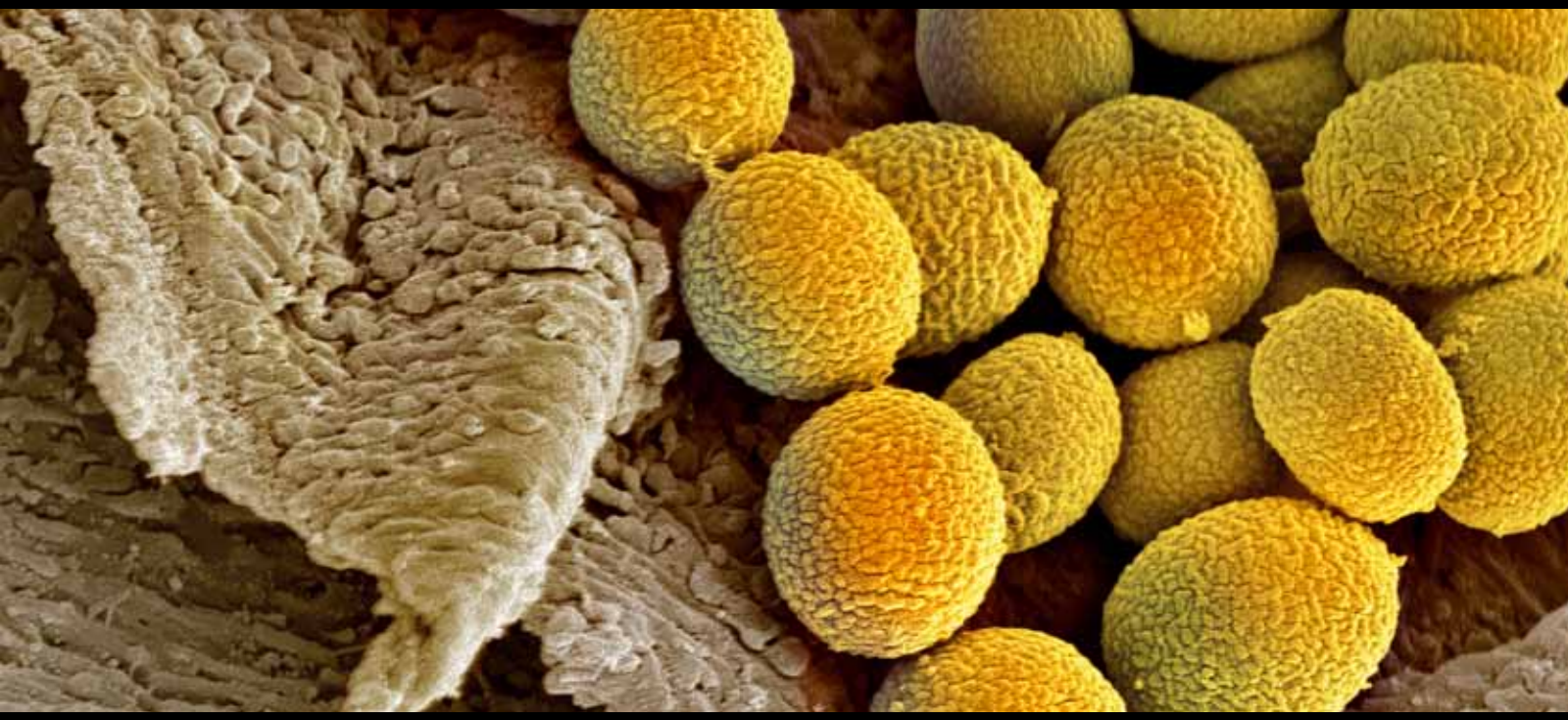
Dermatology Research and Practice

Skin Barrier Protection

Guest Editors: Georgios N. Stamatas, Alex Zvulunov, Paul Horowitz, and Gary L. Grove



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Editorial Board

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Editorial
Skin Barrier Protection

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The largest organ of the human body is the skin with its ~2 m^2 surface area that envelopes the whole organism defining its physical border and which most importantly provides a barrier against internal organ dehydration and external penetration of noxious substances. The critical importance of the skin barrier is appreciated when it is lost such as in skin burns or compromised such as in atopic dermatitis, affecting the overall wellbeing of the individual. Moreover, it has been shown that the skin barrier function undergoes a maturation process during the first years of life. It is therefore of interest to identify skin care routines such as washing and bathing that would not be damaging to the skin barrier and if possible enhancing its protection. Furthermore, barrier enhancement aids in the prevention and treatment of certain conditions such as atopic dermatitis. Recent scientific discoveries in skin biology and formulation science have advanced the understanding of the regulatory mechanisms that control skin barrier homeostasis as well as our knowledge of skin-product interactions. Application of this knowledge has led to the design of appropriate skin care products and the design of tests that can demonstrate barrier-related benefits. This special issue of the Dermatology Research and Practice addresses these issues.

The paper by L. Telofski et al. titled "*The infant skin barrier: can we preserve, protect, and enhance the barrier?*" provides an introduction to the recent findings on skin barrier maturation after birth that lasts for the first few years of life. The authors present on healthy skin barrier development as well as problems that can arise during infancy related to abnormal skin conditions and barrier integrity. They then discuss appropriate cleansing routines that should respect the distinct nature of infant skin and the use of emollients to protect and enhance the infant skin barrier function.

In the paper titled "*Management of patients with atopic dermatitis: the role of emollient therapy*" by M. Mack Correa and J. Nebus, the authors discuss in more detail the use of emollients as baseline support therapy to the use of corticosteroids or calcineurin inhibitors. Prevention strategies are also presented and include appropriate skin care routines, avoiding allergic triggers, and regular use of emollients to improve the skin barrier function. Y. Valdman-Grinshpoun et al. present the dermatologist's point of view in treating and managing atopic dermatitis in their contribution titled "*Barrier-restoring therapies in atopic dermatitis: current approaches and future perspectives*." This paper makes the link between skin barrier dysfunction and atopic dermatitis. It goes on to discuss the importance of skin barrier therapy approaches for its management including the use of corticosteroids and immunomodulators, as well as the potential requirement of short-term topical or systemic use of antibiotics in cases of infected lesions.

Another barrier-related disease, contact dermatitis, is reviewed in the paper by Y. Yoshihisa and T. Shimizu titled "*Metal allergy and systemic contact dermatitis: an overview*." Known metals common in our environment, such as nickel, cobalt, zinc, and chromium can result in allergic contact dermatitis. The authors present *in vivo* and *in vitro* diagnostic tests of metal sensitivity.

Other aspects of skin barrier protection are covered by the following two papers: "*Cleansing formulations that respect skin barrier integrity*" by R. Walters et al. and "*Methods to assess the protective efficacy of emollients against climatic and*

chemical aggressors" by R. Roure et al. The former presents information about innovations in mild surfactant technologies used in cleansing products. As cleansing is an everyday activity that brings these products in contact with the skin, it is important to understand what makes a surfactant potentially aggressive to the lipids of the stratum corneum that provide a large part of the skin's barrier function. The use of hydrophobically modified polymers as surfactants in skin cleansing products is being introduced to enhance the stability and size of micelles and therefore the mildness to the skin. The latter mentioned paper deals with *in vivo* skin protocols that are being used to assess the protective action of emollients on the skin. Such models simulate skin exposure to cold wind or to an irritant such as sodium lauryl sulfate. Data are then presented to demonstrate how these investigative methods can be used to show how exposures can impact skin barrier and skin protection.

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Review Article

Management of Patients with Atopic Dermatitis: The Role of Emollient Therapy

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Atopic dermatitis is a common inflammatory skin disorder that afflicts a growing number of young children. Genetic, immune, and environmental factors interact in a complex fashion to contribute to disease expression. The compromised stratum corneum found in atopic dermatitis leads to skin barrier dysfunction, which results in aggravation of symptoms by aeroallergens, microbes, and other insults. Infants—whose immune system and epidermal barrier are still developing—display a higher frequency of atopic dermatitis. Management of patients with atopic dermatitis includes maintaining optimal skin care, avoiding allergic triggers, and routinely using emollients to maintain a hydrated stratum corneum and to improve barrier function. Flares of atopic dermatitis are often managed with courses of topical corticosteroids or calcineurin inhibitors. This paper discusses the role of emollients in the management of atopic dermatitis, with particular emphasis on infants and young children.

1. Introduction

Atopic dermatitis (AD) is a skin disease characterized by inflammation, pruritus, and chronic or relapsing eczematous lesions. As one of the most common childhood skin diseases, AD afflicts approximately 17% of children in the United States [1]. Worldwide, the prevalence of symptoms for AD has generally risen, although countries with previously high rates appear to have reached a plateau [1, 2]. The increased prevalence over the last few decades is reflected in more recent data from a survey of Greek schoolchildren (Figure 1) [3]. Onset often occurs during early childhood, with 45%, 60%, and 85% of children presenting with clinical symptoms by 6 months, 1 year, and 5 years of age, respectively [4]. In the adult population, AD has an estimated lifetime prevalence of 2%–10% [4]. Although AD is a chronic disease, it resolves in about 60% of patients before adulthood.

Patients with AD frequently develop other forms of atopy. In addition to AD, food allergies are common during the first 2 years of life, with improvement during the preschool years [5]. Children with these conditions typically develop allergic rhinitis and asthma in childhood, which can persist or resolve with age [6]. The progression from AD to other forms of atopic disease is referred to as the atopic march; AD, allergic rhinitis, and asthma comprise the atopic triad. In one study, 87% of children with AD showed improvement in AD by 7 years of age, but 43% and 45% developed asthma and allergic rhinitis, respectively, by age 7 years [7]. Another study reported that rhinitis and wheezing were present in 32% and 24% of children with AD between the ages of 3 and 5 years, with mites and grass pollen identified as the most common sensitizing allergens [8].

Atopy—the propensity to develop hypersensitivity (overproduction of immunoglobulin E [IgE] antibodies) to allergens—is thought to underlie this progression from AD and food allergies to allergic airway diseases. There is confusion about the terms "dermatitis" and "eczema," both of which are used interchangeably and are often associated with AD. Eczema is a broader term that is used often to describe skin diseases, including AD, allergic and irritant contact dermatitis, and seborrheic dermatitis [9]. Confusion is compounded by the medical literature, which will occasionally use the terms "AD," "atopic eczema," and "eczema" interchangeably. Making a clear distinction between "eczematic" skin conditions and the specific disease state of AD will help minimize confusion for patients in

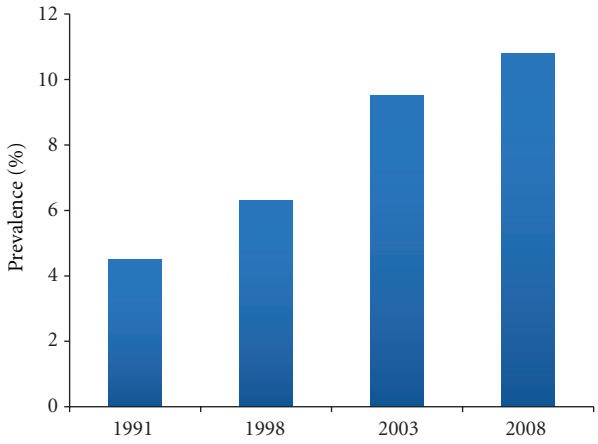

Figure 1: Prevalence of atopic dermatitis in Greek schoolchildren, 1991–2008 [3].

clinical practice. In the USA, the term "atopic" or "atopy" is used generally to describe a clinical phenotype that is associated with AD. Although "atopy" and "AD" are used interchangeably, Flohr et al. demonstrated in a systematic review that up to two-thirds of individuals with AD are not atopic (determined by IgE sensitization) [10]. These findings imply that use of the term "AD" is not accurate [10].

Differentiating AD from other forms of eczema is the first step in receiving a proper diagnosis. The presence of at least three major and three minor symptoms is necessary for an accurate diagnosis of AD. Major symptoms include a history of chronic or relapsing dermatitis, personal or family history of atopy, pruritus, and typical lesional morphology and distribution [11]. Whereas papules, lichenification, and excoriations characterize chronic AD, intensely pruritic erythematous papulovesicular lesions with excoriation and serous exudate characterize acute lesions in infants and young children [12]. AD rashes typically appear on the face, neck, and extensor surfaces in infants and young children, whereas AD rashes and lichenification generally appear on flexural surfaces in older children or adults with chronic disease. Early age of onset, atopy, xerosis, food intolerance, elevated IgE, and facial pallor are examples of minor symptoms that are supportive of a diagnosis [11].

Complications of AD can include secondary bacterial and viral infections, ocular abnormalities, scarring, eczema herpeticum, alterations in skin pigmentation, and sleep disturbances [13]. Sleep disturbances in infants with severe AD have been associated with behavioral changes that persist into childhood [14] and may contribute to delayed growth in children with AD [13, 15].

This narrative review provides a summary of the peer-reviewed literature that discusses AD and emollients or lotions. Studies reporting data on AD and emollients that were published between 1 January 1970 and 30 March 2012 were identified by conducting comprehensive electronic searches in PubMed. The following search terms were used individually or in combination: "atopic dermatitis," "atopic eczema," "atopy," "baby," "ceramide," "child," "children," "colloidal oatmeal," "corneocyte," "eczema," "emollient," "filaggrin," "hygiene hypothesis," "infant," "kallikrein," "lotion," "neonate," "oatmeal," "skin surface pH," or "stratum corneum." Priority was given to randomized controlled trials, but clinical studies that included small groups of participants were considered for inclusion, especially if they contained data collected from infants or children. Small clinical and in vitro studies that investigated biological phenomena underlying the etiology of AD were also considered for inclusion.

2. Risk Factors for Atopic Dermatitis

Genetics play a major role in AD, with parental history of atopic disease associated with both the development and severity of AD in infants. Genetic screening studies have identified more than 40 genes that have a positive association with AD [16]. Of particular interest are a cluster of genes on chromosome 1q21 that are involved in regulating epidermal homeostasis. Filaggrin, which is encoded by *FLG*, is a protein involved in the formation of natural moisturizing factor (NMF) and plays a critical role in corneocyte termination and epithelial barrier function [17, 18]. Filaggrin variants have shown a strong association with early onset and severe AD [19, 20]. In addition to being the most common gene associated with AD risk, *FLG* mutations are associated with other atopic diseases, including asthma and rhinitis [17, 21]. Other genetic mutations associated with AD include polymorphisms of lymphoepithelial Kazal-type 5 serine protease inhibitor (LEKTI or SPINK5) and human kallikrein (KLK) serine protease [22]. Both SPINK5 and KLK are involved in regulating stratum corneum (SC) structure or function [22]. SPINK5, which plays a role in the terminal differentiation of keratinocytes and epithelial formation, is colocalized with KLK proteases in the SC where it inhibits KLK5 and KLK7 [23]. Mutations in the *SPINK5* gene have been associated with AD in studies of Japanese [24, 25] and Caucasian populations [26]. Evidence of an association between KLK7 gain-of-function polymorphism and AD also has been reported [27]. Further exploration of these results and the contribution of genetic variants to AD pathophysiology is warranted.

Environmental factors contribute to the expression and severity of AD. Aeroallergens (e.g., pollen, pet dander, dust mites), food allergens, hard water, and soaps and detergents have been associated with AD [18, 28]. In one study, children with AD exhibited higher levels of sensitization to allergens compared with children without skin disorders [29]. Moreover, the severity of AD was directly associated with the degree of sensitization, particularly to dust mites and cat epithelium.

Although the prevalence of food allergy in children is approximately 6%–8%, its prevalence in children with AD ranges from 33% to 63% [30]. Development of food allergy (cow's milk, hen's egg, fish, wheat, or soybean) by 3 years of age was reported in 61% of children with AD, of whom 92% progressed to develop airborne allergies [7].

Prevalence fluctuates with severity of AD and patient age, with younger children exhibiting a higher prevalence than older children, many of whom are likely to outgrow food allergies. However, food allergy predicts persistence of AD symptoms during childhood. Avoidance of known food allergens has been reported to improve symptoms, whereas exposure can exacerbate disease.

Irritants that can exacerbate disease upon direct contact include abrasive materials such as wool and products with a propensity for causing excessive dryness, such as detergents, soaps, harsh cleansers, astringents, or alcohol. In addition, fragrance and extracts may irritate skin [6]. Studies have reported an association between hard water and increased prevalence of AD [31, 32]. It has been suggested that hard water may exacerbate AD, though a causal link has not been demonstrated [33]. The role of hard water as a contributing factor in AD is thought to be due to the presence of irritants or excessive amounts of detergents that are used frequently in hard water to produce a lather [18].

Other reports provide insight into the interplay between genetics and exposure to environmental factors (i.e., aeroallergens) in the risk for developing AD. In one study, the hazard ratio for developing AD was 2.26 for young children with filaggrin loss-of-function variants and 11.11 for young children with the loss-of-function variant plus neonatal cat exposure [34]. However, the presence of *FLG* mutations alone is insufficient to cause AD in all cases: 40% of children with filaggrin loss-of-function variants do not develop AD and 50% of children with AD do not have *FLG* mutations [20]. Together, these results indicate that the development of AD is a complex process that involves intrinsic and extrinsic factors that remain poorly understood.

The "hygiene hypothesis" postulates that the increase in AD and other atopic diseases is associated with improved hygiene over the decades, resulting in young children having less exposure to infectious agents, endotoxins, noninfectious microbes, and other insults [35]. Such exposure is thought to be critical in priming the maturing immune system of infants and young children. In the absence of early stimulation, the immune system overreacts to interaction with harmless agents such as dander or pollen. This hypothesis is supported by studies reporting that development of atopic disease is associated with high levels of home hygiene [36] and inversely related to multiple acute respiratory infections in young children [37, 38], the presence of older siblings, and exposure to daycare [38, 39]. However, this association remains controversial [40]. In patients with AD, an allergen can initiate an immediate IgE-mediated response as well as a delayed T-cell-mediated response [30]. The interplay between the developing immune system, environment, and genetics continues to evolve; more research is needed to elucidate the mechanisms responsible for the development and onset of atopic disease.

3. Physiology of Lesional and Nonlesional Skin in Atopic Dermatitis

Epidermal barrier function principally falls to the SC as the outermost skin layer. This layer has many functions, including regulating permeability and retaining moisture; protecting against ultraviolet irradiation and microorganisms; relaying mechanical and sensory signals [41]. The SC is composed of corneocytes surrounded by a continuous phase of lipids. The intercellular lipids are a mixture of ceramides, cholesterol, and free fatty acids organized into tightly packed lamellar formations [18, 42]. The amount of intercellular lipids and their organization contribute to overall SC barrier function. Corneocytes consist primarily of tightly packed keratin bundles surrounded by a cross-linked protein envelope. Ceramides are covalently bound to the outer surface of the corneocyte envelope, forming a barrier to water loss. Corneocyte hydration is also maintained by the production of NMF [18], a collection of highly hygroscopic, low-molecular-weight compounds [43, 44]. The primary source of NMF within corneocytes is the breakdown of filaggrin to its component amino acids and the derivatization of two of these amino acids, glutamine to pyrrolidone carboxylic acid, and histidine to urocanic acid [44, 45]. Urea and lactate, two compounds that are produced outside of corneocytes, comprise approximately 20% of NMF [46]. Maintenance of highly organized lipid lamellae and sufficiently hydrated, tightly bound corneocytes is critical to ensuring SC integrity.

The impaired epidermal barrier function in AD is multifactorial in nature and manifests as dysfunction in both the permeability and antimicrobial barriers of the SC. Transepidermal water loss (TEWL) has been shown to be higher than normal in skin with AD that lacks overt clinical manifestations of disease [47, 48], which indicates that the permeability barrier is disrupted even in the absence of a lesion. Increased TEWL is reported in both the presence and absence of *FLG* mutations in patients with AD, but it is higher in AD patients with *FLG* mutations [49]. This increased water loss contributes to the characteristically dryer and rougher skin of patients with AD versus those without AD. The significantly greater increase in TEWL in filaggrin-related AD versus non-filaggrin-related AD [49] is not surprising because of the role of filaggrin in production of NMF. Thus, loss-of-function mutations in the *FLG* gene leads to reduced corneocyte hydration in the SC [49, 50]. However, additional pathways also contribute to the compromised permeability of the SC.

The lipid content of the SC has been shown to be altered in AD, particularly in lesional skin. Studies have shown that in AD, the amount of ceramides in the SC is reduced [51–54], concentrations of specific ceramides species are altered [54–56], and the organization and packing of SC lipids are different than in non-AD skin [56, 57]. These changes to the SC lipid barrier contribute to increased TEWL in the skin of patients with AD [58]. Microfissures, scaling, and itching may lead to excessive scratching, which can further compromise epidermal barrier function and allow penetration of irritants and allergens [59]. Another contributing factor to the impaired permeability barrier is that corneocytes of patients with AD are significantly smaller than those in healthy individuals [60], resulting in a shorter penetration pathlength through the SC. When the barrier is compromised, allergens or microbes can penetrate

the epidermal barrier, interact with antigen-presenting and immune-defector cells, and cause inflammation and itching (Figure 2). Interestingly, a fluorescence study has demonstrated that pollen penetrates the epidermal barrier via both hair follicles and the SC in healthy individuals [61]. One might extrapolate that this penetration occurs with greater ease in the skin of patients with AD.

In addition to functioning as a barrier to transport, the SC functions as an antimicrobial barrier. In AD, the antimicrobial barrier is compromised, contributing to the higher incidence of skin infections [62]. Skin surface pH, the presence of commensal microbial species, and the endogenous production of antimicrobial peptides (AMPs) are contributing factors to the antimicrobial barrier function of the SC. Skin surface pH becomes more acidic over the first several weeks of life and becomes more adult-like during the first year of life [18]. Skin surface pH in patients with AD is higher than in patients without AD [63] and is even higher in patients with flares [64]. Alterations in the skin microbiome are often observed concurrently with increased skin surface pH [65]. The microbiome of healthy skin is characterized by wide variability; commensal bacteria help to deter the growth of pathogenic bacteria (e.g., inhibition of *Staphylococcus aureus* colonization) [66]. Patients with AD demonstrate less variety in the skin microbiome, and active AD lesions are associated with particularly low bacterial diversity. Whereas *S. aureus* constitutes <5% of the microbiome in healthy individuals [65], it is the predominant microorganism in patients with AD [67] and is associated with disease severity [68]. During flares, an increase in Firmicutes (particularly *S. aureus* and *Staphylococcus epidermidis*) and a concomitant decrease in Actinobacteria (Corynebacteria, Propionibacteria) has been reported [69]. Interestingly, treatment appears to restore the diversity of the microbiome and improve the clinical measures of AD severity [69]. Although endogenous production of AMPs was once thought to be reduced during AD [70], recent evidence suggests that AMP production and expression are similar to levels observed in normal, healthy skin [71]. However, normal production of AMPs in AD may not be sufficient to counteract the increase in bacterial colonization on the skin surface.

In addition to modulating the skin microbiome, an elevated skin surface pH has been associated with delayed epidermal barrier recovery [72], as well as activation of serine proteases that lead to corneodesmosome degradation and compromised SC function [73]. A number of serine proteases are involved in desquamation, including KLK5, KLK7, and KLK14, which are localized in granular keratinocytes and the SC [18]. In the presence of a neutral or slightly alkaline pH, inactive precursors of these enzymes are cleaved into active proteases, which in turn activate other members of the cascade, leading to desquamation. Other proteases involved in corneodesmosome degradation are active in more acidic pH, including cysteine proteases (cathepsin L2, SC cathepsin-L-like enzyme) and an aspartate protease (cathepsin D) [18]. Maintenance of a skin pH gradient is necessary to regulate protease and protease inhibitor activity, thus maintaining optimal desquamation.

