
Canadian Consensus on Skin Barrier Repair Therapy in Atopic Dermatitis

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Atopic Dermatitis and the Skin Barrier

Although skin barrier defects may be present in many skin conditions, the focus of this supplement is atopic dermatitis (AD). AD poses a common challenge to those of us in clinical practice, and emerging evidence suggests that the frequency of this skin disease has been increasing, at least in the industrialized world, although the reasons why remain unclear.

Not only is the epidemiology of AD unclear, the pathogenesis is also complicated and multifactorial. Although our understanding of the condition is improving, it remains incomplete. What we do know is that for many of our patients, AD is part of an atopic syndrome that includes asthma and hay fever. Furthermore, genetic, immunologic, and environmental factors are known to be relevant in the development of AD, and there is discussion about the “atopic march,” starting with AD and progressing to asthma and then allergic rhinitis of adulthood.

Our recent understanding of the mechanisms responsible for producing a barrier within the epidermis may

shed light on factors fundamental to the pathogenesis of AD. Additionally, the development of an “inside-outside” hypothesis of AD, where immunologic factors initiate the process, has evolved to an “outside-inside” theory, which centers around a defective epidermal barrier that permits the entry of irritants and possibly allergens, which initiate a knock-on effect on immunologic responses. These immunologic responses, in turn, fuel an inflammatory reaction within the epidermis.

It has long been understood by clinicians that moisturizing is a critical component of skin care in patients with AD. Traditional emollients essentially seal in water in the stratum corneum (SC) or are able to attract water from the outside or from the dermis to hydrate the skin surface. Basic science has shown that the SC lipids are critical for the skin to retain water, preventing desiccation of the skin and resisting surface infection while allowing the normal skin flora to exist. Understanding the role of the extracellular lipids, ceramides, cholesterol, and free fatty acids has enabled the development of a new generation of “barrier repair” or “barrier maintenance products.” These preparations, unlike their predecessors, become incorporated into the actual structure of the skin surface and contribute to improved barrier capability.

This supplement discusses, in some detail, the science of the epidermal barrier and the pathophysiology of AD. It is well known that the severity of this chronic condition fluctuates, which generally means that the degree of skin inflammation varies from low grade in normal-looking atopic skin to very brisk in an acute flare. New evidence has shown that intermittent use of topical antiinflammatory prescription preparations can minimize disease flares. Furthermore, as the following illustrates, although the inflammatory component of AD fluctuates, the basic defective barrier of the SC persists, and various external factors, such as surfactants, pH of cleansers, or climate, can alter an already defective skin barrier.

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Finally, quality of life for our patients with AD can be improved by regular use of emollients, particularly the newer generation of lipid-enhanced products, making the skin less itchy and reducing the risk of inflammatory flares. We review these products in the following pages.

We hope that you will be enthused by this supplement and that this translates into encouraging your patients to understand their condition, allowing them to optimally care for their skin barrier and reduce the burden of their disease.

Pathophysiology

Structure of the SC

The epidermis is a semipermeable barrier that provides both protective and defensive functions mediated via its uppermost layer, the SC. These functions include water retention to prevent desiccation and the maintenance of an antimicrobial barrier that resists pathogenic organisms while supporting normal flora.

Brick Wall

A model of a “brick wall” is often used to illustrate the composition of the SC (Figure 1). The bricks of the SC are made up of anucleate corneocytes, which are highly differentiated keratinocytes located in a bed of extracellular matrix.¹ The impermeable plasma membrane encasing the corneocytes is called the cornified envelope and contains insoluble proteins such as loricrin, filaggrin, involucrin, and proline-rich proteins.¹

Humectants such as urocanic acid, lactic acid, and urea are found within the corneocytes and are cross-linked with calcium-dependent transglutaminase.² This mixture of hygroscopic compounds is collectively referred to as natural moisturizing factor (NMF) and is essential as it maintains intracellular water levels and optimal volume, thereby preventing gaps from appearing between the corneocytes.²

The matrix or the mortar of this brick wall is lipid rich and provides a water-resistant barrier layer that is arranged in multiple bilayers called lamellar sheets. Part of this lipid lamellae is extruded from the corneocytes in the form of lamellar bodies. The extracellular matrix of lipids is made of



Figure 1. Structure of the stratum corneum: bricks and mortar. Courtesy of Dr. Miriam Weinstein.

an equimolar concentration of ceramides, cholesterol, and free fatty acids. The lipids, hydrolases, and antimicrobial peptides also have antibacterial activity and prevent water-soluble materials from penetrating the spaces between the corneocytes.³

The corneocytes are linked by corneodesmosomes, which are in turn encapsulated by lipid lamellae. As corneocytes mature and move toward the surface of the SC, the surrounding corneodesmosomes are degraded by proteases and kept in check by protease inhibitors, causing the corneocytes to disengage, which allows for their shedding: this process is referred to as desquamation. The pH of the SC is critical as it promotes increased protease activity.¹ The disintegration of the SC occurs in the upper, outer layers. By contrast, the lower part of the SC is where the integrity of the epidermal barrier is greatest, where primary prevention of the penetration of allergens and irritants occurs.⁴

The SC is, on average, 20 cells deep, but this varies according to the location. For example, areas such as the eyelids have a much thinner layer of SC, which explains a skin more vulnerable to irritation.

Some epidermal barrier functions

- Limits transepidermal water loss (TEWL)
- Preserves epidermal water homeostasis
- Allows optimal lipid synthesis
- Maintains orderly SC desquamation
- Helps in providing pH balance

Normally, the SC contains between 20 and 35% water, although this varies depending on the location. For example, although the sebum-rich areas of the face appear moist, they actually have reduced water content.⁵ If the SC water content drops below 20%, disruption of the enzymes needed for desquamation occurs. As water content drops below 10%, the epidermis will start to appear dry.⁵

The functional measure of the SC water barrier is called TEWL and was first described by Kligman as insensible water loss through the skin (not perspiration).⁶ TEWL measures the loss of water through the skin by measuring

the humidity gradient at the skin surface and water conductance of the skin, which is altered by hydration.

Lipids make up 10% of the weight of the SC. The lipids are secreted as a mixture of precursors from the hydrophobic lamellar bodies. Three SC lipids are required for barrier function, namely, ceramides (40–50%), cholesterol (25%), and free fatty acids (15%). Equimolar 1:1:1 concentrations of these lipids are necessary for normal barrier repair.⁷ Significantly, recent evidence shows an improvement of barrier repair if any one of these lipids is increased threefold.⁷

At least nine subclasses of ceramides have been identified within the SC. They consist of a fatty acid bound to a sphingoid base. Ceramide 1 contains a fatty acid called linoleic acid and binds the lipid bilayer. Fatty acids can be free or bound to triglycerides, ceramides, or phospholipids.

