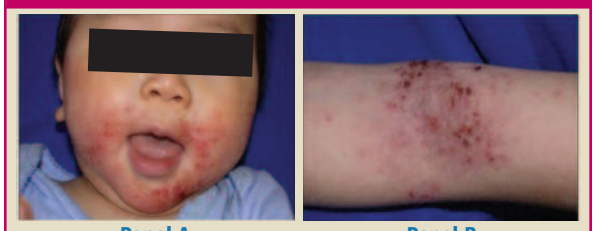
BEST PRACTICES IN: Pediatric Atopic Dermatitis

Atopic dermatitis (AD, also called eczema) is a common, chronic, pruritic, and inflammatory disease. For individuals with AD, it is associated with significant impairments in quality of life, sleep patterns, and psychosocial functioning, as well as comorbidities (such as secondary bacterial and viral infections) and other atopic diseases (such as asthma, allergic rhinitis, and extrinsic allergies).

Depending on definitions and study methodologies, estimates for the prevalence of AD vary from 10% to 20% of the total population.[1] However, it most commonly occurs in children, and up to 90% of pediatric patients are diagnosed by 5 years of age. The disease is characterized by pruritus and erythematous, inflamed eczematous papules and plaques, often with a serous exudate (**Figure 1**). The pruritus may be intense and lead to a cycle of itch-scratch-itch that exacerbates the patient's already compromised epidermal barrier, facilitating water loss, dry skin, and infection.

Although the pathophysiology of AD is not yet fully understood, emerging research indicates important genetic components to AD. Understanding how the disease manifests and its underlying causes may help improve treatment strategies for adult and pediatric patients.

Figure 1. Typical Cutaneous Signs of Childhood Eczema



Panel A Panel B

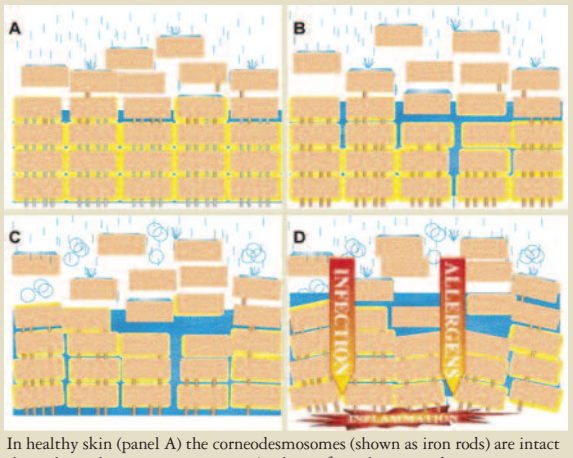
The face is often the first area to be affected in infants (panel A), and the antecubital fossa is commonly affected in older children (panel B).
Photos courtesy of Lawrence F. Eichenfield, MD.

Genetic Underpinnings of AD

AD often coexists with ichthyosis vulgaris—another dermatologic disease characterized by dry, scaly skin—which is thought to contribute, at least in part, to the dry skin tendency in AD. In 2006, two common loss-of-function mutations to the filaggrin (filament-aggregating protein) gene were identified as a cause of ichthyosis vulgaris. These mutations were also recognized as predisposing factors for the development of AD.[2-4] Subsequently, a large set of filaggrin mutations have been found in patients with AD around the world. Patients with AD and filaggrin mutations have been found to suffer from more severe and persistent AD, as well as a higher incidence of atopic comorbidities including asthma and allergic rhinitis.

The filaggrin gene has a variety of functions that contribute to maintaining skin barrier integrity. In the inner stratum corneum, within the cytoskeleton of keratinocytes, filaggrin aggregates several keratins and other intermediate filaments to induce keratinocyte compaction (a type of programmed cell death) during cornification. This process helps maintain the barrier integrity of the stratum corneum. Filaggrin is also an important part of the protein-lipid cornified cell envelope—a barrier that is permeable to water but blocks microbe, allergen, and irritant infiltration.[4,5] During desquamation of the outer stratum corneum, filaggrin is a source of amino acid degradation products, known as natural moisturizing factor (NMF), which contribute to the hydration of these outer layers and likely contribute to the acid mantle. Along with stratum corneum lipids, NMF has a significant influence on water flux and retention in the skin.

Figure 2. Stratum Corneum Disruption in Atopic Dermatitis



In healthy skin (panel A) the corneodesmosomes (shown as iron rods) are intact throughout the stratum corneum. At the surface, the corneodesmosomes start to break down as part of the normal desquamation process, analogous to iron rods rusting. In an individual genetically predisposed to AD (panel B), corneodesmosomes prematurely break down, leading to enhanced desquamation and weakening the barrier, allowing penetration of environmental agents like soap, further reducing barrier integrity (panel C). Finally, allergens and microbes that increase the risk for secondary infection enter (panel D).
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Lawrence F. Eichenfield, MD
Professor of Pediatrics and Medicine (Dermatology)
University of California, San Diego
Rady Children's Hospital, San Diego

Filaggrin and Stratum Corneum Dysfunction

Filaggrin is a central actor in the maintenance of stratum corneum integrity, and mutations predispose individuals to AD and other cutaneous diseases (**Figure 2**). To date, almost 50 loss-of-function mutations have been identified. All are nonsense or frameshift mutations that truncate the profilaggrin molecule.[4-6] Mutations range from deficiencies and mild filaggrin dysfunction to a complete absence of filaggrin. All mutations undermine barrier function and cause the dry skin, inflammation, and decreased NMF that characterize AD.

