

Approach to the Assessment and Management of Adult Patients With Atopic Dermatitis: A Consensus Document.

Section I: Pathophysiology of Atopic Dermatitis and Implications for Systemic Therapy

Mark G. Kirchhof, Ian Landells, Chuck W. Lynde, Melinda J. Gooderham, and Chih-ho Hong

Journal of Cutaneous Medicine and Surgery
2018, Vol. 22(1S) 6S–9S
© The Author(s) 2018
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1023475418803626
journals.sagepub.com/home/jcms



Abstract

Atopic dermatitis (AD) is a chronic, relapsing, and remitting inflammatory skin disease whose onset typically occurs early in life. AD pathophysiology includes genetic, immune, and environmental factors contributing to chronic inflammation. A rapidly evolving understanding of the pathogenesis of AD has led to the development of several treatment options for AD in adults, including topicals, phototherapy, and systemic therapies. Here, we provide a concise summary of AD pathophysiology with a focus on implications for systemic therapy.

Keywords

atopic dermatitis, pathophysiology, systemic therapy

Atopic dermatitis (AD) is a chronic, relapsing, and remitting inflammatory skin disease characterized by erythema, edema, xerosis, erosions/excoriations, oozing and crusting, and lichenification, with pruritus as the hallmark of the condition. These specific clinical features may vary with patient age and chronicity of lesions.^{1,2} The American Academy of Dermatology has published diagnostic criteria for AD with a list of clinical features to be considered for assessment and diagnosis.^{1,3} Broadly, these include the characteristics described above and may also include early age of onset and personal or family history of atopic disease.

Disease onset typically occurs early in life, with 60% of cases presenting by 1 year and 90% presenting by 5 years of age.⁴ The prevalence of AD in the adult population varies regionally but is estimated to be up to 10.2%.⁵ While most cases of pediatric AD do resolve, a significant proportion do not, and in fact a small percentage of patients may first develop symptoms in adulthood.¹

Adult AD can present differently than in children and may require different treatment strategies, in part because patients tend to have thicker, more lichenified skin.⁶ The most common areas of involvement in adult AD are the flexural surfaces of arms and legs, the nape of the neck, and the hands. AD can be

severely problematic for adult patients, particularly when the exposed areas of the body are involved, such as the hands and face, and due to significant effects on overall quality of life.⁶

The pathophysiology of AD is complex and includes genetic, immune, and environmental factors contributing to chronic inflammation. A simplified representation of the pathophysiology of AD is shown in Figure 1. The current paradigm suggests that skin barrier dysfunction contributes to increased allergen penetration and microbial colonization, resulting in an immune response primarily driven by the type 2 inflammatory pathway.⁷ The type 2 inflammatory pathway underlies the pathogenesis of many allergic and fibrotic disorders and is characterized by the

Affiliations/acknowledgments: This paper is part of a series published as a Sanofi Genzyme sponsored supplement. All author affiliations, conflicts of interest statements, and acknowledgements are available in the introduction of this issue (Gooderham JG, Hong C, Albrecht L et al. Approach to the assessment and management of adult patients with atopic dermatitis: a consensus document. *J Cutan Med Surg*. 2018;22(supple 1):3-4.).

Corresponding Author:

Mark G. Kirchhof, Division of Dermatology, Department of Medicine, The Ottawa Hospital Civic Site, Parkdale Clinic, 737 Parkdale Avenue, Ottawa, ON K1Y 4M9, Canada.