Cholesterol can be synthesized from acetate in keratinocytes and can be absorbed from the circulation. Manufacture of epidermal cholesterol increases when barrier function is reduced.^{8,9}

Recently, filaggrin, or filament-aggregating protein, has been shown to play an important role in the epidermal barrier.¹⁰ The gene *FLG* has been identified on chromosome 1q21 and is expressed in the SC and the cornified layer. Filaggrin peptide is derived from profilaggrin, which is found in the keratohyalin granules. It plays a role in developing a cornified cell envelope, which is a critical element in maintaining barrier function related to water, allergen, and microbe regulation, as well as contributing to mechanical strength. Filaggrin disintegration also produces amino acids that retain water, or NMF. These amino acids include L-histidine and glutamine. L-Histidine is a precursor of urocanic acid, and glutamine is converted to pyrrolidone carboxylic acid (PCA). In the setting of downregulated filaggrin, a decrease in these amino acids leads to a reduction in urocanic acid and PCA, resulting in a pH change.¹⁰

Which Dermatologic Conditions Have Dysfunctional Barrier Function?

AD, irritant dermatitis, psoriasis, ichthyosis vulgaris, and Netherton syndrome have all been identified as having SC barrier defects. Interestingly, alopecia areata associated with eczema does not show an *FLG* null mutation. Finally, acne, rosacea, and photodamage may be associated with reduced barrier function.¹ In this supplement, we deal with AD, the most common condition.

Pathogenesis of AD and Epidermal Barrier Dysfunction

In AD, the epidermis is thinner and there is increased permeability with more TEWL through the SC. Furthermore, there is a defective cornified envelope, lower levels of NMF, and a reduction in the ceramide content of the lipid lamellae.

Reduced filaggrin activity results in dry, scaly skin and increased clinical severity of AD. Low filaggrin activity also enhances the activity of epidermal antigen-presenting cells. Moreover, there is a reduction in protease inhibitor activity, resulting in degradation of corneodesmosomes and an elevation of surface pH. Together, these changes result in less water content in the SC with increased water evaporation and increased penetration of irritants and allergens. This epidermal barrier disruption enhances the inflammatory response. In turn, inflammation through T-helper (Th)2 cytokines inhibits barrier function by reducing ceramide and filaggrin, involucrin, and desmoglein 3 production.¹

What Causes AD?

AD is a heterogeneous disease with a multifactorial pathogenesis arising from gene–gene and gene–environment interactions.¹ It involves skin barrier defects, an altered immune response (Th2), and exacerbated inflammation. Changes in genes that affect the structure and function of the epidermal barrier as well as the activity of the immune system may result in the development of varying severities of AD.¹

For decades, AD has been divided into two subtypes, intrinsic and extrinsic, based on the presence of allergic sensitization. However, it is now believed that the two subtypes represent two phases of AD, the first manifesting in infancy as a nonatopic condition and the second presenting later. A defective epidermal barrier that allows the penetration of allergens is considered a significant event in the transition between the first and second phases.² Furthermore, the development of AD is considered a primary step in what is called the “atopic march.”¹¹

The atopic march refers to a hypothetical model where a defective skin barrier allows penetration of allergens, initially resulting in the development of pediatric atopic eczema. As a child with atopic eczema grows into adulthood, an immunoglobulin E (IgE)-mediated autosensitization develops, contributing to the development of asthma in youth and allergic rhinitis in adulthood.¹¹

The hygiene hypothesis of atopic dermatitis can be considered an inside-outside theory (see below) for AD. This hypothesis is based on the fact that a lower prevalence of atopic diseases is seen in rural areas such as Africa and China with “lesser hygiene” and a higher prevalence in urban centers. The theory is that exposure to microorganisms early in life would drive a change from a Th2 response (the predominant immune response from birth) to a Th1 response, lessening the development of AD. In urban environments in which there is less exposure to microorganisms, the Th2 response would be predominant and maintained, leading to an increased incidence of AD, with Th2 cytokines causing inflammation and further damaging the epidermal barrier.¹¹

Inside-Outside and Outside-Inside Theories

Initial disease models of AD were based largely on the inside-outside paradigm, which suggests that a combination of genetic and external triggers sets off an inflammatory cascade of T-helper cells and inflammatory cytokines within the skin.¹² These, in turn, contribute to the development of pruritus and erythema. Patients, predictably, respond to the itching sensation by scratching, which causes excoriation and disturbance of the epidermal barrier. Further disruption of the epidermal barrier function occurs through TEWL, and, eventually, physiologically mediated dysfunction occurs via the penetration of antigens, allergens, and microbes, which further exacerbate the existing inflammatory response. This disease model led to the treatment of inflammatory response in AD, which was believed to be present in early- and late-stage disease.¹²

More recently, however, the outside-inside model was put forth. It suggests that the permeability of the epidermal barrier in people with AD is mediated by genetic abnormalities.¹⁰ These abnormalities are characterized by decreased levels of lipids, ceramides, and the protein filaggrin, which is necessary for corneocyte synthesis. These deficiencies render the epidermal barrier susceptible to penetration by allergens, antigens, and microbes, which subsequently trigger the recruitment of inflammatory cytokines and antimicrobial peptides. Notably, an increased incidence of loss of function mutations in the gene encoding filaggrin has been confirmed in people with AD.¹² Subclinical inflammation of uninvolved skin is also a feature of AD. This is determined by low-grade Th2 perivascular lymphocytic presence with elevated levels of inter-

leukin (IL)-4 and IL-13.¹¹ The skin is dry and less resilient to irritants. Uninvolved skin has an elevated TEWL and increased surface pH. These conditions appear to prime the skin for an inflammatory flare—a feature of AD being the fluctuating course of flares and remissions.¹

Although both the inside-outside and outside-inside models provide reasonable explanations of the possible mechanisms involved in disease progression, neither fully explains the pathogenesis of AD.

Genetic Factors

Between 14 and 56% of patients with eczema have a loss of function mutation in filaggrin. This is found particularly in severe and persistent eczema. *FLG* null mutations have also been identified in ichthyosis vulgaris and predispose to AD but not contact dermatitis or hand eczema. It has been suggested that a filaggrin defect facilitates penetration of allergens.¹⁰

Hyperactivity of degradatory proteases is also implicated in AD. Proteases within the epidermis, which are subsequently contributed to by exogenous proteases from environmental factors such as house dust mites and *Staphylococcus aureus*, contribute to barrier breakdown as they facilitate the cleavage of the corneodesmosome junctions.⁴ This allows for the penetration of allergens, which in turn can promote the release of proinflammatory cytokines and elevated IgE levels.⁴

How Do Filaggrin Mutations Provoke Barrier Abnormality in AD?

Filaggrin is an intracellular protein, but it is not felt that the barrier abnormality provoked with loss of function mutations in filaggrin is due to structurally defective corneocytes. It appears that the barrier dysfunction is primarily due to pH in the SC.

