Research Review
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Moisturization in the Management of Paediatric Atopic Dermatitis

About the Expert

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This article is an overview of the pathogenesis and management of atopic dermatitis in infants and children. The focus of the article is the contribution of epidermal dysfunction to the development of atopic dermatitis and the role of moisturizers in the treatment of paediatric atopic dermatitis and potentially in its prevention. The review concludes with commentary from Paediatric dermatologist Dr. Sandipan Dhar

Atopic dermatitis (AD), also known as atopic eczema, is a chronic relapsing pruritic inflammatory skin disease that is associated with substantial psychosocial and economic burden.[1-6] AD usually starts in infancy or early childhood and is one of the most common skin diseases affecting infants and children.

Epidemiology

The lifetime prevalence of AD in developed countries is considered to have plateaued at 10–20%; in contrast, it is lower but continues to increase in many developing countries, especially in younger groups.[7,8] In India, epidemiological data on AD is largely hospital derived and community prevalence rates have only been assessed for certain centers.[9] The prevalence of AD is believed to be increasing in India but still remains low compared with developed countries.[10] As part of the International Study of Asthma and Allergies in Childhood (ISAAC) phase I, the prevalence of AD in children aged 13–14 years was assessed at 14 single centers in India.[11] All centers had 12-month period prevalence rates of 2–6%, except one center for which the rate was 9%. In phase III of ISACC, the prevalence of eczema was 2.8% in Indian children aged 6–7 years age and 3.7% in children aged 13–14 years.[12] A clinico-epidemiological study conducted at a city hospital in Eastern India by Dhar et al. found a prevalence of 0.55%.[13]

Disease burden

AD adversely affects quality of life (QOL) for both children and parents.[14-16] Emotional distress, fatigue, and sleep disturbance contribute greatly to the deterioration in QOL and are directly correlated with severity of AD. Moreover, the development of AD in childhood often precedes progression to other allergic disorders, such as food allergy, allergic rhinitis, and asthma (i.e. the 'atopic march').[9,17,18] In terms of its economic burden, a recent single-centre study estimated the mean total cost of care of AD in Indian children (aged <10 years) in an outpatient setting to be approximately Rs. 12,000–13,000.[19] Most of the cost burden fell on the families of affected children, mainly in the form of cost of medicines and travel costs.

Pathophysiology

In an infant, the skin barrier has not matured and is less protective against environmental challenges than in an older child or an adult.[20,21] Therefore, infants are more vulnerable to diseases that are caused by a defective skin barrier.

The pathogenesis of AD is complex and multifactorial, with skin barrier dysfunction, environmental factors, genetic predisposition, and immune dysfunction playing a role in its development.[4,9,10,22]

Immune dysfunction in AD has received considerable attention, especially with T cell (lymphocyte) dysregulation and elevated immunoglobulin E (IgE) levels contributing to the development of various allergic skin conditions.[4,5] For example, in a hospital-based study of Indian children (aged ≤15 years) with AD, approximately two-thirds were found to have increased serum levels of IgE.[23] A significant correlation between disease severity and increased serum IgE levels has also been demonstrated in Indian children and adults with AD.[24]

However, dermatological research has established a key role for skin barrier dysfunction in the onset of AD and possibly allergic sensitisation.[2,4,5,25]

The primary function of the skin is to act as a barrier to restrict water loss (transepidermal water loss; TEWL) and prevent the entry of allergens, irritants, and pathogenic microbes.[4,5] Higher TEWL has been demonstrated in healthy neonates compared with adults by Indian researchers, suggesting that neonatal skin is still adapting to life outside the uterus and hence is more vulnerable to environmental challenges than adult skin.[26]

The outermost layer of skin, the stratum corneum, is important to maintain the integrity of the skin barrier. Abnormalities of the stratum corneum are associated with AD, including increased TEWL and reduced hydration, altered lipid composition (including low levels of ceramide), and reduced presence of filaggrin (**Figure 1**).[4,5,27]

