

Review Article

The Use of Emollients for Atopic Eczema

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Abstract

Atopic Eczema (AE) is a frequent inflammatory skin disease with chronic relapsing course. It can affect patients of all ages and have dramatic impact on their quality of life.

The baseline therapy of AE is represented by environmental interventions together with topical treatment: moisturizers and emollients, corticosteroids or calcineurin inhibitors. Systemic therapy and phototherapy are reserved for severe cases.

Emollients are the mainstay of first-line intervention: they hydrate and soften the skin and act as restorers or replacers of the epidermal barrier, which is often damaged or impaired in AE. Over and above the varying ingredients, formulations, strategy of action, costs and innovation, the three key-points of both the older and the latest emollients are: hydration against dryness, protection from pathogen bacterial colonization, relief from pruritus and from other symptoms.

The purpose of our review was to describe the classes of emollients (first-generation, second-generation and third-generation emollients, together with most innovative products) and their composition (oils, ointments, creams, rich-in-water substances), and also to illustrate the main trials that established their efficacy and safety in adults and children.

The use of emollients in AE is currently recommended with a Grade of Recommendation A and Level of Evidence I, and they can be administrated for primary prevention, as well as for acute treatment and for secondary prevention and maintenance.

In conclusion, emollients are an optimal source for baseline therapy against AE, as they are appropriate and suitable for long-term schedules and for all ages. Moreover their use can lead to the control of the disease or reduce the need of topical steroids and of systemic drugs.

Emollients must be used daily and consistently and they are especially appropriate for mild-moderate chronic AE.

Keywords: Atopic eczema; Atopic dermatitis; Emollients; Moisturizers; Xerosis; Epidermal barrier function

Abbreviations

AE: Atopic Eczema; AD: Atopic Dermatitis; NMF: Natural Moisturizing Factor; FLG: Filaggrin; LEKTI or SPINK5: Lymphoepithelial Kazal-Type 5 Serine Protease Inhibitor; TEWL: Transepidermal Water Loss; PED: Prescription Emollient Device; SCORAD: Scoring Atopic Dermatitis Index; IGA: Investigator Global Assessment; QoL: Quality of Life; EASI: Eczema Area and Severity Index

Introduction

Atopic Eczema (AE), is a chronic inflammatory skin disease, characterized by pruritic and eczematous lesions and often associated with other forms of atopy, such as food allergies, asthma and rhinitis. AE mainly affects children, although it also occurs in many adolescents and adults.

Atopic Dermatitis (AD) is synonymous with AE; its persistent and often relapsing course can dramatically deteriorate the quality

of life of patients and their families. Due to its high prevalence in industrialized countries, which has been increasing rapidly in recent years, AE has become a major worldwide medical and socio-economic issue.

A large number of studies have documented that the pathogenesis of AE is primarily related to the disruption of the epidermal barrier function. This impairment involves the skin of the entire body surface, which carries intrinsic and/or externally induced abnormalities [1-4]. In view of this, over the last decades numerous trials have focused on the use of topical emollients for AE. Many new devices were and are being developed and validated by pharmaceutical companies, with the introduction of innovative ingredients and enriched formulations directed to restore the barrier components. In particular, the newest products include substances that act to preserve the lipid layer.

When applied to the whole body surface, emollients represent an optimal and effective treatment of AE, both for their therapeutic properties and for their primary and secondary preventive action.

Moreover, they are well tolerated and suitable for both adults and children. Therefore, in all the most recent guidelines worldwide, emollients are described as an effective source for the prevention and therapy of AE, together with other moisturizers and preservatives of the skin barrier.

However, no standardized measures for using epidermal barrier restorers have yet been validated, and no specific instructions about the frequency and the amount of substances to use for each application have been established for baseline acute or maintenance treatment of AE, nor for its prevention.

The Role of Epidermal Barrier Dysfunction in the Pathogenesis of AE

Epidermal barrier dysfunction has been described by several studies as the primary contributor to the multifactorial development of AE, as well as of other allergic diseases. Xerosis, which consists of markedly dry skin, is a main clinical feature of AE and it results from a disrupted skin barrier function.

In particular the stratum corneum is the most important layer of the skin in retaining water and regulating permeability. Physiologically it is composed of corneocytes and continuous intercellular lamellar formations consisting of lipids: cholesterol, ceramides and free long-chain saturated fatty acids [5-6]. Lipids and corneocytes are bound together and represent the two backbones of the epidermal barrier integrity. A poor lipid content of the stratum corneum is more likely associated with AE, where in particular the amount of ceramides is reduced [6-11].

The Bowstra's group demonstrated in particular the reduction in the carbon chain length of free fatty acids and ceramides, together with an increase in unsaturated free fatty acids, in the stratum corneum of AE patients (both in lesional and non-lesional skin) [12].

Corneal hydration is also essential for the integrity of the barrier function and it is guaranteed by the production of Natural Moisturizing Factor (NMF), a highly hygroscopic substance mainly derived from a protein named Filaggrin (FLG) [5-8,13,14].

The integrity of the skin barrier can be weakened by alterations of the gene encoding FLG. FLG represents the main component of epidermal keratohyalin granules; its role is essential for the epidermal differentiation program as well as for the maintenance of skin hydration [5,13-15]. In particular there is experimental evidence about the indispensable role of FLG in epidermal differentiation process, derived from both "*in vivo*" and "*in vitro*" studies. One very interesting investigation on a three-dimensional reconstructed human epidermis for example was carried out by Pendaries et al., evidencing deficient keratinocyte differentiation due induced FLG downregulation [16]. Moreover FLG expression was widely recognized as a differentiation marker of the transcriptional program of cultured as well as stem-cell derived human epidermal keratinocytes [17,18].

