Moisturisation in the Management of Paediatric Atopic Dermatitis

This article is an overview of the pathogenesis and management of atopic dermatitis in infants and children. The main focus of the article is the contribution of epidermal dysfunction to the development of atopic dermatitis and the role of moisturisers in the treatment of paediatric atopic dermatitis and potentially in its prevention.

Atopic dermatitis (AD), which is a type of eczema, is a chronic relapsing pruritic inflammatory skin disease that is associated with substantial psychosocial and economic burden. AD usually starts in infancy and is one of the most common skin diseases affecting infants and children. Epidemiological studies indicate that the prevalence of paediatric AD in Australia and New Zealand is 15–20%. AD negatively affects quality of life for both patients and parents. Emotional distress, fatigue, and sleep disturbance contribute greatly to the deterioration in quality of life 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’).

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. 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 all playing a role in its development. 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. However, dermatological research has established a key role for skin barrier dysfunction in the onset of AD and possibly allergic sensitisation.

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. The outermost layer of skin, the stratum corneum, is crucial to 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. Atopic dermatitis and the role of moisturisers in the treatment of paediatric atopic dermatitis and potentially in its prevention.

Figure 1. Role of skin barrier dysfunction in the development of AD and the how skin barrier protection might prevent AD. Abbreviation: FLG = filaggrin
Filaggrin is a key structural protein involved in the formation of the stratum corneum. Loss-of-function mutations in the FLG gene, which codes for the production of filaggrin, have been identified in patients with AD and appear to be a strong predisposing factor for AD. In 2006, Irwin McLean and colleagues in the UK were the first group of researchers to link loss-of-function mutations in the filaggrin gene with AD and to identify an important role for impaired skin barrier function in the development of atopic disease. 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. Allergen exposure via the epidermis may initiate systemic allergy and predispose individuals to the atopic march.

Moisturisation

The rationale for moisturisation 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. Regular and generous use of moisturisers reduces TEWL, reduces xerosis, and supports skin barrier repair. Indeed, a recently published Cochrane review and meta-analysis concluded that most moisturisers demonstrate some beneficial effects in the treatment of people with eczema. It also noted that moisturisers 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.

Preterm infants have an especially immature epidermal barrier that is not fully functional and hence susceptible to skin disease. 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.

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. One of these studies demonstrated the ability of moisturisation to have a moderating effect on flares in infants and children with established AD but no active lesions at study enrollment. Daily application of a colloidal oatmeal-containing moisturising body cream for 6 months significantly reduced both the incidence of flare (21 vs 65%; p=0.006) and 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 moisturiser 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 moisturiser, as an adjunct treatment, in the management of AD in infants and children have been previously demonstrated, including improvements in xerosis, itch, and quality of life (QOL).

Diagnosis

Diagnosis of AD is based primarily on clinical features and clinical history, as no reliable biomarker or specific laboratory findings have been established. Important features that support the diagnosis are early age of onset, personal or family history of atopy, IgE reactivity, and xerosis. The preliminary clinical signs of AD are generalised skin dryness and roughness. The essential symptoms are pruritus and eczematous lesions. 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.

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

Treatment

There is no cure for AD so the objective of treatment is to reduce symptoms and achieve long-term disease control. The main principles of treatment are moisturisation, control of inflammation, control of itch, and control of infection. Treatment involves a stepwise approach based on increasing severity of the AD (i.e. emollients → topical anti-inflammatory agents → phototherapy or oral immunosuppressant agents), as recommended in international guidelines.

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. The QOL improvement in the children was accompanied by significant (p<0.001 vs baseline) reductions in skin dryness and pruritus.

Frequent moisturisation 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 moisturising therapy in infants and young children with AD. 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.

Adding skin cleansing to moisturisation

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

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

The mechanism of action and specific uses of the main classes of moisturiser are summarised in Table 1. In general, moisturiser choice should consider an individual’s characteristics and needs including age, body area, skin properties, environment (especially climate), and preferences relative to moisturiser formulation.\textsuperscript{4,15}

All moisturisers are essentially mixtures of lipid (in semi-solid or liquid form) and water and are available in three main forms.\textsuperscript{3} Ointments contain the highest proportion of lipid and provide the greatest lubrication and occlusion.\textsuperscript{4,15} 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 stabilisers 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.