Filaggrin is a key structural protein involved in the formation of the stratum corneum.[4,5,9,28] Loss-of-function mutations in the FLG gene, which codes for the production of filaggrin, have been identified in patients with

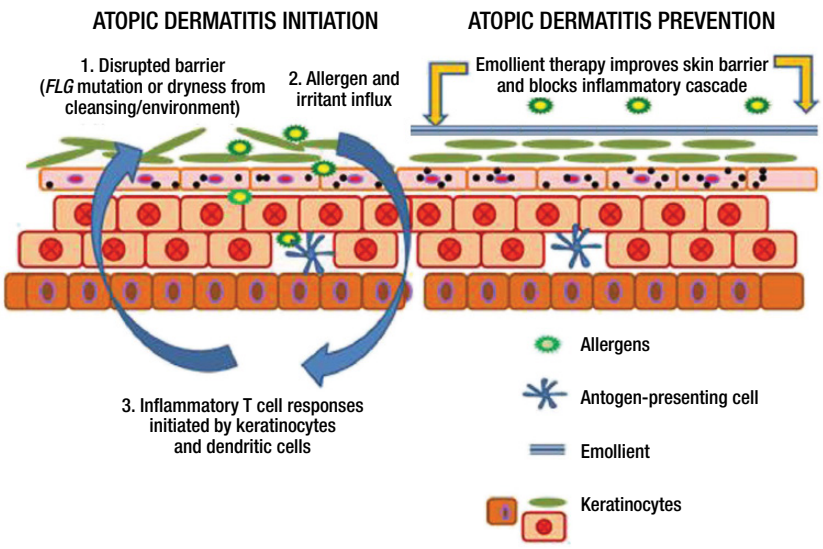

Figure 1. Role of skin barrier dysfunction in the development of AD and the how skin barrier protection might prevent AD.[27] Abbreviation: FLG = filaggrin

AD and appear to be a strong predisposing factor for AD.[29-32] Hence, it has been hypothesized that skin barrier defects caused by FLG mutations allow allergens to penetrate the epidermis and to interact with antigen-presenting cells (immune cells), triggering an inflammatory response.[4,5] Allergen exposure via the epidermis may initiate systemic allergy and predispose individuals to the atopic march.[18,33]

Inadequate filaggrin production impairs the ability of the stratum corneum to restrict TEWL and maintain hydration (via a reduced level of natural moisturizing factor, which is a water-attracting breakdown product of filaggrin), leading to xerosis (skin dryness) and an associated higher risk of developing AD.[4,5,28] Furthermore, the filaggrin deficiency results in an increase in the pH of the skin barrier (via loss of natural moisturizing factor, which maintains a low skin pH) leading to increased barrier breakdown (due to higher skin pH-induced activation of proteolytic enzymes) and/or over-growth of bacteria, such as *Staphylococcus aureus*, which can trigger an innate immune response and the development of inflammatory lesions. *S. aureus* secretes toxins that act as superantigens, which activate T cells and contribute to inflammation.[34]

Diagnosis

Diagnosis of AD is based primarily on clinical features and clinical history, as no reliable biomarker or specific laboratory findings have been established.[4,10,35] Important features that support the diagnosis are early age of onset, personal or family history of atopy, IgE reactivity, and xerosis.[4,10,35,36]

The preliminary clinical signs of AD are generalised skin dryness and roughness.[5] The essential symptoms are pruritus and eczematous lesions.[4,5,35] Eczematous lesions can persist for long periods or follow a relapsing-remitting pattern with repeated flare-ups. The appearance and location of the eczematous lesions generally depends on age. The most commonly affected areas are the face and extensor extremities in infancy and the flexural areas in early childhood. This pattern was reflected in a study of a North Indian paediatric population in which 79% of those with infant AD had facial involvement, 52% had extensor involvement, 42% had flexors affected, and 5.7% had both flexors and extensors affected.[37] In those with childhood AD, the corresponding figures were 74.5%, 35.5%, 56.3% and 8.2%, respectively.

