11.1 episodes each year. These patients experienced exacerbated symptoms for more than half the year (192 days) and sleep disruption nearly half the nights in a year (162 nights).²¹

Psychosocial dysfunction is increased among patients with AD. Patients of the ISOLATE study reported that the AD flare caused concern about their appearance, affected their self-confidence, and led to feeling unhappy or depressed. Patients with moderate-to-severe AD report feelings of embarrassment and low self-confidence, problems with personal and social relationships, and problems with work.²¹ In a study of 102 patients who self-rated their AD as severe, 47% reported being frustrated by the disease, 39% were embarrassed by their appearance, and 35% were angry about their appearance.²² A cross-sectional study of patients (N = 266) with moderate-to-severe AD and their partners revealed that 58% experienced a decrease in sexual desire

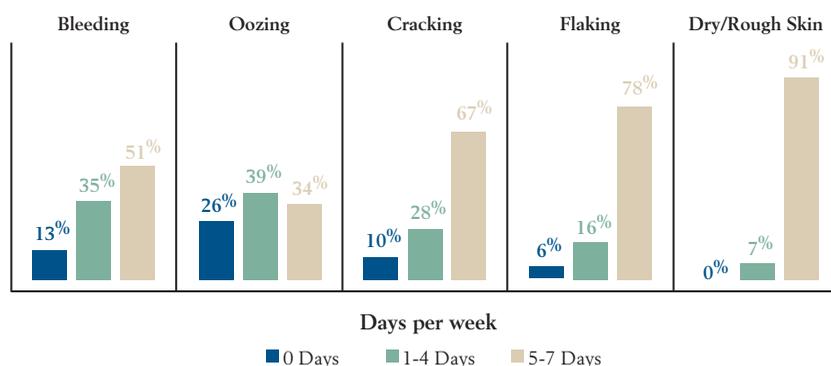
Figure 2. Cumulative Proportion of Subjects Reporting No Symptoms¹²



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Figure 3. Patient-Reported Signs and Symptoms of AD Can Occur on a Daily Basis—Study of 380 Adults With Moderate-to-Severe AD¹³



AD indicates atopic dermatitis.

Reprinted from Simpson EL, Bieber T, Eckert L, et al. *J Am Acad Dermatol*. 2016;74(3):491-498, with permission from Elsevier.

at least occasionally. In addition, 55% said that the appearance of skin affects their sex life, and 47% said that the disease treatment affects their sex life.²³

Behavioral, emotional, and psychological disorders are also increased in patients with AD. AD is independently associated with stress-related, behavioral, affective, and schizophrenic disorders.²⁴ Anxiety, as measured by different clinical scales, is increased in patients with AD.²⁵⁻²⁷ Depressive symptoms are also increased in patients with AD.²⁶

Disease Assessment

Disease assessment is largely based on clinical judgment. A plethora of instruments are used to assess severity in clinical trials. However, they are rarely used in clinical practice. Clinicians should ask patients general questions about the impact of AD on daily activity and use available scales mainly when practical.⁹ More than 25 disease severity scales are available, including:

- Severity Scoring of Atopic Dermatitis (SCORAD)
- Eczema Area and Severity Index (EASI)
- Investigators' Global Assessment (IGA)
- Six-Area, Six-Sign Atopic Dermatitis (SASSAD)
- Leicester Sign Score (LSS)

- Total Severity Score (TSS)
- Atopic Dermatitis Severity Index (ADSI)
- Total Body Severity Assessment (TBSA)
- Three-Item Severity Scale (TISS)^{9,28}

Two commonly used quality-of-life scales across AD and other diseases include:

- Dermatology Life Quality Index (DLQI)
- 36-Item Short-Form Health Survey (SF-36)^{28,29}

THE ROLE OF INFLAMMATION IN AD

AD is a systemic, immune-driven disease. Researchers have proposed 2 hypotheses in AD pathogenesis: an epidermal-based model (“outside-in”) and an immune-based model (“inside-out”). Regardless of initiation, in either model, the result is a state of disease.¹