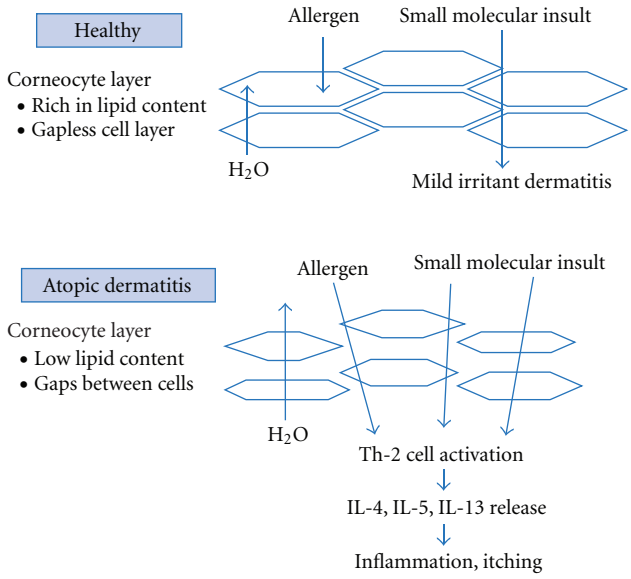

Figure 2: Skin of individuals with atopic dermatitis is fundamentally different compared with healthy skin.

Most KLK proteases, particularly KLK7, exhibit increased expression in patients with AD [74]. Other proteases that contribute to skin barrier dysfunction are associated with the inflammatory response and increase with the level of severity of AD episodes. The levels of mast cell chymase (a serine kinase) were found to be similar between healthy individuals and those with AD, but significantly higher in the lesions of patients with AD [75]. Chymase is overexpressed in both lesional and nonlesional AD skin and is proposed to contribute to compromised barrier function [75]. These abnormalities contribute to a dysfunctional epidermal barrier and altered cutaneous microbiome, which makes the skin of patients with AD more prone to bacterial, fungal, and viral infection.

There are important differences in the skin of infants versus older children and adults [76]. The SC and epidermis of infants (6–24 months of age) are 30% and 20% thinner, respectively, versus adults [77]. Compared with adults, corneocytes and keratinocytes are smaller in size. SC hydration, which is more variable among infants, is generally lower than adult SC during the first month of life, yet SC hydration is greater than adult during infancy [76]. In a significant portion of patients, the developing skin barrier function during the first few years of life may be related to the prevalence of AD in infants and the resolution of the disease with age.

4. Topical Options for Management of Clinical Symptoms

Treatment options for AD typically address skin barrier repair, barrier protection, or inflammatory or immunomodulatory components of disease.

4.1. Barrier Protection and Repair. The primary agents used as skin protectants in AD include colloidal oatmeal and petrolatum-based products. According to the US Food and Drug Administration (FDA), colloidal oatmeal has skin protectant properties and soothing effects that are indicated for the relief of itching and irritation due to eczema [78]. Colloidal oatmeal, an ingredient that is used in bath powders, cleansers, and moisturizers, contains a broad spectrum of components that provide a number of skin care benefits (Table 1). Colloidal oatmeal not only forms a protective film on the skin but also aids in the water-binding and moisture-retention properties in the SC. In addition, colloidal oatmeal also can serve as a pH buffer helping to maintain skin surface pH. There is a long-standing history of safety for colloidal oatmeal as a topical treatment to relieve itch and irritation associated with various xerotic dermatoses. Twice-daily use of colloidal oatmeal cream and use of a colloidal oatmeal cleanser for bathing of babies and young children with AD reported significant improvement in itching, dryness, roughness, and severity at 2 and 4 weeks of treatment compared with baseline [79]. A similar study performed in adults with AD reported that this regimen also significantly improved symptoms and severity of eczema [80]. After 4 weeks of using the colloidal oatmeal regimen, both studies demonstrated that an overall improvement in skin condition resulted in an improved quality of life (QoL) as measured by standardized QoL indices.

There are nearly two dozen compounds recognized by the FDA as having skin protective activity, including dimethicone (1%–30%), mineral oil (50%–100%, or 30%–35% when used with colloidal oatmeal), petrolatum (20%–100%), sodium bicarbonate, cocoa butter (50%–100%), glycerin (20%–45%), and lanolin (12.5%–50.0%) [78]. The important distinction between all these skin protectants is that only colloidal oatmeal, when used within specific levels, is allowed to make claims pertaining to skin protection and relief of minor skin irritations and itching due to eczema [78].

Emollients are moisturizers with properties that make skin soft or supple. They may contain a variety of components, including hygroscopic substances or humectants and lipids that help skin retain water and improve skin barrier function. Humectants (i.e., lactate, urea, and glycerin) are molecules with water-attracting properties that contribute to water retention within skin. Nemoto-Hasebe et al. proposed that low SC hydration in filaggrin-related AD could be related to a deficiency of water-binding filaggrin breakdown products (i.e., NMF) [49]. Given this consideration, inclusion of humectants in topical formulations may help compensate for the lower levels of SC hydration in filaggrin-related AD. Furthermore, inclusion of lipids in emollients may supplement the lipid component that is diminished in the SC of patients with AD. Ceramides, essential lipids that are derived from sphingolipids [82], are involved in barrier function. One study has shown that ceramide (and essential lipid) levels are lower in AD lesions [52].

Emollients may be formulated as lotions, creams, ointments, or bath products, most of which are available as cosmetic or over-the-counter (OTC) products. Emollient therapies are generally categorized as cosmetic moisturizers, OTC skin protectant creams, or cosmetic moisturizers and prescription barrier repair creams (BRCs). Although not all emollient products are indicated specifically for the treatment of AD, emollient therapy is recommended as a first-line treatment in multiple guidelines for AD [28, 83, 84]. Emollient therapy has been reported to improve AD symptoms and to have good tolerability in children as young as 6 months of age [85]. Cosmetics are more lightly regulated than drugs or devices; they are not subject to premarket review and approval, and manufacturers are not required to test products for their effectiveness [86]. However, many products are effective in treating or managing AD.

Table 1: Composition and beneficial properties of colloidal oatmeal [81].

Component	Benefit
Proteins	Help maintain the skin barrier
Polysaccharides and lipids	Replenish the skin barrier
Vitamin E	Antioxidant
Saponins	Cleansing
Enzymes	Antioxidants

Prescription and nonprescription barrier devices indicated for the treatment of AD include Atopiclair (Sinclair IS Pharma, London, United Kingdom), Eletone (Mission Pharmacal Company, San Antonio, TX, USA), EpiCeram (PuraCap Pharmaceutical LLC, South Plainfield, NJ, USA), MimyX (Stiefel Laboratories, Inc., Research Triangle Park, NC, USA), PruMyx (Prugen, Inc., Scottsdale, AZ, USA), and Neosalus Foam (Quinnova Pharmaceuticals, Inc., Newton, PA, USA).

BRCs contain a mixture of ingredients that are reported to help alleviate inflammation and pruritus associated with AD and other forms of dermatitis, as well as repair the skin barrier. For example, EpiCeram contains a 3 : 1 : 1 ratio of ceramides, cholesterol, and free fatty acids, and it helps to manage and relieve burning and itching associated with various dermatoses, including AD. In a study of children 6 months to 18 years of age, EpiCeram and 0.05% fluticasone propionate treatment for 28 days led to a statistically significant improvement in AD severity [87].

One study analyzed the effect of an emollient and two barrier ointments on SC reservoir closure (i.e., the ability to prevent percutaneous absorption into the SC) [88]. Petrolatum, bees wax, and an oil-in-water emulsion containing waxes and surfactants were placed on test areas of skin in healthy volunteers, and a hydrophilic dye was applied to the surface of skin. Petrolatum and bees wax provided complete protection from dye penetration, but the commercial oil-in-water emulsion did not. The authors suggested that barrier ointments or creams used liberally may be useful for protecting against low-grade irritants, but they do not offer complete protection against insult penetration. This study highlights the importance of a barrier ointment or cream composition and the importance of creating an appropriately formulated emollient.

Although many emollients may be beneficial to skin barrier function, some emollients contain ingredients, such as the surfactant sodium lauryl sulfate (SLS), which can be disruptive to skin barrier function [89–92]. Aqueous Cream BP, a paraffin-based emollient that is registered with the British Pharmacopoeia, contains approximately 1% SLS. The surfactant SLS is an effective anionic surfactant that helps emulsify oils into cream formulations, but it can also be irritating and may induce an immune response in skin [93, 94]. Tsang and Guy showed that the Aqueous Cream BP caused a statistically significant increase in TEWL (with or without tape stripping) and a decrease in SC thickness on the left and right volar forearms of healthy adult volunteers [89]. Mohammed et al. showed that the Aqueous Cream BP applied twice daily for 28 days to the left and right volar forearms reduced the size and the progression of corneocyte maturation and led to increases in TEWL [90]. Protease activity increased, and the total amount of protein removed from skin via tape stripping decreased [90]. Danby et al. studied the effect of applying Aqueous Cream BP twice daily to the volar forearms of 13 adult volunteers with a previous history of AD [92]. Topical application of Aqueous Cream BP increased baseline TEWL by a statistically significant margin and led to a decrease in SC integrity [92]. Cork and Danby noted that the negative effects of Aqueous Cream BP on the skin barrier are most likely attributed to the presence of SLS (1% w/w), which disrupts the skin barrier by several mechanisms, including corneocyte swelling, keratin denaturation, and elevation of skin surface pH [91]. Despite its effect on the skin barrier, the Aqueous Cream BP is widely prescribed to individuals with eczema to relieve skin dryness [91].

4.2. Anti-Inflammatory and Immunomodulatory Therapies. Emollient therapy may be useful to help maintain skin barrier function and control symptoms of AD, but emollient use alone rarely leads to complete resolution of AD, especially in severe cases. Anti-inflammatory and immunomodulatory therapies may be necessary for moderate-to-severe AD until symptom resolution in skin (e.g., lesions, patches of dryness, or areas that are prone to flare). Prescription and OTC topical corticosteroids are the principal anti-inflammatory agents used in AD. Topical corticosteroids exert anti-inflammatory effects [84]. Studies of topical corticosteroids have investigated the effect of corticosteroid potency on symptom improvement in children with AD [84]. Topical corticosteroids are normally used for first-line treatment of acute exacerbations of moderate-to-severe AD [95]. The use of anti-inflammatory topical corticosteroids may lead to improvement or resolution of acute flares within a matter of days.

In a postmarketing safety review of children who used topical corticosteroids, the most common adverse effects (>10%) included local irritation, skin discoloration/depigmentation, and skin atrophy [96]. Use of lower potency compounds in children with AD is recommended to minimize the risk of adverse events and systemic effects [28, 84]. Concerns with topical corticosteroids include their potential for systemic effects, growth retardation, striae, telangiectasias, hypopigmentation, ocular effects, and skin atrophy, particularly on sensitive areas such as the face or neck [83, 97]. Despite these risks, a systematic review reported that physiologic changes and systemic complications were uncommon when the appropriate use instructions and dosing regimen of topical corticosteroids were followed [98].

Topical calcineurin inhibitors, such as tacrolimus and pimecrolimus, are options for the second-line treatment of moderate-to-severe AD in patients as young as 2 years of age [84]. Calcineurin inhibitors exert their immunomodulatory effects by inhibiting calcineurin, which in turn inhibits the activation of T-cells and cytokine expression. These effects are thought to be more selective than the effects of topical corticosteroids [41]. Topical calcineurin inhibitors have been associated with cases of malignancy, leading to a black box warning regarding risk of cancer with the use of these agents [99]. Although a causal relationship has not been demonstrated [41, 100], calcineurin inhibitors are reserved for second-line treatment only and are not recommended for children under 2 years of age [13, 84].

5. Maintenance of Skin Barrier

Management strategies for AD focus on maintaining the skin barrier and are recommended by medical societies worldwide [12, 28, 83, 84, 101, 102]. Use of mild, appropriately formulated emollients may provide benefits without interfering with skin barrier function. However, emollients alone may not control eczema or aspects of this skin disorder, especially in severe cases. Although emollient use alone may not be sufficient, prescription treatments (e.g., topical corticosteroids) are often considered to be less ideal for treatment of eczema in infants and young children. Given some of the unique challenges associated with topical corticosteroid treatment in young children [103], guidelines advocate for frequent and consistent use of emollients and avoidance of triggering factors as the foundation of AD management. As the underlying strategy of AD care, a more thorough discussion of optimal skin maintenance is warranted.

5.1. Mild Cleansing. Bathing offers an opportunity for the cleansing and removal of excess scale, as well as improved skin hydration and increased penetration of topical therapies. However, bathing also can cause dryness and further impair the skin barrier. Bathing in lukewarm water for several minutes and using a moisturizing cleanser is recommended, as is gently patting skin dry followed by the liberal application of emollients [97]. Bathing in lukewarm water for 20 minutes followed by use of an occlusive emollient can also help provide symptomatic relief [12]. Guidelines note that addition of baking soda or colloidal oatmeal to the bath may provide an antipruritic effect [12].

Soaps are typically alkaline and can irritate the skin of patients with or without lesional AD. In one study, washing was shown to reduce the thickness of the SC and

intracellular lipids in skin with AD, which suggests further impairment of epidermal barrier function [104]. In a study of individuals with and without AD, the penetration of SLS, a common ingredient used in soaps, shampoos, and bubble bath formulations, was examined *in vivo* using TEWL and tape stripping [48]. Study results showed significant penetration of SLS into the SC of uninvolved skin of patients with AD versus healthy control subjects, despite the finding that the SC thickness was the same in both groups. Additionally, in healthy skin, penetration was directly related to SC thickness, whereas SC thickness did not correlate with penetration in patients with AD. Diffusivity was twice as high in patients with AD versus controls; it was also higher in patients with active AD. This study provided further evidence that uninvolved skin in patients with AD has a defective skin barrier, which allows entry of chemicals and susceptibility to insults. These concerns are of greater importance for infants whose skin barrier and immune system has not matured fully.

Non-soap-based cleansers that support optimal skin surface pH are recommended for patients with AD [28, 102]. Guidelines recommend the use of mild synthetic detergents (syndets) with a pH of 5.5–6.0 to protect the skin's acid mantle [28]. In a 28-day study of children (≤15 years of age) with mild AD, the use of a syndet bar in place of the normal cleansing product (e.g., soap bar) resulted in less severe lesions, improved skin condition, and hydration [105]. Another study examined the effect of bathing and moisturizer combinations [106]. Results showed that the greatest level of skin hydration occurred with moisturization without a bath, whereas bathing alone reduced skin hydration, and bathing followed by moisturization provided modest hydration. It was concluded that the focus of moisturizer or emollient use should be on frequent application, regardless of the absence or presence of bathing.

Oftentimes, water contains a variety of substances that can be irritating; hard water can be especially irritating. Explanations for this association include excessive use of soap and detergent necessary to create a lather, or the presence of calcium that reacts with soap to form irritant chalk particles that enable allergen penetration and increase in cutaneous bacterial colonization [33]. The relationship between hard water and onset of AD is not understood fully. A correlation between water hardness and lifetime prevalence of eczema has been reported in several studies, but a causal relationship has not been established [31, 32, 107]. In a study that sought to address the effect of hard water, two groups of children received the same usual care, but one group also received a home water softener. Comparison of AD symptoms found no significant benefit between children receiving usual care plus the water softener versus children receiving only usual care [33].

Bathing with water alone may exacerbate clinical symptoms of AD. In a study of adults using water alone for cleansing, persistence of AD lesions was reported [108]. Even in healthy babies, bathing in water alone is not recommended due to water's drying effect on skin [109]. Babies with AD are recommended to receive regular bathing to provide skin debridement and help prevent bacterial infection. However, soap-free moisturizing liquid cleansers that do not alter skin surface pH or cause irritation or stinging are recommended [109].

5.2. Emollient Therapy. Guidelines recommend the consistent and liberal use of emollients and skin protectants for the prevention and maintenance of the epidermal skin barrier in patients with AD; their use may even reduce the need for topical corticosteroid use [28, 83, 84]. Emollients and skin protectants help soften the texture of skin and relieve pruritus due to excessive dryness [12]. Emollients also add a protective layer that helps aid corneocyte water retention and inhibits irritant entry [84]. A number of studies have demonstrated the benefits and safety of emollients in different age groups of patients with AD (Table 2) [79, 80, 85, 87, 110–124].

Composition of emollients can vary greatly, making one product more or less suitable for a particular individual's circumstances. Multiple emollients have been shown to improve skin barrier function, and many studies have investigated potential benefits of additional ingredients with varying mechanisms of action [126–128]. It is important to note that emollient creams, as well as cleansers, should be free of all potential allergens or irritating ingredients [12, 91].

Both prescription BRCs and OTC emollients/skin protectants can improve dry skin symptoms of AD as they protect the skin and provide irritation and pruritus relief. Emollients with ingredients such as humectants, skin conditioners, and ceramides work to moisturize the compromised dry skin barrier. Although prescription products are often assumed to be more efficacious than emollient therapy or OTC products, comparative studies provide an alternative view.

Studies have been published comparing the safety and efficacy of emollients with prescription barrier emollients. In an equivalence study, a moisturizer containing mineral oil, petrolatum, paraffin, and ceresin (Albolene, DSE Healthcare Solutions, Edison, NJ, USA) was compared with a BRC-containing glycerin, palmitoylethanolamide, pentylene glycol, olive oil, and vegetable oil (MimyX) in adults with mild-to-moderate AD [117]. Those with moderate AD also received 0.1% triamcinolone cream. All treatments were used twice daily for 4 weeks. AD parameters (erythema, desquamation, lichenification, excoriation, itching, stinging/burning, and overall severity) were assessed at baseline and weeks 1, 2, and 4. Results demonstrated that both treatments significantly improved symptoms to the same degree and with the same timing of resolution and demonstrated parity of treatments. Both treatments were well tolerated with no adverse experiences reported. Study authors noted a significant cost disparity between the therapies.

In another study, the efficacy and cost of the glycyrrhetinic acid-containing barrier cream (BRC-Gly, Atopiclair), ceramide-dominant barrier cream (BRC-Cer, EpiCeram), and OTC petroleum-based moisturizer (OTC-Pet, Aquaphor Healing Ointment, Beiersdorf Inc., Wilton, CT, USA) were compared as monotherapy for mild-to-moderate AD in children 2–17 years of age [122]. Treatments were applied three times daily for 3 weeks, with assessments

Table 2: Summary of studies of emollient use in neonates, infants, children, and adults with AD.

Study population	Treatment	Study duration	Efficacy	Safety
		Neonates		
Neonates ($N = 22$) at high risk for AD [124]	Petrolatum-based emollient barrier cream (Cetaphil, Galderma Laboratories, Fort Worth, TX, USA)	At least once daily for up to 2 years	Observed cases: 15% developed AD. Intent-to-treat: 23% developed AD	No adverse events related to treatment
		Infants		
Infants with moderate-to-severe AD, age <12 months ($N = 173$) [120]	Oat extract-containing emollient (Exomega, Laboratories Pierre Fabre, France)	Twice daily for 6 weeks	Significantly reduced use of high-potency topical corticosteroids and improved SCORAD index and QoL	Good/Very good tolerance in 94% of infants at study end. Two serious adverse events
		Children		
Children with mild-to-moderate AD, age 2 months–6 years ($N = 25$) [79]	Occlusive colloidal oatmeal cream and colloidal oatmeal glycerin cleanser (AVEENO, JOHNSON and JOHNSON Consumer Companies, Inc., Skillman, NJ, USA)	Cream: twice daily for 4 weeks. Cleanser: all bathing	Significantly improved IGA scores, dryness, roughness, and mean itch scores at 2 and 4 weeks. Significantly improved QoL scores at 4 weeks	Well tolerated; no serious adverse events related to treatment
Children with mild-to-moderate AD, age 3 months–16 years ($N = 65$) [125]	Ceramide-dominant barrier emulsion (EpiCeram)	Twice daily for 3 weeks	Improved IGA, patient satisfaction, and QoL	No serious adverse events related to treatment
Children with AD, age 6 months–12 years ($N = 76$) [85]	Moisturizer milk (Exomega) versus control	Twice daily for 2 months	Significantly improved xerosis, pruritus, and QoL	Tolerance rated as satisfactory or excellent in 97%
Children with mild-to-moderate AD, age 6 months–12 years ($N = 142$) [114]	Glycyrrhetinic acid-based cream (Atopiclair) versus vehicle	Three times daily for 43 days	Significantly improved IGA, reduced use of rescue medication (topical corticosteroid)	No serious adverse events related to treatment
Children with moderate-to-severe AD, age 6 months–18 years ($N = 121$) [87]	Ceramide-dominant barrier emulsion (EpiCeram) versus fluticasone cream (Cutivate, PharmaDerm, Melville, NY, USA)	Twice daily for 28 days	Significantly improved SCORAD index. Comparable efficacy between treatment arms	No serious adverse events related to treatment
Children with stubborn-to-recalcitrant AD, age 1.5–12.0 years ($N = 24$) [116]	Ceramide-dominant barrier emollient (TriCeram, Osmotics Corp, Denver, CO, USA) replaced prior moisturizer. Topical tacrolimus or corticosteroid was continued	Twice daily for 12 weeks, then once daily for 9 weeks	Significantly improved SCORAD in 92% of patients by 3 weeks, 100% by 21 weeks; decreased TEWL; improved SC hydration and integrity	No serious adverse events related to treatment
Children with mild-to-moderate AD, age 2–17 years ($N = 39$) [122]	Glycyrrhetinic acid-based cream (Atopiclair) versus ceramide-based barrier cream (EpiCeram) versus petrolatum-based ointment (Aquaphor Healing Ointment, Beiersdorf Inc, Wilton, CT, USA)	Three times daily for 3 weeks	All treatment arms improved, with no significant difference between treatments. Petrolatum-based ointment had greatest improvement across assessments	Well tolerated; no serious adverse events related to treatment

Table 2: Continued.