Email: kirchhof.mark@gmail.com

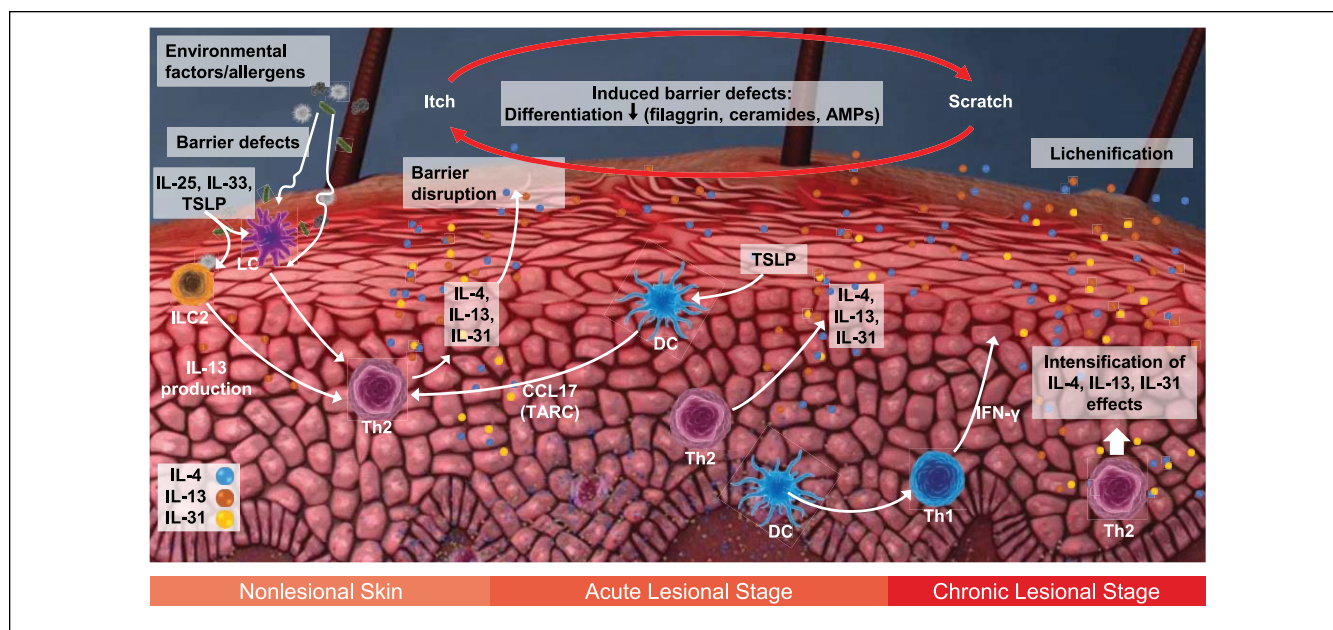


Figure 1. Pathophysiology of atopic dermatitis. (A) Nonlesional skin with underlying barrier defects is susceptible to immune activation in response to environmental factors/allergens. Immune activation by resident innate immune cells leads to type 2 inflammation, led by inflammatory cytokines IL-4, IL-13, and IL-31. (B) Type 2 inflammation mediates barrier disruption, promotes further inflammation, and increases itch, leading to acute skin lesions. (C) Chronic disease is characterized by intensification of the effect of type 2/Th2 cytokines as well as involvement of Th1 inflammation, resulting in lichenification of the skin. AMP, antimicrobial peptide; CCL17, chemokine ligand 17; DC, dendritic cell; IFN, interferon; IL, interleukin; ILC2, type 2 innate lymphoid cell; LC, Langerhans cell; TARC, thymus and activation regulated chemokine; Th, T helper cell; TSLP, thymic stromal lymphopoietin.

production of cytokines such as interleukin (IL)-4, IL-5, and IL-13.⁸ These cytokines may be produced by cells of the innate or adaptive immune system such as type 2 innate lymphoid cells (ILC2) and T helper 2 (Th2) cells, respectively.⁹

Filaggrin gene (*FLG*) mutations resulting in barrier dysfunction are among the strongest risk factors for the development of AD.^{7,10} Filaggrin is known to be downregulated in adult patients with AD irrespective of *FLG* mutation status, highlighting the importance of the skin barrier in the development of the disease.⁷ It is important to note that evidence of barrier dysfunction is observed even in nonlesional skin in patients with AD, which underscores the systemic nature of the disease.¹¹ Accordingly, early intervention from birth to maintain or repair skin barrier dysfunction through daily application of emollient may be protective against the development of AD in high-risk individuals.^{12,13}

Barrier dysfunction may result in increased allergen penetration, microbial colonization, and metabolic disruption of the skin, the consequence of which is stimulation of the immune system primarily characterized by type 2 inflammation.¹⁴⁻¹⁷ The type 2 cytokines increased in AD include IL-4, IL-5, IL-13, IL-31, and thymic stromal lymphopoietin (TSLP).^{7,18,19} These cytokines are increased in lesional skin of patients with AD, suggesting a central role of the type 2 response in disease pathogenesis.²⁰

Type 2 inflammation leads to the downregulation of proteins important in maintaining normal epidermal barrier

functions, including filaggrin.⁷ Type 2 immune activation is also associated with increased mast cell activation, IgE production, and eosinophilia, which may predispose patients to allergic reactions.^{21,22} Type 2 inflammation may also contribute to alterations of the skin microbiome as well as pruritus.^{7,21-23} Oetjen et al²⁴ recently demonstrated that chronic pruritus is dependent on neuronal IL-4Rα signalling, suggesting a central role for IL-4 and IL-13 in the development of disease.