Therefore, patients with mutations of FLG are more likely to develop dry skin, known as xerosis, and are more susceptible to come into contact with allergens [15,19-22]. Some particular Anatomical patterns of dermatitis, together with abnormalities in corneocyte morphology, have also been associated with FLG mutations [23-26].

The expression of FLG can also be reduced by the action of epigenetic factors, such as the environment, lifestyle and infections. In particular, recent studies affirm that low humidity, low temperatures and lack of UVB exposure lead to a general decrease in skin barrier function [27,28].

Other important factors causing epidermal barrier dysfunction are: reduced synthesis of omega-3 and omega-6-derived fatty acids, depletion of sphingosine, loss of inhibition of serine protease due to polymorphisms of Lymphoepithelial Kazal-Type 5 Serine Protease Inhibitor (LEKTI or SPINK5) and Human Kallikrein (KLK) protease, or gain of protease activity leading to aberrations of the metabolism of lipids, especially ceramides [5,29]. In particular, a gained expression of the enzyme sphingomyelinase has been reported to entail a depletion of ceramides in the skin stratum corneum. In fact this enzyme is indispensable for converting sphingolipids into mature ceramides [30].

All these factors disrupt the epidermal barrier function, determining an increase in Transepidermal Water Loss (TEWL), even before the onset of AE. This process often leads to dryness of the skin, which in turn often determines inflammation of eczematous skin.

For this reason, any dysfunction of the epidermal barrier represents an etiopathogenic contributor to the development of a vicious cycle culminating in AE, inducing skin dehydration and increased susceptibility to allergens, microbes as *Staphylococcus aureus*, leading to the release of cytokines and other inflammatory mediators. The inflammation of the skin can induce excessive scratching, which further damages the barrier function [31-33].

Moreover, the pH of the skin surface is often increased in patients with AE. Alkaline conditions can determine abnormal modulations of the skin microbiome and delay the processes of skin repairing. For example they can facilitate the colonization by *Staphylococcus Aureus* [3,6,34,35].

It has been demonstrated that infants develop definitive adult-like functions of water-sustaining skin barrier only after their first year of life, although their skin stratum corneum is intact since birth [36-37]. This is due to varying compositions of the skin layer in the different phases of life. In particular, the epidermis of infants is thinner than that of adults, and composed of smaller corneocytes and keratinocytes. Skin hydration is poor among infants in their first month of life, but higher than in adults after the second month of life [6]. An electron microscopy isotropy score was recently developed by Fluhr JW et al, investigating the distribution of corneodesmosin and corneodesmosomes in different age groups. It was confirmed the poorly controlled process of corneocyte desquamation in infants and immaturity of the epidermal barrier up to 1-2 years after birth [38].

The impairment of the skin barrier function is probably the reason why the incidence of AE is higher among infants than in adults, usually healing after childhood. Since these data were documented, some clinical trials have tested the preventive role of the protectors of the skin barrier in predisposed infants, to prevent the AE development [19].

Moisturizers-Emollients: Mode of Action and Classes of Products

Emollients are substances that have a softening and soothing effect on the skin. They have the power to moisturize and restore the epidermal barrier functions, performing a therapeutic action on AE symptoms. Their main action is directed against xerosis and TEWL, which are two mainstays of the pathogenesis of AE.

Besides emollient, topical moisturizers can have occlusive and humectant effect. In particular:

-Most agents have the power to soften and lubricate the skin: for example propylene glycol, soy sterols and glyceryl stearate. These substances act as emollients.

-Substances with a more specific occlusive action, creating a barrier that reduces TEWL, include petrolatum-based products, colloidal oatmeal, mineral oils and dimethicone [39].

-Some other ingredients may exert a wetting action, attracting water molecules and enhancing fluid retention, such as glycerol, urea and ammonium lactate. Wetting agents represent a first-line therapeutic choice against skin xerosis in AE. The percentage of hydrophilic substances that are contained in these products can vary. For example, the level of urea used in AE ranges from 5 to 20% depending on the type and site of lesions and on the age of the patient [6,40,41].

Emollient, occlusive and/or humectant agents can be contained separately or together in the topical devices specific for AE.

Their water amount has only a short-term restoring effect on the skin.

Topical moisturizers can be incorporated in formulations with different viscosity: creams, lotions, oils, ointments, gels. Most emollients are commercialized as emulsions. Traditional emulsions consist of a mixture of lipids in water, with different percentages, bound together by an emulsifier. All these traditional products are often named oil-in-water emollients. Several specific agents, such as thickeners, perfumes and preservatives, may be added.

It is important that patients with AE use an emollient of their choice, in order to obtain better compliance and effectiveness with the treatment. An ideal emollient product should be able to replace the lipids of the barrier and to implement skin hydration, to calm pruritus and burning sensation, to have an anti-inflammatory action and to contrast pathogen microbes. Moreover, it should have a good scent, be as sterile as possible, not contain irritant preservatives or topical allergens, and contain perfumes only when tested and approved. Its application should be easy for patients of all ages, being not too greasy and not interfering with any other treatment.