Loss of function null mutations in filaggrin decrease the amount of filaggrin in the SC corneocytes. This decreases corneocyte osmolytes, including urocanic acid and PCA, and decreases in these acids affect pH in the SC. The pH has four main actions: it increases serine protease activity, which in turn increases cytokine activation, increasing inflammation in the epidermis. The serine proteases directly damage the epidermal barrier by dissolving corneodesmosomes, and this leads to decreased SC cohesion. Increased

serine proteases appear to directly decrease lamellar body secretion (as demonstrated in flaky tail mice who are filaggrin deficient), leading to decreased lamellar bilayers and a decreased permeability barrier. Finally, the increase in pH inhibits enzymes such as β -glucocerebrosidase and acid sphingomyelinase, which are necessary for ceramide production, and decreased ceramides also decrease the permeability barrier of the SC.¹⁰

Immunologic Factors

Dendritic cells within the dermis take up allergens and present them to helper T cells, which then recruit CD4⁺ T cells. Activated dendritic cells and CD4⁺ T cell-expressed (IL-4 promotes switching from Th1 to Th2) cells affect the subsequent release of proinflammatory cytokines and elevated IgE levels.⁴

Th1, Th2, IL-14, IL-15, IL-13, and IL-31 are key functional subsets of T cells implicated in the pathogenesis of AD. Th1 mostly produces interferon- γ , whereas Th2 produces IL-4, IL-5, and IL-13. The Th2-mediated cytokine IL-4 reduces permeability barrier recovery following an acute assault.¹³ Additionally, Th2 cells are known to stimulate B cells to become IgE-producing plasma cells.

The T cell-derived cytokine IL-31 is also present in AD, and large studies are currently under way to better define its precise role. It is known, however, to be highly pruritic and is thought to play a significant role in the development of itch in T cell-mediated chronic inflammation of AD.¹⁴

IgE, also present in atopic conditions other than AD, is associated with severe pruritic, erythematous papules. Patients with AD who do not have IgE involvement tend to have milder symptomatic AD.¹⁴

Environmental factors known to contribute to and/or exacerbate barrier dysfunction through the breakdown of the epidermal barrier include house dust and scabies mites and cockroaches, and any possible exposure to *S. aureus*.¹⁵ House dust mites and *S. aureus* produce exogenous proteases and lipases, which may directly interfere with the formation of lipid lamellae.

An elevated acid mantle also contributes to barrier dysfunction and is present in AD.

Although anywhere between 25 and 30% of patients presenting with moderate to severe AD may have an increased rate of food allergies compared to the non-AD population, the current data do not support routine testing for IgE. This is largely due to the poor correlation of tests to

Table 1. Soap pH

Cleanser	Type	pH
Aveeno	Syndet	6.9
Burt's Bees	Soap	10
Basis	Soap	10.6
Camay Soap	Soap	9.5
Cetaphil cleanser	Syndet	6.7–7.7
Dermalogica The Bar	Syndet	5.5
Dial soap (liquid and bar)	Soap	9.5
Dove Bar, Baby Dove Bar	Syndet	7.0
Dr. Bonner Liquid Soaps	Soap	8.0
Irish Spring Soap	Soap	9.5
Ivory Soap	Soap	9.5
Johnson & Johnson Baby Wash	Syndet	6.5–7.0
Lever 2000	Soap	9
Neutrogena Extra Gentle Cleansing Bar	Syndet	6.0–7.57
Olay Foaming Face Wash	Syndet	6.85–7.36
Palmolive Soap	Soap	10
Purpose Facial Cleanser	Syndet	6.5–7.0
Zest	Soap	10

Adapted from Sugarman JL.¹⁷

clinical reactions.¹⁶ Therefore, testing for food allergies in AD should be undertaken in patients who do not respond to standard therapies or who may have a history of food reactions that can be confirmed as allergies: estimates suggest that between 50 and 90% of presumed food allergies are not allergies.¹⁵

Surfactants used in skin care products, soaps, and cleansers may also damage lipids and proteins by removing some of the water-soluble NMF and accelerating corneocyte degradation. The water content of the SC increases during washing, and the additional water evaporates after 15 to 30 minutes. However, low humidity and high temperatures enhance the water loss. Most of the water taken up during washing is found in the corneocytes, which swell. Surfactants may increase the swelling effect. Traditional soaps have a greater effect than syndet cleansers (Table 1), and adding surfactants can further increase the swelling of corneocytes.^{16,17}

SC lipids can also be solubilized by surfactants, especially cholesterol and free fatty acids. Ceramides are long alkyl chains less likely to be damaged. As the skin becomes increasingly dry, it also becomes more brittle on the surface and less able to retain water, which is required for enzymes to cleave desmosomes. Elevation in pH, which is inherently present in patients with AD, further increases barrier

dysfunction. Adding emollients at the time of washing may reduce epidermal water loss.

Recently, common moisturizers that have been used for years in patients with AD have been shown to be potentially damaging to the epidermis, leading to increased TEWL. Aqueous cream, a commonly used over-the-counter moisturizer in the United Kingdom (containing a high concentration of sodium lauryl sulfate), was shown by Danby and Cork to increase TEWL and decrease SC integrity when applied to the forearms of patients with a previous history of AD.¹

Topical Calcineurin Inhibitors and Topical Corticosteroids

Although topical calcineurin inhibitors (TCIs) such as pimecrolimus and tacrolimus are used for clinical management of AD instead of topical corticosteroids (TCSs), their effects on barrier function are not fully understood. That said, a growing body of evidence suggests that TCIs likely have a negative effect on epidermal permeability and antimicrobial function, in part by decreasing epidermal lipid synthesis.¹⁸

TCS therapy, however, is well known to negatively affect epidermal barrier homeostasis even with short-term use in just 2 to 3 days. Their prolonged use can induce side effects such as skin atrophy and increased skin infections.¹⁸ It is thought that the means by which TCIs and TCSs affect epidermal barrier function may be similar.¹⁸

TCSs can increase the levels of SC chymotryptic enzyme, which is a protease. The increased protease effects can disrupt normal corneocyte dissolution, leading to a worsening of epidermal barrier dysfunction.¹⁸

Overall, contributing factors common among patients with AD include:

- Thinner epidermis
- Less mature surface corneocytes
- Defective lipid lamellae
- Less water content
- Increased TEWL

Environmental Triggers

Environmental triggers include the following:

- House dust mites
- Elevated acid mantle/pH

- Food
- Soaps and detergents
- Water
- Humidity
- Topical medications

Conclusion

AD is heterogeneous, with a multifactorial pathogenesis. Key factors identified in the development and progression of AD to date include a series of genetic and immunologic dysfunctions in addition to several environmental triggers. Together, they appear to produce varying degrees of symptomatic severity, which require a number of therapeutic strategies to manage if not mitigate. These strategies currently include the use of TCIs and TCSs in combination with general moisturizers for acute flare management. However, given the role of lipids in barrier function, a fundamental approach in long-term disease management should be to restore barrier function with lipid replacement therapy.

