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A Global Review on the Risk Factors and Management of Early Atopic Dermatitis in Children Ages 0 to 2 Years Old

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ABSTRACT

Introduction: Atopic dermatitis (AD) is a chronic, relapsing skin disease starting typically in atopic-prone children between 3–6 months of age, with most children having developed AD by the age of 5 years. Intense itching leads to sleep disturbance, especially in younger children and toddlers.

This review explores early intervention in infants and young children with AD by controlling skin barrier function and inflammation at the earliest time point using a moisturizer and a proactive treatment.

Methods: A working group of experienced clinicians managing pediatric populations with AD convened for a meeting. The panel reviewed the literature surrounding early intervention in infants and young children with AD and developed and discussed clinical questions aimed at optimizing clinical outcomes.

Results: Complex gene/immune system/environment interactions are involved in AD development. Epidermal barrier defects play a central role in the condition, with various studies showing impairment of skin barrier function at birth may precede clinical AD. Dynamic changes take place in the amounts of skin lipids during infancy.

Studies confirm that daily use of a moisturizer from birth onwards may offer benefits in improving skin barrier function and possibly prevention of AD, especially in high-risk, atopic prone newborns. Plant-based moisturizers were shown to be safe and effective when applied in pediatric patients with AD and may provide a TCS-sparing effect while improving skin condition.

Conclusion: Dry skin conditions during infancy may predict the subsequent development of AD. Consequently, emollient therapy from birth represents a feasible, safe, and effective approach for AD prevention. Therefore, parental education and the application of moisturizers are recommended as an integral part of AD prevention, treatment, and maintenance.

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INTRODUCTION

Atopic dermatitis (AD) is a relapsing, inflammatory, pruritic skin disease with a prevalence reported in industrialized countries of over 20% in children and up to 3% in adults.[1,2] The onset of AD is typically between 3–6 months of age, with 90% of atopic-prone children developing AD by the age of 5 years.[2] The clinical diagnosis of AD is based on the presence of one or more signs including pruritus, erythema, scaling, xerosis, edema, excoriations/erosions, oozing, crusting or lichenification.[2] AD usually does not appear in the first weeks of life; the clinical presentation differs with that of adults. In children, AD presents in an age-dependent distribution with facial, scalp, and extensor involvement in infants and young children, and with predominant flexural involvement in older children.[5] Intense itching leads to significant sleep disturbance, especially in younger children and toddlers.[4,5] Poorer sleep than normal occurs even when the children are in remission; this lack of quality sleep may have long-term behavioral and neurocognitive effects.[4,6] Sleep disturbance was reported to be more common in those children with severe disease and

should be considered when assessing the burden of AD on child and family.[4] The social stigma of a visible skin condition can cause distress, anxiety, and embarrassment, which may result in limited social interactions, poor self-esteem, and lack of self-confidence.[5]

The etiology of AD involves complex skin barrier gene/environment interactions that undermine the structural and functional integrity of the skin barrier and its immune function.[7-9] Early recognition of environmental risk factors and their exposure reduction may mitigate AD and support its prevention.[5,7-9]

The current review aims to explore early intervention in infants and young children with eczema and AD-prone skin by improving skin barrier function and controlling inflammation at the earliest time point using a moisturizer and a proactive treatment. This approach may help prevent AD and/or control its evolution; by slowing the atopic march with better control of sensitization emergence, early intervention may provide rapid and possible lasting improvement.[5]

Atopic Dermatitis Impacts Patients and Families

A cost-effectiveness analysis evaluated the average costs of total-body daily moisturizer application with one of seven commonly used moisturizers from birth to 6 months of age.[10] The authors concluded that daily moisturiser use may represent a cost-effective, preventative strategy to reduce the burden of AD.[10]

A 2016 study surveyed 82 caretakers of children aged 6 months to 12 years with moderate to severe AD between 2011–2013 and asked questions about direct and indirect expenses.[11] The authors reported a mean monthly personal cost of AD of US $274, with a high proportion spent on over the counter products, especially moisturizers.[11] Indirect costs comprised the largest portion of the cost, with an average of US $199 expended due to lost caregiver workdays.[11]