It is important to exclude other inflammatory skin conditions, such as contact dermatitis, seborrheic dermatitis, and psoriasis.[5,35] Skin biopsy and laboratory testing may be useful in differential diagnosis.

In terms of rating disease severity and assessing the efficacy of therapeutic interventions in AD, the SCORing Atopic Dermatitis (SCORAD) index was the most commonly used symptom scoring system in randomized controlled trials of AD treatments according to a recent systematic review.[38] Thakur et al. compared SCORAD with the SASSAD (Six Area, Six Sign Atopic Dermatitis) scoring system for AD by correlating values with clinical and haematological parameters. They concluded that SCORAD was a better scoring system for assessing disease severity and monitoring disease progression because it takes into account both subjective and objective parameters.[39]

Treatment

There is no cure for AD so the objective of treatment is to reduce symptoms and achieve long-term disease control.[5] The main principles of treatment are moisturization, control of inflammation, control of itch, and control of infection.[2,4,5] Treatment involves a step-wise approach based on increasing severity of the AD, as recommended in international guidelines. The following is a simplified stepwise approach: emollients (dry skin) → topical anti-inflammatory agents (mild to moderate eczema) → phototherapy or oral immunosuppressant agents (uncontrolled severe eczema).

Moisturization

The rationale for moisturization for continuous restoration and maintenance of epidermal barrier structure and function is based on the presence of generalised skin dryness in patients with AD and research showing a pathogenic role for skin barrier dysfunction in AD.[2,4,5,37]

Regular and generous use of moisturizers reduces TEWL, reduces xerosis, and supports skin barrier repair. Indeed, a recent Cochrane review and meta-analysis concluded that most moisturizers demonstrate beneficial effects in the treatment of people with eczema.[40] It also noted that moisturizers produce better results when used with active treatments, including prolonging the time to flare, reducing the number of flares, and reducing the quantity of topical corticosteroids used.

In India, use of total-body moisturization may be appropriate only in the drier winter months.[37] During the summer and rainy seasons, moisturizer is required only over the dry patches of eczema. Application of moisturizer all over the body during these hot and humid times of the year may result in an uncomfortable sticky feeling of the skin. It has even been suggested that all emollients, especially vegetable oils such as coconut oil, should be used sparingly during warm weather.[41]

Preterm infants have an especially immature epidermal barrier that is not fully functional and hence susceptible to skin disease.[42] Two small prospective studies conducted during the 1990s showed that twice-daily application of emollient ointment for 2 weeks reduced TEWL and the severity of dermatitis in untreated premature neonates.[43,44] Also, twice-daily application of a topical coconut oil, which is traditionally used in India for infant massage, has been demonstrated to significantly ($p<0.001$) reduce TEWL (without increasing bacterial colonization) compared with standard care in very low birth weight Indian neonates.[45]

In infants and young children with AD, emollient therapy has been demonstrated to be effective in statistically significantly reducing xerosis and other symptoms of AD (including pruritus) in two randomised controlled studies.[46,47] One of these studies demonstrated the ability of moisturization to have a moderating effect on flares in infants and children with established AD but no active lesions at study enrollment.[47] Daily application of a colloidal oatmeal-containing moisturizing cream for 6 months significantly reduced the incidence of flare (21 vs 65%; $p=0.006$) and increased the time to flare (180 vs 28 days; $p<0.05$) compared with control. At the end of the 6 months, 79% of subjects in the moisturizer group remained flare-free compared with 35% of the control group, indicating a 44% reduction in risk of flare (**Figure 2**). The benefits of colloidal oatmeal-based moisturizer, as an adjunct treatment, in the management of AD in infants and children have been