Epidermal-Based Model

In the epidermal-based model (“outside-in”), AD is initiated by an epidermal barrier defect that occurs either through a genetic or acquired basis, with subsequent systemic immune activation mediated by memory Th2 cells.^{30,31} An abnormal skin barrier leads to antigen penetration and subsequent immune activation.³² The

epidermal-based model is supported by mutations in structural proteins such as filaggrin, envelope precursor proteins, and claudin.^{31,32}

Immune-Based Model

In the immune-based model (“inside-out”), AD is considered an immunologic disorder, with contributing barrier dysfunction.³³ AD is initiated by activated memory Th2 cells that secrete several systemic cytokines, leading to widespread activation of the immune system.³⁴ Activation of Th2 cells and downstream signaling pathways result in epidermal hyperplasia.^{33,34}

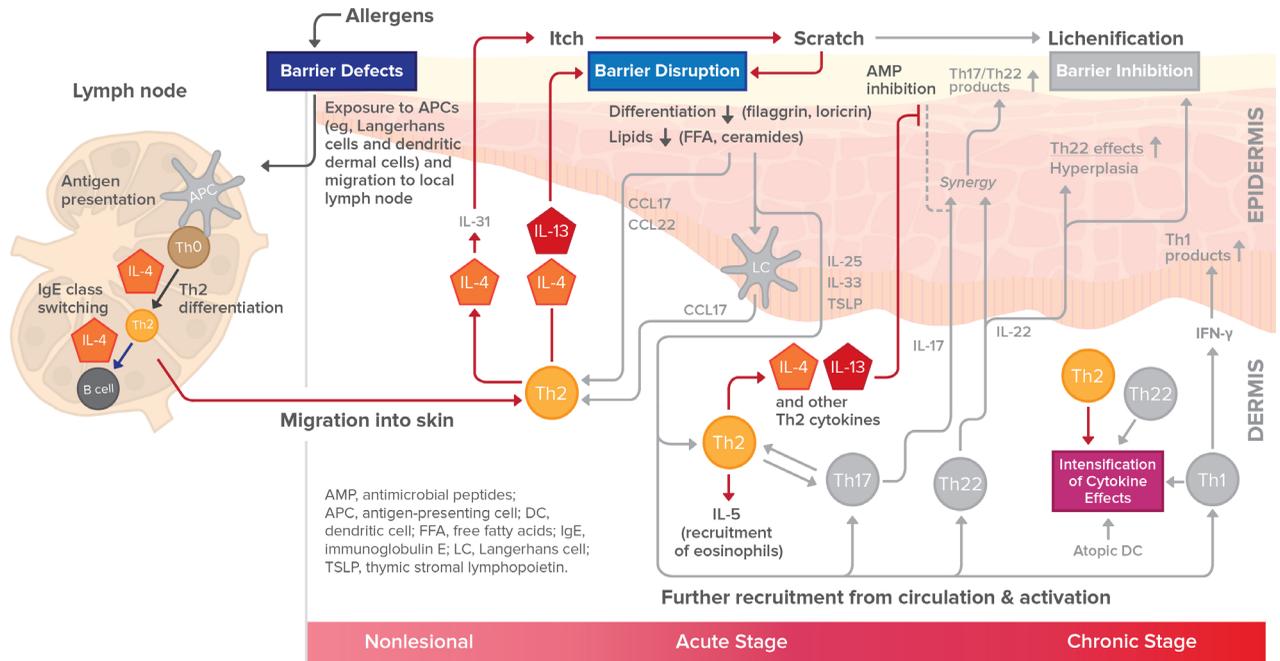
Drivers of Inflammation in AD

Interleukins (ILs) are cytokines secreted by white blood cells that regulate the function of the immune system. IL-4 and IL-13 are key drivers in the underlying inflammatory process that drives itch and lesions.^{35,36} IL-4 and IL-13 represent key upstream drivers in the Th2 pathway that modulate multiple downstream mediators—including IL-5, IL-31, and immunoglobulin E—setting in motion the chronic underlying inflammation of AD (Figure 4).³⁵⁻⁴⁰^{36,37}