Study population	Treatment	Study duration	Efficacy	Safety
		Adults		
Children to adults with mild-to-moderate AD, age 2–70 years [123] (Study 1, $N = 66$; study 2, $N = 127$)	Cetaphil Restoraderm moisturizer (Galderma Laboratories, Fort Worth, TX, USA)	Study 1: Twice daily for 4 weeks; study 2: twice daily for 4 weeks as adjuvant treatment with topical steroid	Study 1: significantly decreased itching and improved hydration and QoL. Study 2: versus steroid only: significantly improved hydration, decreased EASI scores and faster onset of action	No serious adverse events related to treatment
Adolescents to adults with mild-to-moderate AD, age 12–60 years ($N = 25$) [80]	Oat-based occlusive cream and oatmeal-glycerin body wash (AVEENO)	Cream: twice daily for 8 weeks. Wash: once daily	Significantly improved: EASI and IGA scores at 2, 4, and 8 weeks; QoL at 4 and 8 weeks	Well tolerated; no serious adverse events related to treatment
Adults with mild-to-moderate AD, age >16 years ($N = 30$) [111]	Glycyrrhetinic acid-based cream (Atopiclair) versus vehicle	Three times daily for 3 weeks	Significantly improved itch and EASI scores symptoms	No serious adverse events related to treatment
Adults with mild-to-moderate AD, age 2–70 years ($N = 2456$) [119]	PEA-containing barrier (MimyX)	Twice daily for 4–6 weeks	Significantly improved symptoms versus baseline, reduced use of topical corticosteroids	No serious adverse events related to treatment
Adults with AD ($N = 197$) [121]	20% glycerin versus cream base control versus cream with 4% urea + 4% sodium chloride	Once daily for 30 days	Similar improvements in dryness	Moderate-to-severe stinging in 10% of glycerin group and 24% of urea/saline group
Adults with mild-to-moderate AD ($N = 24$) [115]	20% glycerin emollient versus placebo	Twice daily for 4 weeks	Improved SC hydration, restored epidermal barrier function (TEWL)	Not reported
Adults with allergic contact dermatitis, irritant contact dermatitis, or AD ($N = 580$) [112]	Ceramide-3 plus patented nanoparticles with or without corticosteroids	Once or twice daily until clearance (8 weeks)	Significantly improved symptoms in both treatment arms. Significantly improved pruritus, erythema, fissuring, and overall severity in combination arm	Not reported
Adults with mild-to-moderate AD ($N = 100$) [113]	5% urea moisturizer versus 10% urea lotion twice daily	Twice daily for 42 days	Similar reduction in SCORAD from baseline, no difference between products	Both products well tolerated; 5 adverse events possibly related to study treatment; 3 patients withdrew from study because of adverse events
Adults with mild-to-moderate AD ($N = 60$) [117]	Mineral oil, petrolatum, and paraffin-based moisturizer (Albolene) versus barrier cream MimyX (plus 0.1% triamcinolone cream for moderate AD)	Twice daily for 4 weeks	No difference between treatment groups in clinical efficacy	No serious adverse events related to treatment
Adults with mild-to-moderate AD ($N = 20$) [118]	Hyaluronic acid-based emollient foam (Hylatopic, Onset Therapeutics, Cumberland, RI, USA) versus ceramide-containing barrier cream (EpiCeram)	Twice daily for 4 weeks	Significantly improved symptoms at weeks 2 and 4 for foam; at week 4 for cream. Patients preferred foam	No serious adverse events related to treatment
Adults with mild-to-moderate AD ($N = 218$) [110]	Glycyrrhetinic acid-based cream (Atopiclair) versus vehicle	Three times daily for 3 weeks	Significantly improved EASI and IGA, and reduced rescue medication	No serious adverse events related to treatment

AD: atopic dermatitis; SCORAD: scoring atopic dermatitis index; QoL: quality of life; IGA: investigator global assessment; TEWL: transepidermal water loss; SC: stratum corneum; EASI: eczema area and severity index; PEA: palmitoylethanolamide.

performed at baseline and days 7 and 21. Assessments included 5-point Investigators Global Assessment severity scale and body surface area involved (≥1%). Improvement from baseline was noted in all three treatment groups. However, only the OTC-Pet group had statistically significant improvements in all parameters at study end. Although the OTC-Pet group had higher median percentage improvements at days 7 and 21 compared with the other treatment arms, these differences were not statistically significant. The cost of OTC skin protectant and emollient products is substantially below prescription BRCs. In the comparator study, the skin protectant was nearly 50 times more cost effective compared with the prescription BRCs [122].

5.3. Emollient Therapy and Reduction of Corticosteroid Usage. Because topical corticosteroids are associated with a risk of complications, including hypertrichosis, telangiectasia, skin atrophy, and stria [129], guidelines recommend that long-term use be limited [83]. To minimize adverse and systemic effects of topical corticosteroids in infants and young children with AD, appropriate potency (low or moderate, depending upon disease severity and location), duration, and localized application is recommended [84]. However, emollient monotherapy is recommended as the first approach in resolving areas of excessive dryness in very young children with AD [84].

A number of studies report a steroid-sparing effect of emollients when used in conjunction with topical corticosteroids. In a 3-week study of children with mild-to-moderate AD, once-daily hydrocortisone 2.5% cream plus an emollient (water in oil) was compared with twice-daily hydrocortisone 2.5% [130]. Skin symptoms and lesion size were significantly improved by 7 days in both treatment groups, with no significant between-group differences. These results demonstrated that the use of an emollient can be used to reduce the exposure to topical corticosteroids while providing the same degree of improvement.

In a study of infants (<12 months of age) with moderate-to-severe AD, the effect of an oat-extract containing emollient used in combination with either a moderate- or high-potency corticosteroid was examined [120]. In this 6-week study, emollient use decreased the amount of high-potency corticosteroid use by 42% ($P < .05$). The 7.5% decrease in moderate-potency steroid use was not significant. Another study in children (4–48 months of age) with moderate AD examined the effect of an oil-in-water-containing emollient on desonide 0.05% use [131]. This study found that use of topical corticosteroid every other day as adjuvant to twice-daily emollient use was as effective as monotherapy with once- or twice-daily topical corticosteroid.

5.4. Controlling Clinical Symptoms of Atopic Dermatitis Through Maintenance of the Skin Barrier. Maintaining optimal hydration and addressing aspects of skin barrier dysfunction in AD may reduce the incidence of excessive dryness and irritation in AD. The fundamental approach to helping address the skin care needs of those with AD includes routinely using skin protectants and emollients, avoiding known irritants, identifying and addressing specific triggering factors, and maintaining optimal skin care [28]. A combination of approaches may be optimal for some patients.

A consensus document recommends using skin protectants/emollients at a minimum of twice daily in the presence and absence of active disease; emollients also should be applied after bathing or showering [132]. For areas of active irritation and excessive dryness, more frequent-than-normal application of skin protectants/emollients or use of an emollient with higher hydration properties can be used for management of AD [128]. There is consensus among guidelines that, regardless of which emollient is chosen, the critical aspect is that it is used consistently. Patient preference is perhaps the most important aspect of choosing an emollient, as one that is disliked will not be used. Guidelines recommend that patients with AD continuously use emollients to prevent dry skin and irritation [28, 84], with adults generally using 500–600 g per week and children using 250 g per week [128]. One set of guidelines states that the quantity of emollient used should exceed steroid use by a ratio of 10 : 1 [133]. Skin protectants and emollients should be applied generously all over the body, not just on localized areas of dry skin [84].

Although the primary function of emollient therapy is to keep skin hydrated and to maintain the skin barrier, other benefits of emollient therapy have also been reported. A pilot study enrolled 22 neonates who were considered at high risk for developing AD owing to family history [124]. Parents were advised to apply an oil-in-water petrolatum-based emollient at least once daily to their infant and to minimize soap exposure. By 24 months, only 15% of babies had developed AD, which occurred at a mean age of 11 months. In contrast, a systematic review reported that 30%–50% of high-risk babies developed AD by the age of 2 years [134]. The results of this pilot study indicate the need for further research in this area.

Given that emollient therapy alone is insufficient to prevent all irritation associated with eczema, other approaches to decrease the likelihood of flare recurrence have been examined. One approach may be to use a low-dose topical corticosteroid with an emollient. In one such study, patients (12–65 years of age) were maintained on a regimen of daily emollient therapy and either topical fluticasone propionate (0.05% cream or 0.005% ointment) or placebo used twice weekly in skin areas that were prone to flares [135]. Time to relapse was 16 weeks in the treatment group versus 6 weeks in the control group. The risk of relapse was 5.8 times lower and 1.9 times lower in the treatment groups for cream and ointment, respectively, compared with control groups.

6. Conclusion

Atopic dermatitis is a prevalent inflammatory skin disorder characterized by intense pruritus and inflamed skin. AD can develop in very early childhood, yet resolution may occur as an infant ages. There is no known cure for AD, but the fundamentals of a daily skin care routine (e.g., use of a

mild, non-soap-based cleanser followed by at least twice-daily liberal use of an emollient or OTC skin protectant) are essential for hydration and maintenance of the skin barrier. Although patients with AD may be tempted to discontinue use of emollient therapy when symptoms subside, such action is contraindicated. Consistent, frequent, and liberal use of emollients is recommended to maintain skin barrier function in patients with mild AD, even in the absence of lesions. Long-term management focuses on minimizing potential exacerbations by avoiding triggers and adhering to appropriate cleansing and moisturizing regimens. Topical corticosteroids and topical calcineurin inhibitors are used to treat acute flares for patients with moderate to severe cases of AD who do not respond to more aggressive emollient use. Safety concerns regarding topical corticosteroid use, especially in children, has led to efforts to minimize exposure. To this end, steroid-sparing approaches should be sought when severity necessitates the use of a topical corticosteroid.

The care of patients with AD has evolved considerably over the last decade. Increased understanding of skin barrier dysfunction in AD has led to the formulation of a variety of new products. The role of prescription BRCs, OTC and cosmetic emollient formulations, and anti-inflammatory compounds provides diverse options for managing symptoms associated with AD. Elucidation of other mechanisms involved in barrier dysfunction is expected to result in new targets for therapies and may lead to revision of best practices for the management or treatment of AD. The role of emollients as the foundation of treatment, especially in infants and young children, is not likely to be challenged. The benefits of improving barrier function and hydration, coupled with steroid-sparing effects, render emollients a safe and effective option for managing patients with AD, particularly for infants and young children who have a continuously maturing epidermal barrier.

Conflict of Interests

M. Catherine Mack Correa and Nebus are employees of JOHNSON & JOHNSON Consumer Companies, Inc. Their division manufactures consumer products, including lotions and emollients (JOHNSON'S Baby Lotion, JOHNSON'S Baby Oil, JOHNSON'S NATURAL Baby Lotion, JOHNSON'S Baby Cream, JOHNSON'S Vanilla Oatmeal Baby Lotion, and other products). Other divisions within JOHNSON & JOHNSON Consumer Companies, Inc., including the AVEENO brand and NEOSPORIN brand, manufacture consumer products that help treat eczema, including AVEENO Eczema Therapy Moisturizing Cream, AVEENO Baby Eczema Therapy Moisturizing Cream, AVEENO Baby Eczema Therapy Soothing Bath Treatment, and NEOSPORIN ESSENTIALS Eczema Care. The editorial support for this review was funded by JOHNSON & JOHNSON Consumer Companies, Inc.

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Review Article

The Infant Skin Barrier: Can We Preserve, Protect, and Enhance the Barrier?

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Infant skin is different from adult in structure, function, and composition. Despite these differences, the skin barrier is competent at birth in healthy, full-term neonates. The primary focus of this paper is on the developing skin barrier in healthy, full-term neonates and infants. Additionally, a brief discussion of the properties of the skin barrier in premature neonates and infants with abnormal skin conditions (i.e., atopic dermatitis and eczema) is included. As infant skin continues to mature through the first years of life, it is important that skin care products (e.g., cleansers and emollients) are formulated appropriately. Ideally, products that are used on infants should not interfere with skin surface pH or perturb the skin barrier. For cleansers, this can be achieved by choosing the right type of surfactant, by blending surfactants, or by blending hydrophobically-modified polymers (HMPs) with surfactants to increase product mildness. Similarly, choosing the right type of oil for emollients is important. Unlike some vegetable oils, mineral oil is more stable and is not subject to oxidation and hydrolysis. Although emollients can improve the skin barrier, more studies are needed to determine the potential long-term benefits of using emollients on healthy, full-term neonates and infants.

1. Introduction

Skin barrier function resides primarily within the stratum corneum (SC), the top layer of the epidermis. Although the SC is only 7–35 μm thick [1, 2], it plays a vital role in forming a protective barrier and helps to prevent percutaneous entry of harmful pathogens into the body [3, 4]. In addition to serving as a physical barrier, the SC has other important functions, including engaging in thermoregulation, gas exchange, and maintenance of proper hydration. The SC also serves important functions in innate immunity [5] and its slightly acidic pH [6] provides additional protection against pathogens.

Maintenance of the skin barrier is essential for survival [1]. This is especially true for neonates and infants because their skin differs from mature adult skin in structure, function, and composition [1, 2, 7] and is particularly susceptible to infection [3]. During the late fetal period (20 weeks to birth), skin becomes functional and develops a protective barrier [8]. Although full-term infants are born with a competent skin barrier [9, 10], their skin is still developing through the first year of life [2, 11]. During the postnatal period, even the composition of commensal bacteria residing on the skin surface differs from that of adults and continues to evolve over the first year of life [12].

Given that skin continues to develop through the first year of life, the use of appropriate, evidence-based skin care practices is important. Maintaining skin barrier function is critical to preventing organ dehydration [13]. The SC water content is involved in maintaining SC structural integrity and functionality [14]. It is generally accepted that recommendations for infant skin care regimens should be evidence-based [15]. Although several studies have evaluated nonprescription emollient strategies to improve barrier

function [16, 17] or improve fluid and electrolyte balance [18] in neonates, infants, or children with compromised skin, limited information is available on skin care regimens that enable maintenance or enhancement of skin barrier integrity in normal neonatal or infant skin [19, 20].

Skin cleansing and emollient use are two simple strategies that can help keep skin healthy. Proper skin cleansing helps keep infant skin free of unwanted irritants, including saliva, nasal secretions, urine, feces, fecal enzymes, dirt, and microbial pathogens. Exposure to such factors for long periods, especially in the diaper region, can lead to discomfort, irritation, infection, and skin barrier breakdown. In many cases, water alone is not sufficient to cleanse skin during bathing [21]. Epidemiologic studies and anecdotal reports have even suggested a possible link between household use of hard water and atopic eczema in children [22, 23], though a causal relationship has not been shown [24, 25].

In addition to using cleansers during bathing, emollient use during or after bathing also may have benefits [16–20, 26–29]. Emollients decrease transepidermal water loss (TEWL) [16, 17, 26], improve skin condition [17, 26], and may even lead to reduced mortality in extremely premature infants [28]. In adults, 7 weeks of emollient use led to improvement in skin barrier function [27].

In this paper, we discuss the unique structure, function, and composition of infant skin, the importance of maintaining skin barrier integrity, and best practices for maintaining or improving infant epidermal barrier function, including use of appropriately formulated cleansers and emollients. We also discuss various neonatal and infant skin care guidelines from around the world and some controversies surrounding these guidelines. Finally, we will explore the idea that the onset of emollient use from birth may play a role in preserving and protecting the infant skin barrier later in life.

2. Infant Skin: Structure, Function, and Composition

Infant skin is different from adult skin: it undergoes a maturation process through at least the first year of life [2, 7, 11]. Several groups have measured or compared the epidermis of infants and adults [1, 2, 9, 30]. In one study, the epidermis of full-term neonates at birth was found to have 4.3 ± 0.7 cell layers that were vertically stacked from the basal layer to the stratum granulosum (excluding the SC), whereas the epidermis of preterm neonates at birth had only 2.9 ± 0.5 cell layers [9]. In their review of the literature, Chiou and Blume-Peytavi [1] reported that SC thickness ranged from 5.6 μm to 35.4 μm for infants and 15.2 μm to 35.4 μm for adults. Our group found that the suprapapillary epidermis and the SC had respective thicknesses that were on average 20% and 30% thinner in infants than in adults [2]. On the lower thigh area, infant SC was determined to be 7.3 ± 1.1 μm, whereas adult SC on the same region was 10.5 ± 2.1 μm [2].

At birth, full-term neonates have competent barrier function [10, 13] and an epidermis that appears to be fully differentiated [9], but closer examination reveals subtle structural and morphologic differences between infant and adult skin [2]. These differences may lead to observable functional differences between infant and adult skin [11]. Table 1 contains an overview of the major similarities and differences between infant and adult skin.

The water-handling properties of infant skin are unique and distinct from adult skin. Figure 1 shows a schematic of infant and adult SC hydration and their respective water-holding properties. Neonatal skin after birth is considerably drier compared with that of adults [31, 32]. However, during the first month of life, the difference in SC hydration between infants and adults is reversed [32, 33], leading to increased skin hydration in older infants (aged 3–24 months) relative to adult skin [11, 34]. As skin becomes more hydrated, the SC that is initially rough smoothens [32].

In addition to undergoing structural and functional changes, the composition of the cutaneous microflora evolves over the first year of life [12]. Although adult skin is colonized mostly by the phyla Proteobacteria, Actinobacteria, and Firmicutes, the order of predominance changes in infant skin to Firmicutes (predominantly *Staphylococci*), followed by Actinobacteria, Proteobacteria, and Bacteroidetes [12]. Although the implications of these findings are not yet known, early microbial colonization is expected to influence the development of immune function in skin. It also will be important to characterize the further evolution of the human skin microbiome during the first few years of life to determine if commensal bacteria play a role in the maintenance of skin barrier function beyond serving as sentinels of innate immune defense [35].

3. The Skin Barrier Is Competent at Birth in Healthy, Full-Term Neonates

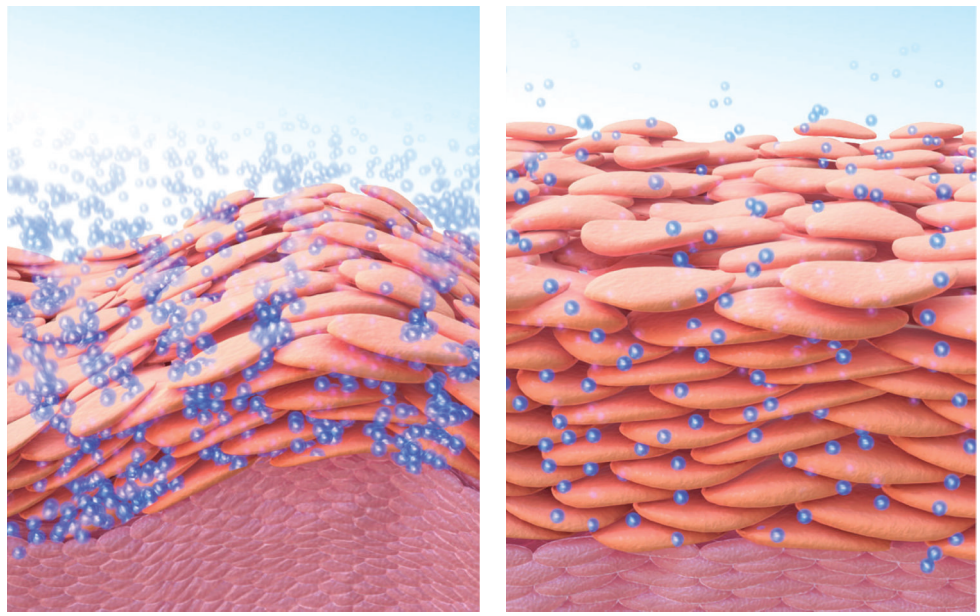
After birth, skin barrier function is influenced by the shift from an aqueous, warm environment in utero to a cooler, arid, and more variable extrauterine world [11, 36]. Skin development is contingent on gestational age. As gestation increases, the thickness and the number of cell layers in the epidermis increase [9]. Morphologic changes also occur, including the formation of an increasingly undulated dermoepidermal junction [9]. Histologically, a well-developed epidermis emerges at 34 weeks of gestation [9], though the period required for complete SC maturation has been reported to vary between 30 and 37 weeks [10].

Although infant skin is different from adult skin [2, 11], studies assessing the histologic and biophysical properties of the SC have demonstrated that the skin barrier is competent at birth in healthy, full-term neonates to prevent organ dehydration [9, 10, 13]. The barrier properties of the skin depend greatly on the thickness and integrity of the SC [8, 9]. As would be expected, preterm infants have a skin barrier that is underdeveloped compared with full-term neonates [9]. In one study [9], the epidermal thickness of full-term neonates at birth was 43 ± 7 μm versus 31 ± 7 μm for preterm infants (24–30 weeks of gestation).

In addition to SC thickness, other parameters can be used to assess barrier function, including skin water-handling

Table 1: Infant and adult skin: similarities and differences.

Structural differences	Infant skin	Adult skin	Reference
Epidermis			
Corneocytes	Smaller	Larger	[2]
Granular cells	Smaller	Larger	[2]
Stratum corneum and epidermis	Thinner	Thicker	[1, 2]
Microrelief lines	More dense	Less dense	[2]
Depth of surface glyphics	Similar to adult	—	[2]
Facultative pigmentation (melanin)	Less	More	[142, 143]
Dermis			
Dermal papillae (density, size, and morphology)	More homogeneous	Less homogeneous	[2]
Distinct papillary-to-reticular dermis transition	Absent	Present	[2]
Compositional differences			
Epidermis			
Natural moisturizing factor concentration	Lower	Higher	[11]
pH	Higher (newborn only)	Lower	[6, 32, 34]
Sebum	Lower (7–12 month-old infant)	Higher	[144]
Stratum corneum water content	Higher	Lower	[11]
Dermis			
Collagen fiber density	Lower	Higher (young adult)	[2, 145]
Functional differences			
Rate of water absorption	Higher	Lower	[11]
Rate of water desorption	Higher	Lower	[11]
Skin barrier function	Competent	Competent	[9, 10]
Transepidermal water loss	Higher	Lower	[11]



(a) (b)

Figure 1: Infant and adult skin: stratum corneum (SC) hydration and water transport properties. The SC of infant skin (a) and adult skin (b) is hydrated (small blue spheres) under normal conditions. Infant SC is more hydrated but also loses water at higher rates than adult SC [11].

properties [11, 34]. Water barrier function and skin hydration status are interdependent factors, the former of which is influenced largely by the organization and composition of the intercellular lipid matrix [37], natural moisturizing factor [38], and the permeation path length through the SC [39]. Skin water content also influences skin barrier function by regulating the activity of hydrolytic enzymes that are involved in SC maturation and corneocyte desquamation [40].

Researchers can assess the skin's capacity to absorb and retain water with sorption-desorption tests that use electrical measurements (e.g., skin surface conductance or capacitance) before and after topical application of water on the skin surface [1, 41]. Water barrier function, which affects rates of water absorption and desorption, is localized within the SC [42] and has been shown to vary between infants and adults [11, 31]. In addition, water content within the SC can have a profound effect on skin surface morphology [43], desquamation [44], and epidermal expression of keratins and cornified envelope proteins [45].

Newborn skin has been reported to have lower skin surface hydration and increased water loss compared with skin from 1- to 6-month-old infants or adults [31]. Our group also found that infant skin (3–12 months) on the upper ventral arm and lower dorsal arm gained and lost water at significantly faster rates than the same regions on adult skin [11]. Skin surface hydration on the upper ventral arm and lower dorsal arm was greater in infants than adults. The distribution of water in the SC varied between infants and adults based on water concentration profiles calculated using confocal Raman microspectroscopy. Infants had more water on the skin surface, more water within the SC, and more water distributed throughout the first 26 μm below the skin surface. Infant SC also had a steeper water gradient compared with adult skin.

TEWL is a noninvasive method that can be used to monitor changes in SC barrier function [46]; it also enables dynamic measurement of water loss [11]. High basal TEWL is suggestive of incomplete skin barrier function and is indirectly proportional to the integrity of water barrier function. This method has been used to confirm that epidermal permeability barrier function is developed fully at birth in full-term neonates [6, 10]. In older infants (3–12 months) our group found that TEWL was significantly higher compared with adult skin ($P < .0005$; 3–6 and 7–12 months old versus adult) [11].