For example, devices with a higher percentage of lipids and fatty substances are more appropriate for the colder months. In particular, ointments are usually well tolerated by the skin, because they contain less preservatives that could cause irritation. However, some patients with AE may not tolerate too greasy substances, preferring lotions or gels, which are lighter and richer in water. On the other hand, these highly hydrated delivery systems can be less effective because of faster evaporation once they are applied on xerotic epidermis [41].

Some products have been commercialized including two or more formulations each, varying the degree of viscosity: for example, one specific for the face and the other more suitable for the remaining body areas. Moreover, some formulations can be specific for the phases of AE: for example, some lines of products include specific formulations for secondary prevention and for flares.

Emollients of all classes usually need preservation, in order to avoid deterioration and contamination. Physical preservation consists in creating an external environment that is hostile for microbes. This method should be preferred to chemical agents. It can be obtained mainly by reducing the "Water Activity" of the substance, which represents the amount of water that is available for bacterial growth [42]. Several substances, for example glycols, alcohol, polysaccharides, glycerin, xanthan and carbomer, reduce the "Water Activity". Another option for obtaining physical preservation is the use of patented devices, as the D.E.F.I® air-tight closure. This is a "steril" packaging closure technology, with a cap that consists of four parts including a supple membrane that rises when pressure is applied to the tube and then resumes the closed position when pressure is released [43].

FDA has recognized several compounds that have skin protective activity [44].

In particular, emollients are classified into 3 different classes:

First-generation emollients

Vaseline or paraffin oil, lanoline, fatty acids, fatty alcohols, together with hydrophilic polymers. Some often-used molecules from the first group are: octyldodecanol, hexyldecanol and isostearyl alcohol encompassed in the group of the fatty alcohols; stearic, isostearic, oleic and palmitic acids in the group of fatty acids. On the other hand, the group of polymers includes glycosaminoglycans, like hyaluronic acid and chitosan, collagen, gelling polysaccharides like xantan or gums, and other high weight macromolecules.

First-generation emollients mainly act as hygroscopic and/or occlusive factors. Occlusive factors must be used carefully to avoid maceration as a possible undesired effect.

Second-generation emollients

Humectants such as glycerol, sorbitol, urea (3, 5 or 10-20%), ammonium lactate, polyethylene glycol; NMF substitutes; carboxylic pyrrolidonate derivate; amino acids as L-isoleucine. These agents work as real restorers of the epidermal barrier function and of skin hydration.

Third-generation emollients

physiological lipids that act as a barrier repair therapy, such as ceramides, cholesterol, omega-3 or omega-6 polyunsaturated fatty acids (for example, respectively alfa-linolenic and alfa-linoleic acids). These products protect the integrity of the skin barrier; in particular they induce the epidermal differentiation process and replace the gaps between the corneocytes.

Most recent advances in barrier repair therapy developed the 3:1:1 ceramide-dominant formula as the correct proportion of epidermal lipids to be included within emollients: respectively ceramides, cholesterol and fatty acids [45].

Table 1: Classes of emollients.

Emollients in AD: strength of recommendation A, level of evidence I	Substances	Features and mode of action
First-generation emollients	Vaseline or paraffin oil, lanoline, fatty acids, fatty alcohols and hydrophilic polymers	They act as hygroscopic and/or occlusive factors. Occlusive factors must be used carefully to avoid maceration as a possible undesired effect
Second-generation emollients	Humectants as glycerol, sorbitol, urea (3, 5 or 10-20%), ammonium lactate, polyethylene glycol; NMF substitutes; carboxylic pyrrolidone derivative; amino acids as L-isoleucine	They work as real restorers of the epidermal barrier function and of skin hydration
Third-generation emollients	Physiological lipids that act as a barrier repair therapy, such as ceramides, cholesterol, omega-3 or omega-6 polyunsaturated fatty acids	They protect the integrity of the skin barrier; they induce the epidermal differentiation process and replace the gaps between the corneocytes
New formulas	3:1:1 ceramide-dominant formula -BioMimic® -Lipigenium® -Cer-omega® and I-modulia®	The main aim of newest emollient formulas is to mimic and replace the native components of human epidermis

New products have been recently commercialized, including the BioMimic® and the Lipigenium® formulas. The Lipigenium® formula is one of the most innovative emollients developed for the therapy of AE. Its composition consists in biomimetic lipids, such as ceramides and phytosphingosine, and essential fatty acids, that induce the creation of a healthy and lasting skin barrier. Lipigenium® was included in different formulations and tested both *in vivo* and *in vitro*.

Features of different classes of emollients are summarized in Table 1.

The range of emollients for AE consists of two groups: a part of them is comprised within the class of cosmetics. Products of this class include barrier repair creams and other moisturizers. They can be sold over-the-counter, and the most innovative of them contain FLG and/or ceramides, in order to restore the correct barrier function of the skin. On the other hand, some other products are identified as "Prescription Emollient Devices" (PEDs) and they are sold as actual medical devices, so the cost of these products may be refunded. They are usually enhanced with specific substances, such as natural anti-inflammatory agents and replacers of the lipids of the barrier.

Other active ingredients that can be added to emollients are lenitive substances, such as thermal water, oatmeal and bisabolol, which is extracted from chamomile, and/or anti-inflammatory substances, like licochalcone A, glyceryl inositol phosphate, sorbityl furfural palmitate, calendula and glycyrrhetic acid, which is extracted from liquorice. Substances like allantoin, calendula, and bioflavonoids have a regenerative cutaneous and vasotonic action, while vitamin B5 and pantenolol increase skin hydration, as do karité butter and glucoglycerol.

