along with upregulation of Th1 cytokines such as interferon gamma.[24] In addition, the Th2 immune response is involved in driving the synthesis of immunoglobulin E (IgE); however, IgE is not consistently elevated in patients with AD.[25] Recent therapeutic advances have focused on targets along the Th2 immune response.

In the majority of children, AD starts before 1 year of age and before 5 years of age in nearly all children.[1] Many will outgrow the disease, but the specific predictors of prognosis are not yet understood. A prospective study in a cohort of children followed longitudinally indicated that approximately 60% of children who developed AD by the age of 2 years had resolution of their symptoms by 4 years of age.[26] Those who have mutations in the filaggrin gene are more likely to have persistent disease.[27]

COMORBITIES

The effects of AD extend beyond the skin, influencing quality of life and mental health. AD impacts quality of life in multiple domains in affected children and their families.[28] Itching, treatment burden, sleep, embarrassment related to appearance of the skin, and ability to participate in sports have the most bearing on quality of life.[29] Not surprisingly, impact on quality of life correlates with severity of disease. AD also affects mental health and has been linked to depression and anxiety in both patients and parents.[30–32] Cognitive behavioral therapy may be effective in reducing self-reported symptoms of eczema and anxiety.[33]

Sleep disturbance affects approximately two-thirds of pediatric patients with AD, and disturbed sleep is associated with increased depression, anxiety, and inattention.[34] Lower nocturnal melatonin secretion was also associated with sleep disturbance in children with AD.[35] A randomized, double-blinded, placebo-controlled trial of melatonin in children 6 to 12 years old demonstrated subjective improvement in AD severity and sleep quality.[36] Behavioral therapy, including progressive muscle relaxation and optimization of sleep hygiene, can serve as an effective adjunct in the care of patients with AD.[37]

Although sedating antihistamines have historically been used as adjunctive treatment of eczema, there is limited evidence to support their efficacy in the treatment of AD.[38] Children with AD have increased attention-deficit symptoms compared with healthy controls, which have been linked to sedating antihistamine use. It is unclear whether there is a causal relationship between early antihistamine exposure and increased attention deficit, or whether antihistamine use is a surrogate for more severe AD or poor sleep quality.[39] Infantile exposure to H1-antihistamines has been linked to development of attention-deficit/hyperactivity disorder (ADHD).[40] Nonsedating second-generation antihistamines are not associated with the same side effect profile as first-generation antihistamines and have been shown to be safe to use long-term, particularly in patients who also have comorbid environmental allergies.[41]

AD has been viewed as the first step in the "atopic march," whereby the defective skin barrier leads to immune sensitization to antigens, resulting in food allergy, asthma, and allergic rhinitis.[42] Although parents may suspect food allergies as a cause of AD, food-induced AD is rare. Instead, the conditions tend to co-occur in patients with atopic disease, and up to 40% of children with AD develop food allergy.[42] Food allergy typically manifests with IgE-mediated hypersensitivity, with symptoms including urticaria and angioedema. In the rare patient in whom food allergy drives eczematous dermatitis (delayed-type hypersensitivity), an immediate-type hypersensitivity reaction has preceded it.[43] Food allergy testing should only be pursued in children with a history consistent with immediate-type allergy, because more than half of children with AD will have high food-specific IgE concentrations (even without true food allergy).[44] Overemphasis on food allergy as a cause of AD leads to unnecessary, and potentially dangerous, elimination diets[45] and may result in intolerance of previously tolerated foods.[43] Avoidance diets should only be recommended in patients who have failed a diagnostic food challenge. Treatment should instead focus on skin-directed therapies.

Increasing rates of food allergy prompted the hypothesis that decreased exposure to antigens leads to decreased immune tolerance and, thus, increased sensitization (the "hygiene hypothesis"). The Learning Early About Peanut allergy (LEAP) trial demonstrated that early exposure to peanut in a cohort of at-risk infants reduced the risk of peanut allergy compared with a control group.[46] The effect was persistent after 12 months of peanut avoidance, strengthening the argument for induction of immune tolerance via early exposure to the antigen.[47] This landmark study led to changes in clinical practice, emphasizing early antigen exposure to the gastrointestinal tract (rather than through the skin) to induce tolerance. New guidelines from the National Institute of Allergy and Infectious Disease (NIAID) for early peanut introduction[48] relied heavily on the results of the LEAP trial. In these guidelines, infants are stratified based on their risk for peanut allergy, which is determined by the presence and severity of AD as well as the presence of egg allergy. In the highest-risk group—infants with severe eczema and/or egg allergy—a peanut-specific IgE and/or skin prick test is recommended before introduction of peanut; if infants do not show evidence of sensitization, then peanut introduction is recommended at 4 to 6 months of age. Infants with mild to moderate eczema comprise the moderate-risk group, and introduction of peanut-containing foods is recommended around 6 months of age to reduce the risk of peanut allergy. In low-risk infants (infants without eczema or any food allergy), peanut-containing foods may be introduced according to family preference.