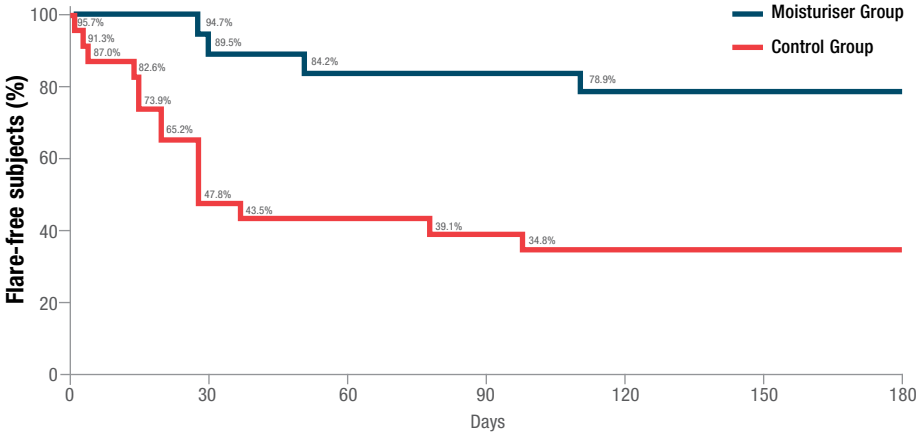

Figure 2. Kaplan-Meier plot showing the proportions of paediatric patients with AD (n=45) who remained flare-free over a 6-month period.[47]

previously demonstrated, including improvement in xerosis, itch, and quality of life (QOL).[48]

QOL improvements typically result from reductions in symptoms of AD. For example, in a multicentre, non-blinded trial, twice-daily application of an emollient for 3 months in children with mild to moderate AD produced significant ($p<0.001$ vs baseline) improvements in the QOL of both the child and their parents.[49] The QOL improvement in the children was accompanied by significant ($p<0.001$ vs baseline) reductions in skin dryness and pruritus.

Frequent moisturization also has the potential to mitigate the use of pharmacologic interventions. Several randomised controlled studies have demonstrated reduced use of topical corticosteroids (i.e. a steroid-sparing effect) during moisturizing therapy in infants and young children with AD.[50-53] In one of the studies, adjunctive treatment with an oat-extract-based emollient for 6 weeks resulted in a significant ($p<0.05$ vs control) reduction in the amount of high-potency corticosteroid used in infants with AD.[51]

Class	Mechanism of action	Biological equivalent	Uses	Examples
Emollients	Softens and smoothens the skin by filling cracks between desquamating corneocytes (terminally-differentiated keratinocytes)	Natural lipids and sebum on skin surface	To maintain the condition of normal skin; not intended to repair damaged skin	Collagen, colloidal oatmeal, cetearyl alcohol, elastin, glyceryl stearate, isopropyl palmitate, shea butter, stearic acid
Humectants	Attract and bind water from deeper epidermis to the stratum corneum	Natural moisturising factor in corneocytes	To maintain the condition of normal skin; absorbed more quickly than occlusives providing an aesthetic advantage	Alpha hydroxy acids, glycerine, hyaluronic acid, lactic acid, sodium PCA, sorbitol, urea
Occlusives	Forms a hydrophobic film or barrier to prevent TEWL from the stratum corneum	Intercellular lipid bilayers: ceramide, cholesterol, free fatty acids	Used on dry and/or damaged skin to promote moisture retention and protect skin from external irritants	Carnauba wax, dimethicone, jojoba oil, lanolin, mineral oils, olive oil, petrolatum, silicone

Table 1. Mechanism of action and uses of different classes of moisturizer.[58-60]

Adding skin cleansing to moisturization

Combining moisturization with gentle skin cleansing using a fragrance-free non-soap-based cleanser is often recommended for good routine skin care.[22,54,55] Skin cleansing helps to remove excess scale, dirt, and debris. Two studies have demonstrated that daily cleansing alone (a double-blind comparison of a syndent bar vs soap bar),[56] and daily cleansing (using a body wash product) in combination with a moisturizer (an open-label baseline comparison)[57] improved skin condition and hydration in children with AD and in infants and toddlers with a history of AD, respectively.