Other substances have antibacterial and immunomodulatory properties: for example decandiol, phytosphingosine, climbazol, and echinacea. Innovative products like Cer-omega® and I-modulia® combine antibacterial properties with anti-pruritus and natural and/or adaptive immunomodulatory activities.

Antioxidant agents can also be incorporated in emollient devices, such as ACE vitamins, polyphenols, furfuryl-palmitate and grape seed oil, as well as anti-pruritus agents like calamine, zanthalene, menthol, PP vitamin or nicotinamide, polidocanol and cannabinoids.

Emollients and in particular PEDs can be quite expensive; in some cases not enough controlled comparative studies have been

performed on these latter products [45-50].

Therefore no PED has yet been identified as more efficient than other emollient agents against AE, and vice versa. Most of the studies that have compared the action of different-generation emollients showed more or less equally positive results, with no significant adverse effects. It is not clear whether formulations with special components added, such as ceramides, are better restorers of the skin barrier than simple petrolatum-based emollients [6,45,51].

Emollients for AE: Recommendations and Efficacy

Topical therapies represent the mainstay of skin care for patients affected by AE, as well as the core of the management of the disease. They may be used as monotherapy in less severe cases, or also in combination with phototherapy or systemic drugs when stronger interventions are needed.

Topical interventions for AE include both non-pharmacologic and pharmacologic measures.

The group of non-pharmacologic topical intervention includes: emollient devices and other moisturizers, detergents, additives and specific bathing practices and wet-wrap therapy.

On the other hand, the group of pharmacologic topical therapies mainly includes: corticosteroids, calcineurin inhibitors, antihistamines, antiseptics and antimicrobials [40].

Each class of topical agents is aimed to tackle distinct aspects of the pathogenesis of AE. Therefore, using combinations of different topical agents may increase the therapeutic effectiveness of the topical treatment.

Our review focused on the class of non-pharmacologic topical devices, in particular moisturizers and emollients.

Their efficacy in patients with AE has been proved by several controlled and randomized clinical trials that were performed in the last decades. All reported a strong action in hydrating the skin and reducing symptoms of AE such as pruritus, fissuring, lichenification, erythema and also in calming inflammation.

One clinical and microscopic study reported that an enhancement in skin hydration was perceived by most patients on whom the application of moisturizers was performed. This subjective data was

Table 2: Summary of the main studies that tested emollient AE. The table was modified, extended and updated from the work of Catherine Mack Correa M and Nebus J [6].

Authors	Population	Intervention	Follow up	Results
NEONATES (<1 months)				
<i>Simpson EL et al</i> [47]	-N = 22 -population at high risk for AE	Daily application of petrolatum-based emollient cream: Cetaphil (Galderma Laboratories, Fort Worth, TX, USA)	2 years	Observed cases of AD: 15% (versus 23% in the intent-to-treat group)
<i>Simpson EL et al</i> [37]	-N = 124 -population at high risk for AE	-UK: sunflower seed oil, liquid paraffine 50% in white soft paraffin or Doublebase gel (Dermal Laboratories, Hitchin, United Kingdom), (UK) -USA: sunflower seed oil, Cetaphil Cream (Galderma Laboratories, Fort Worth or Aquaphor Healing Ointment (Beiersdorf, Chester, Ohio, Tex)	6 months	Risk reduction of developing AE: 50%
<i>Horimukai K et al</i> [19]	-N = 118 -population at high risk for AE	Daily application of moisturizer-emollient (2e [Douhet] emulsion)	32 weeks of life	Incidence of AE: in the intervention group 32% lower than in the control group
INFANTS (<12 months)				
<i>Kvenshagen BK et al</i> [62]	-N = 56 -6-weeks-old infants with dry skin	Regular application of Cerdal® together with daily oil baths	6 months	-Improved skin conditions -lower incidence of AE
<i>Grimalt R et al</i> [56]	-N = 173 -population with moderate-to-severe AE	Twice daily application of oat extract-containing emollient: Exomega (Laboratories Pierre Fabre, France)	6 weeks	-Significantly reduced use of high-potency topical corticosteroids -improved SCORAD index, QoL
CHILDREN (<18 years)				
<i>Nebus J et al</i> [76]	-N = 25 -2 months-6 years children with mild-to-moderate AE	Occlusive colloidal oatmeal cream used twice daily for 4 weeks and colloidal oatmeal glycerin cleanser used for bathing (Aveeno, Johnson and Johnson Consumer Companies, Inc., Skillman, NJ, USA)	4 weeks	Significantly improved QoL, IGA scores, dryness, roughness, itch
<i>Boguniewicz M et al</i> [78]	-N = 142 -6 months-12 years children with mild-to-moderate AE	Cream with Glycyrrhetic acid: Atopiclair applied three times daily, versus vehicle	43 days	-Significantly improved IGA -reduced use topical corticosteroid
<i>Sugarman JL et al</i> [48]	-N = 121 -6 months-18 years children with moderate-to-severe AE	Twice daily application of ceramide-dominant barrier emulsion: EpiCeram, versus fluticasone cream: Cutivate (PharmaDerm, Melville, NY, USA)	28 days	-Significantly improved SCORAD index -equal efficacy between the two groups
<i>Chamlin SL et al</i> [50]	-N = 24 -1.5-12 years children with stubborn-to-recalcitrant AE	Twice daily application for 12 weeks, then once daily for 9 weeks, of ceramide-dominant barrier emollient: TriCeram (Osmotics Corp, Denver, CO, USA) instead of prior moisturizer, together with continuation of topical tacrolimus or corticosteroid	21 weeks	-Significantly improved SCORAD in 100% of patients, decreased TEWL; increased epidermal integrity and hydration
<i>Miller DW et al</i> [45]	-N = 39 -2-17 years children with mild-to-moderate AE	Three times daily application of Atopiclair versus EpiCeram versus Aquaphor Healing Ointment (Beiersdorf Inc, Wilton, CT, USA)	3 weeks	Improvement in all three groups
<i>Canpolat F et al</i> [92]	-N = 83 -6 month-2 years children with mild to moderate AE	Twice daily application of hydrocortisone ointment versus hydrocortisone and mupirocin or emollient ointment	1 week	-Best SCORAD and EASI scores improvement in patients treated with combined therapy (74%) versus the other groups
<i>Gelmetti C et al</i> [80]	-N = 191 -1-12 years children with mild to moderate AE	Twice daily application of emollient containing La Roche-Posay spa water, Shea butter or Karite butter, glycerin, and rapeseed oil: Lipikar Baume La Roche-Posay Pharmaceutical Laboratories, Asnie ´res, France)	3 months	-Significantly improved SCORAD of the patients -improved QoL and favourable opinions in most parents of the children
<i>Patrizi A et al</i> [81]	-2 months-15 years children with mild to moderate AE with associated pityriasis alba	Application of cream containing AR-GG27® (sorbityl furfural palmitate)	30 days	Significantly improved IGA score and reduced itching
<i>Evangelista MT et al</i> [82]	-N=117 -children with mild to moderate AE	Application of virgin coconut oil or mineral oil	2 months	Significative improved SCORAD score, capacitance and TEWL in both group, with better results using Virgin coconut oil than mineral oil
<i>Schario M et al</i> [63]	-N = 38 -2-6 years children with dry skin or predisposed to DA	Application of emollient containing pressed ice plant juice or petrolatum-based emollient	16 weeks	-Skin conditions significantly improved in all children -pressed ice plant juice-based emollient showed significantly higher stratum corneum hydration and lower TEWL
<i>Lucky AW et al</i> [71]	-N = 25 -3-15 years children	Adjunctive regimen of a once-daily application each of hydrocortisone 2.5% cream and of a water-in-oil cream versus comparative regimen of twice-daily applications of hydrocortisone 2.5% cream	2 weeks	Two regimens were equivalent in efficacy