In acute and chronic lesions, the combined effects of IL-4 and IL-13 create a positive feedback loop. Increased expression of IL-4 and IL-13 decreases the production of structural proteins and antimicrobial proteins, resulting in a weakened skin barrier and increased susceptibility to infection. Keratinocytes are also affected, resulting in decreased keratinocyte differentiation. The number of infiltrating immune cells increases, in turn causing increased expression of IL-4 and IL-13.⁴⁰ Increases in IL-4 and IL-13 activity correlate with the appearance of acute lesions; expression of these cytokines is also elevated in chronic disease.³⁶

Elevated cytokine expression is persistent in skin lesions. In 1 study, expression of IL-4 and IL-13 was measured with reverse transcriptase-polymerase

Figure 4. IL-4 and IL-13: Key Drivers in the Underlying Inflammatory Process That Drives Itch and Lesions³⁵⁻⁴⁰



IL-4 and **IL-13** represent key upstream drivers in the Th2 pathway that modulate multiple downstream mediators—including IL-5, IL-31, and IgE—setting in motion the chronic underlying inflammation of atopic dermatitis.

AMP indicates antimicrobial peptide; APC, antigen-presenting cell; CCL, chemokine (C-C motif) ligand; FFA, free fatty acids; IFN, interferon; IgE, immunoglobulin E; IL, interleukin; LC, Langerhans cell; Th, T helper; TSLP, thymic stromal lymphopoietin.

Adapted from Mollanazar NK, Smith PK, Yosipovitch G. *Clin Rev Allergy Immunol*. doi: 10.1007/s12016-015-8488-5. Gittler JK, Shemer A, Suárez-Fariñas M, et al. *J Allergy Clin Immunol*. 2012;130(6):1344-1354. doi: 10.1016/j.jaci.2012.07.012. Biedermann T, Skabytska Y, Kaesler S, Volz T. *Front Immunol*. 2015;6:353. doi: 10.3389/fimmu.2015.00353. Guttman-Yassky E, Dhingra N, Leung DY. *Expert Opin Biol Ther*. 2013;13(4):549-561. doi: 10.1517/14712598.2013.758708. Noda S, Krueger JG, Guttman-Yassky E. *J Allergy Clin Immunol*. 2015;135(2):324-336. doi: 10.1016/j.jaci.2014.11.015. Guttman-Yassky E, Nogales KE, Krueger JG. *J Allergy Clin Immunol*. 2011;127(6):1420-1432. doi: 10.1016/j.jaci.2011.01.054.

chain reaction testing of intrapersonal biopsy samples from acute and chronic skin lesions and nonlesional skin of patients with moderate-to-severe AD (N = 17).³⁶ Expression of IL-4 was significantly higher in acute lesions than in nonlesional skin ($P < .05$), and expression of IL-13 was significantly higher in chronic lesions than in nonlesional skin ($P < .01$) (Figure 5³⁶).

Abnormalities in Atopic Skin

AD causes genomic, immunologic, and epidermal abnormalities in both lesional and nonlesional skin. In 1 study, biopsy samples from nonlesional and lesional skin of patients with

moderate-to-severe AD (n = 15) were compared with skin from normal, healthy volunteers (n = 10). Genomic profiling revealed that gene expression patterns in nonlesional and lesional skin in patients with AD differ from normal skin. In AD, nonlesional skin and lesional skin have similar differential gene expression in moderate-to-severe disease. In the same study, nonlesional skin in AD demonstrated immune and epidermal abnormalities. The cluster of differentiation 3 cutaneous T-cell population was significantly (86%) higher in nonlesional atopic skin than in normal skin from healthy volunteers ($P < .001$). Ki-67 cell pro-