Moisturizer types

The mechanism of action and specific uses of the main classes of moisturizer (emollients, occlusives, and humectants) are summarised in **Table 1**. In general, moisturizer choice should consider an individual patient's characteristics and needs, which includes age, body area, skin properties, and environment (especially climate).[5,21]

All moisturizers are essentially mixtures of lipid (in semi-solid or liquid form) and water and are available in three main formulations: ointments, creams, and lotions.[4] Ointments contain the highest proportion of lipid and provide the greatest lubrication and occlusion.[5,21] Consequently, they feel greasy when applied to the skin. Ointments are typically used for treatment of areas of skin that are dry, thick, and leathery. Creams are emulsions of water in lipid, which makes them less greasy than ointments. However, they also contain preservatives and stabilizers to prevent separation of the ingredients, which can produce a burning or stinging sensation on atopic skin. Creams are suited to large areas. Lotions are emulsions with a higher proportion of water than creams and thus require frequent application to maintain skin hydration. Having a high-water content, they can be used to cool or dry inflamed and oozing lesions.

Moisturizer safety

Safety considerations when selecting a moisturizer should relate to preservatives, fragrances, labelling, and packaging (**Practice Tips 1**). The ideal moisturizer is one that is fragrance free and has the least possible number of preservatives since fragrances and preservatives are potential irritants and allergens.[4] The EU's Scientific Committee on Consumer Safety has highlighted 26 fragrance ingredients, including linalool and limonene, that have the potential to cause skin reactions in susceptible individuals.[61] Preservative-free moisturizers are generally not recommended as moisturizers lacking effective preservatives are at higher risk of contamination.[4]

It is also worth noting that 'natural' does not always mean 'safer'.[21] Most plant extracts are mixtures of compounds from different chemical

classes, e.g. alkaloids, phenolics, and terpenes, some of which could be pharmacologically active and hence increase the potential for adverse effects.[62,63] For example, plant extracts of lavender, rosemary, and tea tree have been shown to cause allergic contact dermatitis.[64-66]

Control of inflammation

Cases of AD not controlled by moisturizers alone should be treated with topical anti-inflammatory agents, corticosteroids and calcineurin inhibitors.[4,5] Topical corticosteroids form the first line of management in mild to moderate AD.[67]

Topical corticosteroids are effective and safe when used appropriately, i.e. short-term adequate treatment of flares, which includes awareness of known potential cutaneous atrophy-related adverse effects and systemic effects such as adrenal suppression.[4,5] Topical corticosteroids are classified according to their potency, with risk of adverse effects directly correlated with potency. A recent comprehensive systematic literature review by Siegfried et al. supports the long-term safety of low-to-mid potency topical corticosteroids in paediatric patients with AD, with no evidence of cutaneous atrophy or systemic exposure.[68] For acute flares, and moderate to severe cases, corticosteroids can be applied under wet wrap dressings to facilitate penetration and skin hydration.[4,5] It has been suggested that wet wraps should be used with caution in India's hot and humid climate due to the increased potential for occlusive adverse effects.[37] Oral steroids are not indicated because of their tolerability profile and risk of rebound dermatitis.[4,5]

Topical calcineurin inhibitors, tacrolimus and pimecrolimus, are immunosuppressive agents that inhibit T cell function, i.e. they ameliorate immune response.[4] The recent systematic literature review by Siegfried et al. also supports the long-term safety of topical calcineurin inhibitors in paediatric patients with AD.[68] As they do not cause skin atrophy they are appropriate options for delicate skin areas such as the face and in patients in whom the long-term use of corticosteroids is a concern.[4,5] A study by Dhar et al. has shown that topical tacrolimus is effective and safe in the treatment of children with mild to moderate AD.[69]

Once an acute flare has responded to anti-inflammatory treatment, maintenance of the remission should be attempted with continued moisturizer treatment,[5] and some clinicians may advocate a period of proactive infrequent anti-inflammatory agent use.