<i>Szczepanowska J et al</i> [72]	-N = 52 -2-12 years children	Application of 0.1% methylprednisolone aceponate cream on lesional atopic skin once daily for 2 weeks and observation for other 4 weeks in both Groups A and B. Group B used additionally emollients for the whole study period.	42 days	The additional use of emollient showed better results in improving xerosis, pruritus and in the maintenance
<i>Janmohamed SR et al</i> [91]	6 months-10 years children with severe AE	Wet-wrap treatment with diluted corticosteroids (1:3 mometasone furoate 0.1% ointment and for the face 1:19 mometasone furoate 0.1% ointment under a mask) versus emollient (petrolatum 20% in cetomacrogl cream)	4 weeks	Wet-wrap treatment with diluted corticosteroids acted faster and was more efficacious than Wet-wrap treatment with emollients
ADULTS				
<i>Barba C et al</i> [64]	-N = 9 (in vivo study) + in vitro study	Two different emulsions containing physiological lipid mixture applied daily	1 week	Both studies showed protecting and repairing effects in healthy and in artificially disrupted skin
<i>Nebus J et al</i> [77]	-N = 25 -12-60 years adults with mild-to-moderate AE	Twice daily application of oat-based occlusive cream and once daily oatmeal-glycerin body wash (Aveeno)	8 weeks	Significantly improved: EASI, IGA scores and QoL
<i>Belloni G et al</i> [79]	-N = 30 ->16 years adults with mild-to-moderate AE	Three times daily application of Atopclair versus vehicle	3 weeks	Significantly improved symptoms, itch and EASI scores
<i>Eberlein B et al</i> [49]	-N = 2456 -2-70 years adults with mild-to-moderate AE	Twice daily application of palmitoylethanolamide-containing barrier (MimyX)	4-6 weeks	Significantly improved symptoms and reduced use of topical corticosteroids
<i>Breternitz M</i> [52]	-N = 24 -adults with mild-to-moderate AE	Twice daily application of 20% glycerin emollient versus placebo	4 weeks	Improved SC hydration and restored epidermal barrier function (TEWL)
<i>Berardesca E et al</i> [86]	-N = 580 -adults with allergic contact dermatitis, irritant contact dermatitis, or AE	Once or twice daily application Ceramide-3 plus patented nanoparticles with or without corticosteroids	8 weeks (until clearance)	-Significantly improved symptoms in both treatment arms. -significantly improved pruritus, erythema, fissuring, and overall severity in combination arm
<i>Berth-Jones J et al</i> [95]	-N = 376 -12-65 years adults with moderate to severe AE who were experiencing a flare	Application of fluticasone propionate (0.05% cream or 0.005% ointment once or twice daily) for 4 weeks. After stabilisation a 16 week maintenance treatment was continued, applying emollient daily with a bath oil and either the same formulation of fluticasone propionate or its placebo base (emollient alone) twice weekly	20 weeks	The addition of fluticasone propionate twice weekly to maintenance treatment with emollients significantly reduced the risk of relapse
<i>Bissonnette R et al</i> [89]	-N = 100 -adults with mild-to-moderate AE	Twice daily application of 5% urea moisturizer versus 10% urea lotion	42 days	Similar reduction in SCORAD from baseline with no difference between the two products
<i>Draeos ZD et al</i> [46]	-N = 60 -adults with mild-to-moderate AE	Twice daily application of mineral oil, petrolatum, and paraffin-based moisturizer (Albolene) versus barrier cream MimyX (plus 0.1% triamcinolone cream for moderate AD)	4 weeks	Similar clinical efficacy between the two treatment groups
<i>Draeos ZD et al</i> [85]	-N = 20 -adults with mild-to-moderate AE	Twice daily application of hyaluronic acid-based emollient foam: Hylatopic (Onset Therapeutics, Cumberland, RI, USA) versus ceramide-containing barrier cream: EpiCeram	4 weeks	Significantly improved symptoms at weeks 2 and 4 for foam; at week 4 for cream
<i>Hon KL et al</i> [84]	-N = 24 -adults with AE	Twice daily application of emollient containing ceramide-precursor lipids and moisturizing factors: LMF moisturizer: Cetaphil Restoraderm™ Lotion (Galderma Canada Inc., Thornhill, ON, Canada) and moisturizing wash (Cetaphil Restoraderm™ Wash; Galderma Canada Inc.)	2 weeks	Improvement of SCORAD score and skin hydration in the group of patients that found the acceptability of the LMF moisturizer good or very good
<i>Angelova-Fisher I et al</i> [83]	-N = 20 -adults with mild to moderately severe AE	-For 1 week: application of a formulation with licochalcone A (Glycyrrhiza Inflata root extract), decanediol, menthoxypropanediol and ω-6-fatty acids (emollient arm) or 1% hydrocortisone (HC arm). -Then: application of the emollient formulation on both arms for 3 weeks	4 weeks	Significantly improved symptoms and TEWL in both arms and decrease of <i>Staphylococcus Aureus</i> colonization with no difference between the two arms
<i>Park SB et al</i> [69]	-N = 28 -adults with AE	Application of lactobacillus sakei probio 65-containing emollient	4 weeks	Significant improved TEWL and VAS
<i>Lodén M et al</i> [90]	-N = 197 -adults with AE	-Once daily application of 20% glycerin versus cream base control versus cream with 4% urea + 4% sodium chloride	30 days	The treatment arms showed similar improvements in xerosis

