

Revolutionizing Atopic Dermatitis

Jonathan I. Silverberg, MD, PhD, MPH

Impressive progress has been made in recent years in the management and treatment of atopic dermatitis (AD) and its comorbidities; however, there is a major need for state-of-the-art, evidence-based, multidisciplinary education for AD management. To address this need, the first Revolutionizing Atopic Dermatitis (RAD) Conference (<https://revolutionizingad.com>) was held in April 2019 in Chicago, Illinois, featuring cutting-edge research presented by globally recognized experts in dermatology, allergy and immunology, sleep medicine, ophthalmology, and nursing care. The following is a recap of the latest topics in AD research presented at the conference.

Diagnosis and Assessment of AD:

Jonathan I. Silverberg, MD, PhD, MPH

Although diagnosis of AD typically is straightforward in children, it can be challenging in adults, even for expert clinicians. These challenges stem from the different lesional distribution and morphology of AD in adults vs children.^{1,2} Additionally, the conditions included in the differential diagnosis of AD (eg, allergic contact dermatitis, cutaneous T-cell lymphoma, psoriasis) are far more common in adults than in children. Formal diagnostic criteria can be useful to improve the diagnosis of AD in clinical practice.³ It is important to note that flexural lesions and early disease onset are diagnostic criteria in AD; nevertheless, neither are essential nor sufficient on their own to make the diagnosis.

Patch Testing: Jacob P. Thyssen, MD, PhD, DmSci, and Noreen Heer Nicol, PhD, RN, FNP, NEA-BC

Patch testing can be used in AD patients to rule out contact dermatitis as an alternative or comorbid diagnosis.⁴⁻⁶ Because contact dermatitis can mimic AD, patch testing is recommended for all patients with adolescent and adult-onset AD.⁵ Additionally, refractory cases of AD across all ages, especially prior to initiation of systemic therapy, warrant patch testing. The unique challenges of patch testing in AD patients were reviewed.

Patient Panel

Atopic dermatitis can be a considerable disease burden on both patients and society in general. At the 2019 RAD Conference, a panel of patients bravely shared their AD journeys. Their eye-opening stories highlighted opportunities

for improving real-world assessment and management of AD. Some key takeaways included the importance of adequately assessing the symptom burden of AD and not merely relying on visual inspection of the skin. The need for long-term treatment approaches beyond quick fixes with steroids also was discussed.

Pathogenesis of AD: Mark Boguniewicz, MD

There have been many advances in our understanding of the complex pathogenesis of AD,⁷⁻¹¹ which is characterized by an altered skin barrier and immune dysregulation. Filaggrin deficiency in the skin has structural and biological consequences. A subset of patients with AD has filaggrin loss-of-function genetic polymorphisms inherited in an autosomal-semidominant pattern; however, many other genetic polymorphisms have been identified that affect different components of the skin architecture and immune system. Many cytokine pathways have been found to be upregulated in AD lesions, including IL-13, IL-4, IL-31, and IL-5 in acute and chronic lesions, and IFN- γ and other helper T cell (T_H1) cytokines in chronic lesions. IL-4 and IL-13 (T_H2 cytokines) have been shown to decrease epidermal expression of filaggrin and lead to lipid abnormalities in the skin of patients with AD. Even normal-appearing, non-lesional skin has substantial immune activation and barrier abnormalities in patients with moderate to severe AD. Activation of different immune pathways may contribute to the heterogeneous clinical presentation of AD. There also is an increasingly recognized role of superantigen-producing *Staphylococcus aureus* and decreased microbial diversity in AD.

Therapies for AD

The advances in our understanding of AD pathophysiology have led to the development of 2 recently approved therapeutic agents.⁷⁻¹⁰ Crisaborole ointment 2% is a topical phosphodiesterase 4 inhibitor that was approved by the US Food and Drug Administration in 2016 for treatment of mild to moderate AD. Treatment with crisaborole ointment 2% demonstrated improvement in lesion severity, itch, and quality of life in children and adults with AD. Dupilumab, an injectable biologic therapy that inhibits IL-4 and IL-13 signaling, was approved by the US Food and Drug Administration in 2017 for adults and in 2019 for adolescents aged 12 to 17 years with moderate to severe AD.

From the Departments of Dermatology, Preventive Medicine, and Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, Illinois. Dr. Silverberg is the conference chair for the Revolutionizing Atopic Dermatitis Conference.

Correspondence: Jonathan I. Silverberg, MD, PhD, MPH, Department of Dermatology, Ste 1600, 676 N Saint Clair St, Chicago, IL 60611.

The expert panel of speakers at the 2019 RAD Conference discussed many practical clinical pearls regarding patient education, optimization of both short- and long-term efficacy, and prevention and management of treatment-related adverse events. The discussion included evidence-based guidelines for bathing practices and topical therapy in AD, as well as practical pearls for patient and provider education in AD, reviewed by Dr. Nicol. Evidence-based guidelines for use of phototherapy and systemic and biologic therapy for AD also were highlighted by Dr. Silverberg.

After decades of limited therapeutic options, there is a large therapeutic pipeline of topical, oral, and biologic agents in development for the treatment AD.⁷⁻⁹ Dr. Boguniewicz reviewed the state-of-the-art treatments that are the furthest advanced in development. Many of these agents may be approved within the next couple of years and look promising in terms of their potential to improve the care of patients with AD.