AD significantly impacts patients and their families' quality of life, burdening them financially and emotionally.[12] Financial expenses can be divided into direct and indirect costs: Direct costs could include prescriptions, over-the-counter treatments, physician visits and hospitalizations, while indirect costs can consist of absenteeism from school or work, decreased productivity, and emotionally decreased quality of life.[13]

AD has profound effects on the lives of children due to scratching, pain, and sleep difficulties and is associated with secondary effects on caregivers.[14] Reports have shown patients with AD have difficulties with sleep, work, and interpersonal relationships.[4] AD is also associated with potential risk factors for obesity and high blood pressure, chronic inflammation, sleep disturbances, and mental health comorbidities, including suicide.[14]

Atopic Dermatitis Development in Early Childhood

The first phase or initial phase of AD commonly occurs in early childhood and may present without signs of sensitization; this phase is also referred to as non-atopic or intrinsic AD.[5] A genetically predisposed child may present with non-pathological xerosis only, in the absence of positive specific serum immunoglobulin E (IgE) serology.[5] The atopic child, in a second phase, also called true or extrinsic AD, presents as sensitive to allergens in the presence of an IgE response to environmental allergens, such as aeroallergens.[5] There is a third phase, also referred to as auto-allergic AD, which only seems to affect those patients suffering from AD with sensitization and is characterized by the appearance of IgE response to endogenous proteins. This third phase involve very severe forms of AD.

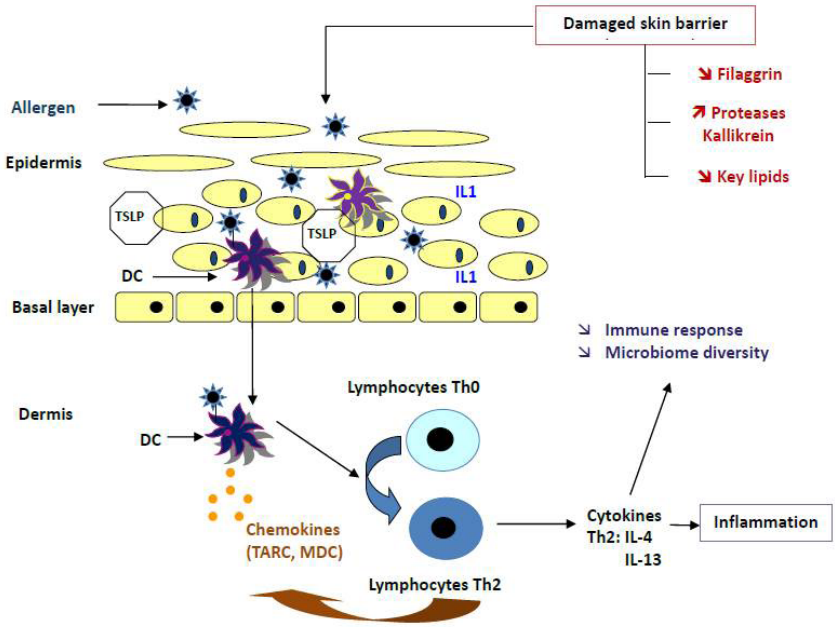
AD may be regarded as a lifelong condition in which defects of the epidermal barrier play a central role (Figure 1).[15,16] AD has been described as having genetic predispositions, including null mutations in FLG and having reactions to environmental triggers, climate, urban living, and diet.[8,9,15]

Kelleher and colleagues[17] evaluated infants at 6 and 12 months of age for the presence of AD and assessed disease severity using SCORing Atopic Dermatitis (SCORAD) at 6 months and both SCORAD and Nottingham Severity Score (NSS) at 12 months. A total of 1903 infants were enrolled in the study and 1300 infants were genotyped for filaggrin (FLG) mutations. At 6 months, 18.7% of the infants presented with AD, and at 12 months, 15.53% had symptoms. The researchers concluded that enhanced TEWL at birth and at 2 months was shown to precede clinical AD.[15]