Pruritus, microbiome alterations, and environmental triggers collectively contribute to chronic inflammation and barrier dysfunction in AD. The skin in patients with AD has been shown to have increased innervation and decreased sensory nerve activation thresholds, thereby promoting pruritus.²⁵⁻²⁷ Patients with AD also have decreased antimicrobial peptide (AMP) production resulting in increased microbial colonization and rates of skin infection, particularly with *Staphylococcus aureus*.^{7,28-30} Disease flares may be associated with both increased *S aureus* colonization and decreased microbial diversity in the skin microbiome.^{29,30} Finally, the skin of patients with AD is more prone to sensitization to environmental irritants and allergens.³¹⁻³³ Tobacco smoke and pollutants are associated with disease development.³² Dry weather and hot showers that result in transepidermal water loss (TEWL), a hallmark of AD, are also known to exacerbate disease.³⁴⁻³⁶

Other immune pathways have also been demonstrated to be important in AD pathogenesis. These include the Th22- and Th17-mediated inflammatory pathways, as well as the Th1 pathway in chronic disease.^{7,37-40} However, their contribution to the development of AD is less well understood and seems to be less central than the type 2 pathway, as current evidence shows poor efficacy of drug candidates targeting the Th22, Th17, and Th1 pathways.^{41,42}

The complex interplay between skin barrier dysfunction, microbial and allergen penetration, and immune dysregulation has several implications for the prevention and management of disease, as targeted therapies may affect more than one element of disease. The goal of any therapy is therefore to reduce skin inflammation and pruritus and to restore skin barrier function.

There are several options for the treatment of AD in adults, including topical therapies, phototherapy, and systemic therapies. Several groups have published detailed treatment guidelines or algorithms to assist health care providers in the diagnosis, assessment, and treatment of AD, with a main focus on moderate-to-severe disease.⁴³⁻⁴⁸ The selection criteria for candidates for systemic therapy in adults are quite similar among the guidelines and algorithms, which broadly defined candidates as patients with moderate-to-severe AD who have failed topical therapy and for whom phototherapy is unsuccessful or unsuitable.^{45,46,48} With recent advances in our understanding of the complex pathophysiology of AD, the development of targeted therapeutics has become a reality and is leading the way to better clinical outcomes for patients with AD.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The authors received funding from Sanofi Genzyme to attend a summary review meeting. Research and writing assistance provided by Tracy Chew was funded by Sanofi Genzyme.