later confirmed by microscopic inspection of the skin cells and by measuring the conductance and capacitance of the tissue [6,39,52-56].

For this reason emollient topical devices have been included in guidelines worldwide as the baseline therapy for AE. In the most recent American and global guidelines for AD their use is currently recommended with a Grade of Recommendation A and Level of Evidence I [40,41,46,57-60].

Emollients are appropriate and suitable for both children and adults, and their use can be personalized in relation to the type of

patient and to the severity of the disease, for either therapeutic or preventive purposes. In fact, emollients can be applied: to healthy infants, as primary prevention, to patients with AE both as secondary prevention and as maintenance therapy, and also as a treatment of AE flares.

The main trials that tested the use of emollients in AE are summarized in Table 2.

Primary prevention

Some recent trials have tested the role of skin barrier protection since birth in preventing genetically predisposed infants from the

development of AE. After the preliminary introduction of this concept by Macharia et al. in 1992 [61], Simpson et al in 2010 carried out the first pilot study to assess the role of emollients within the preventive strategy of AE. The oil-in-water petrolatum-based cream Cetaphil (Galderma Laboratoires, Fort Worth, TX) was applied since birth in a very high-risk cohort of 22 newborns, resulting in quite encouraging data: the emollient was excellently tolerated and it achieved the preservation of the skin barrier, and the expected incidence of AE was reduced in the cohort [47]. More specific results were later obtained by the same group of research in a wider and multicenter randomized controlled trial jointly performed in the USA and UK: a cohort of 124 high-risk newborns underwent since birth the application of an emollient on their entire body surface. This could be chosen from among an oil, a cream-gel or an ointment. In particular: in the United Kingdom products choices were sunflower seed oil (William Hodgson and Co, Congleton, United Kingdom), Double base Gel (Dermal Laboratories, Hitchin, United Kingdom), and liquid paraffin 50% in white soft paraffin. In the United States parents were offered the same sunflower seed oil as used in the United Kingdom, Cetaphil Cream (Galderma Laboratories, Fort Worth, Tex), or Aquaphor Healing Ointment (Beiersdorf, Chester, Ohio). At 6 months, the relative risk of developing AE was reduced by 50%. The compliance of the infants and their families was optimal and no significant severe adverse effects occurred [37].

Horimukai et al. concurrently conducted a similar randomized controlled trial, evaluating the effects of a daily emulsion-type moisturizer-emollient application (2e [Douhet] emulsion) in a group of 59 neonates with high risk for developing AE. At 32 weeks of life, the incidence of AE in the intervention group was 32% lower than in the control group, which included another 59 neonates with high risk for AE that did not undergo the emollient application. Moreover, this latter study evaluated the serum levels of allergen-specific IgE at the end-point in the two groups. Allergic sensitization was higher in infants that developed AE, but no significant association with the use of emollients was found [19].