An infant's stratum corneum (SC) is not fully developed and has an elevated pH of approximately 6.0, which acidifies in order to reach a physiological pH range of (4.1–5.8). During the first year of life, the SC's function and thickness will develop gradually.[16] An in-vivo study on the physiology of infant epidermal skin and its adaptation after birth investigated the molecular composition of the SC and its water content using Raman spectroscopy, as well as non-invasive assays for measurement of transepidermal water loss (TEWL), SC hydration and skin surface pH.[18] The 108 subjects were divided into six age groups: Full-term newborns (1–15 days), babies aged 5–6 weeks, babies aged 6±1 months, children aged 1–2 years, children aged 4–5 years and adults aged 20–35 years. The study showed skin surface acidification and changes in hydration take place during the first weeks after birth.[18] A decreased water content was observed in newborns compared to all age groups.[18] The investigators concluded that dynamic changes in the amount of natural moisturizing factor (NMF) take place during infancy, with lowest NMF amounts occurring at 6 months.[18]

A further study evaluated the maturation and organization of

FIGURE 1. Inflammation and skin barrier impairment in atopic dermatitis.



the SC after birth using an electron microscopy isotropy (EMI) score and immunocytochemical corneodesmosomes labelling.[19] Subjects were allocated according to their age: full-term newborns (1–15 days), babies aged 5–6 weeks, babies aged 6±1 months, children aged 1–2 years, children aged 4–5 years and adults aged 20–35 years. The lowest EMI scores were noted in neonates, who together with the youngest groups of babies displayed irregular and thick cell clusters comprising poorly individualized cells versus the older groups, where a more regular distribution of superficial corneocytes was observed.[19] The immunocytochemical corneodesmosome assay showed a correlation between age and structural maturation, and confirmed the relative immaturity of the epidermal barrier up to 1¬2 years after birth under basal condition. Authors concluded these findings reveal the relative immaturity of the epidermal barrier from birth to 1–2 years, which may contribute to explaining the fragility of children's skin, its susceptibility to chemical, physical and microbial aggression and also its well-known relative permeability. Consequently, the skin of neonates, infants and young children requires special caution with topical skin care regimens.[19]

Studies demonstrated that certain infants with epidermal barrier breakdown at birth are predisposed to the development of AD.[20-22] A randomized controlled study including 115 neonates evaluated biophysical, biological and functional properties of the developing neonatal SC from birth to 4 weeks of age.[20] The study indicated the presence of impaired barrier function correlated with elevated protease activity and reduced NMF at birth and may explain the development of skin barrier dysfunction and AD.[20] A cohort study showed that those with an impaired skin barrier function in early infancy and at 2 years of age demonstrated a higher risk for food allergy.[22] The authors concluded that neonatal skin barrier dysfunction may predict food allergies, while skin barrier dysfunction may also support possible transcutaneous food allergen sensitization. The study showed TEWL measurements in the first few days of life may be useful in predicting AD development.[22] An overview of the discussed literature is displayed in Table 1.

Prevention of Atopic Dermatitis in Babies and Toddlers Using a Moisturizer

Working with a hypothesis that improving the properties of the skin barrier early in life by applying moisturizers from birth may protect against the onset of AD in infants and early childhood, investigators developed various trials. Results from two prospective, randomized controlled trials demonstrated the daily use of a moisturizer prevented AD in 32% of Japanese and 50% of Anglo-American high-risk newborns.[23,24] Horimukai and colleagues further suggested allergic sensitization during this time period is associated with the presence of AD but not with moisturizer use.[24] However, a larger study may find using a moisturizer reduces allergic sensitization by preventing the development of AD.

Data from 116 infants in a randomized controlled study[24] were analyzed evaluating skin barrier function measuring TEWL, stratum corneum hydration (SCH), and skin surface pH, as well as the association between skin barrier function and time-to-AD development.[25] The Kaplan-Meier survival function (estimate

TABLE 1.