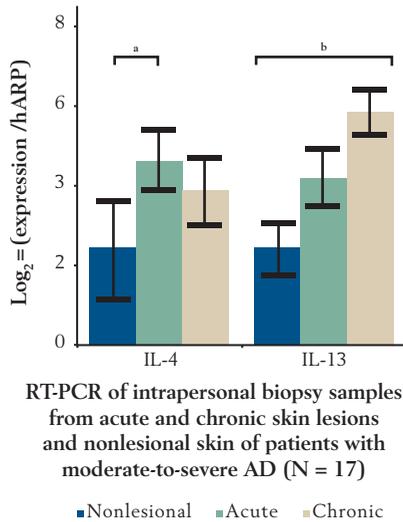
liferation was 218% higher in nonlesional atopic skin than in normal skin from healthy volunteers ($P < .05$). In the histological analysis, hematoxylin and eosin staining revealed differences in both nonlesional and lesional atopic skin compared with non-atopic normal skin (Figure 6⁴¹).

MANAGEMENT STRATEGIES

Traditional Strategies

Traditional management strategies for AD are reactive, and focus on treating disease flares as they arise.⁴² As the intensity of disease increases, therapies are added in a stepwise

Figure 5. Elevated Cytokine Expression Is Persistent in Skin Lesions³⁶



AD indicates atopic dermatitis; hARP, human acidic ribosomal protein; IL, interleukin; RT-PCR, real-time polymerase chain reaction.
^a*P* < .05.
^a*P* < .01.

Reprinted from Gittler JK, Shemer A, Suárez-Fariñas M, et al. Progressive activation of T(H)2/T(H)22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. *J Allergy Clin Immunol.* 2012;130(6):1344-1354, with permission from Elsevier.

fashion. Patients with dry skin only receive basic treatment which focuses on skin hydration and emollients, avoidance of irritants, and identification and addressing of specific trigger factors. Patients with mild-to-moderate AD are prescribed low- to mid-potency topical corticosteroids and topical calcineurin (for patients over 2 years), with higher-potency formulations used as the disease progresses to moderate-to-severe AD. Patients with recalcitrant, severe AD receive systemic or UV therapy (Figure 7⁴³).⁴³

With traditional management strategies, patients receive anti-inflam-

Figure 6. Nonlesional Skin in AD Demonstrates Immune and Epidermal Abnormalities⁴¹



AD indicates atopic dermatitis; H&E, hematoxylin and eosin.

Suárez-Fariñas M, et al. Nonlesional atopic dermatitis skin is characterized by broad terminal differentiation defects and variable immune abnormalities. *J Allergy Clin Immunol.* 2011;127(4):954-964. © Elsevier Editeur. All rights reserved.

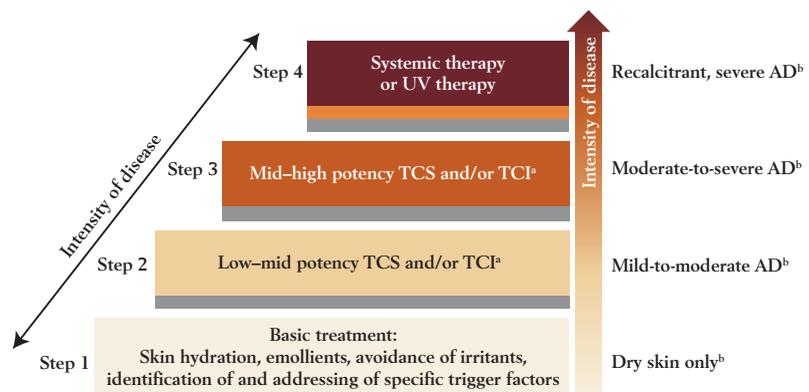
matory treatment of visible lesions only.⁴² The underlying disease remains unchanged, and symptoms of AD recur after each treatment cycle ends (Figure 8A^{44,45}).⁴⁴⁻⁴⁶