Table 1. Mechanism of action and uses of different classes of moisturiser.\textsuperscript{44-46}

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

Safety considerations when selecting a moisturiser should relate to preservatives, fragrances, labelling, and packaging (Practice Tips 1). The ideal moisturiser is one that is fragrance free and has the least possible number of preservatives since fragrances and preservatives are potential irritants and allergens.\textsuperscript{3} 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.\textsuperscript{47} Preservative-free moisturisers are generally not recommended as moisturisers lacking effective preservatives are at higher risk of contamination.\textsuperscript{5}

It is also worth noting that ‘natural’ not always mean ‘safer’.\textsuperscript{15} 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.\textsuperscript{48,49} For example, plant extracts of lavender, rosemary, and tea tree have been shown to cause allergic contact dermatitis.\textsuperscript{50-52}

Control of inflammation

Cases of AD not controlled by moisturisers alone should be treated with topical anti-inflammatory agents, corticosteroids and calcineurin inhibitors.\textsuperscript{3,4}

Topical corticosteroids are effective and safe when used appropriately.\textsuperscript{3,4} Higher-strength topical corticosteroids can be used for flares, with a lower strength used for maintenance in appropriate cases. Awareness of potential side effects is important but patients and parents should be advised sensibly about them. Concerns about topical corticosteroid use (‘corticophobia’ or ‘steroid phobia’) are common among parents of children with AD, potentially leading to non-adherence and poor disease control.\textsuperscript{53,54} However, the consensus of Australasian dermatologists is that the use of topical corticosteroids in paediatric AD does not cause atrophy, hypopigmentation, hypertrichosis, osteoporosis, purpura, or telangiectasia when used according to guidelines.\textsuperscript{55,56} In a 2016 survey of Australasian College of Dermatologists fellows, 75% of the respondents strongly agreed that topical corticosteroids do not cause skin atrophy when used appropriately and under clinical supervision in the treatment of paediatric AD.\textsuperscript{57}

Topical corticosteroids are classified according to their potency, with risk of adverse effects directly correlated with potency.\textsuperscript{4} A recent comprehensive systematic literature review 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.\textsuperscript{58} For acute flares, and moderate to severe cases, corticosteroids can be applied under wet wrap dressings to facilitate penetration and skin hydration.\textsuperscript{4,59} Oral steroids are not indicated because of their tolerability profile and risk of rebound dermatitis.

Topical calcineurin inhibitors, e.g. pimecrolimus, are immunosuppressive agents that inhibit T cell function.\textsuperscript{3} The previously mentioned recent systematic literature review also supports the long-term safety of topical calcineurin inhibitors in paediatric patients with AD.\textsuperscript{56} 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.\textsuperscript{4}

Once an acute flare has responded to anti-inflammatory treatment, maintenance of the remission should be attempted with continued moisturiser treatment,\textsuperscript{4} and often clinicians will advocate twice-weekly maintenance topical corticosteroid or calcineurin inhibitor use.

Control of itch

Pruritus contributes substantially to the loss of QOL in patients with AD.\textsuperscript{3,19} 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.

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.\textsuperscript{3,19} Twice-weekly bleach baths may be a good 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.

Refractory disease

In patients who are refractory to conventional treatment, the use of phototherapy or systemic immunosuppressant therapy may be indicated under supervision of a dermatologist.\textsuperscript{3,4} If topical treatment and phototherapy fail, systemic immunosuppressive therapies are required.\textsuperscript{4}
Adherence to treatment

Treatment failure in AD is often due to non-adherence to treatment, which is particularly common with topical therapy. 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: 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. These same researchers have also emphasised the need to direct patients and carers towards high-quality information on AD and its treatment available on the internet. Decisions regarding the use of infant skin care products in preterm and term infants should be evidence based. Written action plans and education and training programmes (e.g. nurse-led clinics) can also help to improve adherence. 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.

Better education of healthcare professionals, especially pharmacists, about the use of topical corticosteroids is also called for to help to improve adherence and treatment outcomes. For example, a survey of Australian pharmacists showed that 46% believed that side effects would occur from topical corticosteroid use and 54% would instruct patients to use topical corticosteroids sparingly. However, topical corticosteroids do not cause atrophy and other adverse effects in the treatment of paediatric eczema if used appropriately and there is no requirement to apply topical corticosteroids sparingly. Dermatologists can play an important role in the education of other healthcare professionals regarding the safe and effective use of topical corticosteroids.

Prevention

An effective primary prevention strategy for AD has yet to be established. 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. In addition to allergen avoidance, moisturisation may also have a secondary preventative effect.

**PRACTICE TIPS 1: MOISTURISER SELECTION**

- The relative moisturising 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.

Two randomised controlled studies provide preliminary evidence that daily full-body moisturising from birth helps to primarily prevent the development of AD in high-risk infants. One of these 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. During the first 8 months of life, significantly fewer infants who received the moisturiser (32%) than infants who received the control (47%) developed AD. The moisturiser group maintained healthy skin for a significantly longer period than the control group. Higher levels of stratum corneum hydration were observed in the moisturiser group versus the control group (p<0.12) 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 moisturiser group vs 43% in the control group) in 124 infants with a parent or sibling with AD.