Literature Review Summary on Atopic Dermatitis Development in Neonates, Infants, and Toddlers			
Reference	**Population**	**Study Type**	**Details**
[5]Bieber T: Atopic dermatitis. *N Engl J Med* 2008; 358: 1483–1494.	Infants	Review	A genetically predisposed child may present with non-pathological xerosis only.
[8]Kantor R, et al. *Exp Rev Clin Immunol.* 2016 (6): 15-26.	AD	Review	The genetic predisposition and exposure to environmental triggers may lead to AD flares.
[9]Agrawal R, et al. *Curr Allergy Asthma Rep.* 2014 May;14(5): 433-9.	Skin barrier defects in AD	Review	Skin barrier defects in AD.
[15]Flohr C, et al. *Allergy* 2014;69:3-16.	Childhood AD	Review	New insights into AD epidemiology.
[17]Kelleher MM, et al. *J Allergy Clin Immunol.* 2015 Apr; 135(4): 930–935.	Over 1900 infants evaluated at 6 and 12 months of age	Cohort study	Impairment of skin barrier function at birth and at 2 months was shown to precede clinical AD.
[18]Fluhr JW, et al. *Br J Dermatol.* 2012 Mar;166(3):483-90.	N = 108 Subjects: Full-term newborns (1-15 days); Babies: Aged 5-6 weeks and 6±1 months; Children: Aged 1-2 years and 4-5 years; Adults: Aged 20-35 years.	In-vivo study on infant epidermal skin physiology and its adaptation after birth.	Dynamic changes in the amounts of the natural moisturizing factors take place during infancy, with lowest amount at 6 months of age.
[19]Fluhr JW et al. *Br J Dermatol.* 2014 Nov;171(5):978-86.	Population as in reference[18]	*In-vivo* study on maturation and organization of the SC after birth.	There is relative immaturity of the epidermal barrier from birth to 1–2 years old. The skin of neonates, infants and young children requires special caution with topical skin care regimens.[19]
[20]Chittock J. *Br J Dematol. 2016;* 175(3):713-720.	One hundred and fifteen (115) Neonates	Randomized controlled study on biophysical, biological and functional properties of neonatal SC from birth to 4 weeks of age.	The presence of impaired barrier function was correlated with elevated protease activity and reduced natural moisturizing factors at birth and may explain the development of AD.
[22]Kelleher MM	Early infancy and evaluation at 2 years of age.	Cohort study on longitudinal impact of transcutaneous exposure to food allergens evaluating neurological and nutritional endpoints and skin barrier function.	Neonatal skin barrier dysfunction may predict food allergies and support possible transcutaneous food allergen sensitization.

Atopic dermatitis (AD)

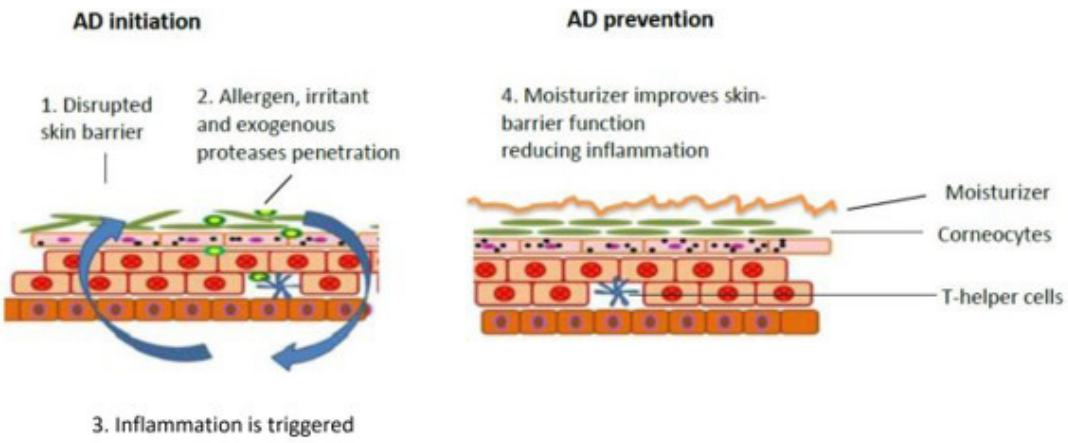
of incidence) of the time-to-AD development and hazard ratios were estimated. Allergic sensitization to egg white and ovomucoid at 32 weeks was assessed, and study results showed that measurements of TEWL on the forehead could contribute to identifying neonates at high risk of developing AD.[25]