Proactive Treatment Strategies

Improved management strategies focus on reducing the severity and

incidence of flares. There is a recent trend toward proactive treatment in AD with topical corticosteroids or topical calcineurin inhibitors.⁴⁵ With this strategy, patients receive an induction course of treatment that continues until symptoms are in remission. Twice-weekly maintenance therapy is aimed at keeping symptoms at or

Figure 7. Traditional Management Strategies Versus Disease Severity⁴³

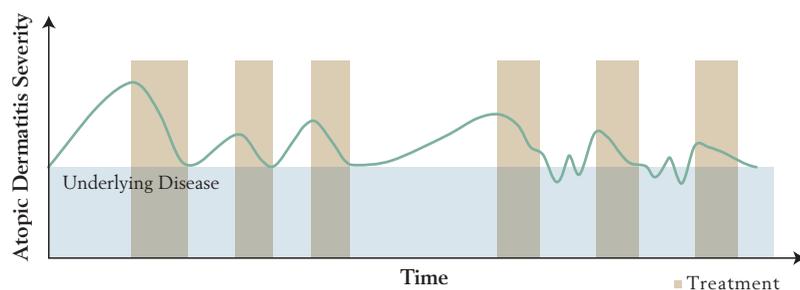
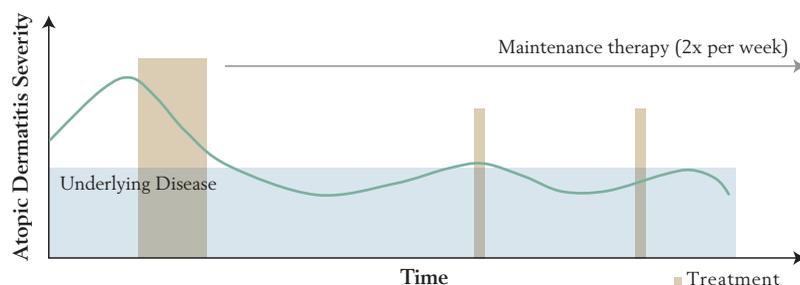


AD indicates atopic dermatitis; TCI, topical calcineurin; TCS, topical corticosteroid; UV, ultraviolet.

^aPatients older than 2 years.

^bDisease severity assessed individually by clinician.

Reprinted with permission from Akdis CA, Akdis M, Bieber T, et al; European Academy of Allergology; Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Group. Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report. *Allergy.* 2006;61(8):969-987.

**Figure 8 (A).** Reactive Treatments: Anti-inflammatory Treatment of Visible Lesions Only^{44,45}**Figure 8 (B).** Conceptual Representation of Proactive Therapy^{42,44}

below the threshold of symptomatic disease (Figure 8B^{42,44}).^{42,44}

Opportunities to Optimize Management

Future management of AD can be improved by creating practical, clinically relevant definitions and methods to assess disease severity and control.^{47,48} There is a need for more specific long-term treatments that target the immune-mediated inflammatory nature of AD.³⁸ During a question-and-answer session with an editor from the *American Journal of Managed Care*, Dr Silverberg remarked, “I think that for patients who require longer-term control ... there has to be a balance between regulating costs and ensuring that patients have access to these drugs, especially when they are suffering.” Also, increased patient education on the disease course and treatment of AD may optimize management.⁴⁹

SUMMARY

- AD is a common, chronic, inflammatory skin disease that may require continuous, long-term management in moderate-to-severe cases.
- In addition to barrier dysfunction, current understanding of the pathophysiology of AD has identified specific inflammatory mediators, including the Th2 cytokines IL-4 and IL-13, which are central to perpetuating the disease.
- AD has a significant impact on patients’ physical and emotional health, which can affect their quality of life.