Formation of an acidic SC is essential for epidermal barrier maturation and repair processes [10]. Many factors contribute to formation of the acid mantle, including sebum secretion, sweat (lactic acid), amino acids and amino acid derivatives (urocanic acid and pyrrolidone carboxylic acid), and exocytosis of lamellar body contents at the stratum granulosum/stratum compactum interface [47]. At birth, full-term neonates have a skin surface pH that varies between 6.34 and 7.5 [6, 48]. Within the first 2 weeks of life, skin surface pH falls to approximately 5 [3, 48], which is similar to the skin surface pH that has been observed during adulthood (pH range: 4.0 to 6.7) [6, 49]. Discrepancies in skin surface pH between studies could be the result of differences in participant age (infant versus child), gender mismatch, body location (volar forearm versus buttock), or instrumentation. It should be noted that adult skin surface pH also has been shown to vary by a wide margin [49]. Taken together, published data indicate that skin surface pH is close to neutral at birth and becomes more acidic over the first few days of life. Within a matter of weeks, skin surface pH is similar to levels observed in adults. However, consensus has not been reached on the duration of this transition period.

4. Maintenance of Skin Barrier Integrity Is Essential to Overall Health and Wellness

Skin barrier function is essential for survival [1] and is critical to preventing percutaneous entry of bacteria and other pathogens into neonatal skin [50]. If the skin barrier is disturbed, bacteria or bacterial factors will have access to living epidermal keratinocytes and can induce defensive immune responses [4]. Keratinocytes produce antimicrobial peptides (AMPs), including the cathelicidin-derived peptide LL-37 and human β-defensins 1-3 [4]. In the absence of AMPs, pathogenic microorganisms can invade the surface of skin, leading to infection or an imbalance of commensal flora versus pathogenic bacteria. For example, patients suffering from burns, chronic wounds, surgery, or injuries that are associated with skin barrier dysfunction are more susceptible to infections caused by *Pseudomonas aeruginosa* [4], yet this opportunistic pathogen rarely causes infections on healthy human skin [4].

5. Abnormal Infant Skin Conditions and Barrier Integrity

5.1. Atopic Dermatitis (AD). During childhood, skin disorders that are characterized by skin barrier dysfunction are common. Compromised skin barrier integrity is thought to be critical to the early onset and severity of AD, which is often accompanied by dry, scaly skin. AD is an inflammatory skin condition that occurs in 15–20% of children [51, 52]. Alterations in skin barrier properties that are observed in AD include increased TEWL [53], changes in skin surface pH [54], increased skin permeability [55], increased bacterial colonization [56], alterations in AMP expression [57], and compromised skin permeability barrier integrity [58]. Once the skin barrier is compromised, allergens, irritants, and other unwanted agents can penetrate skin, leading to aggravation of symptoms associated with AD.

There are several guidelines that discuss how caregivers can manage and treat AD [59, 60]. Recommendations to relieve AD include using warm water in lieu of hot water, taking short baths (5–10 minutes), and using a liquid cleanser with emollient that does not compromise skin barrier integrity, followed by gentle dry patting with a soft towel and immediate application of a skin emollient [29, 61].

The Royal College of Paediatrics and Child Health (RCPCH) presented a tiered approach to the management of mild, moderate, and severe atopic eczema [62]. In all three cases, the RCPCH noted that initial treatment should

focus on repairing the skin barrier through the use of emollients for moisturizing, washing, and bathing. Depending on severity, emollient use can be supplemented with topical corticosteroids. In cases of moderate atopic eczema, bandages and topical calcineurin inhibitors (second-line treatment) can be used to supplement emollient use. During severe atopic eczema, emollient use can be supplemented with phototherapy and systemic therapy.

5.2. Irritant Diaper Dermatitis. Irritant diaper dermatitis is a complex skin condition that is characterized by compromised epidermal barrier function occurring on the buttocks, perianal region, inner thighs, and abdomen. Skin occlusion, friction, lipolytic and proteolytic activity of fecal enzymes, increased skin surface pH, and prolonged exposure to urine are all contributing factors to the onset of irritant diaper dermatitis [63]. Greater than 50% of infants will have at least one episode of irritant diaper dermatitis during the diaper-wearing phase [64]. Clinical presentation of irritant diaper dermatitis includes skin erythema [65], but severe cases may lead to presentation of papules and edema [66].

Within the past 10 years, there have been several reviews discussing the etiology and management of irritant diaper dermatitis [67–71]. Although use of appropriately formulated cleansers and emollients can help maintain the epidermal skin barrier in the diaper region, good hygiene and adequate protection are necessary to prevent skin barrier breakdown, rash, and infection.

6. Cleansing Is Vital to Maintaining Good Health and Hygiene

6.1. Infant Skin Care Guidelines, Recommendations, and Review of the Literature. Keeping babies clean and good skin hygiene are essential to overall health. Cleansing helps keep skin free of unwanted substances, including irritants (saliva, nasal secretions, urine, feces, and fecal enzymes), dirt, and transient germs. Keeping hands clean, particularly in the case of babies with their hand-to-mouth behaviors, can help reduce or prevent oral transmission of microbial contaminants. Caregivers should give special attention to skin on the facial area, which may be irritated easily by milk, food, and saliva. Skin folds and creases on the face also should be kept clean.

Although the benefits of good hygiene are known, neonatal skin cleansing and the use of cleansers, soaps, or other topicals during the bathing process is controversial. For most of the 20th century there were no formal guidelines on neonatal skin cleansing. In 1974, the American Academy of Pediatrics recommended that caregivers cleanse neonatal skin after the infant's temperature stabilizes [72]. In 1978, Sweden and Great Britain proposed similar recommendations [73]. In 2007, the Second Edition of the Association of Women's Health, Obstetric, and Neonatal Nurses (AWHONN) Neonatal Skin Care Evidence-Based Clinical Practice Guideline recommended that caregivers select mild cleansing bars or liquid cleansers that have a neutral pH (5.5 to 7.0) that are preservative-free or contain preservatives that have a demonstrated safety/tolerance profile [74]. In contrast, the National Institute for Clinical Excellence (NICE) clinical guideline 37 on postnatal care states the following [75]: "Parents should be advised that cleansing agents should not be added to a baby's bath water nor should lotions or medicated wipes be used. The only cleansing agent suggested, where it is needed, is a mild non-perfumed soap." Despite these recommendations, there is limited evidence to support the NICE position on infant cleansing [29]. Water is insufficient for removal of all oil-soluble skin surface impurities [76, 77] and has poor pH-buffering action [78]. Depending on bathing frequency and quality of water used, washing with water alone can have a drying effect on infant skin [29], which may lead to impairment of infant skin condition. Although soap is an effective skin cleanser, it can disrupt skin surface pH, alter skin lipids, and cause dryness and irritation [79–81], all of which may make soap less preferable.

On 13 February 2007, a group of clinical experts in pediatrics and dermatology formed the first European Round Table meeting on "Best Practice for Infant Cleansing." The consensus panel recommended that caregivers use liquid, pH-neutral, or mildly acidic cleansers over traditional alkaline soaps on neonates and infants [29]. In addition, the consensus panel made the following recommendations:

(i) Liquid cleansers are preferable to water alone.

(ii) Liquid cleansers cleanse and hydrate skin better than water alone.

(iii) Liquid preparations, which often contain emollients, are preferable to cleansing bars.

(iv) Liquid cleansers should contain adequate and appropriate preservatives.

(v) An "ideal cleanser" is one that does not cause irritation, alterations to skin surface pH, or eye stinging.

(vi) Skin care products should be selected on the basis of evidence acquired in practical use conditions.

Although the consensus panel recommended using liquid cleansers and believed that liquid cleansers have some desirable properties, to our knowledge no peer-reviewed publications have summarized the results from randomized controlled trials comparing the tolerance or efficacy of liquid or rinse-off cleansers to traditional soaps or syndet bars. In an open-label, controlled, randomized study, Gfatter et al. compared the effects of washing infant skin with a liquid detergent (pH 5.5), compact detergent (pH 5.5), or alkaline soap (pH 9.5) with a control group washing with water alone after a single wash [79]. Their study was designed to assess the effect of skin care regimens on pH, fat content, and skin hydration. Although all cleansing regimens tested (including the control) were shown to influence the parameters studied, the soap bar had the largest influence on skin pH and fat content, resulting in statistically higher pH (more alkaline) and statistically greater loss of fat. The study by Gfatter et al. concluded that the short-term effects from a single wash can disturb the skin acid mantle and its protective function,

which suggests the need to determine the long-term effects of cleansing products and other skin care regimens [81].

Given the lack of harmonization across infant skin cleansing guidelines, bathing practices vary widely. Siegfried and Shah surveyed skin care cleansing practices in 15 neonatal nurseries from 12 hospitals in Missouri, Iowa, Illinois, and California [82]. Of these nurseries, four were defined as "low risk" and 11 were defined as "high risk." Head nurses, nursery directors, or other healthcare professionals were asked questions about bathing practices, cord care, and general infant skin care. Bathing of full-term infants in the low-risk nurseries occurred on the first day when the infant was stable or when the infant's core temperature was 98.6°F. There was little variation in the cleansing products used during bathing. Nine of 15 nurseries used a mild baby cleanser. One nursery used more than one brand, and no information was given about the cleansing products used at the other five nurseries.

Garcia Bartels et al. evaluated the effect of bathing with or without a liquid cleanser on skin barrier function in healthy, full-term neonates [19]. TEWL, SC hydration, skin surface pH, and sebum were measured on the forehead, abdomen, upper leg, and buttock on day 2, week 2, 4, and 8 of life. After 8 weeks of life, skin surface pH was significantly lower in neonates who were bathed with a liquid cleanser versus those who were bathed with water alone. Bathing with a liquid cleanser did not lead to significant differences in median TEWL values or SC hydration on any of the tested body sites versus those who were bathed with water alone. Moreover, use of a liquid cleanser did not lead to statistically significant changes in sebum measurements. The use of a liquid cleanser was well tolerated in healthy, full-term neonates during the first 8 weeks of life. The study by Garcia Bartels et al. did not include premature neonates or infants with abnormal skin conditions and it is not known if similar observations would be made in premature neonates or those with compromised skin.

In a randomized, investigator-blinded clinical study, Dizon et al. compared the effects of twice-daily washing with water alone versus washing with water and a mild cleanser or water with a comparator cleanser for 2 weeks in 180 healthy infants [83]. After 2 weeks, cleansing with water alone led to a significant increase in erythema from baseline. In contrast, there was no change in skin erythema from baseline in the group that was cleansed with water and mild cleanser.

6.2. Formulation Considerations. Many traditional soaps contain detergents that are derived from saponification (e.g., the process of mixing a strongly alkaline solution with a fatty substance such as vegetable oil or tallow, leading to soap formation) [76]. Alkaline soaps can increase skin surface pH beyond what is considered an ideal range [76, 79]; they can also dissolve fat-soluble and water-soluble barrier components from the surface of skin [79]. Unlike traditional soaps, many of which can be irritating, infant cleansers should be mild to accommodate the maturing skin barrier. Infant cleansers should also wash away dirt, sebum, saliva, urine, fecal matter, and fecal enzymes with minimal effort [66, 80, 81].

Although most cleansers and soaps are suitable for adult bathing, cleansers for neonatal or infant skin should be formulated specifically for that population and its special needs. An ideal infant cleanser should contain at least one "surface-active agent" (surfactant), a molecule with both hydrophilic and oleophilic (lipophilic) properties that reduces the interfacial tension between oil and water. Surfactants enable formation of oil-in-water, water-in-oil, and more complex, multiphasic systems. By reducing interfacial tension, cleansers help to emulsify oils and other skin surface impurities into water [77], making their removal easier without requiring excessive friction or mechanical force during bathing.

Several classes of surfactants are used often in cleanser formulations, including anionic surfactants such as sodium lauryl sulfate (SLS) or sodium laureth sulfate (SLES), nonionic surfactants (e.g., poloxamers), and amphoteric surfactants (e.g., cocamidopropyl betaine). Foaming action and mildness are influenced by the charge of a surfactant's hydrophilic head group and the formation of spherical structures (micelles) that enable solubilization of oils and lipids from the skin surface [21]. Although anionic and amphoteric surfactants facilitate foam formation (a desirable aesthetic property for shampoo), they are usually less mild than nonionic surfactants such as polyethylene glycol (PEG)-80 sorbitan laurate.

Surfactant selection represents a tradeoff between functionality, aesthetics, and mildness. Due to their charge and ability to form smaller micelles relative to other surfactants, some anionic surfactants can be disruptive and irritating to skin [21, 81]. For example, SLS is an effective emulsifying and foaming agent, but in certain circumstances it may cause irritation [81, 84]. In contrast, PEGylated nonionic surfactants (e.g., PEG-80 sorbitan laurate or polyethylene oxides) can lead to micelle stabilization, potentially increasing cleanser mildness [21]. Cleansers containing sulfated ethoxylated alcohols (e.g., SLES), surfactants that have large head groups and have the ability to form larger micelles, may be formulated to have improved mildness compared with those containing SLS [84, 85]. In 20 healthy adult volunteers, patch testing revealed that SLES was milder and caused significantly less damage to the epidermal barrier compared with SLS [84]. After 7 days, no significant irritation was observed with SLES, even at the highest tested concentration (2.0%). Regeneration after skin irritation occurred much faster with SLES compared with similar concentrations of SLS [84]. In 2010, the Cosmetic Ingredient Review (CIR) panel concluded that SLES is safe as a cosmetic ingredient when used appropriately in products formulated to be nonirritating [86].

Mild moisturizing cleansers are expected to provide cleansing benefits without negatively altering the hydration and viscoelastic properties of skin [81]. Formulators can combine surfactants to create milder cleansers [21], which may be particularly ideal for individuals with AD [87]. For example, liquid body cleansers that contain a blend of anionic and amphoteric surfactants can be milder than

a liquid cleanser that contains an equal proportion of anionic surfactant alone. The blending of hydrophobically-modified polymers (HMPs) with surfactants also may lead to increased cleanser mildness [88]. HMPs can interact with and associate with the hydrophobic tails of other surfactants, leading to self-assembly and the formation of larger surfactant/polymeric structures. The creation of micelles with a larger hydrodynamic diameter has been shown to have lower irritation potential and may ultimately allow for the creation of milder surfactant systems and better tolerated cleansers [88].

The properties of an ideal infant cleanser are summarized in Table 2. Traditional cleansers are formulated to have a pH that is similar to that of the skin surface. Liquid cleansers should be nonirritating and should enable maintenance of normal skin surface pH [29]. If the pH of a cleanser is acidic but does not perturb skin surface pH, it may be preferable to one that is pH neutral that causes a greater shift in skin surface pH. Solutions that are not pH neutral are not necessarily more irritating to skin. Moreover, it could be argued based on the weight of the evidence that alkaline cleansers would be least appropriate. Alkaline soap can disrupt skin surface pH [79], decrease SC thickness [89], decrease SC intracellular lipids [89], and lead to dryness and irritation [80, 81]. Buffer solutions with varying pH (4.0 to 10.5) were shown to be nonirritating to skin irrespective of pH [90]. In addition, detergents buffered at pH 3.5 or 7.0 caused similar levels of skin irritation [90]. Although cleansers can alter skin surface pH, temporary pH fluctuations may be stabilized by the skin's large buffering capacity [90]. A cleanser's effect on skin surface pH may be more important than the pH of the formulation itself in determining product mildness.

There are conflicting reports in the literature about the effect of cleansers on cutaneous commensal bacteria. Maintaining a skin surface pH between 4.0 and 4.5 facilitates cutaneous commensal bacterial attachment to the surface of skin [49]. Larson and Dinulos hypothesized that inappropriately formulated soaps could alter the delicate balance between cutaneous commensal and pathogenic bacteria [3]. da Cunha and Procianoy investigated the effect of using a pH-neutral soap during bathing on cutaneous bacterial colonization in infants admitted to a neonatal intensive care unit [91]. After 1 week, the use of a pH-neutral soap did not have an effect on cutaneous bacterial colonization compared with infants who were bathed with water alone. Given the importance of cutaneous commensal bacteria to innate immunity [92], the use of mild cleansers that do not cause alterations in skin surface pH may be important for normal skin maturation and innate immune function.

6.3. Noninvasive Approaches to Predict Skin Irritation Potential. Interleukin-1α (IL-1α) and prostaglandin E_2 mediate inflammation in skin via cytokine-dependent and arachidonic acid-dependent pathways, both of which play a role in the development of erythema and edema. Proinflammatory markers (including IL-1α) that are indicative of subclinical inflammation (i.e., erythema) may be useful in predicting the skin irritation potential of a skin cleansing product [93, 94].

Bernhofer et al. demonstrated that IL-1α can be a useful predictor of skin mildness and irritation potential [93]. Levels of subclinical irritation—even in the absence of visible erythema—can be determined using a noninvasive epidermal tape-stripping technique and enzyme-linked immunosorbent assay [95, 96]. IL-1 receptor antagonist (IL-1ra), IL-1α, and the ratio between these two molecules are useful for assessing skin reactivity [95] and measuring skin inflammation [95, 97]. The IL-1ra/IL-1α ratio increases during infancy, irritant diaper dermatitis, heat rash, and erythema [96]. By extension, the IL-1ra/IL-1α ratio also may help predict the irritation potential of skin cleansers [93]. It is anticipated that skin treated with a mild skin cleanser would have a lower IL-1ra/IL-1α ratio compared with skin treated with a more irritating cleanser, possibly leading to a more normalized skin condition. Table 3 shows the proinflammatory activity of several commercially available cleansing products whose irritation potential was assessed by measuring IL-1α release using *in vitro* skin tissue equivalents (EpiDerm, MatTek Corporation, Ashland, MA, USA). A mild baby cleanser and mild baby shampoo caused less IL-1α release compared with a commercial sensitive skin syndet bar. Moreover, MTT cell proliferation (cell viability) assay data revealed that there was more cell cytotoxicity associated with the sensitive skin syndet bar. Although these data are from *in vitro* skin equivalents, the mild baby cleanser and mild baby shampoo would be expected to cause minimal release of IL-1α from infant skin, possibly leading to less skin irritation. Other methods for assessing cleanser mildness include measuring the percutaneous transit time, protein solubilization, or collagen-swelling potential [98].

7. Emollients Can Improve Skin Barrier Function in Healthy, Full-Term Neonates

Dry, scaly skin is common in neonates [31] but can occur at any stage of development. Although many factors contribute to skin surface hydration, the environment (i.e., dry, cold weather or wind) can accelerate the loss of moisture from the SC. Emollients have been used for centuries to protect the integrity of the SC and to maintain skin barrier function [99]. Appropriately formulated emollients can preserve, protect, and enhance the infant skin barrier by supplying the SC with water and lipids and by helping to inhibit water loss. Emollients also supply lipids to epidermal keratinocytes, where they can be transported through the cell membrane and metabolized within the cell [100]. Keratinocytes can then use lipids (including linoleic acid) as components to build a functional epidermal barrier [101].

Several studies have shown that emollient use can improve skin barrier function [16, 17] or improve fluid and electrolyte balance [18] in preterm infants, but very few studies have investigated the use of emollients on healthy, full-term neonates [19, 20]. Garcia Bartels et al. investigated the effect of applying topical emollients on healthy, full-term neonates after bathing with or without liquid cleanser on skin barrier function during the first 8 weeks of life [19]. After 8 weeks, median TEWL was significantly lower on the

Table 2: Ideal properties of appropriately formulated cleansers for neonates and infants.

Property	Traditional cleanser	Infant cleanser
Surfactant systems	Amphoteric, anionic	Amphoteric, nonionic, and ethoxylated anionic
Micelle diameter	Smaller	Larger
pH	Slightly acidic to neutral pH	pH should cause minimal changes to skin surface pH
Estimated IL-1ra/IL-1α ratio	Larger	Smaller
Preservative system	Some claim preservative-free	Product should be "microbiologically robust"
Fragrance (parfum/perfume)	Higher concentration level	Lower concentration level; restrictions on specific fragrance components; fragranced product clinically evaluated for irritation and sensitization potential
Other	—	Product should be efficacious and should be demonstrated to be well tolerated

IL-1α: interleukin-1α, IL-1ra: interleukin-1 receptor antagonist.

Table 3: Proinflammatory activity of commercially available cleansing products.

Cleanser	IL-1α (pg/mL)	MTT cell proliferation assay
Mild baby cleanser	100.5 ± 35.0	99.5%
Sensitive skin syndet bar	1150.1 ± 0.1	6.5%

Mean (± standard deviation) IL-1α (pg/mL) released from *in vitro* skin tissue equivalents (EpiDerm, MatTek Corporation, Ashland, MA, USA) after exposure to various cleansing products. MTT cell proliferation (cell viability) assay data are also shown. The sensitive skin syndet bar had significantly more cell death than the mild baby cleanser, IL-1α: interleukin-1α.

front, abdomen, and upper leg of neonates who received an emollient after taking a bath with liquid cleanser ($P < .001$ for all regions versus infants who bathed with water alone and did not receive an emollient after bathing). After 8 weeks, median TEWL also was significantly lower on the forehead, abdomen, upper leg, and buttock in neonates who received an emollient after bathing with water alone ($P < .001$ for all listed regions versus infants who bathed with water alone and did not receive an emollient). Emollient use after bathing with or without a liquid cleanser led to an improvement in SC hydration on the forehead and abdomen ($P < .001$ versus infants who bathed with water alone and did not receive an emollient). Moreover, use of an emollient did not affect skin surface pH or sebum production.

Many healthcare practitioners and caregivers understand the utility of incorporating mild, appropriately formulated cleansers into the bathing routine, yet far fewer caregivers recognize the importance or benefits of emollient use for application on healthy neonatal and infant skin. In a recent study, 90% of the mothers surveyed believed that their child's skin was not dry, yet clinical evaluation revealed that only 37% of these children had nondry skin, whereas the remaining children exhibited clinical signs of low to moderately dry skin [102].

7.1. Formulation Considerations. Similar to the case of cleansing products, appropriate formulation of emollient products need to take into account the particular nature of infant skin properties [7, 11]. Some considerations that may be important when selecting a skin care emollient product are summarized in Table 4. Although this table is not meant to be an exhaustive list, we have attempted to provide practical considerations relating to preservative systems, fragrances, and the reasons behind other formulation considerations.

It has been postulated that emollient products containing a physiologic balance of epidermal lipids (3 : 1 : 1 : 1 molar ratio of cholesterol/ceramide/palmitate/linoleate) are optimal for barrier repair [103]. Furthermore, many compounds (used alone or in combination with other molecules) have been reported to have beneficial effects on skin barrier function. However, due to the complex nature of emollient formulations and differing individual needs, designing emollients that are optimized for a particular individual and tailoring the emollient for maximum efficacy are still active areas of research [104].

Oils are used traditionally in some countries as emollients during the bathing process [105–109], to treat hypothermia in newborns, [110], or to remove impurities from neonatal skin hours after birth [111]. Some dermatologists have recommended using bath oils for their ability to leave a film on the skin surface or to reduce xerosis [106–108]. One study [109] found that bath oils can be beneficial to infants, yet another double-blind, randomized study showed that some bath or shower oils can be irritating to skin [112]. More recently, an analysis of systematic review found that there was no benefit associated with using oils to treat conditions like atopic eczema [113]. As noted by Shams et al. [113], there is an absence of evidence demonstrating a benefit of using bath emollients in addition to directly applied emollients in the treatment of atopic eczema. Furthermore, Tarr and Iheanacho [114] were not able to find a randomized controlled trial that showed the benefit of using bath emollients. Although the benefits of

Table 4: Practical considerations for emollient product selection.