References

1. 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.
2. Weidinger S, Novak N. Atopic dermatitis. *Lancet*. 2016;387(10023):1109-1122.
3. Eichenfield LF, Hanifin JM, Luger TA, et al. Consensus conference on pediatric atopic dermatitis. *J Am Acad Dermatol*. 2003;49(6):1088-1095.
4. Kay J, Gawkrödger D, Mortimer M, et al. The prevalence of childhood atopic eczema in a general population. *J Am Acad Dermatol*. 1994;30(1):35-39.
5. Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. *J Invest Dermatol*. 2013;132(5):1132-1138.
6. Elias PM, Schmuth M. Abnormal skin barrier in the etiopathogenesis of atopic dermatitis. *Curr Opin Allergy Clin Immunol*. 2009;9(5):437-446.
7. Brunner PM, Leung D, Guttman-Yassky E. Immunologic, microbial, and epithelial interactions in atopic dermatitis. *Ann Allergy Asthma Immunol*. 2018;120(1):34-41.
8. Wynn TA. Type 2 cytokines: mechanisms and therapeutic strategies. *Nat Rev Immunol*. 2015;15(5):271-282.
9. Eberl G, Colonna M, Di Santo JP, McKenzie AN. Innate lymphoid cells. Innate lymphoid cells: a new paradigm in immunology. *Science*. 2015;348(6237):aaa6566.
10. Palmer CN, Irvine AD, Terron-Kwiatkowski A, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet*. 2006;38(4):441-446.
11. Seidenari S, Giusti G. Objective assessment of the skin of children affected by atopic dermatitis: a study of pH, capacitance and TEWL in eczematous and clinically uninvolved skin. *Acta Derm Venereol*. 1995;75(6):429-433.
12. Simpson EL, Chalmers JR, Hanifin JM, et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol*. 2014;134(4):818-823.
13. Horimukai K, Morita K, Narita M, et al. Application of moisturizer to neonates prevents development of atopic dermatitis. *J Allergy Clin Immunol*. 2014;134(4):824-830.e6.
14. Kawasaki H, Nagao K, Kubo A, et al. Altered stratum corneum barrier and enhanced percutaneous immune responses in filaggrin-null mice. *J Allergy Clin Immunol*. 2012;129(6):1538-1546.e6.
15. Fallon PG, Sasaki T, Sandilands A, et al. A homozygous frame-shift mutation in the mouse Flg gene facilitates enhanced percutaneous allergen priming. *Nat Genet*. 2009;41(5):602-608.
16. Jeong S, Kim H, Youm J-K, et al. Mite and cockroach allergens activate protease-activated receptor 2 and delay epidermal permeability barrier recovery. *J Invest Dermatol*. 2008;128(8):1930-1939.
17. Thyssen JP, Kezic S. Causes of epidermal filaggrin reduction and their role in the pathogenesis of atopic dermatitis. *J Allergy Clin Immunol*. 2014;134(4):792-799.
18. Oyoshi MK, Larson RP, Ziegler SF, Geha RS. Mechanical injury polarizes skin dendritic cells to elicit a TH2 response by inducing cutaneous thymic stromal lymphopoietin expression. *J Allergy Clin Immunol*. 2010;126(5):976-984.e1-5.
19. Onoue A, Kabashima K, Kobayashi M, Mori T, Tokura Y. Induction of eosinophil- and Th2-attracting epidermal chemokines and cutaneous late-phase reaction in tape-stripped skin. *Exp Dermatol*. 2009;18(12):1036-1043.
20. Gittler JK, Wang JF, Orlow SJ. Bathing and associated treatments in atopic dermatitis. *Am J Clin Dermatol*. 2017;18(1):45-57.
21. Werfel T, Allam J-P, Biedermann T, et al. Cellular and molecular immunologic mechanisms in patients with atopic dermatitis. *J Allergy Clin Immunol*. 2016;138(2):336-349.
22. Hönzke S, Wallmeyer L, Ostrowski A, et al. Influence of Th2 cytokines on the cornified envelope, tight junction proteins, and β -defensins in filaggrin-deficient skin equivalents. *J Invest Dermatol*. 2016;136(3):631-639.
23. Sonkoly E, Muller A, Lauerma AI, et al. IL-31: a new link between T cells and pruritus in atopic skin inflammation. *J Allergy Clin Immunol*. 2006;117(2):411-417.