In addition to filaggrin mutations, lipids and other components of the epidermis contribute to maintaining skin barrier integrity. Of these, ceramides have been shown to be of great importance. Ceramides are combinations of fatty acids and a sphingoid base, and account for 50% of intracellular lipids. Reductions in ceramides disrupt the balance between the stratum corneum's other two key lipids—cholesterol and free fatty acids—and ceramide levels are often reduced in patients with AD. In addition, barrier function can be affected by changes in pH, protease activity in the skin, and inflammation.

As barrier function is increasingly compromised, complications of AD set in. These include physical breaks in the skin leading to secondary bacterial and viral skin infections, as well as possible soft tissue, bone, or systemic infections. The skin's appearance and the intense pruritus also significantly disrupt sleep, worsen psychosocial functioning, and generally worsen the quality of life for patients of all ages. AD is also an entry to other atopic abnormalities such as asthma, food allergy, and allergic rhinitis, and severe disease may adversely affect growth and development.

Treatments

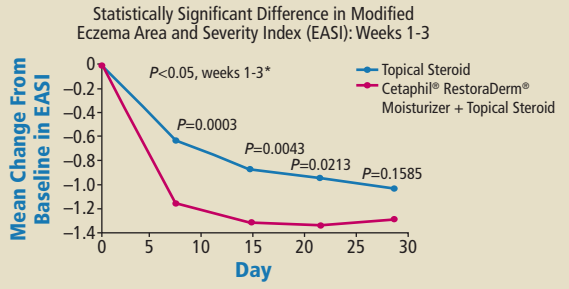
The goal of AD treatment is to improve the skin's health with a combination of bathing and moisturizing regimens, as well as prescription anti-inflammatory and anti-infective agents, as needed. A large variety of moisturizers, emollients, and targeted barrier repair products are available that effectively minimize the consequences of barrier dysfunction in AD and help control and suppress the typical pruritus, dry skin, and secondary complications.

There is increasing evidence of the utility of over-the-counter (OTC) agents to improve barrier function in individuals with AD. Recently, Simpson and Dutronc[7] summarized four independent studies that measured the effects of Cetaphil® RestoraDerm® Moisturizer (CRM; Galderma Laboratories) on skin hydration and signs of AD, when used alone or in conjunction with other topical treatments. These studies enrolled a total of 223 men, women, and children with AD, and CRM was compared with several other topical OTC products (Physiogel® Al cream [PAl cream; Stiefel Laboratories] or Eucerin® Calming Creme [ECC; Beiersdorf]), as well as topical corticosteroids in one study, and controls.

CRM is an OTC moisturizer designed to improve barrier function through the use of ceramides and supplemental filaggrin breakdown products that increase skin hydration. CRM also contains humectants, emollients, and occlusives that may improve skin barrier integrity. Across the four studies, CRM was associated with statistically significant improvements in skin hydration, skin barrier integrity, quality of life, and reduced AD symptoms, and the product was well tolerated.[7]

Of particular interest is the study assessing CRM in conjunction with topical corticosteroids, as compared to topical corticosteroids alone. This multicenter, evaluator-blinded, randomized, and intraindividual comparison enrolled 127 patients with mild to moderate AD. All patients applied topical steroids to all affected areas of the body. Steroids of class I to III potency were used in 23.8% of the patients. Patients applied CRM to lesions and normal skin on one complete side of the body. No moisturizers were allowed on the opposite side. After 4 weeks of treatment, skin hydration was significantly improved on both sides of the body as compared to baseline ($P<0.05$), but the side treated with adjunctive CRM had a greater improvement than the steroid-only side. Eczema Area and Severity Index (EASI) also decreased on both sides of the body, but, again, the side treated with adjunctive CRM had a more rapid onset of action and significantly lower EASI at multiple time points (**Figure 3**).[7]

Figure 3. CRM as an Adjunct to Corticosteroid Treatment in Atopic Dematitis



*Between-group difference in EASI was analyzed by ANCOVA.
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Management Strategies

AD cannot be cured. However, it can be effectively managed with a combination of good bathing habits, avoidance of known irritants and allergens, routine and sufficient application of base therapy (moisturizers, emollients, and barrier repair products), and early symptom recognition. As symptoms emerge and AD flares, topical corticosteroids and anti-inflammatory agents can be added until symptoms regress. Patients with severe disease may require more routine use of anti-inflammatory agents, including intermittent topical corticosteroids, calcineurin inhibitors, and other adjunctive therapies. Patients should be monitored for infections and treated with systemic and/or topical antimicrobial agents as needed. Bleach baths may be used for patients with high rates of colonization. The most severely ill patient may require phototherapy or systemic anti-inflammatory therapy. Education and patient self-care practices are essential for controlling AD. Internet resources such as the Rady's Children's Hospital's Eczema Center (www.eczemacenter.org) and National Eczema Association (www.nationaleczema.org) are reliable and useful.

Conclusions

AD is caused by fundamental genetic defects in skin barrier function. These underlying causes emphasize the pressing need for developing and correctly using topical products that restore skin barrier function and strategies for overall good skin care. A variety of products are available to minimize the dryness, pruritus, and inflammation that individuals with AD suffer, and they are associated with improved quality of life.

References

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