Efficacy considerations
(i) Appropriate tests should testify to the efficacy of the product formulation
Safety considerations: overall
(i) The margin of safety for each ingredient at the concentration used in the formulation should be considered
(ii) Ingredients in a product can behave differently than in isolation; therefore, it is important to evaluate the full formulation for safety and potential dermal effects, including irritation and sensitization
Safety considerations: fragrance
(i) The use of fragranced products for healthy neonates and infants should be supported by evidence for safety and tolerance
(ii) Fragrances should be compliant with the International Fragrance Association (IFRA), which is a body that helps to ensure the safety of fragrance materials
Safety considerations: preservatives
(i) Products should be microbiologically robust
(ii) "Natural" does not always mean safer (e.g., some natural oils (eucalyptus, sage, and tea tree oils) can be toxic at certain levels)
(iii) Preservative ingredients can be natural or synthetic as long as their safety profile is documented; identical chemical structure means identical safety profile
Safety considerations: labeling and packaging
(i) Directions for product use should communicate and educate parents on safe and appropriate use
(ii) Package design should help to minimize product contamination (e.g., loose top or seal could expose product to microbes)

using oils to improve the skin barrier remain equivocal, bath oil use may have a soothing or calming effect on infants when used during massage or bathing [115, 116]. Moreover, the incorporation of emollients into the bathing routine may provide emotional benefits such as reinforcement of the parental or caregiver bond through touch [29].

While bath oils may not have an obvious benefit, some emollient formulations contain essential fatty acids (e.g., linoleic acid) that can provide systemic benefits to neonates [117]. Not all vegetable oils are appropriate for use on skin [118]. Vegetable oils can vary in composition, for example, in the ratio of linoleic to oleic acid. Some vegetable oils, including certain olive, soybean, and mustard oils, can be detrimental to the integrity of the skin barrier [119]. Some unsaturated free fatty acids can act as permeation enhancers [120], an effect that may cause contact dermatitis in adults [121–124]. In addition, many vegetable oils are unstable and degrade by hydrolysis and oxidation. Degradation can increase the likelihood of microbial growth and spoilage, especially in hot, humid environments. Cutaneous *Propionibacterium acnes* and *Propionibacterium granulosum* secrete lipases, enzymes that hydrolyze sebum triglycerides to free fatty acids [125]. By extension, *Propionibacterium acnes*, *Propionibacterium granulosum*, and possibly other cutaneous bacteria may hydrolyze vegetable oils present in topicals into free fatty acids, accelerating the degradation of vegetable oils on the skin surface. Use of unstable emollients or those that degrade quickly may lead to undesirable effects, especially on infant skin that is undergoing SC maturation and expansion of innate immune function.

Emollients that contain inert, stable ingredients such as mineral oil are preferable for use on the maturing infant skin. Mineral oil, a semiocclusive ingredient that penetrates the upper layers of the SC [126], is immiscible with water. It is noncomedogenic [127], has a long record of safe use [128], and is unlikely to go rancid even in hot, humid climates. Mineral oil helps to enhance the skin barrier as shown by a reduction in TEWL following topical application of the oil [126]. By reducing the amount of evaporated water, it helps keep the SC more hydrated, leading to an improved appearance on the skin surface. Other favorable physical properties of mineral oil include a low viscosity and a low specific gravity relative to water.

The semiocclusive mineral oil layer on the skin surface helps to retain water by retarding water evaporation [126]. In an unpublished experiment, our group investigated the effects of mineral oil on water retention in excised human SC. Equal weights and sizes of human SC were dehydrated at a constant temperature and humidity for 48 hours. After dehydration, the weights of the human SC samples were recorded. One set of samples (group 1) underwent full hydration by placing the samples in a closed chamber (90% humidity) for 48 hours. At the end of this period, the "wet" sample weight was recorded. A second set of samples (group 2) was allowed to equilibrate to room temperature. Once complete, sample weights in group 2 were recorded. The weight of the hydrated samples was calculated by taking the average percentage of the wet sample weight (group 1) minus the average percentage of the room equilibrated sample weight (group 2). A third set of samples (group 3; control) was maintained at dry weight until use. Mineral oil was applied to the fully hydrated samples in group 1, while two other moisturizing lotions were applied to the samples in group 2. Mineral oil and test lotions were weight-adjusted to ensure that equivalent weights of oil, lotion, and water were applied to human SC (some of the lotions contained water,

whereas mineral oil contained none). Weight measurements were taken immediately after product application on all samples; weights also were recorded periodically until there was no further decline in sample weight (i.e., complete evaporation of SC water). In the absence of mineral oil, SC moisture evaporated quickly, whereas samples with mineral oil showed higher water retention. Figure 2 shows a hypothetical model for how a semiocclusive layer of mineral oil could improve the water barrier. In the left panel, no mineral oil is present. In the right panel, water evaporation from the surface of skin slows in the presence of mineral oil, leading to reduced TEWL.

Another approach to enhance the skin barrier of infant skin is to combine the emollient ingredients within the liquid cleanser formulation [29]. More studies are needed to determine specifically which types of emollient formulations will be optimal for neonatal and infant skin.

8. Use of Emollients on Compromised Skin

8.1. Premature Infants. Gestational age is strongly linked to epidermal barrier function. The skin barrier of premature infants is injured easily and can serve as a portal of entry for agents, causing serious bacterial infections [13, 129]. Several groups have investigated using vegetable seed oils to improve skin barrier function in premature infants of various ages [28, 100, 119, 130]. Although several studies have shown that emollient use can decrease the frequency of dermatitis or improve skin integrity in very premature newborns [16, 17, 26, 131], there is controversy about the use and effectiveness of emollients in high-risk neonates and infants.

In 2004, Conner et al. [132] reviewed the effectiveness of prophylactic application of topical ointments on nosocomial sepsis rates and other complications in premature births. In their meta-analysis, they included infants (n = 1304) with a gestational age <37 weeks who received an emollient within 96 hours of birth. They found that prophylactic application of topical ointments increased the risk of coagulase negative staphylococcal infection (typical relative risk (RR) 1.31, 95% confidence interval (CI) 1.02–1.70; typical risk difference 0.04, 95% CI 0.00–0.08), any bacterial infection (typical RR 1.19, 95% CI 0.97–1.46; typical risk difference 0.04, 95% CI 0.01–0.08) and nosocomial infection (typical RR 1.20, 95% CI 1.00–1.43; typical risk difference 0.05, 95% CI 0.00–0.09). One limitation of this paper was that it included only four studies [16, 17, 26, 131], which reflects the limited number of studies that had been published at that time. It remains to be seen if the conclusions of the meta-analysis would be applicable for other topicals or emollients.

In the studies that observed higher rates of infection [16, 26, 131], several possible explanations have been proffered as to the cause. Conner et al. [132] speculate that contamination may have occurred during application of the preservative-free petrolatum ointment or that its use may lead to conditions suitable to proliferation of bacterial organisms. Visscher [133] posits that skin occlusion on extremely low birth weight neonates may have delayed barrier maturation.

It might be further reasonably speculated that increased rates of nosocomial infections could have been due to use of a preservative-free petrolatum-based ointment that was opened and exposed to pathogenic organisms. Although it is unlikely that a preservative-free petrolatum-based product manufactured using good manufacturing practices would become contaminated, inadvertent addition of excessive moisture from a damp environment (i.e., bathroom) could lead to product contamination. Similar to petrolatum, mineral oil is anhydrous, yet there is evidence that it can become contaminated by improper handling [134]. Given these considerations, formulators should select an effective preservative system, even when formulating low water activity emollients.

Several studies have found very high concentrations ($>10^4$ colony-forming units (CFU)/g) of microbial contaminants in consumer products that are poorly preserved or preservative-free [135, 136]. Use of a poorly preserved, contaminated emollient led to an outbreak of *P. aeruginosa* in a neonatal intensive care unit [137]. Furthermore, use of preservative-free white petrolatum has been linked to systemic candidiasis [138].

Since publication of the meta-analysis in 2004 [132], other studies have also investigated emollient use in premature infants or neonates. In a randomized controlled trial, Darmstadt et al. evaluated the efficacy of a petrolatum-based emollient and a sunflower seed oil with high-linoleate content on neonatal mortality rates among hospitalized preterm infants (≤33 weeks gestation) at a large tertiary hospital in Bangladesh [28]. Massaging high-risk infants with the petrolatum-based emollient or the high-linoleate sunflower seed oil led to a reduction in nosocomial bloodstream infections (reduction rates for the respective treatments were 71% (95% CI: 17%–82%) and 41% (95% CI: 4%–63%) relative to no treatment). Moreover, massage with either product led to a significant decrease in neonatal mortality (32% and 26% for the petrolatum-based emollient and the high-linoleate sunflower seed oil, resp.) relative to the standard of care for premature neonates (no treatment). In contrast, use of the same petrolatum-based emollient on extremely premature infants (birth weight 501 to 1000 g) in the United States (and other countries) did not have an effect on neonatal mortality [131]. Darmstadt et al. [28] proposed that differences in trial design, study population, treatment (i.e., access to life-saving interventions), and environmental factors could help explain the differences in neonatal mortality rates observed between the two studies [28, 131].

LeFevre et al. [139] used a Monte Carlo simulation on the data generated by Darmstadt et al. [28] and found that use of the petrolatum-based emollient or sunflower seed oil with high-linoleate content was a cost-effective strategy to improve clinical outcomes. Relative to untreated premature infants, the petrolatum-based emollient and sunflower seed oil had respective costs of US$162 and US$61 per death averted and respective costs of US$5.74 and US$2.15 per year of life lost averted [139]. Although both products were cost-effective strategies to reduce neonatal mortality in a hospital setting, it is not known whether a reduction in mortality

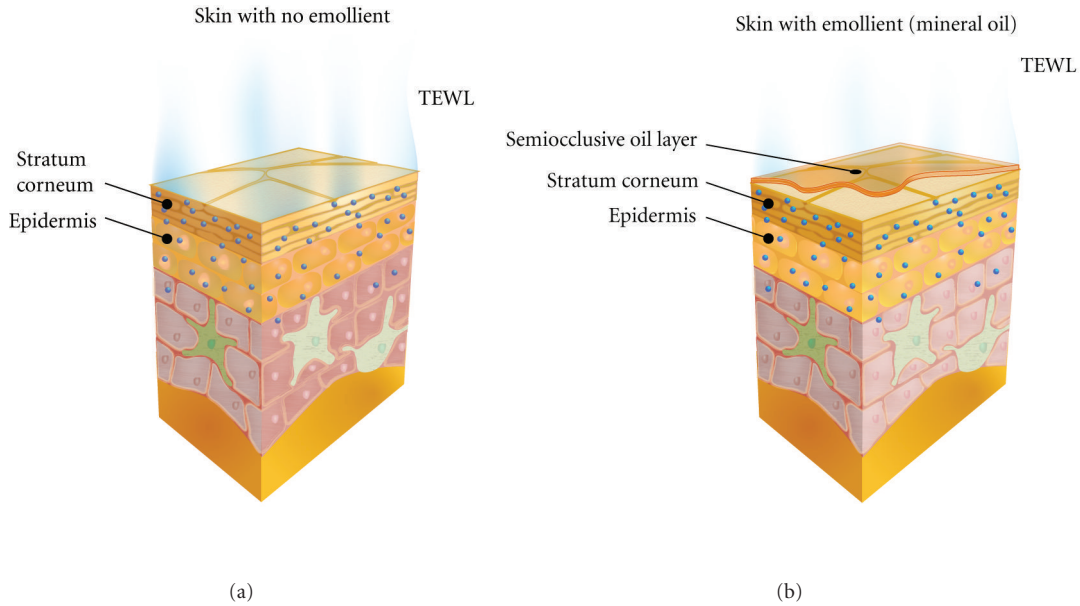


Figure 2: Stratum corneum (SC) moisture retention following application of mineral oil emollient. In (a), transepidermal water loss (TEWL) from the SC is shown under ambient temperature, humidity, and pressure. In (b), TEWL is reduced following emollient application. Oils in the emollient create a semiocclusive layer. The reduction in water evaporation leads to greater water retention in the SC.

also would be observed in a low-resource community setting outside the hospital, which is more typical of a normal birthing environment in Bangladesh and other developing countries [140].

Brandon et al. compared the effects of a composition containing water, polymers, and odorless, nonalcoholic evaporating agents or a petrolatum-based emollient on skin barrier integrity over the first two weeks of life in premature (<33 weeks gestation) infants [141]. A nine-point neonatal skin condition score (NSCS) was used to assess skin dryness, erythema, and skin breakdown. TEWL declined significantly over time; there were no differences in TEWL between treatment groups. The neonatal skin condition scores for infants receiving the petrolatum-based emollient were statistically better than those for infants receiving the aqueous polymeric composition, yet both scores were within normal range. Few infants in either treatment group had skin breakdown.

Although many studies have investigated the use of emollients in children or adults with eczema or AD, very few studies have investigated the use of emollients in healthy, premature, or full-term neonates. A summary of studies that have investigated the use of emollients in healthy, preterm or full-term neonates (0–4 weeks old) or infants (1–6 months old) is shown in Table 5.

9. Emollient Use May Lead to Long-Term Improvement in Skin Condition

To our knowledge, there are no randomized controlled trials that have investigated the long-term use of emollients on skin barrier function or overall skin condition. Nevertheless, prophylactic use of emollients that are appropriately formulated for use after birth may produce measurable benefits later in life. To test this hypothesis, some members of our team conducted a 6-week study on 51 infants (aged 3 to 12 months) that consisted of giving the infant participants twice-daily baths with a mild baby cleanser, followed by twice-daily application of one of three marketed lotions (unpublished data). Infants were randomized to receive one of three oil-in-water emollient formulations, each of which contained different types of surfactants and other ingredients. Skin barrier function was assessed indirectly by measuring TEWL and SC hydration (skin conductance) on the upper volar arm and lower dorsal arm. The effect of each lotion varied among the three groups. Results indicated that skin barrier function and SC hydration improved with daily use of only one of the emollients over a period of six weeks. These results suggest that emollient efficacy is related to the specific chemistry and ingredients of the formulation. Although no studies have investigated the long-term use of emollients on infants, long-term emollient use could improve the epidermal skin barrier and improve overall skin condition relative to untreated skin.

10. Summary

Although the need for and benefits of good skin hygiene are clear, recommendations for best cleansing and bathing practices remain debated during infancy and early childhood. As infant skin continues to change throughout the first years of life, its dynamic properties need to be addressed with appropriate skin care routines. Use of mild surfactant systems in cleansers can enable maintenance of skin barrier integrity; these cleansers may also be minimally disruptive to

Table 5: Emollient therapy in healthy, full-term, or premature neonates (0–4 weeks old) or infants (1–6 months old) on skin barrier function: literature review[†].

Study	Cohort	Treatment	Study duration	Endpoints/ measurements	Primary outcome(s)
		Healthy, full-term infants			
Garcia Bartels et al. [19]	64 healthy, full-term neonates (gestation ≥37 weeks aged ≤48 hours)	Body wash; body wash with emollient use after bathing; water alone, followed by emollient after bathing	8 weeks	TEWL, SC hydration, skin surface pH, sebum, NSCS, and bacterial colonization	Wash with emollient improved skin condition; in some cases, lower TEWL and higher SC hydration were observed; no adverse events
Garcia Bartels et al. [146]	44 healthy, full-term infants (≥37 weeks gestation) aged 3–6 months old	Lotion was applied after a swimming lesson once weekly or no treatment	5 weeks	TEWL, SC hydration, skin surface pH, and sebum	Reduced TEWL in both groups; site-specific differences in the treatment group were observed
Lowe et al. [147]	10 healthy, full-term neonates (0–4 weeks old; gestation ≥36 weeks) with a family history of allergic disease	Emollient consisting of ceramides, cholesterol, and free fatty acids at a 3 : 1 : 1 ratio and 2% petrolatum (applied once daily)	6 weeks	TEWL, SC hydration, skin surface pH, and sebum	Emollient use reduced TEWL
Simpson et al. [20]	22 full-term infants (≥37 weeks gestation) considered to be at high risk for developing atopic dermatitis	Oil-in-water, petrolatum-based emollient cream	Up to 2 years	TEWL and skin capacitance	Skin barrier measurements remained within normal range; only three participants developed atopic dermatitis
		Premature Infants			
Beeram et al. [18]	54 infants (≤27 weeks gestation)	Petrolatum-based emollient applied every 6 hours or no treatment	2 weeks	Fluids, electrolytes, bilirubin, and sepsis	The petrolatum-based emollient led to a significant reduction in the need for fluids; it also led to better urine output, more stable electrolytes, and lower bilirubin values
Brandon et al. [141]	69 infants (<33 weeks gestation)	Polymer, liquid-based film (applied twice) or petrolatum-based emollient (twice-daily application)	2 weeks	Total fluid intake, TEWL, and neonatal skin condition	Both treatments were well tolerated; both led to a decrease in TEWL

Table 5: Continued.

Healthy, full-term infants					
Study	Cohort	Treatment	Study duration	Endpoints/ measurements	Primary outcome(s)
Darmstadt et al. [28, 100, 148]	497 premature infants (≤72 hours old; gestation ≤33 weeks)	Sunflower seed oil or petrolatum-based emollient (3 times daily for 14 days, then twice daily until hospital discharge) or no treatment	≥14 days	Survival rate and rate of nosocomial infection	Sunflower seed oil and petrolatum-based emollient reduced mortality by 25–30%; sunflower seed oil reduced nosocomial infection rates by a statistically significant margin
Lane and Drost [16]	34 neonates (29–36 weeks gestation)	Twice-daily application of a water-in-oil emollient; no treatment	16 days	TEWL, NSCS, and quantitative microbiology	Emollient decreased dermatitis of the hands (days 2–11), feet (days 2–16), and abdomen (days 7–11); no changes in microbial flora
Nopper et al. [17]	60 neonates (<33 weeks gestation)	Petrolatum-based emollient (applied twice daily); no treatment	2 weeks	Temperature, TEWL, fluid intake, weight analysis, skin condition, microbiology, and blood/urine analysis for cerebrospinal fluid cultures	Emollient use led to statistically significant decrease in TEWL; significant improvement in infant skin condition on days 7 and 14; less colonization of the axilla on days 2, 3, 4, and 14; statistically significant reduction of positive findings in blood and cerebrospinal fluid

TEWL: transepidermal water loss, SC: stratum corneum, NSCS: neonatal skin condition score.

† Studies published between 1 January 1960 and 1 June 2012 were identified by searching peer-reviewed literature indexed in PubMed. The titles and abstracts of indexed publications listed in PubMed were searched using the following words: "newborn OR neonat* OR infant*" (group 1), "emollient OR lotion OR cream OR topical" (group 2), and "skin" (group 3). These three groupings were connected using the Boolean operators "AND". The titles and abstracts were also searched using the word "vitro" and the Boolean operator "NOT". Finally, only the titles of PubMed-indexed publications were searched using a fifth group of words and were connected to the search string using the Boolean operator "NOT": "injury OR wound OR burn OR damage OR eczema OR dermatitis OR psoriasis OR disease* OR pain OR hemangioma* OR syndrome OR sepsis OR antisepsis." Review articles, publications that were printed in a language other than English were also excluded. Although our search generated 220 publications, only 9 (summarized in Table 5) met the search criteria described above.

skin surface pH and have minimal potential to stimulate the production of IL-1α and other proinflammatory molecules. Emollients can provide benefits to premature infants or infants with compromised skin barrier function. Few studies to date have demonstrated the benefits of emollient use on healthy, full-term infants. In addition to providing short-term benefits such as maintaining or improving skin barrier function, it is hypothesized that long-term use of emollients may produce lasting benefits to skin barrier function and overall skin condition. In the future, harmonization of neonatal and infant skin care guidelines—including use of properly formulated cleansers and emollients—is warranted.

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Review Article

Barrier-Restoring Therapies in Atopic Dermatitis: Current Approaches and Future Perspectives

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Atopic dermatitis is a multifactorial, chronic relapsing, inflammatory disease, characterized by xerosis, eczematous lesions, and pruritus. The latter usually leads to an "itch-scratch" cycle that may compromise the epidermal barrier. Skin barrier abnormalities in atopic dermatitis may result from mutations in the gene encoding for filaggrin, which plays an important role in the formation of cornified cytosol. Barrier abnormalities render the skin more permeable to irritants, allergens, and microorganisms. Treatment of atopic dermatitis must be directed to control the itching, suppress the inflammation, and restore the skin barrier. Emollients, both creams and ointments, improve the barrier function of stratum corneum by providing it with water and lipids. Studies on atopic dermatitis and barrier repair treatment show that adequate lipid replacement therapy reduces the inflammation and restores epidermal function. Efforts directed to develop immunomodulators that interfere with cytokine-induced skin barrier dysfunction, provide a promising strategy for treatment of atopic dermatitis. Moreover, an impressive proliferation of more than 80 clinical studies focusing on topical treatments in atopic dermatitis led to growing expectations for better therapies.

1. Introduction

Atopic dermatitis (AD) is a multifactorial, chronic relapsing, inflammatory disease, characterized by xerosis, eczematous lesions, and pruritus. AD usually begins in infancy or early childhood, about 90% of cases start in first five years of life [1]. The disease has significant morbidity and it adversely affects the quality-of-life of the child and his family in both social and emotional aspects [2]. The most dominant physical symptoms experienced by affected children are sleep disturbances and pruritus/scratching. It is important to notice that pruritus usually leads to an "itch-scratch" cycle that may compromise the epidermal barrier, resulting in transepidermal water loss (TEWL), xerosis, or secondary infection, especially with *Staphylococcus aureus* [3].

There are many theories regarding the pathogenesis of AD. The pathogenesis of AD involves skin barrier dysfunction, environmental and infectious agents, and immune abnormalities. In 1999 Elias and Taieb proposed that failure of the skin barrier may be the primary factor in the development of AD [4, 5]. Subsequent studies demonstrated epidermal barrier abnormalities in AD dysfunction that correlate with the disease severity. TEWL is greater in areas with clinical disease. Even clinically uninvolved sites of skin show abnormal skin barrier function and greater TEWL compared to healthy individuals [6–9]. However, it must be noted that TEWL is only relevant when regarding the penetration of molecules less than 500 daltons, such as water, irritants, and haptens.

2. Skin Barrier Dysfunction in AD

Skin is a barrier that protects the body from the outside world. Defense functions are localized in the stratum corneum (SC), which typically includes about 9–15 corneocyte cell layers that consist of packing of keratin filaments and filaggrin of corneodesmosomes [10]. Elias depicted the SC as a brick wall, with the corneocytes analogous to bricks

and lipid lamellae acting as mortar [11]. These lipids are composed of approximately 50% ceramide, 25% cholesterol, and some long-chain free fatty acid. Lipid lamellae play a crucial role in the barrier function [12]. Sphingosine, ceramide metabolite, exhibits potent *in vitro* antimicrobial activity [13, 14], and is reduced in AD patient's skin [15–17], predisposing to pathogen colonization.

The pathogenesis of AD is not completely understood. Nevertheless, congenital and acquired defects in each part of the SC structure are associated with pathogenesis of AD. Furthermore, skin barrier abnormalities in AD may result from mutations in the gene encoding for filaggrin, which plays an important role in the formation of cornified cytosol. The products of filaggrin breakdown are important for hydration and acidification of the SC, which are both impaired in AD [9]. Abnormal maturation and secretion of lamellar body in AD results in reduction of lipids and ceramides content and increased cholesterol levels in AD as compared to nonatopic subjects [18, 19]. These barrier abnormalities render the skin more permeable to irritants, allergens, and microorganisms [20]. Conversely, pathogen colonization further impairs the abnormality of the permeability barrier [21]. *Staphylococcus aureus* colonization on the skin may be found in up-to 90% of AD patients [22]. Moreover, *Staphylococcus aureus* may produce ceramidase, which additionally undermines the barrier function [15].