Key Points

- The mixture of hygroscopic compounds within the SC that maintains intracellular water levels is referred to as natural moisturizing factor or NMF.
- The functional measure of the SC water barrier is called transepidermal water loss or TEWL.
- The lipids ceramide, cholesterol, and free fatty acids are central to maintaining normal skin barrier function. Degradation of any of these three lipids, but ceramides in particular, results in compromised epidermal barrier function through TEWL.
- Filaggrin or filament-aggregating protein plays a key role in epidermal barrier homeostasis. Low filaggrin activity results in dry, scaly skin and increased clinical severity of AD.
- Elevated IgE is associated with severe pruritis in AD.
- The pathogenesis of AD is multifactorial and involves skin barrier dysfunction, an altered immune response, and an exacerbated inflammatory response.
- The pH of the epidermis affects protease inhibition activity, which is important in the desquamation process.

Correcting SC Barrier Function in AD

Given the multifactorial pathogenesis of AD, various options for treatment and management exist, the first and obvious being the removal or minimization of factors known to worsen epidermal barrier function. Appropriate medical therapy with epidermal barrier repair and support of the SC is the primary therapeutic objective. These could involve restoration of the pH of the SC, use of serine protease inhibitors, use of nonspecific moisturizers, and targeted lipid replacement therapy. To that end, correction of TEWL and the ceramide deficiency resulting from the defective skin barrier is essential.¹⁹

Factors known to exacerbate barrier dysfunction, including house dust mites, cockroaches and scabies mites, and any possible exposure to *S. aureus*, should be minimized or eliminated as they contribute to barrier breakdown. Avoiding exposure to these factors, whenever possible, plays an important role in long-term disease management. Avoiding exposure to surfactants used in personal care products, household cleansers, and certain emollients is also recommended as they are known to cause significant barrier disruption through loss of key lipids and acceleration of corneocyte degradation.¹

Support and Repair of the SC

Barrier Support

For decades, the mainstay of therapy for AD has involved concomitant administration of moisturizers and anti-inflammatory therapy using TCSs.¹⁷ TCSs promote altered gene expression, which may lead to altered SC protease activity. Their prolonged use is associated with worsening of AD.

Importantly, the concomitant use of nonphysiologic emollients has been shown to reduce the need for TCSs. Petrolatum, an occlusive agent often found in emollients, works to partially restore barrier function in models of acute injury; however, the benefits are short-lived, with no cumulative effect, thus requiring its repeated application. Petrolatum works by forming a hydrophobic shield on the surface of the skin, trapping water underneath; it does not permeate the SC. Petrolatum has shown efficacy in concentrations as low as 2 and 4%.¹⁷

Humectants such as glycerin, glycol, and propylene are common ingredients in moisturizers and work by drawing out moisture from the surrounding environment into the SC.¹⁷

Providing Barrier Repair

To provide “barrier repair” or “barrier recovery,” emollients have been developed that replace lost cholesterol, free fatty acids, and ceramides in varying molar ratios.⁷ These physiologic lipid-based treatments have a different mechanism of action than nonphysiologic lipid-based therapy, such as petrolatum, in that they are absorbed by the keratinocytes and then converted into lamellar bodies to be resecreted to lamellar bilayers.

In 1993, Mao-Qiang and colleagues showed that administration of an equimolar mixture of cholesterol, ceramide, and free fatty acids provides normal barrier recovery in both animal models and damaged human skin.⁷ However, later studies found that the recovery rates in barrier function were significantly accelerated when any one of the three lipids was increased beyond 1:1:1, with optimal recovery occurring at about a threefold increase, suggesting an optimal molar ratio of 3:1:1.

The four prescription products currently approved for the treatment of AD that claim to repair skin barrier function are EpiCeram, Atopiclair, Mimyx, and Eleteone. At the present time, only EpiCeram is available in Canada. TriCeram, also a barrier repair product, contains a greater concentration of ceramides to free fatty acids and cholesterol, in the 3:1:1 ratio.¹⁷ Data from pediatric patients with AD show improved scores for SCORing Atopic Dermatitis (SCORAD) and TEWL in patients using TriCeram.¹⁷

EpiCeram EpiCeram skin barrier emulsion distinguishes itself from its precursor, TriCeram, by providing the three essential lipids with a higher ratio of ceramides, in the 3:1:1 ratio. In addition to restoring physiologic lipids within the SC, EpiCeram also forms a vapor-permeable barrier that allows for metabolic responses that repair the skin and helps normalize pH in the SC. It has demonstrated clinical efficacy in restoring SC function in patients with AD (Table 2).²⁰

In 2009, the results from a five-center, randomized, investigator-blinded study comparing EpiCeram barrier repair cream to a mild-potency topical steroid, fluticasone

Table 2. EpiCeram Activities

Formulation	Physiologic lipid-based emulsion Buffered pH 5.5
Physiologic lipid ratio	Ceramide-dominant 3:1:1 molar ratio
Activities within skin barrier	Prevents TEWL through barrier creation Provides bulk replenishment of ceramides, cholesterol, and free fatty acids
Benefits of ceramide in AD	Ceramide treatment reduced TEWL in AD Ceramide improves SC integrity
Importance of TEWL	TEWL an indicator for AD severity

Adapted from Elias et al. 2000.

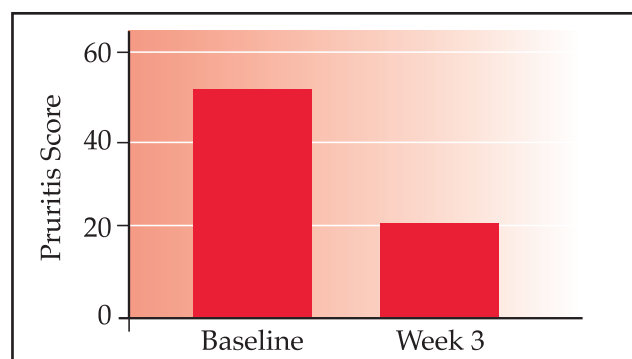
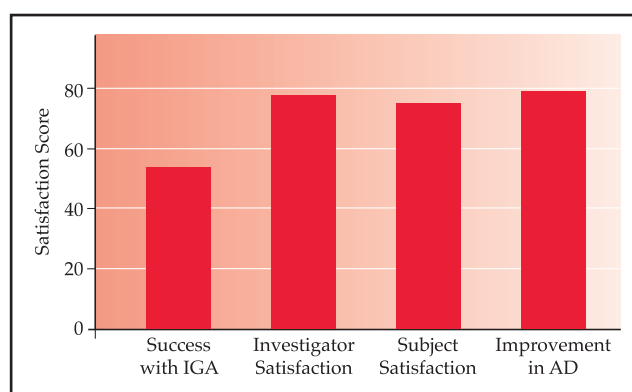
AD = atopic dermatitis; SC = stratum corneum; TEWL = transepidermal water loss.

propionate 0.05% cream (Cutivate), in 121 patients (6 months to 18 years) with moderate to severe pediatric AD showed comparable efficacy between the two treatments following 28 days of treatment.²⁰ Significant improvements were seen in clinical end points as measured on SCORAD (0–72) in patients using EpiCeram at both days 14 and 28, with a 56% reduction in SCORAD from baseline at day 28 ($p < .0001$). Similarly, EpiCeram monotherapy demonstrated significant improvements from baseline at days 14 and 28 in measures of pruritus and sleep habits. No adverse events were reported in either the EpiCeram- or the fluticasone-treated patients.