Another randomized controlled trial examined the effects of the twice-daily application of a ceramide-containing emollient for the first six months of life on the incidence of AD and skin barrier dysfunction in high-risk infants up to 12 months of age.[26] Eighty infants with a family history of allergic disease were recruited. Clinical follow-up of infants by a blinded assessor occurred at 6 weeks, 6 months and 12 months of age. Among the intervention group, children who developed food sensitization had a later initiation of treatment.[26] Results showed twice-daily prophylactic use of the ceramide-containing moisturizer may have a stronger potential to prevent the development of food sensitization than once-daily application of emollients used in previous trials.[26]

A pilot study evaluated frequent oil baths and facial moisturizer application in 56 six-week-old children with xerosis. Seventy-five percent (75%) of the 24 children comprising the intervention group had normal skin condition after 6 months of more frequent product use than did the children in the control group (37.5%) with fewer oil baths and facial moisturizer use.[27]

Parental education and the application of moisturizers are recommended as an integral part of AD prevention, treatment and maintenance (Figure 2).[5] Studies on prevention of allergy and sensitization in infants and children, such as for AD, have shown

FIGURE 2. Defective epidermal barrier in individuals with AD.



positive trends; however, conclusive evidence on long-lasting results is lacking.[21] Rather than allergen avoidance in infants, stimulation of allergen tolerance by controlled exposure may be a more productive strategy, together with optimizing skin barrier properties and function.[3,23-28] A therapeutic strategy to prevent allergy could be developed by focusing on safe skin treatment, oral tolerance induction and environmental controls including lifestyle changes.[29]

Benefits of the Use of Natural Oils for Skin Moisturization

Vegetable oils can be derived by different methods such as distillation, or solvent extraction from roots, stems, and leaves. Based on their properties two categories can be distinguished: Fixed oils and essential oils.[30] An overwhelming proportion of herbal and vegetable oils exist for various skin conditions compared to the inadequate proportion of studies pertaining to oils.[30] Robust studies of plant oils efficacy in AD are particularly limited;[30] a literature review on vegetable oils for pruritus selected 29 publications. Of these, the following articles concentrated on clinical trials: Two on moisturizers containing Cocos nucifera, two on Sunflower oleo distillate, one research paper on Helianthus annuus, and two reviews on Ricinus communis and on Sclerocarya birrea containing moisturizer.[30] Ahn and colleagues concluded plant oils have the potential to alleviate pruritus when used as a component in a moisturizer.[30]

Evangelista et al.[31] studied the effect of full body-applied topical virgin coconut oil compared to mineral oil on pediatric patients with AD for 8 weeks. The results at 8 weeks were analyzed based on the SCORAD index, TEWL, and skin capacitance values.[31] The topically applied virgin coconut oil showed efficacy in all three categories; the study conclusions suggested that virgin coconut's efficacy resulted from its anti-inflammatory activity.[31]

Another study compared the effects of extra virgin coconut oil as a moisturizer in individuals with dry skin to those of mineral oil; the study concluded both were equally effective and safe.[32] Sunflower seed oil was proposed as an effective moisturizing agent, either in direct topical application[33] or incorporated in a topical as an active ingredient.[34,35]

Sunflower oil distillate is a by-product of the original oil extracted by molecular distillation. It contains 90% essential fatty acids, mainly oleic and linoleic acids, as well as 5% phytosterols and1% vitamin E.[34] As an agonist of the peroxisome proliferator activated receptor-alpha (PPARα), sunflower oil distillate decreases inflammation, restores filaggrin expression, activates ceramides 3, and regulates kallikrein expression.[34]