Severe pruritus is the most disturbing symptom of AD. The scratching severely compromises the skin barrier, enhancing inflammatory reacting that subsequently results in the vicious itch-scratch cycle.

3. Therapeutic Aspects

Treatment of AD must be directed to control the itching, suppress the inflammation, and restore the skin barrier. There are various strategies and medical efforts that can help us achieve these goals. In addition, it is extremely important to educate the parents, emphasizing the chronic nature of the disease, the importance of continued maintenance therapy, and the need for prompt suppression of flare-ups. Patients should also be provided with written instructions regarding appropriate medical care in order to reinforce learning [20, 23–25].

4. Emollients

Emollients are widely used in conservative local treatment of AD. There are few objective studies based on clinical evidence demonstrating their efficiency [26–28]. Emollients, both creams and ointments, improve the barrier function of SC by providing it with water and lipids. Nevertheless, the exact mechanism by which this process works is still unknown [29]. Ghadially et al. showed that petrolatum lipids may replace SC bilayers and accelerate barrier recovery in human skin [30].

A case-control study by Macharia et al. demonstrated that the use of topical petrolatum in infants may protect against AD development [31]. Additionally, several studies have demonstrated a reduction in incidence of "dermatitis" or improved skin condition in premature neonates treated with emollients [32–36]. One recent pilot study on primary prevention of AD by emollients therapy starting in infancy has shown some promising results [37].

Emollients have been shown to enhance the effects of topical corticosteroids (TCS) therapy in children with AD in a randomized comparison study [38] and lead to reduced usage of TCS [39].

Though usually effective in a short range, most of emollient moisturizers contain nonphysiologic lipids, such as petrolatum, lanolin mineral oil, and silicone. These substances may impede, rather than correct, the underlying biochemical response of the skin barrier's flawed structure in AD [40]. A 1996 study proclaimed that application of petrolatum in damaged skin results in a partially restored barrier function in acute injury models, but this benefit is fairly short [41].

5. Barrier Repair Therapy

Recent advances in the understanding of pathophysiology of the epidermal barrier and its critical role in the pathogenesis of AD led to increased interest in barrier repair therapies. But what does "barrier repair therapy" mean? Ideally, the emollients should normalize the epidermal barrier function by reducing TEWL and improving SC hydration [42].

Properties of physiologic lipid-based products are different from nonphysiologic agents. Lipids are taken up by keratinocytes, packaged into the lamellar bodies, and then resecreted to form lamellar bilayers. Equimolar ratio of 1 : 1 : 1 of ceramide, cholesterol, and FFA induces barrier recovery in acute injure models [41].

Studies on AD and barrier repair treatment, either in animal models or in humans, showed that adequate lipid replacement therapy reduces the inflammation and restores epidermal function comparable to topical fluticasone cream [23, 43–47].

Urea, a well-known humectant used in various topical emollients, has been very recently shown to normalize barrier function and antimicrobial peptide (LL-37 and β-defensin-2) expression in a murine model of AD [48].

There are several nonprescription products that proclaim barrier repair properties [42, 49]. Chinese herbal mixtures (CHM) had been often claimed beneficial in treatment of AD. A recent study had demonstrated that topical CHM accelerated barrier recovery following acute barrier disruption by increased epidermal lipid content and mRNA expression of fatty acid and ceramide synthetic enzymes, mRNA levels for the epidermal glucosylceramide transport protein, and mRNA expression of antimicrobial peptides both *in vivo* and *in vitro* [50].

Skin care products that contain high lipid substances are frequently applied for the care of dry skin and inflammatory skin conditions [51]. Oils, both pure and integrated, are commonly applied for skin care. The oils assist the native lipids of the SC to provide a better barrier function and consequently help moisturizing the skin [52]. The decreased

TEWL values specify that the use of the oils leads to a semiocclusion of the skin surface. Similar results were attained for both mineral and vegetable oils [53]. Paraffin, jojoba, and almond oils were shown to penetrate equally into layers of SC [52], while coconut oil, used as a moisturizer, was found to be as effective and safe as paraffin oil [54]. Proksch et al. found that bathing in magnesium-rich (5%) Dead Sea salt solution improves skin barrier function, augments skin hydration, and decreases inflammation in atopic dry skin [55]. A recent study revealed that treatment of atopic dermatitis by a Dead Sea mineral enriched body cream, improves physiologic and clinical severity scores of the disease, and may serve as a maintenance therapy for AD patients [56].

6. Topical Corticosteroids and Immunomodulators

The inflammatory response of AD is mediated by lymphocytes, mast cells, eosinophil, dendritic cells, and monocytes/macrophages [23, 57]. TCS may inhibit many aspects of inflammation in AD, thus it is still being used as a standard therapy, especially for acute flare-ups. The effects of TCS are facilitated by cytoplasmic glucocorticoids receptors in various types of cells, such as keratinocytes and fibroblasts, as well as in immune cells. When activation occurs, the receptor binds to glucocorticoids response elements in the promoter region of target genes. Consequently, the receptor inhibits the transactivating function of transcription factors, which results in reduced expression of proinflammatory genes [58].

Recently, nerve growth factor (NGF), substance P, and eosinophil count, were all found elevated in the plasma of AD patients. These are considered possible mechanisms of itch in AD [59, 60]. The treatment of AD with TCS results in NGF reduction and in relief of pruritus [59].

Tacrolimus and Pimecrolimus are topical calcineurin inhibitors (TCI). These steroidal-free alternatives in the treatment of the inflammatory response in AD constitute the second line therapy in AD [61]. The action mechanism of TCI is limited to immune cells only, thus skin atrophy or telangiectasia are not observed, contrary to TCS [62]. Consequently, we may use TCI in sensitive affected area, such as face, eyes, neck, and genitalia, without concern of systemic absorption or skin atrophy [3, 24].

Although effectively reducing inflammation by suppressing immune reaction in AD, TCS, and TCI do not correct the primary skin barrier abnormality that principal the pathogenesis of the disease [44]. Recent studies have shown that the use of TCI or TCS may compromise skin barrier function in normal skin [25, 63, 64].

One recent study demonstrates that betamethasone and pimecrolimus improve clinical and biophysical parameters of barrier function, but differ in their effects on the epidermal barrier.

Betamethasone employed a more effective antiproliferative and anti-inflammatory result, leading to a faster reduction in TEWL, but causing epidermal thinning.

Pimecrolimus indicating renovation of the epidermal barrier by inducing regular lipid layer formation and lamellar body extrusion.

7. Treatment of Skin Infections

Following the compromising of antimicrobial barrier in AD, there is colonization of *Staphylococcus aureus* in AD patients, even in nonlesional skin [22]. Furthermore, superantigen produced by *Staphylococcus aureus* strains colonize more commonly in steroid-resistant patients [65].

Recent findings proclaim that barrier skin permeability and antimicrobial function share common structural and biochemical features, and both are coregulated and interdependent [16, 66]. As a consequence, secondary infections may be triggered by failure of the permeability barrier. Contrariwise, pathogen colonization or infection may exacerbate the permeability barrier abnormality [21].

Presence of secondary bacterial infection in AD lesions may require a short-term topical or systemic antibiotic therapy. Conversely, some researchers claim that barrier repair therapy may reduce secondary colonization of pathogenic *Staphylococcus aureus* by targeted correction of lipid biochemical abnormalities [21].

8. Future Perspectives

Inflammation itself may be able to induce a functional dysfunction and induce or aggravate AD [67]. Consequently, efforts directed to develop immunomodulators that interfere with cytokine-induced skin barrier dysfunction, provide a promising "kill two birds with one stone" strategy for treatment of AD.

Potential therapeutic use of phosphodiesterase-4 inhibitors in a variety of inflammatory disease, including AD, has been known for years. However so far, an appropriate molecule devoid of gastrointestinal adverse effects has not been approved. Currently, there are several studies exploring various topically administered PDE4 inhibitors that suppress the release of TNF-α, IL-12, IL-23, and other cytokines [68].

Bissonnette et al. recently reported beneficial clinical effects in adults with AD [69]. This compound is a novel small molecule, derived from metabolites of a unique group of bacterial symbionts (organisms in a symbiotic relationship; the symbiont is the smaller of these and is always a beneficiary in the relationship, while the larger organism is the host and may or may not derive a benefit) of entomopathogenic nematode that has been shown to inhibit inflammatory cytokine secretion by activated T cells, including tumor necrosis factor-α and interferon-χ *in vitro*.

Fucoidan, a sulphated polysaccharide extracted from brown seaweed having a wide range of pharmacological, has been very recently shown to significantly inhibit mRNA expression of TARC, MDC, and RANTES chemokines and improve clinical features of AD in mice model comparable to topical dexamethazone 0.1% [70].

Finally, an impressive proliferation of more than 80 clinical studies focusing on topical treatments in atopic

dermatitis, many of these involving new or novel active ingredients (http://www.clinicaltrials.gov), led to growing expectations for better therapies. These include DPK-060 by DermaGen-AB, BPR277 by Novartis, GW842470X by GlaxoSmithKline, KP-413 by Kaken Pharmaceutical, TS-022 by Taisho Pharmaceutical R&D Inc., LAS41002 by Almirall, S.A., CD2027 by Galderma, BRT-FC-83C by Biomed Research & Technologies, Inc., E6005 by Eisai Co., Ltd., PH-10 by Provectus Pharmaceuticals, V0034CR01B by Pierre Fabre, Mapracorat and ZK245186 by Intendis GmbH, SRD174 by Serentis Ltd., and 0416 and 0417 by Fougera Pharmaceuticals Inc. Unfortunately, for most of these substances, nature and properties are still kept confidential.

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Clinical Study

Methods to Assess the Protective Efficacy of Emollients against Climatic and Chemical Aggressors

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Exposure to harsh environmental conditions, such as cold and dry climate and chemicals can have an abrasive effect on skin. Skin care products containing ingredients that avert these noxious effects by reinforcement of the barrier function can be tested using *in vivo* models. The objective is to use in vivo models to assess the efficacy of emollients in protecting skin against climatic and chemical insults. A first model used a stream of cooled air to mimic cold wind. A second used sodium lauryl sulfate (SLS) under patch as chemical aggressor. In the model with simulated wind exposure, the untreated exposed area had a significant decrease in hydration. In contrast, application of an emollient caused a significant increase in hydration that was maintained after wind exposure. In the second model with SLS exposure, application of a barrier cream before SLS patch significantly reduced the dehydrating effect of SLS with a significant difference in variation between both areas. Application of the cream reduced TEWL, indicative of a physical reinforcement of the skin barrier. The two presented test methods, done under standardized conditions, can be used for evaluation of protective effect of emollient, by reinforcing the barrier function against experimentally induced skin dehydration.

1. Introduction

The skin is the outermost barrier that protects the human body from physical, chemical, and microbial insults and prevents the uncontrolled loss of water among other substances. The epidermal barrier function of the skin resides in the stratum corneum (SC) and is linked to the protein-enriched corneocyte layers and the intercellular membrane lipids mostly composed of ceramides, cholesterol, and free fatty acids [1, 2]. Corneocytes are rapidly and continually replaced to maintain skin integrity and to repair damage.

Exposure to external factors can damage this protective function. Much studied is the cumulative damage of sun exposure as it accounts to a great extent for the permanent changes in skin physiology and morphology over time [3]. Other environmental aggressors that significantly impact on skin properties and may cause acute or chronic damage of the skin barrier include climatic conditions (e.g., wind, low temperatures, low humidity) and chemicals in frequent contact with the skin (e.g., soaps and detergents) [4, 5]. Exposure to such aggressors can reduce the hydration status of the epidermis and compromise the skin barrier function. Skin dryness reflects an abnormal desquamation process, where corneocytes are shed as visible scales, causing the cosmetically unattractive rough texture associated with dry skin and provoking discomfort and itchiness. Compromised skin barrier shows visible irritation (redness) or even inflammation. Moreover, dry and barrier impaired skin favors penetration of microorganisms, allergens, and other irritants. Dryness and impaired barrier function are also symptoms of inflammatory skin diseases such as atopic dermatitis (AD) [6], the etiology of which is determined by a range of factors, including genetic, immunological, environmental factors (such as cold climate), and chemical and mechanical irritants [7, 8].

There is thus a need to protect both healthy and sensitive skin from environmental and chemical aggressors and to preserve or restore its integrity. Cosmetic products containing emollients (also referred to as moisturizers) are specifically formulated to soften and soothe dry skin and to reduce itching sensation and irritation signs. Emollients are delivered in the form of creams, ointments, gels, pastes, or

liquid preparations [9]. They increase the moisture content of the SC by providing an occlusive oily film on the skin surface to reduce transepidermal water loss (TEWL), which is the normal movement of water through the SC, and by serving as humectants, that is, binding water and thus increasing the water holding capacity in the SC. Emollients thus prevent and alleviate skin dryness by increasing skin hydration and reducing TEWL and promote recovery of the damaged skin barrier, including that observed in atopic skin. Formulations contain a combination of ingredients, including emollient lipids (e.g., mineral oils, waxes, fatty acids, and glycerides), humectants (e.g., alpha-hydroxy acids, urea, and glycerin), emulsifiers, and antipruritics (e.g., glycine), as well as inactive components.

A large number of emollient formulations exist, more or less effective in their proposed functions [10, 11]. Standardized, controlled testing conditions are thus crucial in the development of adequately formulated products. The goal of this study was to implement models that allow assessing the efficacy of emollients in protecting skin against climatic and chemical insults under standardized conditions *in vivo*. We designed two models, one in which the effect of cold and dry wind was mimicked by exposure to a continuous stream of cooled air and the second, with sodium lauryl sulfate (SLS) under patch used as chemical aggressor.

2. Materials and Methods

For the simulation of cold and dry wind, compressed air was led through a temperature controlled rubber tube (stabilized at $13 \pm 2^\circ$) and the airflow maintained constant was blown onto the skin for 15 minutes. The hydration level of the SC was assessed by determination of capacitance using corneometry (Corneometer, Courage + Khazaka electronic GmbH) and results were expressed in arbitrary units [12]).

To simulate the exposure to chemical aggressors, a patch consisting of 1% SLS solution was applied to the skin for 3 hours. The hydration level of the SC was assessed by determination of capacitance using corneometry (Corneometer, Courage + Khazaka electronic GmbH) and results were expressed in arbitrary units [12]). Moreover, the transepidermal water loss (TEWL) was assessed using a Tewameter (Courage + Khazaka electronic GmbH) and results were reported in $g/m^2/h$ [13].

Two studies were conducted to assess the potential of emollient containing skin care products to protect skin from exposure to cold, dry air and to SLS under controlled laboratory conditions. Subjects were acclimated to testing conditions for 15 minutes at a temperature of $20 \pm 2^\circ C$ and a relative humidity of $50 \pm 5\%$ before measurements. All subjects gave their written informed consent prior to study enrolment. The studies were conducted in accordance with the Declaration of Helsinki [14]. All adverse events, whether considered product related or not, were reported during these studies.

2.1. Simulated Exposure to Cold and Dry Wind. Twelve healthy Caucasian women of normal skin type and aged between 53 and 70 years participated in this study. The test product was a lotion containing glycerin and glycine soja as emollients. A fixed quantity ($2\,\mu l/cm^2$) of the test product was applied to the inner forearm on two different test areas of $16\,cm^2$ size. Three test areas were assessed in each subject (1) treated area (with test product), without wind exposure; (2) untreated area, with wind exposure; (3) treated area, with wind exposure. Measurements were taken at the following time points (1) treated area, without wind exposure: before test product application (T_0), 1 hour after application ($T_{\text{after lotion}}$), and 5 minutes after a 15 minutes resting period ($T_{\text{after resting}}$, replacing wind exposure); (2) untreated area, with wind exposure: before wind exposure (T_0) and 5 minutes after 15 minutes wind exposure ($T_{\text{after wind}}$); (3) treated area, with wind exposure: before test product application (T_0), 1 hour after application ($T_{\text{after lotion}}$), and 5 minutes after 15 minutes wind exposure ($T_{\text{after wind}}$). Three consecutive measurements were taken at each test area and at each time point.

Statistical analysis included the calculation of mean values and standard deviation (SD) at all time points, as well as percentage of variation (%) relative to T_0 using Microsoft Excel 2000. The results were compared with the paired bilateral Student's t-test and the level of statistical significance was set at $P \leq 0.05$. Variance analysis was performed to compare the variation between $T_{\text{after wind/lotion}}$ to T_0 between the three assessed areas using the Fisher's least significant difference (LSD) test (StatGraphics Plus 5.1 software).

2.2. Exposure to a Chemical Aggressor (Sodium Lauryl Sulfate (SLS)). Fourteen healthy Caucasian women of normal skin type and aged between 25 to 68 years participated in this study. The test product was a barrier cream (nappy cream) containing glycerin, sorbitol, and butylene glycol as emollients associated to zinc oxide. A fixed quantity ($2\,\mu l/cm^2$) of the test product was applied to the inner forearm at two different test areas of $16\,cm^2$ size. SLS application consisted of a 1% SLS solution applied to the skin under a semiocclusive patch for 3 hours. Three test areas were assessed (1) treated area (with test product), without SLS exposure; (2) untreated skin area, with SLS exposure; (3) treated area, with SLS exposure. At the test area without SLS exposure an empty patch was applied. Where applicable, the test product was applied before the SLS patch. Three repetitive measurements with Corneometer were taken at each test areas and at each time points. Two consecutive measurements with Tewameter were carried out before (T_0) and one hour after product application ($T_{1\,h}$) on the untreated control area (without product) and the treated area.

Mean values and SD at all time points and variation (%) at $T_{30\,\text{min}}$ relative to the untreated area and T_0 were calculated. Data were compared using the paired Student's t-test for normal distribution and the Wilcoxon signed rank test for not normal distribution. Statistical significance was defined as $P \leq 0.05$. Matlab was used for statistical analysis. Variance analysis was performed to compare the variation between $T_{30\,\text{min}}$ and T_0 between the different test areas using ANOVA.

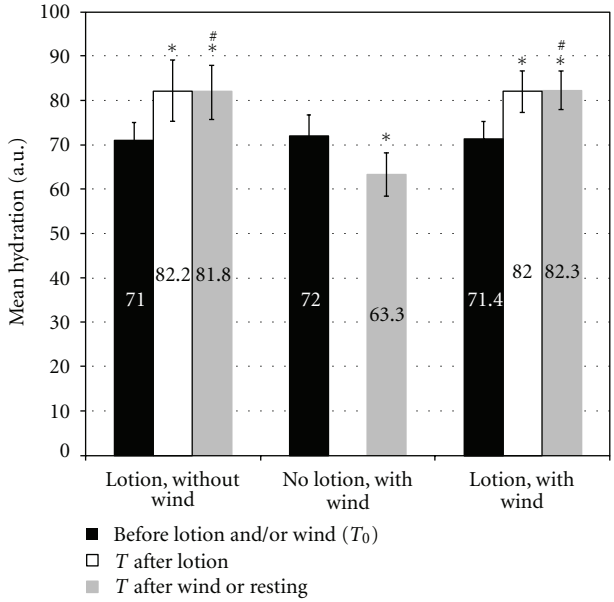

Figure 1: Hydration after wind exposure with and without an emollient lotion. *indicates a statistically significant difference compared to T_0 ($P < 0.001$). #indicates a statistically significant difference in the variation between $T_{\text{after wind/resting}}$ and T_0 between the two lotion-treated test areas (with and without wind) and the untreated area (no lotion, with wind) ($P < 0.05$, variance analysis).

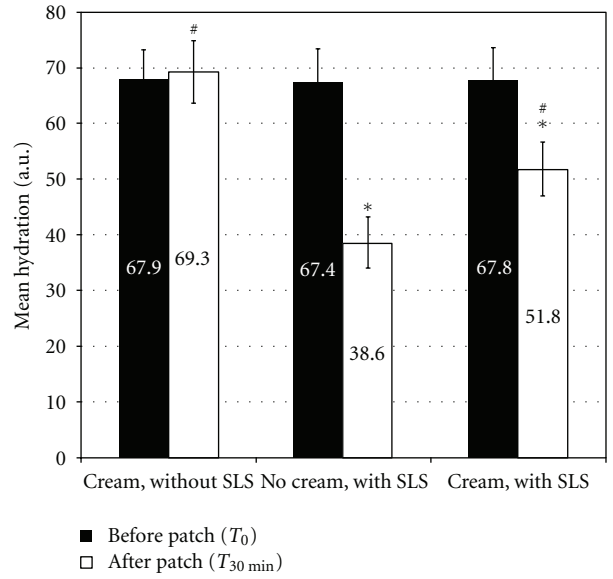

Figure 2: Hydration after SLS exposure with and without an emollient cream. *indicates a statistically significant difference compared to before cream application ($P < 0.001$). #indicates a statistically significant difference in the variation between $T_{30\ \text{min}}$ and T_0 between the two cream-treated test areas (with and without SLS) and the untreated test area (no cream, with SLS) ($P < 0.05$, variance analysis).

3. Results

3.1. Exposure to Cold and Dry Wind. The results of the twelve subjects participating in this study were analyzed. The results of the hydration assessment at the three different test areas are shown in Figure 1. At the lotion treated area, where wind exposure was substituted by a resting period, there was a significant increase in hydration at $T_{\text{after lotion}}$ with a variation of 15.8% ($P < 0.001$) compared to T_0. At $T_{\text{after resting}}$, hydration remained at a similar level compared to $T_{\text{after lotion}}$ (variation 15.1% compared to T_0, $P < 0.001$). At the untreated area, a significant decrease in skin hydration was noted after wind exposure at $T_{\text{after wind}}$ with a variation of -12.1% ($P < 0.001$) compared to T_0. In contrast, hydration measured at the treated test area exposed to wind was significantly increased at $T_{\text{after lotion}}$ and remained at a similar level at $T_{\text{after wind}}$. The variations compared to T_0 were 14.8% and 15.2% ($P < 0.001$ for both time points), respectively, at these two time points and thus similar to the changes observed at the treated area, without wind. The variance analysis showed that the variation between $T_{\text{after wind/rest}}$ and T_0 was significantly different at the treated, with wind area as well as at the treated, without wind area compared to the untreated, with wind area ($P < 0.05$).

3.2. Exposure to SLS under Patch. The results of the 14 subjects participating in this study were analyzed. Hydration assessment showed the following results for the three test areas (Figure 2): test product application without subsequent SLS exposure led to a nonsignificant increase in hydration with a variation of 2.1% at $T_{30\ \text{min}}$ compared to T_0. When the test area was exposed to SLS without previous test product application, there was a significant decrease in skin hydration at $T_{30\ \text{min}}$ with a variation of -41.7% compared to T_0 ($P < 0.001$). Application of the test product before SLS exposure resulted in a significant decrease in hydration with a variation of -23.6% compared to T_0 ($P < 0.001$). According to the variance analysis, the change between $T_{30\ \text{min}}$ and T_0 was significantly smaller at the cream treated area with SLS exposure compared to the area not treated before SLS exposure ($P < 0.05$).

The TEWL measurements showed a significant decrease at $T_{1\,\text{h}}$ compared to T_0 when emollient was applied (variation -19.6%, $P = 0.002$). Moreover, the statistical comparison between areas showed a significant difference ($P = 0.002$) (Figure 3).

There were no adverse events reported in either of the two studies.

4. Discussion

Emollient use in the form of bath additives, creams, lotions, or ointments is recommended to relief dry and itchy skin conditions and as adjuvant therapy in the management of skin barrier disorders such as AD [6, 15–17]. It was observed that the beneficial effect of emollients for skin barrier restoration allows for a significant reduction of the use of high-potency topical corticosteroid consumption to diminish disease severity in AD afflicted infants [18].