24. Oetjen LK, Mack MR, Feng J, et al. Sensory neurons co-opt classical immune signaling pathways to mediate chronic itch. *Cell*. 2017;171(1):217-228.e13.
25. Mollanazar NK, Smith PK, Yosipovitch G. Mediators of chronic pruritus in atopic dermatitis: getting the itch out? *Clin Rev Allergy Immunol*. 2015;51(3):263-292.
26. Wilson SR, Thé L, Batia LM, et al. The epithelial cell-derived atopic dermatitis cytokine TSLP activates neurons to induce itch. *Cell*. 2013;155(2):285-295.
27. Tominaga M, Ozawa S, Tengara S, Ogawa H, Takamori K. Intraepidermal nerve fibers increase in dry skin of acetone-treated mice. *J Dermatol Sci*. 2007;48(2):103-111.
28. Ong PY, Ohtake T, Brandt C, et al. Endogenous antimicrobial peptides and skin infections in atopic dermatitis. *N Engl J Medicine*. 2002;347(15):1151-1160.
29. Nakatsuji T, Chen TH, Narala S, et al. Antimicrobials from human skin commensal bacteria protect against *Staphylococcus aureus* and are deficient in atopic dermatitis. *Sci Transl Med*. 2017;9(378):pii:eaah4680.
30. Kong H, Oh J, Deming C, et al. Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. *Genome Res*. 2012;22(5):850-859.
31. Kabashima K, Otsuka A, Nomura T. Linking air pollution to atopic dermatitis. *Nat Immunol*. 2017;18(1):5-6.
32. Kim K. Influences of environmental chemicals on atopic dermatitis. *Toxicol Res*. 2015;31(2):89-96.
33. Kim J, Han Y, Ahn JH, et al. Airborne formaldehyde causes skin barrier dysfunction in atopic dermatitis. *Br J Dermatol*. 2016;175(2):357-363.
34. Sato J, Denda M, Chang S, Elias PM, Feingold KR. Abrupt decreases in environmental humidity induce abnormalities in permeability barrier homeostasis. *J Invest Dermatol*. 2002;119(4):900-904.
35. Goad N, Gawkrödger DJ. Ambient humidity and the skin: the impact of air humidity in healthy and diseased states. *J Eur Acad Dermatol Venereol*. 2016;30(8):1285-1294.
36. Chiang C, Eichenfield LF. Quantitative assessment of combination bathing and moisturizing regimens on skin hydration in atopic dermatitis. *Pediatr Dermatol*. 2009;26(3):273-278.
37. Czarnowicki T, Esaki H, Gonzalez J, et al. Early pediatric atopic dermatitis shows only a cutaneous lymphocyte antigen (CLA)+ TH2/TH1 cell imbalance, whereas adults acquire CLA+ TH22/TC22 cell subsets. *J Allergy Clin Immunol*. 2015;136(4):941-951.e3.
38. Suárez-Fariñas M, Dhingra N, Gittler J, et al. Intrinsic atopic dermatitis shows similar TH2 and higher TH17 immune activation compared with extrinsic atopic dermatitis. *J Allergy Clin Immunol*. 2013;132(2):361-370.
39. Moy AP, Murali M, Kroshinsky D, Duncan LM, Nazarian RM. Immunologic overlap of helper T-cell subtypes 17 and 22 in erythrodermic psoriasis and atopic dermatitis. *JAMA Dermatol*. 1970;151(7):753-760.
40. Kerschenlohr K, Decard S, Przybilla B, Wollenberg A. Atopy patch test reactions show a rapid influx of inflammatory dendritic epidermal cells in patients with extrinsic atopic dermatitis and patients with intrinsic atopic dermatitis. *J Allergy Clin Immunol*. 2003;111(4):869-874.
41. Saeki H, Kabashima K, Tokura Y, et al. Efficacy and safety of ustekinumab in Japanese patients with severe atopic dermatitis: a randomized, double-blind, placebo-controlled, phase II study. *Br J Dermatol*. 2017;177(2):419-427.
42. Khattri S, Brunner PM, Garcet S, et al. Efficacy and safety of ustekinumab treatment in adults with moderate-to-severe atopic dermatitis. *Exp Dermatol*. 2017;26(1):28-35.
43. Ring J, Alomar A, Bieber T, et al. Guidelines for treatment of atopic eczema (atopic dermatitis) part I. *J Eur Acad Dermatol Venereol*. 2012;26(8):1045-1060.
44. Ring J, Alomar A, Bieber T, et al. Guidelines for treatment of atopic eczema (atopic dermatitis) part II. *J Eur Acad Dermatol Venereol*. 2012;26(9):1176-1193.
45. Simpson EL, Bruin-Weller M, Flohr C, et al. When does atopic dermatitis warrant systemic therapy? Recommendations from an expert panel of the International Eczema Council. *J Am Acad Dermatol*. 2017;77(4):623-633.
46. Boguniewicz M, Alexis AF, Beck LA, et al. Expert perspectives on management of moderate-to-severe atopic dermatitis: a multidisciplinary consensus addressing current and emerging therapies. *J Allergy Clin Immunol*. 2017;5(6):1519-1531.
47. Schneider L, Tilles S, Lio P, et al. Atopic dermatitis: a practice parameter update 2012. *J Allergy Clin Immunol*. 2013;131(2):295-299.e1-27.
48. Lynde CW, Bourcier M, Gooderham M, et al. A treatment algorithm for moderate to severe atopic dermatitis in adults. *J Cutan Med Surg*. 2018;22(1):78-83.