Two clinical studies used 2% sunflower oleo distillate (SOD) emollient in AD-affected pediatric patients; results from both studies demonstrated that the emollient improved skin condition and AD symptoms.[34,35]

Another clinical study evaluated the topical corticosteroid (TCS) sparing effect when using a SOD-containing emollient and TCS. Eighty-six pediatric patients with AD, aged 4 months to 4 years, were allocated to one of the five treatment groups (3).[36] More favorable results were shown in the groups that applied the 2% SOD emollient, showing a corticosteroid-sparing effect for the group where a TCS was applied every other day in combination with the emollient, versus TCS application twice a day (Table 4).[36]

In 2011, a further clinical study was conducted, which included 80 atopic children allocated to two groups.[37] Group A applied a TCS and group B applied the 2% sunflower oleo distillate emollient cream, twice a day. SCORAD (SCORing Atopic Dermatitis) was determined at baseline, 1 week, and 3 weeks, with quality of life scored at baseline and at week 3.[37] Results demonstrated the emollient improved skin condition and patients' quality of life comparable to those patients treated with a TCS.[37]

TABLE 2.

Overview of Literature Supporting the Role of Moisturizers in Improving Outcomes in AD

Reference	Population	Study Type	Details
[23]Simpson EL, et al. J Allergy Clin Immunol. 2014;134(4):818–23.	N = 124 high-risk neonates at risk for AD	RCT, primary outcome was the cumulative incidence of AD at 6 months.	The results demonstrated that emollient therapy from birth represented a feasible, safe, and effective approach for AD prevention.
[24]Horimukai K, et al. J Allergy Clin Immunol. 2014;134(4):824–30. e6.	N = 118 neonates at high risk for AD.	RCT, daily use of an emulsion-type moisturizer during the first 32 weeks of life to 59 of the 118 neonates at high risk for AD.	Fewer neonates (32%) who received the moisturizer developed AD by week 32 than control subjects. Allergic sensitization during this time period was associated with AD but not with moisturizer use.
[26]Lowe AJ, et al. Br J Dermatol. 2017;178(1):e19–e21.	N = 80 high-risk infants up to 12 months of age	A parallel, single-blinded RCT on the incidence of AD and skin barrier function after ceramide-containing moisturizer BID use for first 6 months of life. Follow-up to 12 months of age.	Prophylactic use of the moisturizer for the first 6 months of life showed a trend towards reduced incidence of AD and food sensitization at age 12 months, suggesting that the beneficial effects persisted for ≥ 6 months after stopping treatment.
[27]Kvenshagen BK, et al. Allergol Immunopathol (Madr). 2014;42(6): 539–43.	N = 56 six-week-old infants with xerosis.	A controlled intervention pilot study. Skin quality score ranging from 0 (normal skin) to 4 (probable AD), was assessed at inclusion, 3 and 6 months of age, with skin quality at 6 months as main outcome.	Intervention group (n=24) had more often normal skin (75%) at six months than the observation group (37.5%). Regular oil baths in infants seem to reduce xerosis and may possibly reduce AD.
[34]Eichenfield LF, et al. Pediatric Dermatol. 2009;26(6):669–75.	Adults and infants with atopic skin	Review	A marked steroid-sparing effect and improvement of QoL was shown in studies on infants and babies with AD after application of 2% SOD cream.

Randomized controlled trial RCT); Atopic dermatitis (AD); Quality of life (QoL); Sunflower oil distillate (SOD) cream

TABLE 3.

Study Groups Presenting With Mild-To-Moderate Atopic Dermatitis

Reference	A	B	C	D	E
Group Size	18	17	15	17	19
Treatment A.M. P.M.	CT CT	CT + Em CT + Em	CT --	CT + Em Em	CT 1 day/2 + Em
Doses of corticosteroid / 7 days	14	14	7	7	3.5
Corticosteroid-sparing / group A (%)	--	0	50	50	75

CT, corticosteroid; Em, 2% SOD. Each group received a treatment based on different doses of corticosteroids combined or not with application of a 2% SOD emollient[36]

TABLE 4.