Comorbidities of AD

The impact of AD is not just skin deep. Atopic dermatitis is associated with myriad comorbid health conditions.¹²⁻¹⁶ Dr. Boguniewicz reviewed the relationship between AD and atopic comorbidities, including asthma, hay fever, and food allergies, which are common across all AD patients. In addition, a subset of children with AD demonstrated the atopic march, in which AD first appears early in life followed by the development of other atopic comorbidities in later childhood or adulthood. In particular, children with filaggrin null mutations were found to be at increased risk of early-onset, severe, persistent AD with asthma and allergic sensitization.¹⁷ More recently, eosinophilic esophagitis was demonstrated to be a late-onset comorbidity of the atopic march.¹⁸ The allergy guidelines for which patients are appropriate candidates for food and/or aeroallergen testing were discussed,¹⁹ and it was emphasized that patients with AD should not routinely receive this testing.

Atopic dermatitis is associated with many other comorbidities, including sleep disturbances. Phyllis C. Zee, MD, PhD, provided a brilliant review of circadian regulation of physiology and the immune system. Sleep is one of the most important determinants of patients' health and well-being. Atopic dermatitis is associated with disturbances of sleep and circadian rhythms. Sleep disturbances are gaining recognition as an important end point to assess for improvement in clinical practice and trials.

Patients with AD have long been recognized to have increased ophthalmic comorbidities, including allergic conjunctivitis, atopic keratoconjunctivitis, and cataracts. More recently, conjunctivitis has emerged as an important adverse event with dupilumab treatment.²⁰ Jeanine Baqai, MD, reviewed the various ophthalmic comorbidities and shared numerous clinical signs of ophthalmic comorbidities that dermatologists can assess with the naked eye (no slit-lamp examination needed). Pearls to manage dupilumab-related conjunctivitis shared by Dr. Baqai and the speaker panel included elimination of eye rubbing, cold compresses,

avoidance of exacerbating factors, artificial tears, and timely referral to an ophthalmologist. Medications discussed were mast cell stabilizers, antihistamines, and corticosteroids and calcineurin inhibitors.

Final Thoughts

There has been an explosion of new research that has increased our understanding of all aspects of AD, and the standard of care is truly being revolutionized. Clinicians should stay tuned to a wealth of new evidence-based recommendations coming down the pike.

REFERENCES

- Vakharia PP, Silverberg JI. Adult-onset atopic dermatitis: characteristics and management [published online May 28, 2019]. *Am J Clin Dermatol*. doi:10.1007/s40257-019-00453-7.
- Silverberg JI. Adult-onset atopic dermatitis. *J Allergy Clin Immunol Pract*. 2019;7:28-33.
- Hanifin J, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol (Stockh)*. 1980;92(suppl):44-47.
- Hamann CR, Hamann D, Egeberg A, et al. Association between atopic dermatitis and contact sensitization: a systematic review and meta-analysis. *J Am Acad Dermatol*. 2017;77:70-78.
- Owen JL, Vakharia PP, Silverberg JI. The role and diagnosis of allergic contact dermatitis in patients with atopic dermatitis. *Am J Clin Dermatol*. 2018;19:293-302.
- Rastogi S, Patel KR, Singam V, et al. Allergic contact dermatitis to personal care products and topical medications in adults with atopic dermatitis [published online July 25, 2018]. *J Am Acad Dermatol*. 2018;79:1028-1033.e6.
- Vakharia PP, Silverberg JI. New and emerging therapies for paediatric atopic dermatitis. *Lancet Child Adolesc Health*. 2019;3:343-353.
- Vakharia PP, Silverberg JI. New therapies for atopic dermatitis: additional treatment classes [published online December 14, 2017]. *J Am Acad Dermatol*. 2018;78(3 suppl 1):S76-S83.
- Silverberg JI. Atopic dermatitis treatment: current state of the art and emerging therapies. *Allergy Asthma Proc*. 2017;38:243-249.
- Vakharia PP, Silverberg JI. Monoclonal antibodies for atopic dermatitis: progress and potential. *BioDrugs*. 2017;31:409-422.
- Silverberg NB, Silverberg JI. Inside out or outside in: does atopic dermatitis disrupt barrier function or does disruption of barrier function trigger atopic dermatitis? *Cutis*. 2015;96:359-361.
- Silverberg JI. Comorbidities and the impact of atopic dermatitis. *Ann Allergy Asthma Immunol*. 2019;123:144-151.
- Brunner PM, Silverberg JI, Guttman-Yassky E, et al. Increasing comorbidities suggest that atopic dermatitis is a systemic disorder. *J Invest Dermatol*. 2017;137:18-25.
- Silverberg J, Garg N, Silverberg NB. New developments in comorbidities of atopic dermatitis. *Cutis*. 2014;93:222-224.
- Silverberg JI. Selected comorbidities of atopic dermatitis: atopy, neuropsychiatric, and musculoskeletal disorders. *Clin Dermatol*. 2017;35:360-366.
- Silverberg JI, Gelfand JM, Margolis DJ, et al. Association of atopic dermatitis with allergic, autoimmune, and cardiovascular comorbidities in US adults. *Ann Allergy Asthma Immunol*. 2018;121:604-612.e603.
- Henderson J, Northstone K, Lee SP, et al. The burden of disease associated with filaggrin mutations: a population-based, longitudinal birth cohort study. *J Allergy Clin Immunol*. 2008;121:872-877.e879.
- Hill DA, Grundmeier RW, Ramos M, et al. Eosinophilic esophagitis is a late manifestation of the allergic march. *J Allergy Clin Immunol*. 2018;6:1528-1533.
- Boyce JA, Assa'ad A, Burks AW, et al; NIAID-Sponsored Expert Panel. Guidelines for the diagnosis and management of food allergy in the United States. *J Allergy Clin Immunol*. 2010;126:1105-1118.
- Akinlade B, Guttman-Yassky E, de Bruin-Weller M, et al. Conjunctivitis in dupilumab clinical trials [published online March 9, 2019]. *Br J Dermatol*. doi:10.1111/bjd.17869.