REFERENCES

1. Leung DY, Guttman-Yassky E. Deciphering the complexities of atopic dermatitis: shifting paradigms in treatment approaches. *J Allergy Clin Immunol.* 2014;134(4):769-779. doi: 10.1016/j.jaci.2014.08.008.

2. Weidinger S, Novak N. Atopic dermatitis. *Lancet.* 2016;387(10023):1109-1122. doi: 10.1016/S0140-6736(15)00149-X.

3. Welcome to QuickFacts: Arizona. United States Census Bureau website. www.census.gov/quickfacts/table/PST045214/04/embed/accessible. Accessed July 7, 2016.

4. Bieber T. Atopic dermatitis. *Ann Dermatol.* 2010;22(2):125-137. doi: 10.5021/ad.2010.22.2.125.

5. Silverberg JL, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. *J Allergy Clin Immunol.* 2013;132(5):1132-1138. doi: 10.1016/j.jaci.2013.08.031.

6. Data on file. Clinformatics. Sanofi.

7. Data on file. Wei W, Anderson P, Gadhari A, et al. Extent and consequences of inadequate disease control among adults with a history of moderate-to-severe atopic dermatitis (control ID 2466960).

8. Data on file. Adelphi Real World. Atopic dermatitis (AD) 2015 disease specific programme (DSP). Study report: concordance on disease severity. January 2016.

9. Eichenfield LF, Tom WL, Chamlin SL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol.* 2014;70(2):338-351. doi: 10.1016/j.jaad.2013.10.010.

10. Landis ET, Davis SA, Taheri A, Feldman SR. Top dermatologic diagnoses by age. *Dermatol Online J.* 2014;20(4):22368.

11. Hanifin JM, Reed ML; Eczema Prevalence and Impact Working Group. A population-based survey of eczema prevalence in the United States. *Dermatitis.* 2007;18(2):82-91.

12. Margolis JS, Abuabara K, Bilker W, Hoffstad O, Margolis DJ. Persistence of mild to moderate atopic dermatitis. *JAMA Dermatol.* 2014;150(6):593-600. doi: 10.1001/jamadermatol.2013.10271.

13. Simpson EL, Bieber T, Eckert L, et al. *J Am Acad Dermatol.* 2016;74(3):491-498. doi: 10.1016/j.jaad.2015.10.043.

14. Schneider L, Tilles S, Lio P, et al. Atopic dermatitis: a practice parameter update 2012. *J Allergy Clin Immunol.* 2013;131(2):295-299. doi: 10.1016/j.jaci.2012.12.672.

15. Park HY, Kim CR, Huh IS, et al. Staphylococcus aureus colonization in acute and chronic skin lesions of patients with atopic dermatitis. *Ann Dermatol.* 2013;25(4):410-416. doi: 10.5021/ad.2013.25.4.410.

16. Simpson EL. Comorbidity in atopic dermatitis. *Curr Dermatol Rep.* 2012;1(1):29-38. doi: 10.1007/s13671-011-0003-5.

17. Dawn A, Papoiu AD, Chan YH, Rapp SR, Rasette N, Yosipovitch G. Itch characteristics in atopic dermatitis: results of a web-based questionnaire. *Br J Dermatol.* 2009;160(3):642-644. doi: 10.1111/j.1365-2133.2008.08941.x.

18. O’Neill JL, Chan YH, Rapp SR, Yosipovitch G. Differences in itch characteristics between psoriasis and atopic dermatitis patients: results of a web-based questionnaire. *Acta Derm Venereol.* 2011;91(5):537-540. doi: 10.2340/00015555-1126.