Importantly, the authors concluded that EpiCeram monotherapy significantly reduced the need for topical steroids for many of the study participants; only 4 (6.7%) of the 59 patients treated with EpiCeram required steroid rescue therapy. Therefore, it could provide an effective stand-alone treatment option or ancillary treatment for pediatric patients with AD.

In March 2011, the results from a multicenter, open-label, community-based study of EpiCeram were published.²¹ Conducted at 50 sites in the United States, the study evaluated EpiCeram used topically as monotherapy or in combination with a prescription for another topical medication chosen by the investigators. The study participants had mild to moderate AD.

Overall, 207 of 225 patients enrolled completed the study and were evaluable. Efficacy data showed 54% of participants being clear or almost clear by week 3, and they were rated as “treatment success” based on the Investigator

**Figure 2.** Pruritis score decreases with use of EpiCeram.**Figure 3.** Investigator Global Assessment and satisfaction scores.

Global Assessment (IGA). A greater proportion of patients with mild AD at baseline had demonstrable success with EpiCeram compared to participants who had moderate AD. The difference was statistically significant: 62% versus 46%, respectively ($p = .02$). Notably, no statistically significant differences were seen between the success rates in the combination and monotherapy treatment arms, with a 40% reduction in the mean IGA from 2.49 at baseline to 1.47 at week 3 ($p < .001$).⁶

Importantly, the number of participants experiencing severe pruritus decreased significantly between baseline and week 3, from 52% to 21%, respectively ($p < .001$) (Figure 2). Overall, 69% of subjects with mild, moderate, or severe pruritus at the study baseline reported less pruritus by week 3, with a mean reduction in the pruritus score from 2.35 to 1.46, respectively, representing an average reduction of 38%.

The study authors concluded that EpiCeram was effective with or without additional topical therapy in the treatment of mild to moderate AD. Additionally, there was a high level of patient and investigator satisfaction (Figure 3).

The findings from this study are consistent with those from earlier investigations of EpiCeram and, taken together, support the approach of providing initial skin barrier repair therapy either in conjunction with another topical therapy or as initial monotherapy.

Atopiclair Atopiclair is a nonsteroidal, antiinflammatory cream that contains the humectants hyaluronic acid, telmestaine, and glycerin. It also contains botanicals, including grapevine extract, allantoin, and licorice root extracts. The latter is reported to have antiinflammatory properties.

Comparative studies done in pediatric and adult patients with AD using Atopiclair and vehicle have demonstrated clinical efficacy. Data from randomized, double-blind, vehicle-controlled studies in pediatric patients showed that Atopiclair use was associated with an average improvement in the Eczema Area and Severity Index (EASI) score of 5 points after 22 days and a 75% reduction in itch from baseline, which was significantly different from the results in vehicle-treated children. Furthermore, 91% of the children did not need topical steroids after 43 days compared to 71% of patients using the vehicle. Burning was the most common side effect and occurred in 6.9% of those on Atopiclair compared to 7.1% using the vehicle.^{22,23} Similarly, data from a study done in 218 adult patients with mild to moderate AD showed a 66% improvement in the EASI score after 22 days of Atopiclair treatment compared to 3% in the vehicle cream group. Furthermore, 95% did not require topical steroids after 50 days compared to 60% in the vehicle group.¹⁷

Of note, neither study specified the placebo used. Additionally, tests done using Atopiclair for barrier repair in normal skin and in an atopic mouse model showed that this agent actually delayed barrier recovery.²⁴

Finally, a 5-week study in 30 adult patients with mild to moderate AD showed efficacy for Atopiclair compared to the control vehicle. After 22 days of treatment, a significant improvement was seen in the Atopiclair-treated patients, with an improvement in the total body area affected from baseline ($17.2\% \geq 13.2\%$, $p < .001$), itch score ($2.7 \geq 1.3$ on a 10-point scale, $p = .001$), and EASI score ($28.3 \geq 24.3$, $p = .024$).²⁵

Although these studies are underpowered to show superiority or noninferiority, they suggest the effectiveness of this novel type of treatment. Longer-term studies with

greater numbers of patients would strengthen the data supporting the use of barrier repair creams.²⁴

Mimyx Mimyx is also a nonsteroidal, water-based emulsion, antiinflammatory cream. It contains the fatty acid *N*-palmitoylethanolamine (in place of ceramides and the nonphysiologic lipid squalane), olive oil, sarcosine, and pentylene glycol. It has been formulated to manage and give relief of burning and itching in various dermatoses, including AD, allergic contact dermatitis, and radiation dermatitis. Like Atopiclair, data from mouse models with atopic disease show no barrier repair characteristics; however, anecdotal reports indicate some efficacy when used with hydrocortisone 1%.

Eletone Eletone barrier cream, currently available in the United States by prescription, is an occlusive emollient formulated with 70% lipids and 30% water. Specifically, it contains petrolatum, purified water, mineral oil, cetostearyl alcohol, Ceteth-20, citric acid, sodium citrate, propylparaben, and butylparaben. It does not correct pH, has no documented effect on filaggrin, and does not contain ceramides in a 3:1:1 ratio.²¹

Evidence of the efficacy of Eletone comes from a subset intent-to-treat (ITT) analysis of data from a US multicenter, prospective, randomized, vehicle-controlled study, the results of which contributed to Eletone being brought to the market.²¹ The original trial enrolled 260 pediatric patients (aged 3 months to 18 years) with mild to moderate AD who were treated with a new, midpotency topical corticosteroid formulation in a lipid-enhanced, nonsteroidal cream base or vehicle (Eletone) over a 4-week period. The results showed a marked improvement in the signs and symptoms of AD for the vehicle control group ($n = 134$), which resulted in the ITT analysis.