Kvenshagen et al. recruited 56 6-week-old infants with dry skin for another controlled study on the prevention of AE. 24 infants underwent the regular application of an emollient fat cream for the face (Ceridal®), together with daily oil baths. At six months the intervention group of the study showed improved skin conditions and lower incidence of AE than in the observation group [62].

Another similar study was made in older children, aged 2 to 6 years, with dry skin condition and atopic predispositions. After 16 weeks of emollient therapy with pressed ice plant juice-based emollients (Ice Plant Body Care Lotion and Intensive Ice Plant Cream, formulated by Dr. Hauschka Med, WALA Heilmittel GmbH (Bad Boll, Germany)) in one group of 24 patients, or with petrolatum-based devices (German Drug Codex basic cream, WALA Heilmittel GmbH (Bad Boll, Germany)) in a second group of 23 patients, all children showed significantly improved skin condition and reduction of TEWL and skin pH. In particular, pressed ice plant juice-based emollients showed better results than petrolatum-based emollients. These data strengthen the beneficial potential of emollients on dry skin in children [63].

The restoring action of emollients was also proved *in vivo* in

healthy adults, evaluating TEWL and skin hydration, and consistently confirmed with *in vitro* tests. In this trial two different emulsions containing physiological lipid mixture were applied daily, showing beneficial protecting and repairing effects respectively in healthy and in artificially disrupted skin [64].

As developing a safe and effective preventive strategy for AE was defined as an “urgent call for research” in 2000 [65], the data obtained by these trials contain a huge potential for future studies and validate the role of emollients in the primary prevention of AE, as well in its therapy and secondary prevention.

Previous trials had focused on food allergens or aeroallergens avoidance with no significant results. Some encouraging data resulted from studies where the role of probiotic agents in preventing AE was investigated [66-68].

Emollients have now emerged as an appropriate, feasible, safe, well-tolerated and not costly preventive source for AE.

Acute treatment

Moisturizers-emollients are the main and most feasible primary treatment for patients with mild AE. They provide hydration of the skin and they reinforce the skin barrier, preventing the entry of inflammatory and exacerbating factors inducing flares. For moderate and severe cases, they may be combined with topical corticosteroids. [46] Besides reducing inflammation and AE symptoms, such as xerosis and pruritus, emollients have also a beneficial steroid-sparing effect. In fact they reduce the need for topical corticosteroids by up to 50% [69-71].

Moreover, they may enhance the effects of topical corticosteroids, whose use has been subjected to criticism and should be avoided or reduced as much as possible in children, since it can cause severe side effects [6,72]. For all these reasons, the use of emollients often results in improved quality of life of both patients and their families.

Emollients are recommended as monotherapy for the treatment of mild cases of AE: they must be applied full-body and at least twice daily both in the presence or absence of the disease. Moreover, Boralevi et al. recently established the benefits of a long-term therapy with emollients. Two-hundred-and-fifty-one children aged between 2 and 6 years with AD-associated xerosis were included in the study and were 1:1 randomized for a long-term treatment with an emollient combining glycerol and paraffin (Dexeryl®) or its vehicle. The emollient intervention group showed better efficacy, such as the reduction of the xerosis and of the SCORAD index, and an improvement in the response to the emollients themselves, with no significant adverse effect [41,73-75].

Evidence of the efficacy and safety of emollients have been shown by several trials carried out in adults and children with established AE [6,72].

For example, the efficacy was documented in children with mild-to-moderate AE treated twice daily with colloidal oatmeal, resulting in a significant improvement of the quality of life and of all AE symptoms [76]. Similar results were obtained with a ceramide-dominant barrier emulsion given twice daily [77]. Moreover, in 121 children, the efficacy of a ceramide-dominant, triple-lipid barrier repair formulation (EpiCeram®) proved comparable to that of a

fluticasone propionate cream monotherapy as a valid stand-alone or ancillary therapy for pediatric patients [48]. Another device validated on children aged 6 months to 12 years was MAS063DP (Atopiclair), a vitis vinifera and glycyrrhetic acid-based cream. This device was applied on 72 children and showed better efficacy than a vehicle cream applied in the control group, which included 70 children [78]. Comparable results were also obtained in adults [79].

Other ingredients tested and validated as effective in children with mild-to-moderate AE were, for example, shea butter, karité butter, rapeseed oil, sorbityl furfural palmitate, and virgin coconut oil. This latter substance in particular was proved to be more efficient than the traditional mineral oil in a study realized on 117 children aged between 1 and 13 years [80-82].

Substances recently tested and validated in adults were licochalcone A, omega-6 fatty acids, hyaluronic acid, ceramide-3, ceramide-precursor lipids, and *Lactobacillus sakei* probio 65 [69, 83-86].

Lactobacillus is known to improve the performance against AE when incorporated within an emollient. This was reported in animal model studies [87-88] and confirmed by Park et al. in a double human-and-animal controlled study [69]. This group of research derived *Lactobacillus sakei* probio 65 from kimchi, a traditional fermented Korean food. *L. sakei* was added to a traditional emollient and the clinical effects obtained with this enriched emollient were compared with the use of a traditional one, both in rabbits and in humans. The addition of *L. sakei* emerged as a safe and beneficial strategy. Besides having more efficacy in clinical symptom reductions, this probiotic seems to have a great potential in inhibiting *Staphylococcus Aureus* and decreasing IgE and IL-4 levels during the acute phases of AE.

Regardless of their composition, emollients also have an important steroid-sparing role in the acute treatment of AE.