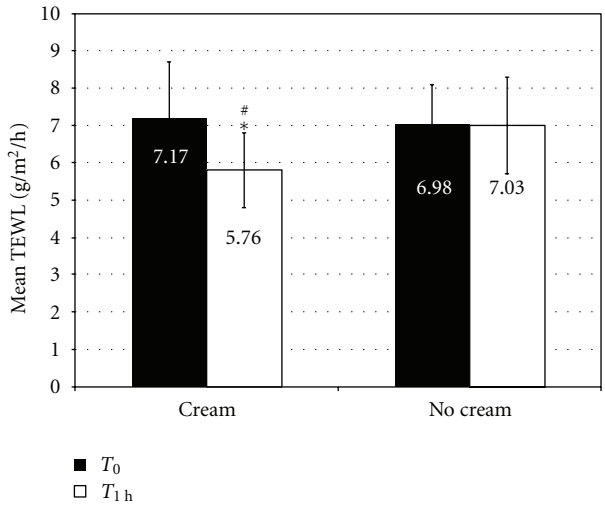

Figure 3: TEWL with and without emollient cream.*indicates a statistically significant difference between $T_{1\,h}$ and T_0 ($P = 0.002$). #indicates a statistically significant difference in the variation between $T_{1\,h}$ and T_0 between the two areas.

The surfactant SLS is a common ingredient in personal care products and is used as a model substance to experimentally elicit skin barrier damage. Depending on the concentration and exposure conditions, SLS can provoke skin dryness, roughness, tightness, erythema, and inflammation. This is related to the potential of surfactants to denature proteins in the SC, solubilize intercellular skin lipids, increase the skin pH, and increase TEWL [19]. Repeated exposure to surfactants, as is the case in frequent hand washing, causes in many individuals irritant contact dermatitis, characterized by inflammation and pruritic lesions of the skin.

Rough climatic conditions also impact on skin integrity, as seen in cold and dry winter months. Exposure of skin to a dry environment reduces the SC water content and induces changes in the skin surface texture [20]. In addition, wind removes water vapor from the skin causing redness and chafing [21]. These changes are usually reversible and skin hydration tends to improve during more humid summer months [22].

Some recent controlled studies have demonstrated the beneficial effect of emollients on skin dryness and irritation associated with exposure to dry and cold climatic conditions and to the irritation potential of repeated hand washing. For example, regular application of an emollient containing body-wash reduced the signs of xerosis associated with dry winter skin compared to a regular bar cleanser [23]. Likewise, regular application of some (but not all) tested moisturizing creams reduced the risk of skin irritation linked to repeated hand washing with soap in healthy skin [10]. In another study, repeated hand immersion into an SLS solution caused barrier dysfunction with increased TEWL and reduced skin hydration, which was prevented when the skin was preventively treated with a moisturizer [24].

The environmental and chemical insults modeled in our studies were rather mild in nature and did not induce skin irritation beyond skin dehydration. In an approach similar to ours, Cheng et al. evaluated the effect of two cosmetic products on skin water content and TEWL under simulated wind exposure [25]. However, the conditions chosen in their study were not harsh enough to induce a significant change in these parameters compared to unexposed skin.

Our model with experimentally induced skin dehydration with cold and dry wind permitted us to distinguish the effect of the emollient containing test product from no treatment. At the area treated with lotion and exposed to wind there was no significant decrease in hydration in contrast to the unprotected area, demonstrating a protective effect of the lotion. Moreover, many tests using this model have been performed on different emollient products since several years. In each test, we observed that, without product, the dehydration is at the same level and the application of product allows protecting the skin from the drying out. However, TEWL measurements were not performed. Indeed, when this model was developed, it has been demonstrated that hydration measurements seemed to be the most relevant measurements for this model, in our experimental conditions. In a long-term study, Black et al. have showed that the TEWL only significantly changed in summer. Decreases in lipids (ceramides and cholesterol) and in hydration (electrical conductance) of the *Stratum corneum* were the main changes observed in winter situation [22]. Many tests using this model have been performed on different emollient products since several years. In each test, we observed that, without product, the dehydration is at the same level and the application of product allows protecting the skin from the drying out.

In the second model, skin dehydration was induced by subirritant exposure to 1% SLS under patch. We found that skin hydration was significantly reduced when no emollient containing test product was applied prior to SLS exposure. In the presence of the cream the loss of skin hydration was significantly smaller, indicating a protective effect of the cream. Besides, the skin barrier function was significantly reinforced in unexposed skin in the presence of the cream, as indicated by reduced TEWL.

Emollients are beneficial for the reinforcement of both normal and sensitive skin. Irritant contact dermatitis is of particular relevance in infants, as they are prone to develop irritant contact dermatitis in the diapered area due to prolonged exposure to urine, feces, high skin pH, and chemical irritants from the diaper. Alkaline conditions activate intestinal enzymes, which together with excessive hydration and friction leads to skin barrier breakdown and irritation [26]. The application of a water repellent emollient is recommended in the management of diaper dermatitis [27].

5. Conclusions

The two devised methods mimicking cold and dry wind and surfactants insults, done under standardized conditions, can be used for evaluation of protective effect of emollient. The protection brought by the emollients can then be assimilated to a reinforcement of the barrier function.

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Review Article

Cleansing Formulations That Respect Skin Barrier Integrity

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Surfactants in skin cleansers interact with the skin in several manners. In addition to the desired benefit of providing skin hygiene, surfactants also extract skin components during cleansing and remain in the stratum corneum (SC) after rinsing. These side effects disrupt SC structure and degrade its barrier properties. Recent applications of vibrational spectroscopy and two-photon microscopy in skin research have provided molecular-level information to facilitate our understanding of the interaction between skin and surfactant. In the arena of commercial skin cleansers, technologies have been developed to produce cleansers that both cleanse and respect skin barrier. The main approach is to minimize surfactant interaction with skin through altering its solution properties. Recently, hydrophobically modified polymers (HMPs) have been introduced to create skin compatible cleansing systems. At the presence of HMP, surfactants assemble into larger, more stable structures. These structures are less likely to penetrate the skin, thereby resulting in less aggressive cleansers and the integrity of the skin barrier is maintained. In this paper, we reviewed our recent findings on surfactant and SC interactions at molecular level and provided an overview of the HM technology for developing cleansers that respect skin barrier.

1. Introduction and History

The general purpose for skin cleansing is to reduce sebum and exogenous contaminants and to control odors and the skin microbiome. The surfactants in cleansers solubilize hydrophobic materials into the aqueous phase and enable their subsequent removal from the skin surface. The amphiphilic structure of surfactants, consisting of both a hydrophilic polar head group and a nonpolar lipophilic tail, drives surfactants to oil/water interfaces to facilitate cleansing.

Figure 1 depicts how the surfactants interact with the stratum corneum (SC) during cleansing. Cleansers are usually formulated with surfactant at concentration much higher than its critical micelle concentration (CMC). At such concentration, the majority of the surfactant molecules self-assemble into micelles [1]. It is desirable for a cleanser to remove unwanted exogenous lipophilic materials; however, the interaction between surfactants and skin is more complicated. Solubilization of skin components such as lipids, enzymes, and natural moisturizing factors weakens the skin barrier function. Additionally surfactants can also remain in the SC even after rinsing and lead to chronic surfactant exposure [2]. SC structure is composed of anucleated corneocytes embedded in an intercellular lipid matrix. These lipids form a highly ordered lamellar structure [3]. As will be discussed later, surfactant molecules that remain in the SC likely insert into the SC lipid lamellae, which is schematically graphed in the inset of Figure 1. The inserted surfactants disrupt SC lipid structural order and cause the continual degradation of the skin barrier [4, 5]. As the result of the barrier impairment, inflammation and oxidative stress occur [6, 7], which can then be perceived by patients as redness, dryness, discomfort, and irritation of the skin.

Humans have been cleansing their skin with surfactants for millennia. Soap was discovered multiple times throughout human history. Figure 2 shows the technical progression of skin cleansing over time. Generally, the progress in cleansing technology has been marked by the creation of cleansing systems that better respect the skin barrier. While the industrial revolution brought purer soap, the high pH and aggressiveness that came with this new product

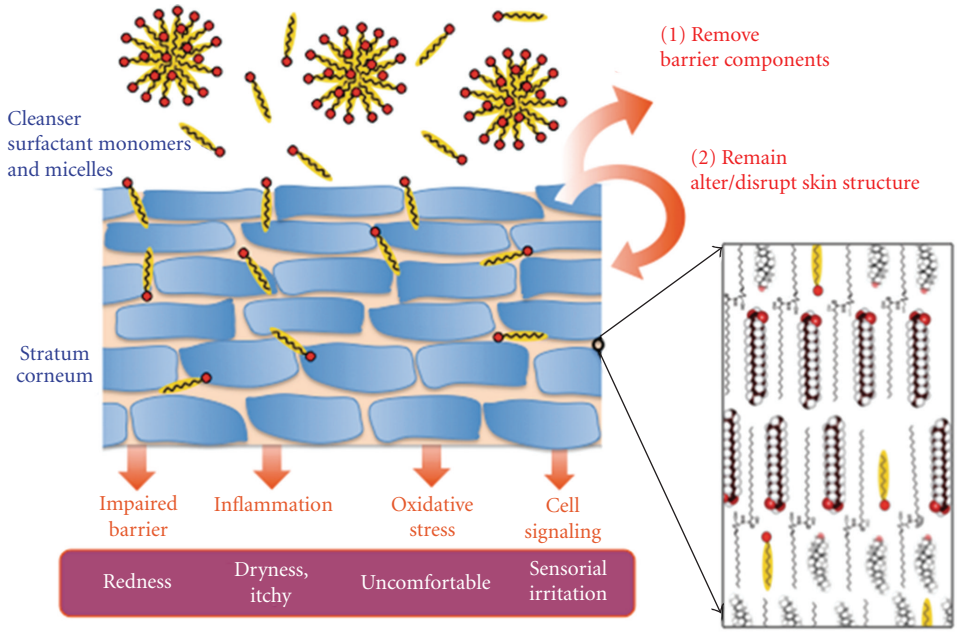

Figure 1: Depiction of how surfactants within a cleanser can remove SC material and also remain in the SC. The lengths scales of the cartoon at the left are inaccurate; corneocytes have diameters ~20 μm, while the micelles sizes are ~5 nm. At the right, a molecular-level illustration of ordered SC lipids (ceramides, cholesterol, and fatty acids) and surfactants from a cleanser inserting into these ordered SC lipids.

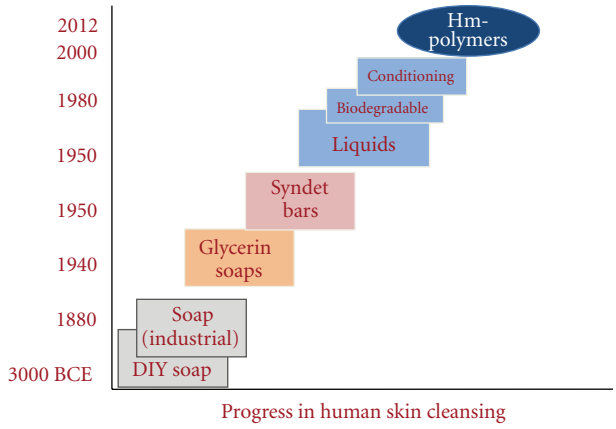

Figure 2: Progress of technology and skin compatibility of human skin cleansing over time. Adapted from Walters 2009.

motivated the development of new, gentler technologies [8, 9]. The addition of glycerin to cleansers, to make for milder cleansing systems, marked the first significant advance in skin cleansing.

After the world wars, the development of new synthetic chemistries enabled many advances in milder cleansing. Developed in the 1950s, the lower pH syndet bar was introduced as an alternative cleanser to soap. The syndet bar has been shown to better respect the skin barrier than soap bars [10]. In the 1960s, polymers were added to cleansers for the first time for multiple benefits [11]. As will be discussed later, the more recent introduction of hydrophobically modified polymers into surfactant systems allows for a new approach to creating cleansers with reduced impact to the skin barrier.

2. Surfactant Penetration into Skin

In order to design a cleansing formulation that respects the skin barrier, it is essential to understand how surfactant penetrates into skin. It has long been believed that only surfactant monomers can penetrate into skin [12, 13], which is known as "surfactant monomer skin penetration model." This model was largely based on the observations that surfactant-induced irritation is positively correlated with the CMC of surfactant mixtures and the CMC is the upper limit of monomer concentration in a solution. In addition, micelles were generally believed not able to penetrate into skin due to their larger size.

The monomer penetration theory drove a desire to decrease the CMC of cleansing systems, which led to the development of surfactant systems with low monomer concentrations or low critical micelles concentrations (CMCs), that were believed to be less irritating [14]. Personal care cleansers are primarily comprised of anionic surfactants (commonly sodium lauryl sulfate), and adding a cosurfactant has reliably reduced their CMCs and lowered the aggressiveness of cleansers to the skin barrier.

More recent discoveries have challenged monomer penetration model to fully explain how surfactants penetrate skin. Following surfactant exposure, skin irritation and barrier disruption increases with increasing concentration of surfactant, even at surfactant concentrations above the CMC,

where the monomer level is constant [15–17]. Additionally, typical dermal exposure occurs at concentrations of 1–10 wt% surfactant, concentrations that are two or three orders of magnitude above the CMC concentrations. At these typical in-use concentrations nearly all of the surfactants exist in micelles with only a small fraction ~0.1% existing as monomers. Finally, the correlation between surfactant CMCs (the monomer level) and aggressiveness was not found in systems studied more recently [18].

Researchers have proposed alternative mechanisms to explain these discrepancies of monomer penetration model. Blankschtein and associates utilized radiolabeled ^{14}C to track the amount of SDS penetrated into epidermis and found it to increase with SDS concentration when applied above the CMC [19]. When polyethylene oxide (PEO) was added to the SDS solution, less SDS was observed in the epidermis. PEO primarily interacts with micelles but not with monomers. The PEO-bound SDS micelles have an average radius of 25 Å, while that of the unbound micelles is ~20 Å. It was suggested that SDS micelles, with its small size, could be capable of penetrating the skin through aqueous pores, while the larger PEO-bound SDS micelles could not and a surfactant micelle skin penetration model was proposed. While the current research is actively evaluating this micelle model, it has already inspired new technologies to think outside of the box of CMC-based cleanser design approach.

3. Effects of Surfactants on Skin at Molecular Level

SC, the outermost layer of the skin, provides most of the skin's barrier function. As discussed previously, it is structured as stratified anucleated corneocytes embedded in an intercellular lipid matrix [20], which is mainly composed of ceramides, long-chain free fatty acids, cholesterol, and cholesterol sulfate [21–24]. SC lipids are organized as multiple lamellae with long and short periodicity [25–30]. In each lamella, the lipids are laterally packed in predominantly orthorhombic and hexagonal phases [31]. Such highly ordered SC lipid structures play an important role in regulating water transport and skin permeability [32, 33]. The disruptions of the SC lipid order by surfactants contribute to the barrier damaging side effects of skin cleansing [34, 35]. Our group and our collaborators have recently studied sodium dodecyl sulfate (SDS) penetration in both isolated SC [36] and excised intact skin [37] with infrared spectroscopy and confocal Raman microscopy to understand the effects of SDS on skin structure at molecular level and the time course of its permeation in skin.

In these studies, acyl chain perdeuterated SDS was utilized to accomplish the simultaneous detection of IR and Raman signals originating from both permeated SDS and endogenous skin lipids and proteins. For experiments conducted with isolated SC, the amount of SDS that permeated into SC became saturated after 2 h SDS soaking. It took longer time for topically applied SDS to permeate into the full thickness skin. Distribution of the absolute SDS concentration in skin cross-section was determined through IR spectroscopic imaging technique with ~10 μm spatial resolution and 5–20% accuracy in concentration measurement. SDS permeated into different skin regions in a time- and temperature-dependent manner. SDS concentration up to 1000 mmol/L, which is much higher than donor solution (40 mmol/L), was observed in SC. The results for a skin sample treated with SDS for 40 h at 34°C are shown in Figure 3, along with the companion microscopic image. The rapid SDS concentration decrease going from SC into viable epidermis demonstrates the barrier function of SC. SDS was observed to permeate into the dermis region at a concentration of ~32 mmol/L.

In addition to tracking SDS penetration, IR spectroscopy offers a convenient approach to evaluate the interaction between surfactants and skin by following skin lipid order and protein secondary structure as well as the physical state of permeated SDS molecules. A set of spectra between 715 and 732 cm^{-1} from isolated SC is plotted in Figure 4 as a function of temperature. The methylene rocking band in this spectral region is sensitive to phase transition between orthorhombically (ortho) and hexagonally (hex) packed lipids. At low temperature, human SC lipids are mainly packed in orthorhombic phase and display two peaks near 729 cm^{-1} and 720 cm^{-1}. As temperature increases, the amount of lipids in hexagonal phase increases, and, as a result, the 729 cm^{-1} peak intensity diminishes and 720 cm^{-1} peak red shifts slightly. Therefore, the 729 cm^{-1} peak is utilized as a signature of orthorhombic phase. Its integrated peak area, normalized by protein Amide II peak area to account for SC thickness difference between samples, is depicted in Figure 4(b) as a function of temperature. After isolated SC was soaked with SDS, the midpoint of this ortho-to-hex phase transition temperature decreases and the initial amount of SC in orthorhombic phase was lower compared to controls. SDS appears to be extracting lipids and/or increasing the amount of hexagonal phase or disordering lipids that were originally in orthorhombic phase.

SDS conformational order can be tracked with methylene stretching frequency, the lower the frequency is the more ordered the acyl chains are. Figure 5(a) shows the asymmetric stretching frequency of SDS in micelles and in SC after 2 h and 6 h soaking as a function of temperature. The frequency increase from 2194 cm^{-1} to 2198 cm^{-1} at ~18°C for SDS solution corresponds to its Krafft point, above which SDS is predominantly in a micellar phase. As shown in the figure, when incorporated to isolated SC, SDS asymmetric frequency was ~1.5–3 cm^{-1} lower comparing to its micellar state. Similar decrease in stretching frequency comparing to SDS micelles was also observed for SDS permeated into the SC regions of full thickness skin. The symmetric methylene stretching frequency between 2090 and 2096 cm^{-1} was monitored for SDS in the SC of intact skin and is shown in Figure 5(b). The decrease in stretching frequency and thus increase in conformational order for SDS in SC indicate that SDS exists in a more ordered state in SC than SDS micelles. The densely packed SC lipids apparently have an ordering effect on permeated SDS. For the SDS that penetrated to the deeper dermis sites of skin, its stretching frequency is comparable to micelles (Figure 5(c)). These

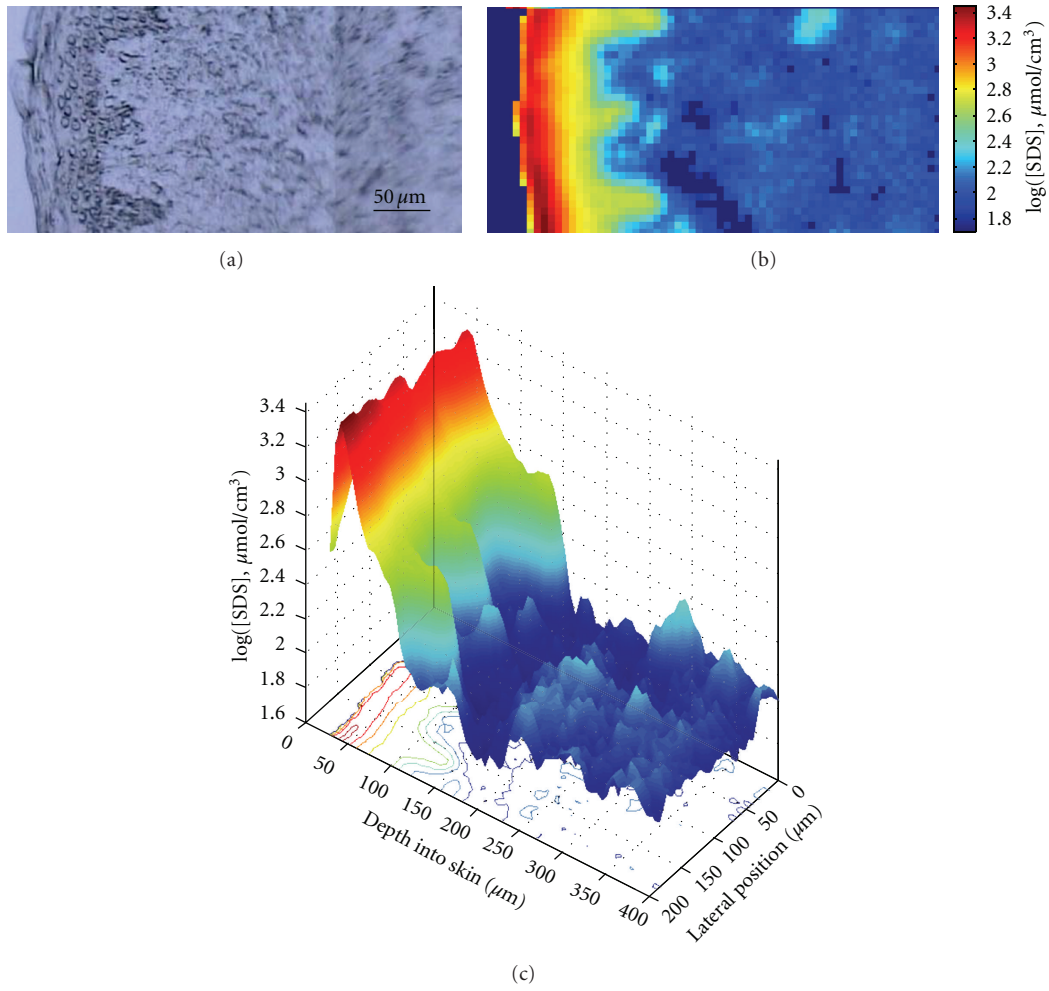

Figure 3: (a) Visible light microscopic image of human skin cross-section, distribution of SDS concentration in the same skin section following 40 h topical SDS treatment at 34°C, (b) shown as an IR image map, and (c) shown as a 2D depth profile.

observations provide some insights into the mode of SDS permeation in skin. SDS can either permeate into skin as a monomer or permeate as micelles but these micelles quickly dissemble to monomers once integrated into SC lipids. The possibility of micelle reformation in dermis is not likely but cannot be excluded based on the above CMC concentration in these sites and the stretching frequency comparable to SDS micellar solution.

Protein secondary structure is commonly monitored with Amide I and Amide II band contours between 1480 and 1730 cm^{-1}. The lack of major changes in this spectral region for isolated SC and SC from full thickness skin before and after SDS treatment demonstrates that SDS has minimal effects on SC keratin structure. The ability of surfactants to solubilize zein protein has been used to access the surfactant harshness. However, it might not be relevant to the actual interaction between surfactant and SC proteins. Zein protein is structured as antiparallel helices clustered within a distorted cylinder [38], while the SC keratin has a more complicated secondary structure and assembles to keratin filaments [39]. Furthermore, the keratin inside cornified envelope of SC is much more difficult to access compared to the zein protein in testing solutions. The surfactant permeates into SC mainly through intercellular lipid pathway and might have minimal contact with keratin inside corneocyte envelope. This hypothesis is consistent with a recent study on naturally fluorescent penetration enhancers [40]. The two-photon fluorescence microscopy images of skin treated with a more hydrophobic molecule, sodium sulforhodamine G (SRG), showed that SRG is mostly confined in the cornified envelope and did not penetrate inside the corneocytes.