The data from 133 patients (one patient's data were disqualified) showed good clinical efficacy in the parameters of pruritis and body surface area (BSA). Specifically, 72 (54%) patients demonstrated some degree of improvement in pruritis: one grade of improvement was seen in 52 patients (34%), two grades of improvement in 25 (19%) patients, and three grades of improvement in 2 (2%) patients. No improvement was seen in 52 (39%) patients, whereas 9 experienced a worsening of itching by one or two grades ($n = 7$; 5%). With respect to BSA, there was a reduction of 43.6% over 29 days in Eletone-treated patients; the aver-

age BSA involvement decreased from 22.6% at baseline to 14% by day 29.

Further data on Eleteone come from a bilateral comparison study of Eleteone and pimecrolimus cream 1% in patients with AD.²⁶ The results showed equivalent efficacy and safety for the medical device cream. Twenty patients aged 2 years and older participated in the randomized, investigator-blinded study. The active treatment period was 4 weeks for each participant. They applied both treatments topically, Eleteone three times and pimecrolimus 1% cream twice daily, to symmetrical target lesions on both sides of the body. Participants were evaluated at baseline and at the 2- and 4-week visits using the Physician Global Assessment (PGA), Target Lesion Symptom Score, subject self-assessment, and digital photography.

After 4 weeks, 75% of participants (15 of 20) were rated “clear” or “almost clear” by the PGA. The percent improvement on PGA from baseline for pimecrolimus cream 1% and the topical medical device cream was 72.50% (15 of 20) and 71.67% (15 of 20), respectively ($p = .9283$). A significant improvement in PGA scores was evident from baseline in both treatment arms ($p = .004$). The results overall showed no statistically significant difference between the Eleteone and pimecrolimus cream 1% by PGA scores throughout the course of the study, and both treatments were found to be safe and well tolerated. The investigators noted that although this study was small, it suggests efficacy for non-steroid-based topical therapy in AD.

Several products make barrier repair in AD claims, based on a lipid replacement strategy. Several over-the-counter lipid replacement moisturizers have been marketed recently (CeraVe and CeraTopic).¹⁷ CereVe contains ceramides, 1,3,6-11 cholesterol, phytosphingosine (a ceramide precursor), occlusive agent petrolatum, and glycerin.³ CeraTopic contains all three lipids (ceramide, cholesterol, free fatty acid). Although both CereVe and CeraTopic contain the lipids for barrier repair, their respective lipid ratios and final concentrations are not known.¹⁷

CeraVe also markets a liquid cleanser incorporating ceramides that are time-released through a patented multilamellar vesicular emulsion (MVE). A 4-week study was recently done to evaluate the efficacy of the MVE ceramide-containing liquid cleanser and moisturizing cream in 60 participants between 5 and 80 years of age who had mild to moderate eczema.²⁷ Specifically, the study sought to determine the efficacy of the products in shortening symptom duration.

The participants were randomized to one of three treatment arms. Treatment group 1 received fluocinonide cream 0.05% twice daily with a mild bar cleanser, treatment group 2 used fluocinonide cream 0.05% twice daily plus an MVE ceramide-containing cleanser as needed, and treatment group 3 used fluocinonide cream 0.05% twice daily plus an MVE ceramide-containing cleanser as needed and an MVE ceramide-containing moisturizer cream twice daily. The results showed a significant improvement in disease clearance between treatment groups 1 and 3: 15 and 76%, respectively ($p = .0001$). The results for disease clearance between treatment groups 1 and 2 were not significantly different, at 15 and 37%, respectively ($p = .155$). The times to disease clearance in treatment groups 1, 2, and 3 were 3.7, 3.4, and 3.0 weeks, respectively.

Furthermore, improvements were evident in disease severity on the PGA. At baseline, no difference in disease severity was evident between the three treatment arms, whereas by the end of the first week, a significant improvement was seen in group 2 compared to group 1 ($p = .012$). By week 4, a further significant improvement was seen in group 2 versus group 1 ($p = .0443$). Group 3 also experienced improvement in disease severity from baseline to week 2 compared to group 1 ($p = .63$).

Some barrier repair products may not work due to the following²⁴:

- A lack of ceramides
- Insufficient total physiologic lipids
- Incorrect formulation (eg, incorrect molar ratio)
- Incomplete mixture of physiologic lipids
- Incorrect free fatty acids (eg, C/10/11 free fatty acids are too short)

Conclusion

Long-term management of AD involves control of environmental triggers known to exacerbate the disease and targeted therapeutic strategy. Although several treatment paradigms exist for the clinical management of AD, the data on barrier support therapy using ceramide-dominant, physiologic lipid-based treatment provide a new and effective option for primary therapy of AD. Coupled with anti-inflammatory treatment initially or as needed in moderate to severe disease, lipid replacement therapy also provides a disease-specific treatment with substantial safety advantages compared to TCSs and TCIs.

Table 3. Diagnostic Criteria for Atopic Dermatitis

<i>Atopic Eczema Diagnostic Criteria</i>	<i>Hanifin and Rajka</i>	<i>UK Working Group</i>	<i>Millennium</i>
Mandatory +++	3/4 ++	1 +++	1 +++
Major ++	3/25 +		2/3 ++
Minor +	++	3/5	
Pruritus	++	+++	++
Typical morphology and distribution of skin lesions			
Chronic or relapsing course	++		++
Personal or family history	++	+	
Presence of allergen-specific IgE			+++
Xerosis	+	+	
History of flexural involvement		+	
Rash under age of 2 years		+	
29 other criteria	+		+

Adapted from Bos JD et al.¹⁴

Key Points

- Barrier recovery therapeutic products that contain an optimal ratio of 3:1:1 for ceramides, cholesterol, and free fatty acids, respectively, have demonstrated significant benefit in recovery of barrier function.
- Ceramide therapy with an appropriate concentration has been shown to reduce TEWL in AD.
- Ceramide therapy with an appropriate ratio improves SC integrity.
- EpiCeram skin barrier emulsion contains the three essential lipids with a higher ratio of ceramides in the 3:1:1 ratio. Its key functions involve restoring physiologic lipids within the SC, forming a vapor-permeable barrier that allows for metabolic responses that repair the skin, and normalizing pH in the SC.
- Clinical study data support the approach of providing initial skin barrier repair therapy either in conjunction with another topical therapy or as initial monotherapy in localized areas of disease.

Table 4. Proposed Clinical and Pathophysiologic Criteria of Atopic Dermatitis

	<i>Yes</i>	<i>No</i>
Clinical criteria		
Itching		
Dry skin		
Topical morphology and flexural involvement		
Chronic course of fluctuation of intensity		
Pathophysiologic subtypes		
Elevated IgE positive		
Filaggrin mutation positive		

Incorporating Skin Barrier Repair Therapy into the Current Management of AD

Diagnostic Criteria

AD has long been considered a syndrome that includes asthma, hay fever, and allergic urticaria. Some feel that elevation of IgE is necessary for making a diagnosis of AD.¹¹ More recent developments have shown that a defect in filaggrin may contribute to barrier dysfunction in some but not all patients with AD. Furthermore, it appears that IL-31 is involved in the development of pruritis.¹

The long-standing criteria for the diagnosis of AD were created by Hanifin and Rajka.¹⁴ Two newer sets of diagnostic features come from the UK Working Group and the Millennium Criteria. The UK Working Group criteria have been validated. The Millennium Criteria require an elevated IgE to use the term *atopic* (Table 3).