Steroid-sparing as well as clinical efficacy was verified in infants with mild-to-severe AE thanks to the use of oat extract-containing emollient [56]. The reduction in steroid use was obtained in several other studies, thanks to both traditional and innovative substances. For example, a reduced use of steroids was observed in adult patients thanks to a treatment with ceramides-added devices. Beneficial clinical results and a good tolerance were also observed by prescribing 5% or 10% urea moisturizers to adult patients with AE (n=100) [46,49,52,85,89-90].

However, for cases of severe AE in adults as in children, topical corticosteroids are usually needed to tackle the disease and are more efficient and faster in action, as shown by a recent trial that compared their combined diluted use in wet-wrap treatment versus emollients alone [91]. A significantly better improvement of SCORAD was also confirmed in infants with mild-to-moderate AE treated with hydrocortisone alone or combined with mupirocin than in emollient-treated infants [92].

The duration of the treatment of acute episodes can vary. In most of the studies described it ranged in all age groups from 3 weeks up to 2 months.

The efficacy and the safety were proved for all emollients regardless of their composition, both in children and in adults [45]: no

significant severe adverse effects have been reported in the Literature, and they are usually associated with good adherence to the therapy.

However, it must be considered that particular clinical conditions of the skin can affect the effect of emollients and cause unwanted reactions. In particular, some Authors consider the direct use of emollients on inflamed skin as poorly tolerated, stating that topical corticosteroids and/or topical calcineurin inhibitors are needed in most cases to treat flares effectively [93]. For this reason, the decision to start an emollient treatment should be taken after clinical evaluation of the patient, considering both overall condition and degree of skin inflammation.

Secondary prevention and maintenance

The maintaining of an optimal skin care is essential for patients with AE, also during disease remission phases. It is important to avoid xerosis and irritation in order to prevent relapses. The most specific and feasible measure to reach this purpose is the use of emollients, as well as the identification and avoidance of allergens, irritants and other precipitating or exacerbating factors. External skin irritation and altered pH may result from the use of cosmetics as detergents, makeup, showering or other cleansing products. Therefore clinicians generally agree that when topical emollient therapy against AE is needed any other non specific agents should be avoided [57]. Emollients can be applied with high frequency to the skin, where they create an additional protectant layer that facilitates hydration and combats allergens entry. Their use is recommended in infants, children and adults. They should be applied at least twice daily, after showering or bathing.

Moreover, to maintain the integrity of the skin barrier, the use of emollients should always be combined with general measures of skin care, in particular with correct mild cleansing and appropriate bathing [6,73].

The application of emollients should be continuous and extended to the entire surface of the body and not only on the areas where xerosis is most pronounced. This is because the entire skin surface of patients affected by AE is predisposed to develop xerosis: despite the normal appearance, uninvolved skin areas conceal altered conditions, as increased surface pH and TEWL, decrease expression of FLG and epidermal barrier impairment. According to most guidelines, the overall amount of the substance of choice used per week should be about 500 g for adults (suggested doses vary between 350-500 g and 500-600 g in Literature) and 250 g for children [94]. In particular, a useful rule for emollient application is counting with fingertip-units. These units equal approximately 0.5 g, which is the amount of product that is usually handled by each fingertip of adults. With one fingertip unit about two palms of the skin surface of the body should be covered. For 3-month-old infants, the entire body skin should be covered with 8 g of device per day, 26 g per week. The same whole-body application can be obtained with 36 g per day and 250 g per week in 12-year-old children, and with 75 g per day and 500 g per week in adults.

The correct adherence of the patient to the consistent application of emollients is facilitated by the use of a product of choice. In fact, no studies have validated any emollient as more effective than the others. Therefore, the aspect of personal preference should not be

undervalued because it is an essential guarantee for the compliance of the patient [6].

However, in some more severe cases, the use of the emollient alone is not sufficiently effective to prevent flares. Here low-dose corticosteroids can be added ("proactive therapy"), with lower frequency than emollients. The efficacy of this combined approach was proved by some trials, which for example tested the association of emollients with fluticasone propionate twice daily [6,95]. It is nevertheless recommended that topical corticosteroids should not exceed the ratio of 1/10 compared to the amount of emollient [96].

More specific studies need to be carried out in order to define precise instructions about the frequency, type and quantity of emollients that should be applied to treat or prevent AE [97].

Conclusion

The potential of emollients as baseline therapy against AD is vast, as they are appropriate and suitable for long-term schedules and for all ages. Emollients and other moisturizers effectively treat the symptoms of AE and prevent flares. Moreover, recent studies have reported encouraging data about their action in the primary prevention of AE.

Patients with AE must use emollients daily and consistently. Emollients are especially appropriate and efficient for mild-moderate chronic AE, which represents the majority of cases. Here the baseline therapy can lead alone to a good and satisfying control of the disease, both in patients with persistent but mild disease, and in those with relapsing course, both during exacerbations and remission periods.

The most important property of emollients is to allow the reduction or even the avoidance of the use of topical steroids. Indeed, when a baseline topical therapy is appropriately performed, systemic drugs can be avoided for the majority of patients with AD, and can be reserved only for those with severe or resistant disease [50,56,98].

Over and above the varying ingredients, formulations, strategy of action, costs and innovation, the three key-points of both the older and the latest emollients are: hydration against dryness, protection from pathogen bacterial colonization, relief from pruritus and from other AE symptoms.

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