19. Silverberg JL, Garg NK, Paller AS, Fishbein AB, Zee PC. Sleep disturbances in adults with eczema are associated with impaired overall health: a US population-based study. *J Invest Dermatol*. 2015;135(1):56-66. doi: 10.1038/jid.2014.325.
20. Torrelo A, Ortiz J, Alomar A, Ros S, Prieto M, Cuervo J. Atopic dermatitis: impact on quality of life and patients' attitudes toward its management. *Eur J Dermatol*. 2012;22(1):97-105. doi: 10.1016/j.jaci.2006.02.031.
21. Zuberbier T, Orlow SJ, Paller AS, et al. Patient perspectives on the management of atopic dermatitis. *J Allergy Clin Immunol*. 2006;118(1):226-232. doi: 10.1016/j.jaci.2006.02.031.
22. Anderson RT, Rajagopalan R. Effects of allergic dermatosis on health-related quality of life. *Curr Allergy Asthma Rep*. 2001;1(4):309-315.
23. Misery L, Finlay AY, Martin N, et al. Atopic dermatitis: impact on the quality of life of patients and their partners. *Dermatology*. 2007;215(2):123-129. doi: 10.1159/000104263.
24. Schmitt J, Romanos M, Pfennig A, Leopold K, Meurer M. Psychiatric comorbidity in adult eczema. *Br J Dermatol*. 2009;161(4):878-883. doi: 10.1111/j.1365-2133.2009.09309.x.
25. Noh S, Kim M, Park CO, Hann SK, Oh SH. Comparison of the psychological impacts of asymptomatic and symptomatic cutaneous diseases: vitiligo and atopic dermatitis. *Ann Dermatol*. 2013;25(4):454-461. doi: 10.5021/ad.2013.25.4.454.
26. Dalgard FJ, Gieler U, Tomas-Aragones L, et al. The psychological burden of skin diseases: a cross-sectional multicenter study among dermatological out-patients in 13 European countries. *J Invest Dermatol*. 2015;135(4):984-991. doi: 10.1038/jid.2014.530.
27. Linnert J, Jemec GB. An assessment of anxiety and dermatology life quality in patients with atopic dermatitis. *Br J Dermatol*. 1999;140(2):268-272.
28. Rehal B, Armstrong AW. Health outcome measures in atopic dermatitis: a systematic review of trends in disease severity and quality-of-life instruments 1985-2010. *PLoS One*. 2011;6(4):e17520. doi: 10.1371/journal.pone.0017520.
29. Ware JE. SF-36 Health survey update. SF-36.org website. www.sf-36.org/tools/sf36.shtml. Accessed July 7, 2016.
30. Elias PM, Hatano Y, Williams ML. Basis for the barrier abnormality in atopic dermatitis: outside-inside-outside pathogenic mechanisms. *J Allergy Clin Immunol*. 2008;121(6):1337-1343. doi: 10.1016/j.jaci.2008.01.022.
31. De Benedetto A, Rafaels NM, McGirt LY, et al. Tight junction defects in patients with atopic dermatitis. *J Allergy Clin Immunol*. 2011;127(3):773-786. doi: 10.1016/j.jaci.2010.10.018.
32. Elias PM, Wakefield JS. Mechanisms of abnormal lamellar body secretion and the dysfunctional skin barrier in patients with atopic dermatitis. *J Allergy Clin Immunol*. 2014;134(4):781-791. doi: 10.1016/j.jaci.2014.05.048.
33. Guttman-Yassky E, Nograles KE, Krueger JG. Contrasting pathogenesis of atopic dermatitis and psoriasis—part I: clinical and pathologic concepts. *J Allergy Clin Immunol*. 2011;127(5):1110-1118. doi: 10.1016/j.jaci.2011.01.053.
34. Malajian D, Guttman-Yassky E. New pathogenic and therapeutic paradigms in atopic dermatitis. *Cytokine*. 2015;73(2):311-318. doi: 10.1016/j.cyto.2014.11.023.
35. Mollanazar NK, Smith PK, Yosipovitch G. Mediators of chronic pruritus in atopic dermatitis: getting the itch out? [published online May 1, 2015]. *Clin Rev Allergy Immunol*. doi: 10.1007/s12016-015-8488-5.