Proposed Clinical and Pathophysiologic Criteria of AD

The determination of a precise clinical definition for AD remains a challenge as the disease has many different clinical phenotypes and is characterized by widely varying severity and an unpredictable and highly individual clinical course. Until uniform diagnostic criteria are developed and validated, a clinical determination of AD will be required (Table 4).

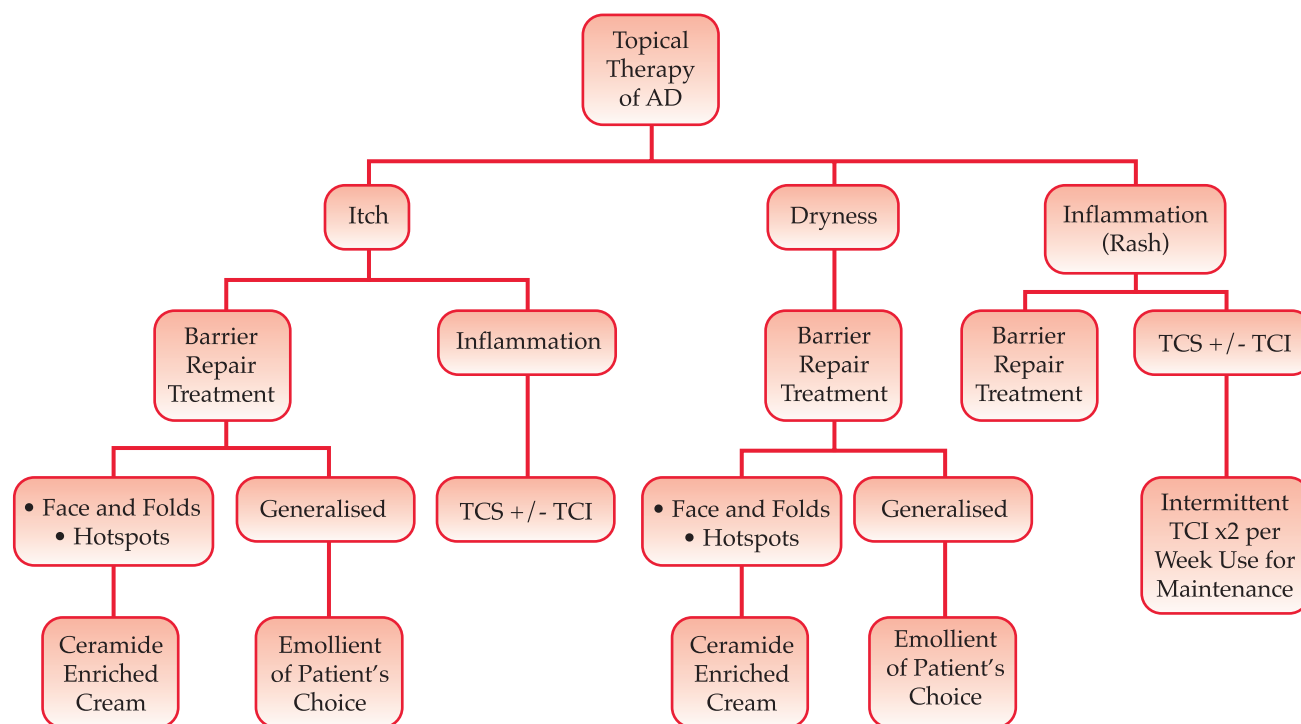


Figure 4. Treatment of clinical signs of AD.

AD = atopic dermatitis; TCI = topical calcineurin inhibitor; TCS = topical corticosteroid.

Pathophysiologic Subtypes

Elevated IgE Positive/Negative

Production of allergen-specific IgE is a fundamental factor in atopy syndrome, which includes atopic eczema (AE), allergic asthma, rhinitis, conjunctivitis, food allergy, and allergic contact urticaria.¹¹ However, where detectable levels of allergen-specific IgE are not present, patients have been diagnosed with nonallergic eczema and intrinsic AE, as opposed to extrinsic AE, in which allergen-specific IgE is present.¹⁴ Bos and colleagues proposed using the term *atopiform dermatitis* (AFD) in these cases as it clearly indicates the presence of the clinical phenotype of AE, but there is no atopy.¹⁴

Filaggrin Mutation Positive/Negative

A loss of filaggrin production, resulting from genetic mutations, is present in roughly 25% of Western, mainly white European, patients presenting with AD. However, no plausible explanation has been postulated for the remaining 75% of patients with AD in whom the filaggrin gene

is not affected. Similarly, there is no explanation as to what is happening in 8% of the population who have a filaggrin null mutation without atopy or AE.¹⁴

Clinical Patterns

Clinical patterns of AD vary with age.

Infantile

- Fifty percent occurs in the first 6 months of life, involving mostly the head and neck and continuing for 2 to 3 years.
- Some feel that a minor diagnostic criterion should include the dermatitis starting in the first years of life.

Juvenile

- This pattern involves the flexures of the knees and elbows and often the neck and lasts until puberty.

Adult

- This pattern involves the flexures as well as the wrists and ankles. Eyelids and hands are also commonly involved.

Therapy must involve treating the various pathophysiologic factors involved in AD.

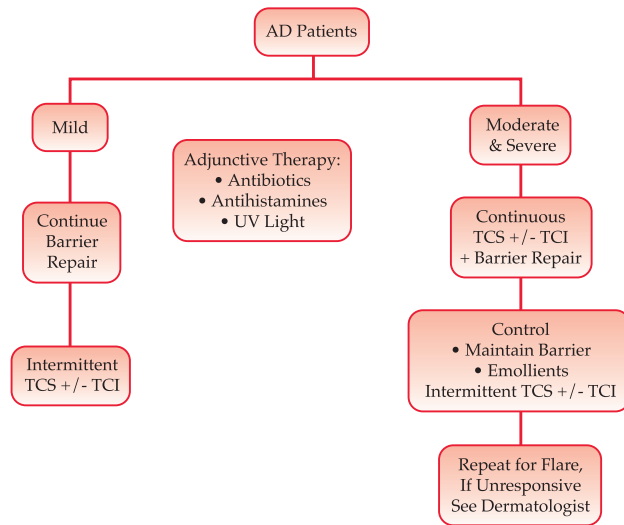


Figure 5. Maintenance therapy for AD. AD = atopic dermatitis; TCI = topical calcineurin inhibitor; TCS = topical corticosteroid; UV = ultraviolet.

