



Atopic dermatitis More than a rash

In the current issue of the *Annals*, Bridgman et al¹ provide an overview on the multidimensional burden of atopic dermatitis (AD). It is clear from this perspective that patients with AD are affected in multiple ways, leading to impaired quality of life and social functioning, low self-esteem, more sick days, reduced physical activity, and academic and work impairment. These effects lead to disruption not only of the patients' lives but that of their families, with increased feelings of helplessness, stress, and low general life satisfaction. This burden of AD is largely driven by the intense itching and skin pain, sleep disturbance, depression, and anxiety with this disease, particularly when poorly controlled by available medications.^{2,3} In 2004, the total annual financial burden of AD was estimated to be \$4.3 billion. Recognition of the multidimensional burden of AD is important in the management of these patients with complex conditions.

During the past decade, there have been major advances in our understanding and management of AD. Importantly, in recent years the focus has shifted from exclusive evaluation of the skin lesion to the nonlesional skin of AD and potential systemic aspects of AD beyond the skin.⁴ Studies now clearly demonstrate that even the normal-looking skin in patients with AD have subclinical inflammation and evidence of skin barrier dysfunction. Importantly, as early as the second day of life before the onset of clinical AD, there is evidence of increased transepidermal water loss, supporting the concept that epicutaneous allergen sensitization with predisposition to food allergy may occur early in life.⁵ Clinically, this means that prevention studies should focus on the perinatal period and that if clinicians wait until patients have overt AD, the path to development of food allergy and possibly pediatric respiratory disease may already be established. Similarly, there is increasing evidence that microbial dysbiosis (eg, reduced beneficial commensal bacteria and increased pathogenic bacteria, such as *Staphylococcus aureus*) of the skin and gastrointestinal tract occurs before the onset of clinical AD and food allergy. This evidence has sparked attention to use of targeted microbiome transplantation as an approach to prevention of allergy.

Clinical and laboratory evidence that the effects of AD are more than skin deep includes the observation that patients with AD have significantly higher IgE responses than any other allergic disease, including food allergy, allergic conjunctivitis, allergic rhinitis, and asthma.⁶ This evidence is not surprising considering that the skin

is an enormous surface area that is continuously engaging external environmental allergens and microbes. Penetration of these allergens through a defective skin barrier that contains high levels of thymic stromal lymphopoietin, interleukin 33, and interleukin 25 creates an ideal environment for high IgE production and other allergic responses.⁷ Although the classic atopic march (AD followed by food allergy, allergic rhinitis, and asthma) occurs in only a few patients, AD is often associated with other allergic diseases (eg, 40% association of AD with food allergy and animal models support a strong link between these 2 conditions).⁸ Several studies have been published that suggest that use of skin emollients can prevent AD, but the optimal treatment needed to prevent food allergy is not known. This treatment may need to include immunomodulatory or anti-inflammatory therapy to shut off the type 2 immune response because emollients will only improve the skin barrier.

There is also evidence that the skin inflammation in AD can spread systemically to contribute to nonallergic conditions. AD has been associated with increased occurrence of suicidal ideation, depression, anxiety, attention-deficit disorders, and autism. It is speculated that the association of AD with neuropsychiatric disorders is attributable to their debilitating itch, but there is also evidence that circulating proinflammatory cytokines can act directly on the brain to affect behavior. Beyond effects on the neuropsychiatric disorders, there is also evidence that AD is associated with an increased prevalence of coronary artery disease. This association has not been reproduced and may involve specific subsets of patients with AD. A recent study indicated that *S aureus* infections in AD not only involve the skin but can involve distant organs and blood, thus leading to increased hospitalizations.⁹

During the past year, a number of publications have appeared in the *Annals* that contribute to optimized AD management.^{10,11} The AD yardstick, published at the beginning of 2018, provides the most recent management guidelines for treatment of AD by the practicing allergist.¹⁰ A novel aspect of the yardstick are recommendations, including the role of biologics in treating moderate to severe AD. As we move toward more targeted therapies, we need to appreciate the complex heterogeneity of AD that occurs as the result of racial and age-related effects on AD, acquired and genetic skin barrier dysfunction, and different immune pathways that are activated in various AD subtypes. Because these biologics affect systemic immune responses, patients with systemic allergy (eg, concomitant AD, asthma, and food allergy) will likely benefit the most from treatment with biologics. Convenient noninvasive biomarkers, however, are needed to identify the different subsets of patients with AD who will benefit from the various targeted

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therapies that are becoming available. Despite these challenges, the future prospects for novel and effective therapies in AD are exciting.

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