36. Gittler JK, Shemer A, Suárez-Fariñas M, et al. Progressive activation of T(H)2/T(H)22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. *J Allergy Clin Immunol*. 2012;130(6):1344-1354. doi: 10.1016/j.jaci.2012.07.012.
37. Biedermann T, Skabytska Y, Kaesler S, Volz T. Regulation of T cell immunity in atopic dermatitis by microbes: the yin and yang of cutaneous inflammation. *Front Immunol*. 2015;6:353. doi: 10.3389/fimmu.2015.00353.
38. Guttman-Yassky E, Dhingra N, Leung DY. New era of biologic therapeutics in atopic dermatitis. *Expert Opin Biol Ther*. 2013;13(4):549-561. doi: 10.1517/14712598.2013.758708.
39. Noda S, Krueger JG, Guttman-Yassky E. The translational revolution and use of biologics in patients with inflammatory skin diseases. *J Allergy Clin Immunol*. 2015;135(2):324-336. doi: 10.1016/j.jaci.2014.11.015.
40. Guttman-Yassky E, Nograles KE, Krueger JG. Contrasting pathogenesis of atopic dermatitis and psoriasis—part II: immune cell subsets and therapeutic concepts. *J Allergy Clin Immunol*. 2011;127(6):1420-1432. doi: 10.1016/j.jaci.2011.01.054.
41. Suárez-Fariñas M, Tintle SJ, Shemer A, et al. Nonlesional atopic dermatitis skin is characterized by broad terminal differentiation defects and variable immune abnormalities. *J Allergy Clin Immunol*. 2011;127(4):954-964. doi: 10.1016/j.jaci.2010.12.1124.
42. Gelmetti C, Wollenberg A. Atopic dermatitis - all you can do from the outside. *Br J Dermatol*. 2014;170(suppl 1):19-24. doi: 10.1111/bjd.12957.
43. Akdis CA, Akdis M, Bieber T, et al; European Academy of Allergology; Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Group. Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report. *Allergy*. 2006;61(8):969-987. doi: 10.1111/j.1398-9995.2006.01153.x.
44. Tang TS, Bieber T, Williams HC. Are the concepts of induction of remission and treatment of subclinical inflammation in atopic dermatitis clinically useful? *J Allergy Clin Immunol*. 2014;133(6):1615-1625. doi: 10.1016/j.jaci.2013.12.1079.
45. Schmitt J, von Kobyletzki L, Svensson A, Apfelbacher C. Efficacy and tolerability of proactive treatment with topical corticosteroids and calcineurin inhibitors for atopic eczema: systematic review and meta-analysis of randomized controlled trials. *Br J Dermatol*. 2011;164(2):415-428. doi: 10.1111/j.1365-2133.2010.10030.x.
46. Novak N, Simon D. Atopic dermatitis - from new pathophysiologic insights to individualized therapy. *Allergy*. 2011;66(7):830-839. doi: 10.1111/j.1398-9995.2011.02571.x.
47. Schmitt J, Spuls P, Boers M, et al. Towards global consensus on outcome measures for atopic eczema research: results of the HOME II meeting. *Allergy*. 2012;67(9):1111-1117. doi: 10.1111/j.1398-9995.2012.02874.x.
48. Langan SM, Schmitt J, Williams HC, Smith S, Thomas KS. How are eczema 'flares' defined? A systematic review and recommendation for future studies. *Br J Dermatol*. 2014;170(3):548-556. doi: 10.1111/bjd.12747.
49. Sidbury R, Tom WL, Bergman JN, et al. Guidelines of care for the management of atopic dermatitis: Section 4. Prevention of disease flares and use of adjunctive therapies and approaches. *J Am Acad Dermatol*. 2014;71(6):1218-1233. doi: 10.1016/j.jaad.2014.08.038.