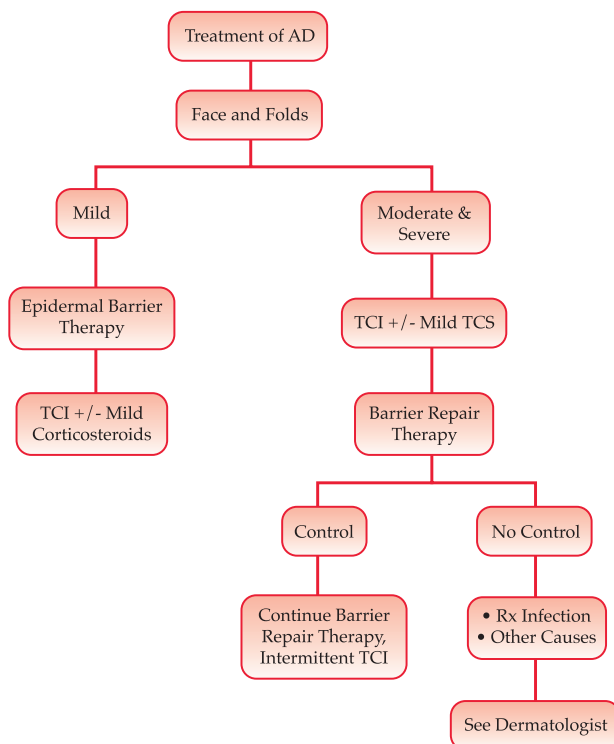


Figure 6. Maintenance therapy for face, folds and hot spots. AD = atopic dermatitis; TCI = topical calcineurin inhibitor; TCS = topical corticosteroid.

Therapeutic Approaches

Treatment of Clinical Signs of AD

Itch, dryness and inflammation are all features that are interdependent but can be thought of as separate in terms of therapy (Figure 4).

Fluctuating Severity

AD is a chronic disease that fluctuates in severity through a cycle of flares and remissions. The combination of a compromised epidermal barrier, together with inflammatory cell infiltrates and increased expression of high-affinity IgE, increases the tendency for inflammatory flares. Given these factors and the propensity for subclinical inflammation, which contributes to further flares, the long-term management of AD has typically involved intermittent use of low-dose TCSs and TCIs to treat disease flares and prolong remissions. However, TCSs contribute to epidermal barrier dysfunction and are associated with skin atrophy and possible rebound flares.

Maintenance Is Key

Given the mounting body of evidence to support the role of underlying epidermal barrier dysfunction in patients with AD, specifically ceramide deficiency, the use of ceramide-rich epidermal barrier repair products may play a primary role in disease management, both in conjunction with TCSs to manage severe flares and with moisturizers and emollients for maintenance of epidermal barrier integrity and function over the longer term. Additionally, removing or mitigating environmental triggers wherever possible is also fundamental to the long-term management of patients with AD. Figure 5 demonstrates the options for AD maintenance therapy.

Suggestions for Maintenance of Therapy for the Face Folds and Hot Spots

Patients frequently have small areas of persistent dermatitis. Figure 6 outlines suggestions for maintenance treatment for these "hot spots," as well as the face and folds.

Five Cardinal Rules in Addition to the Standard Prescription Therapies for Eczema

There are five cardinal rules for treating patients with eczema:

1. Educate
2. Empower
3. Eliminate environmental factors
4. Apply emollients
5. Repair the epidermis

Ideally, treatment of AD should aim at the prevention of flares. To this end, continuous emollient use and barrier repair therapy are critical, especially when the affected area(s) appears to be controlled. A recent study by Wollenberg and colleagues suggested that topical tacrolimus used twice a week is valuable in reducing flares of AD.²⁸

Tacrolimus Twice a Week for Maintenance

In 2008, Wollenberg and colleagues demonstrated significant efficacy with twice-weekly maintenance administration of tacrolimus (Protopic) 0.1% ointment in reducing the frequency of disease flares in adults with AD.²⁸

Conducted at 22 centers in 13 European countries, this 12-month, vehicle-controlled, phase III study consisted of a 6-week open-label treatment phase in which 257 adults with mild, moderate, or severe AD applied 0.1% tacrolimus ointment twice daily until they achieved an IGA score ≤ 2 . Patients were then randomized to the disease control period of the study to either proactive tacrolimus ($n = 116$) or vehicle ointment ($n = 108$) twice weekly for 12 months. During the 12-month period, participants who experienced disease exacerbations returned to the twice-daily tacrolimus regimen until they regained an IGA score ≤ 2 . The primary end point was the number of disease exacerbations during the twice-weekly maintenance period that required substantial therapeutic intervention.

The results clearly demonstrated proof of concept with a significant reduction in the number of disease exacerbations in the tacrolimus arm compared to the control group; the median difference was 2 ($p < .001$). Furthermore, a significant difference was evident in the percentage of disease exacerbation treatment days, with a median difference of 15.2% ($p < .001$) favoring the tacrolimus cohort. A significantly increased time to first exacerbation was also seen: median 142 versus 15 days, respectively ($p < .001$), favoring tacrolimus-treated patients. Wollenberg

and colleagues noted no unexpected adverse events, with the tacrolimus twice-weekly maintenance arm demonstrating a good safety profile.

Topical Ceramide-Rich Barrier Repair

A ceramide-dominant, physiologic lipid-based topical emulsion, such as EpiCeram, can be used with or without additional therapy to provide good clinical efficacy in patients with AD. The data on EpiCeram from the most recent clinical study in patients with mild to moderate AD, who ranged in age from 6 months to 93 years (history of AD), support a currently accepted treatment approach of using a targeted skin barrier repair product for all patients as it targets the underlying defective skin barrier inherent in this disease.²¹

Notably, although additional prescription products may be incorporated to expedite the reduction of cutaneous inflammation and associated symptoms, particularly when disease is severe, EpiCeram may be sufficient as monotherapy in many patients with mild to moderate disease, thereby reducing both the dependence on TCSs and their sequelae. Furthermore, it can be safely applied around the eyes, mouth, and face.

Key Points and Conclusions

- TCSs, although a mainstay of AD therapy, contribute to epidermal barrier dysfunction and are associated with skin atrophy and rebound flares over the long term.
- Persistent, continuous use of emollients and barrier repair therapy is a must.
- Intermittent use of TCI $\pm$ TCS is necessary to prevent disease flares.
- A ceramide-dominant, physiologic lipid-based topical emulsion can be used with or without additional therapy to provide barrier repair and symptom management in patients with AD. EpiCeram may be sufficient as monotherapy in many patients with mild to moderate disease, thereby reducing both the dependence on topical corticosteroids and their sequelae.
- Removing or mitigating environmental triggers wherever possible is fundamental to the successful long-term management of patients with AD.

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