**PRACTICE TIPS 2: MOISTURISER APPLICATION**

- Cleanse the skin with a fragrance-free non-soap cleanser prior to applying moisturiser.
- Moisturise twice daily, more frequently if appropriate.
- Apply immediately after bathing, i.e. while the skin is still warm and damp.
- Apply to the entire body irrespective of whether dermatitis is present.
- Use of a greasier moisturiser may be necessary in low humidity environments.
- Consider use of lighter moisturisers 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 at least 1 hour before topical anti-inflammatory agents, or apply them at different times of the day. If this is not practical, apply anti-inflammatory agents immediately after bathing and then the moisturiser on top.
Moisturisation in the Management of Paediatric Atopic Dermatitis

Since the seminal work by Professor Irwin McLean and colleagues on filaggrin null mutations, there has been a sea-change in our understanding of the pathogenesis of atopic eczema. The renewed focus on improving the skin barrier defect has led to an increased emphasis on moisturising the skin. Preliminary studies in neonates suggest that using regular emollients from birth can prevent atopic eczema in high-risk infants, a significant and exciting finding for both clinicians and patients. More studies are underway.

For the everyday GP, paediatrician, and dermatologist, our responsibility is to ensure that our patients with atopic eczema are treated adequately, with a simple regimen, which is reviewed over time. All too often, we know that parents of children with atopic eczema are given conflicting advice about treatment, particularly with regard to the use of topical steroids, from a wide variety of sources including many health professionals.

Giving patients incorrect information about steroid use undoubtedly leads to non-adherence with treatment and ultimately treatment failure and poorer outcomes. Every day we see patients who have been treated with the wrong strength of steroid, who have been treated with oral antibiotics instead of moisturisers, and not given enough topical treatment to last them more than a week. We need better education for everyone who is managing eczema.

Parents and patients need to be given written eczema plans, including clear instructions about frequency of application and the amount of treatment to be used. Prescriptions should be given in adequate quantities. All healthcare workers should be educated about the safety of topical steroids, to avoid misinformation and undermining confidence in prescribed treatments.

Topical calcineurin inhibitors can very helpful for facial and eyelid eczema, but their use cannot be fully exploited in New Zealand since they are not fully subsidised by Pharmac, and is prohibitively expensive for many patients.

Dermatologists need to use the media to spread the word about what causes eczema and what helps control eczema. The recent Australasian College of Dermatologists Consensus Statement on topical steroids in paediatric eczema (2017) should be read by all healthcare professionals who encounter patients with eczema.

A number of genetic protein and lipid variations, in particular of filagrin and ceramides, have been shown to predispose to impaired skin barrier and AD. Other factors likely also play a role in skin barrier, including other proteins (e.g. involucrin, loricrin), ratios of lipids and proteins, the skin acid mantle, and complex balances of proteases and protease inhibitors of the skin. While it is not currently possible to specifically reverse genetic predisposing factors, there is increasing evidence that routine, early moisturisation has a very important role in therapy, as well as in primary and secondary prevention of AD. Recent studies have shown that routine moisturisation not only improves clinical outcomes but also reduces biochemical markers of inflammation in the skin.

Treatment must be personalized; consideration of social, environmental, personal, body site, and other skin factors is important to optimize effectiveness, minimize intolerance, and ensure compliance with moisturisation regimens. Greasier moisturisers are effective emollients and their occlusive effects are beneficial in areas that are very dry or prone to irritation (e.g. perioral and diaper areas in infants) but lighter moisturisers have advantages in their ease of use in older children and when there is a risk of heat rash and folliculitis. Consistency in the frequent use of moisturisers is key to their beneficial effects.

Use of a safe and well-tolerated cleanser is recommended instead of soap, but overcleansing should be avoided to prevent irritation. Recognition of signs of inflammation and infection is also important, to allow timely use of anti-inflammatories and anti-microbial measures.

Evidence-based structured education programmes can be very helpful. Better communication between families and health professionals will help families to appreciate paediatric skin needs, to adopt effective and sustainable AD treatment plans, and to persevere with optimizing skin care.

**TAKE-HOME MESSAGES:**

- **AD is a common skin disease in Australian and NZ 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 moisturisation can support skin barrier function and integrity.**
- **Regular use of moisturisers reduces symptoms and flares in infants and children with established AD.**
- **Regular use of moisturiser has the potential to be corticosteroid-sparing.**
- **Intensive application of moisturiser from birth may have a role in primary prevention of paediatric AD.**
REFERENCES


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