PRACTICE TIPS 1: MOISTURIZER SELECTION

- The relative moisturizing effects of different formulations are: ointments > creams > lotions.
- Fragrance-free products are best for patients with AD.
- Products should contain the least possible number of preservatives (but still be effective in the prevention of contamination).
- Preservatives can be natural or synthetic, as long as their safety profile is documented.
- Directions for product use should educate parents on safe and appropriate use.
- Package design should help to minimise product contamination.

Control of itch

Pruritus contributes substantially to the loss of QOL in patients with AD.[2,4] The re-establishment of an effective skin barrier to prevent allergen and microbial penetration in addition to effective anti-inflammatory therapy is associated with reduced severity of pruritus. Topical antihistamines are not effective in controlling itch as histamine appears to play only a limited role in the pathophysiology of AD. However, oral sedating antihistamines help to reduce the sensation of itching and may be of most benefit at night when itching is worse. Sedating antihistamines should generally be avoided in infants.

Control of infection

Although the skin of most patients with AD is colonised with *S. aureus*, antibiotic therapy should be reserved for clinically overt infections since the over-use of antibiotics can lead to drug resistance.[2,4] Bleach baths may be an option for patients who are susceptible to recurrent infection and AD flares. As children with AD are at higher risk of skin infection, early recognition and treatment of infection leads to improved outcomes.

PRACTICE TIPS 2: MOISTURIZER APPLICATION

- Cleanse the skin with a fragrance-free non-soap cleanser prior to applying moisturizer.
- Moisturize twice daily, more frequently if appropriate.
- Apply within 5min of bathing, i.e. while the skin is still damp.
- Apply to the entire body irrespective of whether dermatitis is present.
- Use of a greasier moisturizer may be necessary in low humidity environments.
- Consider use of a lighter moisturizer for heat-rash-prone areas (e.g. torso) in warm climates.
- Pay attention to high-risk areas, i.e. lower limbs, heels, and feet.
- Apply anti-inflammatory agents immediately after bathing and then the moisturizer on top.

Refractory disease

In patients who are refractory to conventional treatment, the use of phototherapy or systemic immunosuppressant therapy may be indicated.[4,5] In terms of phototherapy, narrow band UVB is effective and safe in management of children with AD.[70,71] If topical treatment and phototherapy do not produce improvement, systemic immunosuppressive therapies are required.[5]

Adherence to treatment

Treatment failure in AD is often due to non-adherence to treatment, which is particularly common with topical therapy.[5,37,59,72] Reasons for non-adherence include fears related to the potential adverse effects of corticosteroids, a poor or inadequate understanding of AD and its treatment, especially the need for long-term therapy, and the inconvenience of some treatment regimens.

In addition to allaying 'steroid phobia' and simplifying treatment regimens, paediatric healthcare professionals need to take the time to fully explain AD and its treatment to parents and caregivers. A qualitative study conducted in the UK that assessed the views of parents and carers on the use of emollients for paediatric AD found the following:[72]

- A consensus that emollients improve AD but mixed views about long-term use to prevent flare-ups.
- Mixed views on which emollients were of most benefit.
- A need for understanding differences between products and their effective use.

The researchers concluded that providing parents or caregivers of children with AD a scientific rationale for long-term emollient use and emollient choice could help improve treatment adherence and control of AD.[72] These same researchers have also emphasised the need to direct patients and caregivers towards high quality information on AD and its treatment available on the internet.[73] Decisions regarding the use of infant skin care products in preterm and term infants should be evidence based.[74]

Written action plans, education, and training programmes (e.g. nurse-led clinics) can also help to improve adherence.[4,5] In a UK study, a community-based nurse-delivered educational support programme for parents and carers of children with AD resulted in increased emollient use, reduced symptoms, and fewer GP visits.[75]

Prevention

An effective primary prevention strategy for AD has yet to be established.[5] Most interventions evaluated to date have involved allergen avoidance or immunomodulation but no clear evidence for the effectiveness of these measures has emerged. Nonetheless, while it may be impossible to completely avoid triggers that exacerbate AD, minimising exposure to them can be beneficial in some patients.[2,4,5] In addition to allergen avoidance, moisturization may also have a secondary preventive effect.