SCORAD Comparing Baseline, Day 7, and Day 21 Skin Condition After Treatment With or Without the 2% Sunflower Oil Distillate Containing Moisturizer

Groups	Score D0	Score D7	D7-D0	Score D21	D21-D0
A	33.28	13.27	- 60%	12.30	- 63%
B	34.60	13.82	- 60%	9.66	- 72%
C	34.50	10.00	- 69%	14.50	- 58%
D	35.18	12.82	- 64%	9.18	- 74%
E	35.91	16.70	- 56%	9.03	- 75%
			All *P<0.001*		All *P<0.001*

Details of the treatment groups are described in Table 1.[36]
SCORAD (SCORing Atopic Dermatitis)

DISCUSSION

Understanding potentially modifiable environmental risk factors for AD may allow for exposure reduction, mitigation of disease and/or prevention.[8] Management of AD hinges on effective treatment and control for the well-being of the child and the family, while paying attention to psycho-social and comorbidity issues.[6-9,12-14] Important aspects of AD treatment include parental education, avoidance of triggering factors, and daily application of moisturizers.[5,8]

A defective epidermal skin barrier permits the entry of allergens and loss of moisture.[35,8] A better understanding of the neonatal skin barrier development in reaching a physiological pH and in gaining thickness is crucial in order to encourage parents to use moisturizers from birth, especially for those infants at risk for AD.[15,23-26] Ongoing recognition of the central role a defective skin barrier plays in AD, supports the daily and ongoing use of moisturizers as an important part of treatment, prevention, and maintenance of AD.[5,23,24,28]

The need for medical treatments such as TCS and/or topical calcineurin Inhibitors (TCI) and/or phosphodiesterase 4 inhibitors depends on the severity of the AD condition; these treatments should be used in combination with moisturizers.[38]

The choice of moisturizer is dependent on individual preference, should be safe, effective, inexpensive, free of additives, fragrances, perfumes, sensitizing agents, and should be comfortable to use.[39]

Head-to-head trials between specific moisturizers are few in number, and are often underpowered, which may explain the lack of superior outcomes of one moisturizer compared to another.[39]

A Cochrane review on moisturizer use in AD identified 77 relevant studies published to December 2015, with 6603 participants; most patients had mild-to-moderate AD.[40]

The authors concluded that moisturizer use in AD showed beneficial effects, prolonging time to flare, and reducing the number of flares and the amount of TCS needed to achieve similar reduction in AD severity. Moreover, combining active treatment with moisturizer showed better results than with active treatment alone.[40]

Topical natural oils, such as coconut, and sunflower seed oil are frequently chosen to combat dryness and to reduce the use of topical steroids.[41] A moisturizer that contains sunflower oil distillate demonstrated clinical efficacy and safety when applied in pediatric patients with AD.[34,35] Additionally, the moisturizer exhibited a TCS-sparing effect while improving skin condition.[36,37]

Limitations

The cause of AD is poorly understood, although genetic predisposition and environmental triggers appear to be critical to its pathogenesis. Further research is needed to better ascertain the various etiologic contributors to AD development in order to improve understanding of the condition, and to develop effective preventative and therapeutic treatments that may be initiated from birth. Although more studies are needed, daily moisturizer use from birth onwards appears to improve clinical outcomes for atopy-prone infants.

CONCLUSION

AD is a chronic, relapsing skin disease, which impacts not only the child, but also the family unit, impacting both financial burden and emotional effects. Prevention and management of AD hinge on parental education, preventive measures, treatment, and control to improve the well-being of the child and of the family. A defective epidermal skin barrier in AD may benefit from daily moisturizer use, which should start after birth, especially in those infants at risk for AD. Sunflower oil distillate, as a component in a moisturizer, has exhibited clinical efficacy and safety when used in pediatric patients with AD.

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