Two randomised controlled studies provide preliminary evidence that daily full-body moisturizing from birth helps to primarily prevent the development of AD in high-risk infants.[27,76] One of the two studies investigated whether use of an emulsion-type emollient from the first week of life reduced the incidence of AD in infants who had a parent or sibling with AD.[76] During the first 8 months of life, significantly ($p=0.012$) fewer infants who received the moisturizer (32%) than infants who received the control (47%) developed AD. The moisturizer group maintained healthy skin for a significantly ($p=0.012$) longer period than the control group. Higher levels of stratum corneum hydration were observed in the moisturizer group versus the control group ($p<0.05$ at weeks 12 and 24). In the other randomised controlled study, application of an emollient (an oil, cream/gel, or ointment) at least once daily from birth produced a significant ($p=0.017$) 50% reduction in the incidence of AD at 6 months (22% in the moisturizer group vs 43% in the control group) in infants with a parent or sibling with AD.[27]

Preventing the development of AD in neonates and infants has the potential to translate into economic benefit. A recent cost-effectiveness analysis, which was conducted in the US healthcare setting, produced initial evidence that daily total-body moisturization from birth in high-risk neonates may reduce the burden of AD.[77]

EXPERT CONCLUDING COMMENTS – SANDIPAN DHAR

AD is a chronic, relapsing, inflammatory skin disorder characterized by pruritus and inflammation, mostly manifesting in infancy and childhood. Though studies have shown an increase in the prevalence of AD in developing countries like India, the severity is less as compared to the developed countries. This review nicely elucidates the role of epidermal dysfunction in the pathogenesis and the role of moisturizers in restoring the compromised epidermal barrier and preventing flares.

It is well known that filaggrin plays an important role in epidermal barrier function. Filaggrin gene mutation results in decreased to absent epidermal filaggrin, leading to skin barrier dysfunction. However, these filaggrin mutations are seen only in 25% to 50% children with AD. There are no well documented studies regarding filaggrin gene mutation in Indian children, giving rise to the possible role of exogeneous factors in the increased prevalence of AD.

Moisturizers form the cornerstone of management in restoring deranged epidermal barrier function. Moisturizers in AD improve hydration, relieve pruritus, enhance the skin barrier function, reduce exposure to irritants and microbes, prevent flares, and have a steroid-sparing effect. In Indian children, simple petrolatum-based products are economical, safe, and effective in improving skin barrier function. However, in the last few years, there has been lot of hype about the newer moisturizers containing ceramides. This is supposed to be mostly useful for those patients with AD having filaggrin deficiency in their epidermis. Indeed, there are some clinical studies showing that ceramide-containing moisturisers have efficacy in the treatment of children with atopic dermatitis. However, it is still not established that such formulations are better than just ordinary petrolatum products in majority, if not all, the patients.

TAKE-HOME MESSAGES:

- **AD is a common skin disease infants and children.**
- **Abnormalities of skin barrier biology and immune mechanisms underlie the pathophysiology of AD.**
- **A defective skin barrier facilitates allergen penetration and sensitisation, as well as microbial infection.**
- **Daily cleansing and moisturization can support skin barrier function and integrity.**
- **Regular use of moisturizers reduces symptoms and flares in infants and children with established AD.**
- **Regular use of moisturizer has the potential to be corticosteroid-sparing.**
- **Emerging evidence suggests that intensive use of moisturizer from birth may have a role in primary prevention of paediatric AD.**

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