Increases in transepidermal water loss (TEWL) following SDS treatment have been reported [6, 34, 41, 42]. In addition to damaging the skin barrier, SDS permeation causes irritation and inflammation [7, 43] and alters barrier renewing processes by affecting keratinocyte differentiation [44] and desquamation [45]. The disordering effects of SDS on SC lipids help explain the weakened skin barrier and offer a mechanism for the observed TEWL increases following SDS treatment. The fact that it is able to permeate to deep sites in skin can be responsible for the irritation

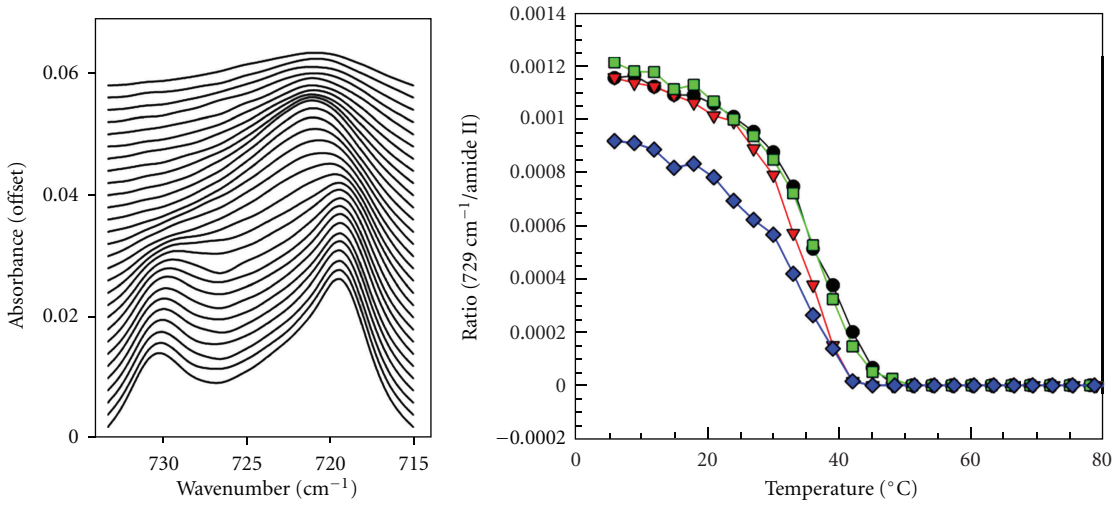

FIGURE 4: (a) CH_2 rocking band contour progression with temperature increase from 6°C (bottom) to 90°C (top) in 3°C increments a in an isolated human SC control sample; (b) integrated peak area of 729 cm^{-1} rocking band normalized by protein Amide II peak area as a function of temperature for 2 h control (circles line), 2 h SDS-d_{25} (down-pointing triangles line), 6 h control (square line), and 6 h SDS-d_{25} (rhombuses line) isolated human SC samples.

and inflammation that are commonly associated with SDS application on skin.

4. Creating Cleansers with Less Barrier Disruption

As discussed, surfactants are capable of disrupting the skin barrier, and creating cleansing formulations with minimal barrier disruption has marked the major advancement in cleansing technologies. By modifying their solution properties, the behavior of the surfactants can be changed, and the effect of surfactants on the skin barrier can be reduced. In addition to the CMC, surfactant solution properties including the surface charge, size, and shape of micelles, as well as the dynamics of the surfactant monomer-micelle equilibrium, are major factors to consider when designing the new generation of skin cleansers.

Surfactant micelles that have a highly negative surface charge (i.e., micelles of anionic surfactants) have been shown to be more aggressive at solubilizing Zein protein [46]. By blending amphoteric surfactants, the micelle surface charge is reduced, and the surfactant system becomes less aggressive. Modifying the aqueous phase can also affect the surfactant behavior. For instance, Ghosh et al. demonstrated that adding glycerin to SDS solution leads to reduced barrier perturbation when compared to SDS control [5, 47].

In an alternate approach, polymers have been used to alter surfactant solution behavior in order to create milder cleansers. Polyethylene oxide (PEO) has been shown to alter micelles and create surfactant systems with less aggressiveness to the skin barrier [17]. The PEO chains bind water molecules and have been shown to wrap around surfactant micelles [48]. These polymer chains with bound water are highly biocompatible, as they present water to biological tissue. This approach to mild cleansing actually was employed decades ago; the original mild cleansing technology in baby shampoo was employed in PEG-80 Sorbitan Laurate to create mild cleansing systems [49, 50].

More recently, alternate polymer architectures have been used to modify surfactant solution behavior. Hydrophobically modified polymers (HMPs) have been shown to associate surfactants in solution. Surfactant self-assembled to the hydrophobic domains of the polymer results in slower surfactant dynamics. By creating these large polymer/surfactant complexes, the cleanser becomes less aggressive [51]. In these HMP/surfactant systems, because less surfactant enters the SC, there is less inflammation, and therefore the skin barrier is less disturbed [52].

In recent work, we have developed a gentle foaming facial cleanser utilizing HMP. The effects on the skin barrier following treatment with this formulation (NUG) compared to a leading dermatologist-recommended lotion facial cleanser (CGSC) were compared. With images obtained from multiphoton laser scanning confocal microscope [53], the benefits provided by HMP technology of minimizing the SC barrier disruption were visualized directly. The skin samples were mounted on a Franz diffusion cell with SC facing the donor chamber and cleansers, diluted with distilled water to a concentration of 80%, were applied and maintained at 37°C for 2 h. A fluorescent dye was then applied to the samples, and its fluorescence in skin was imaged. The penetration of this florescent dye characterized the barrier properties of skin samples treated with different cleansers [54].

Typical photomicrographs of the dye penetration in skin samples after exposure to two cleansers are shown in Figure 6. The images from depths into the skin at 2 and 20 μm are shown in the top and bottom rows,

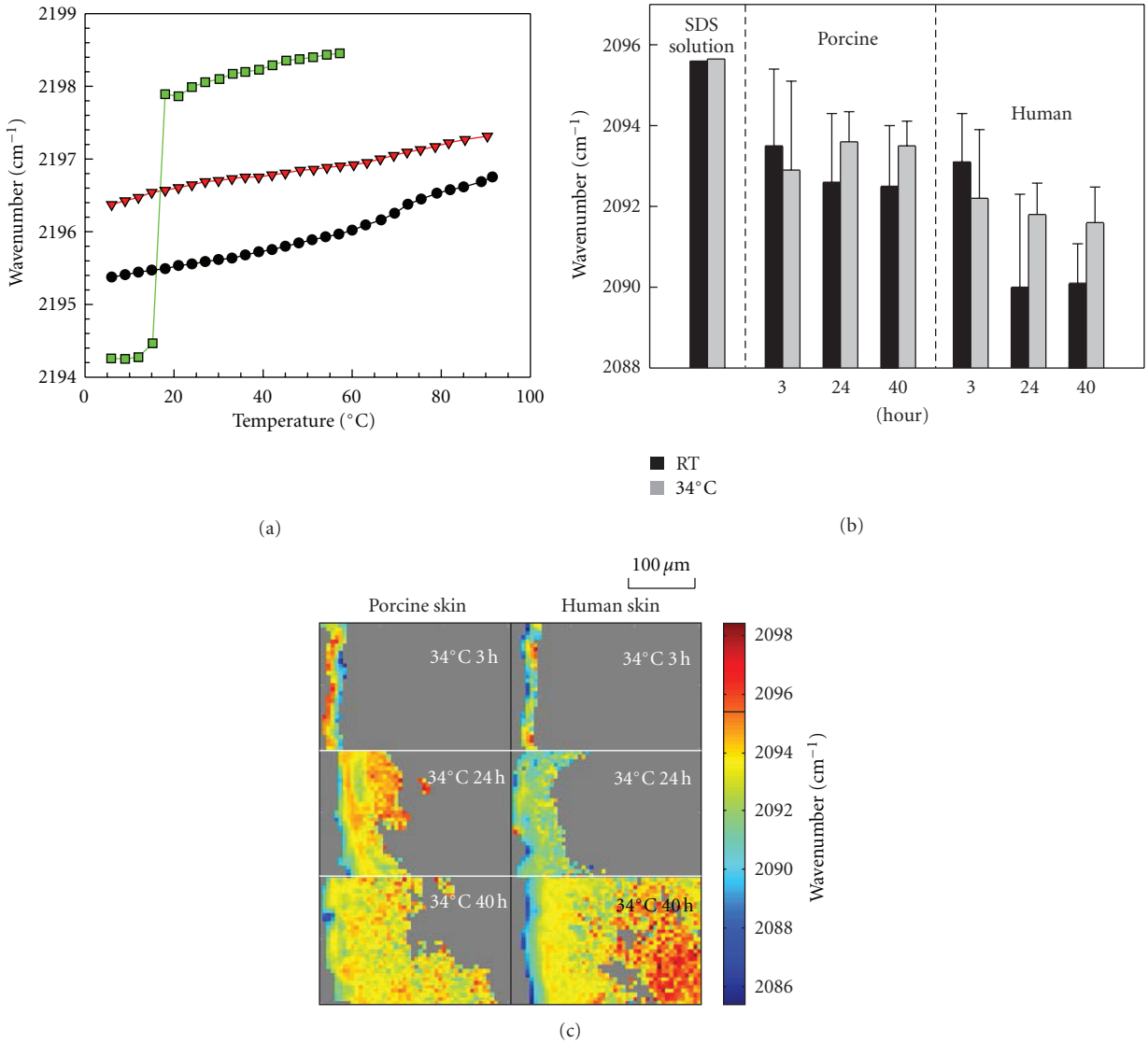

Figure 5: (a) Peak frequency of the SDS-d_{25} CD_2 asymmetric stretching band as a function of temperature in isolated SC after 2 h (circles line) and 6 h (squares line) SDS-d_{25} incubation along with a SDS-d_{25} solution in PBS at 62.5 mg/mL (down-pointing triangles line); (b) average peak frequency of SDS-d_{25} CD_2 symmetric stretching in porcine and human SC after 3, 24, and 40 h treatment at room temperature (gray) and 34°C (black) along with a SDS-d_{25} solution in PBS at 12.5 mg/mL. Error bars (standard deviation) do not reflect lack of precision in the measurement but rather predominantly arise from heterogeneity in the skin; (c) peak frequency of SDS-d_{25} CD_2 symmetric stretching frequency in porcine and human skin after treatment for 3, 24, and 40 h at 34°C.

respectively. Lower intensity of fluorescence indicates a more intact barrier after exposure to the cleansing system, while higher dye penetration signifies a more porous barrier. With both cleansers, images obtained at the 20 μm skin depth, Figures 6(c) and 6(d), show less presence of dye compared to the ones from 2 μm depth into skin, Figures 6(a) and 6(b). Comparing images obtained from skin treated with different cleansers, at the same skin depth, the image from skin treated with NUG clearly had less fluorescence from the dye than that from CGSC treated skin (Figure 6(a) versus Figure 6(b), and Figure 6(c) versus Figure 6(d)). The lower intensities of the dye in the NUG-treated specimens demonstrated the reduced barrier damage caused by cleanser compared to CGSC.

5. Conclusions

Surfactants remove skin components, penetrate into skin, alter skin structure, and therefore degrade skin barrier functions and lead to clinical and subclinical skin conditions. Maintaining the molecular order of the SC lipids is essential to healthy skin. The new understanding of the interactions between SDS, which has entered the SC, and the SC lipids at molecular level reveals the importance of designing cleansing systems that respect skin barrier function.

In order to maintain the skin barrier during cleansing, it is best to maintain the endogenous lipids and the native skin structure. The addition of polymeric species that interact with the surfactants to modern cleanser formulations creates

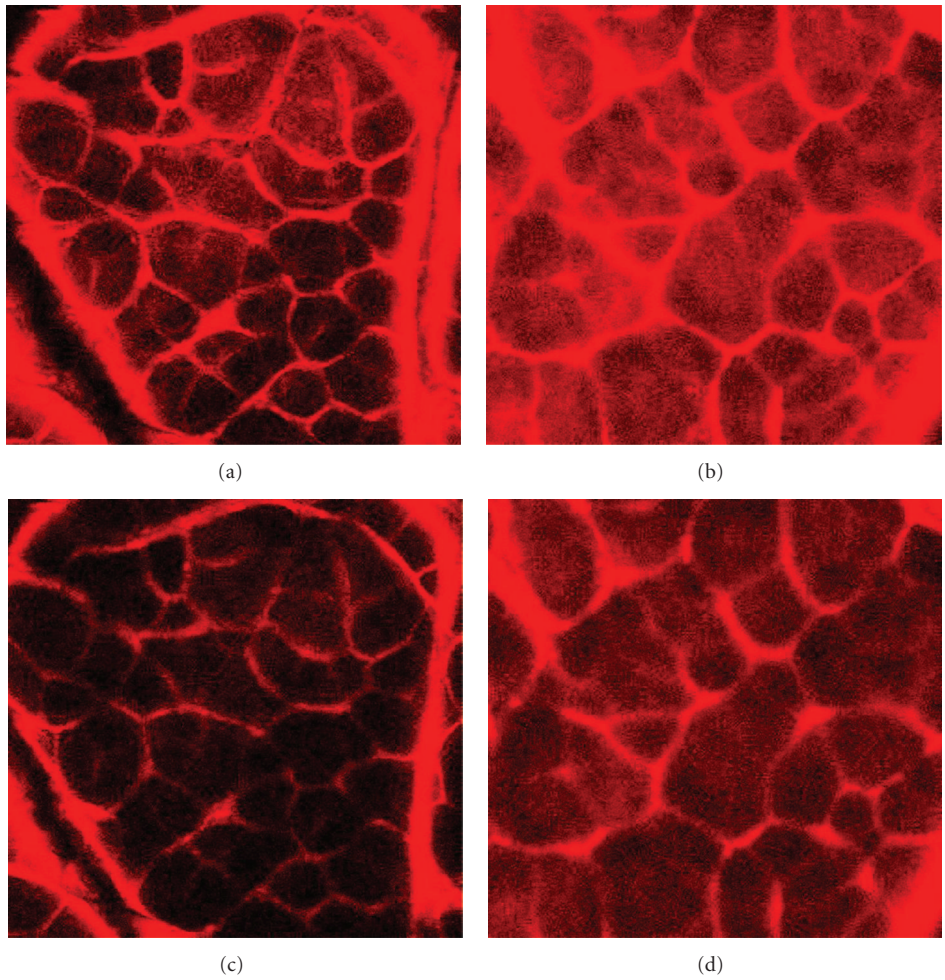

Figure 6: 2-photon fluorescent microscopy images showing skin barrier condition after treatment with NUG facial cleanser, with HMP (a and c) compared to CGSC (b and d) at a depth into the SC of 2 μm (upper row; a and b) and 20 μm (lower row; c and d). The limited dye penetration (lower intensity) indicates a more intact barrier, while more dye penetration indicates a weaker barrier.

less aggressive cleansers. The novel application of hydrophobically modified polymers has been proven to advance current technology to further minimize the damaging effects of cleansers on skin.

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Review Article

Metal Allergy and Systemic Contact Dermatitis: An Overview

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Contact dermatitis is produced by external skin exposure to an allergen, but sometimes a systemically administered allergen may reach the skin and remain concentrated there with the aid of the circulatory system, leading to the production of systemic contact dermatitis (SCD). Metals such as nickel, cobalt, chromium, and zinc are ubiquitous in our environment. Metal allergy may result in allergic contact dermatitis and also SCD. Systemic reactions, such as hand dermatitis or generalized eczematous reactions, can occur due to dietary nickel or cobalt ingestion. Zinc-containing dental fillings can induce oral lichen planus, palmoplantar pustulosis, and maculopapular rash. A diagnosis of sensitivity to metal is established by epicutaneous patch testing and oral metal challenge with metals such as nickel, cobalt, chromium, and zinc. *In vitro* tests, such as the lymphocyte stimulating test (LST), have some advantages over patch testing to diagnose allergic contact dermatitis. Additionally, the determination of the production of several cytokines by primary peripheral blood mononuclear cell cultures is a potentially promising *in vitro* method for the discrimination of metal allergies, including SCD, as compared with the LST.

1. Introduction

Contact dermatitis is usually produced by external exposure of the skin to an allergen; however, sometimes a systemically administered allergen may reach the skin through the circulatory system and thereby produce systemic contact dermatitis. Systemic contact dermatitis (SCD) is an inflammatory skin disease that is known to occur with exposure to drugs, foods, and dental metals. A variety of types of skin eruptions have been reported, including flares of previous patch test sites, symmetrical intertriginous and flexural exanthema, exfoliative erythroderma, and widespread dermatitis [1].

Metals such as nickel, cobalt, chromium, and zinc are ubiquitous in our environment. During the 20th century, industrialization and modern living resulted in increased cutaneous exposure to these metals and hence an increased incidence of metal allergies [2]. Metal allergies may result in allergic contact dermatitis. Metals that are electrophilic have the ability to ionize and react with proteins, thus forming complexes that can be recognized by dendritic cells, which allows for sensitization to occur [3]. Cases of contact dermatitis caused by cutaneous exposure to cosmetics products and jewelry that contain nickel have been reported in the literature. The thinness of the stratum corneum and intermittent exposure to sweat on the eyelids have been associated with increased nickel absorption through the skin from cosmetics, allowing lower nickel concentrations to elicit a reaction [4]. Cobalt is a strong skin sensitizer [5]. Over the years, occupational exposure to cobalt has been primarily observed in metal workers, bricklayers, and pottery workers. Contact dermatitis that results from direct contact to an allergen is the most common and easiest form of metal allergy to identify. However, the timely recognition of the type of systemic skin inflammation known as SCD and its varying presentations is critical as it can result in more chronic and severe symptoms.

2. Metals and SCD

2.1. Nickel and SCD. Nickel is a chemical element found ubiquitously in the environment and is used with a high frequency worldwide. This metal is manufactured into steel and a variety of alloys containing cobalt, palladium, iron, titanium, gold, and magnesium [6]. Sensitized individuals generally experience a predictable localized response

following cutaneous exposure to nickel, including erythema, vesicle formation, scaling, and pruritus. According to recent studies, females have an about 4-fold higher relative risk of developing allergic contact dermatitis to nickel compared with males [6].

Systemic reactions, such as generalized eczematous reactions or dyshidrotic hand eczema, can occur due to dietary ingestion of nickel. In 1984, Andersen et al. coined the term "baboon syndrome" to describe the generalized dermatitis of the buttocks, anogenital area, flexures, and eyelids that is frequently observed in patients with SCD to nickel [7]. Nickel is present in most dietary items, and food is considered to be a major source of exposure to nickel for the general population. Certain foods are routinely found to be high in nickel content. Nickel present in the diet of a nickel-sensitive person can provoke SCD. For example, SCD can be elicited in nickel-sensitive individuals from the consumption of foods with a high nickel content, such as cocoa [8]. In such patients, adherence to a low-nickel diet and avoidance of local exposure to metal objects result in the disappearance of skin symptoms. Silvestri and Barmettler reported the case of a nickel-sensitive patient with a 1.5 year history of treatment-resistant pruritus ani [9]. The patient disclosed a habit of daily peanut butter consumption. His symptoms resolved with a restriction of dietary nickel [9]. A study of systemic nickel allergy found a dose-response relationship between nickel ingestion and the occurrence of dermatitis flare-ups [10]. Of note, for most nickel-allergic patients, a single dose of 4 mg of nickel will result in widespread dermatitis [10]. It is recommend that individuals with food-related flare-ups of nickel dermatitis consume a low-nickel diet [11].

Nickel is considered to be the most frequent contact allergen for patients with AD [12]. A recently published study of a German population showed a positive association between filaggrin mutations, which have been shown to be strongly associated with AD, and contact sensitization to nickel [13]. Another study also reported a positive association between nickel sensitization and AD, in a subanalysis of nonpierced women [14].

It is necessary to be aware of the systemic reactions that occur with SCD, which can be chronic and can produce severe symptoms that may often be mistaken for AD [15]. Initially, Shanon reported that patients with SCD occasionally experience a skin manifestation similar to AD called "pseudoatopic dermatitis" [16]. Hsu et al. recently reported four cases of children with variable presentations of SCD to nickel [15]. For each of these patients, the presence of clinically relevant exposure to nickel was confirmed with dimethylglyoxime testing. One of these patients, 16 years old, had a nine-year history of pruritic dermatitis that began on her infraumbilical area and arms. During the past year, the dermatitis had spread to the remainder of her body, including her face, and the patient was thus believed to have AD [15].

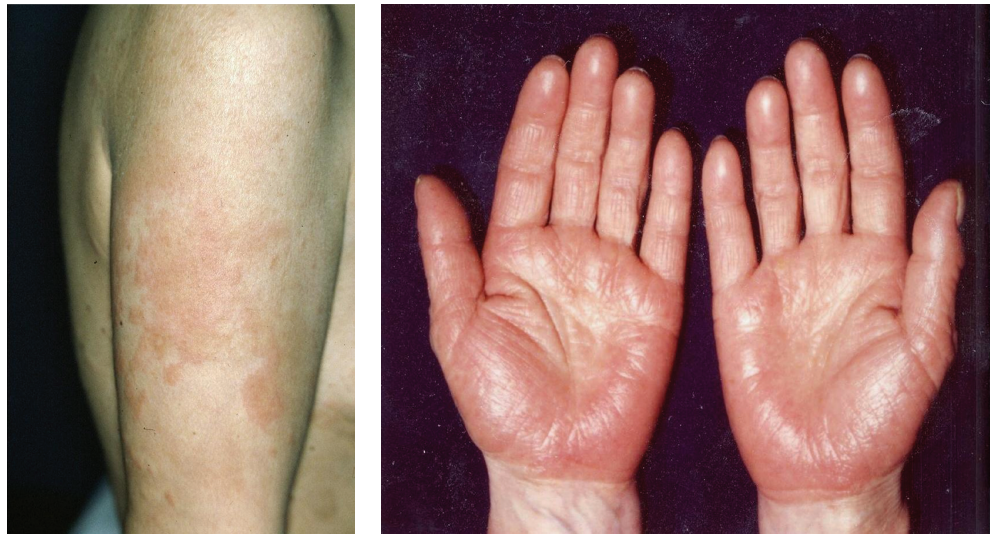
2.2. Cobalt and SCD. Although nickel sensitivity is more common than cobalt sensitivity, the two are frequently linked. Rystedt and Fischer reported that a quarter of nickel-sensitive patients developed a cobalt allergy and patients with simultaneous nickel and cobalt allergies have more severe dyshidrotic eczema [17]. It was proposed that a low-cobalt-diet reduced the dyshidrotic eczema flares in cobalt allergic patients [18]. Therefore, the ingestion of increased amounts of cobalt through food should be added to the list of triggering factors for SCD.

Furthermore, cobalt is contained in a variety of materials. Hard metal is manufactured by means of a powder metallurgical process in which about 90% tungsten carbide, small amounts of other metal carbides, and polyethylene glycol are mixed with about 10% metallic cobalt, which is used as a binding agent. Hard metal manufacturing involves pressing, forming, sintering, grinding, and etching or color marking. Cobalt exposure via inhalation may lead to cobalt-related asthma. Hard metal workers may develop cough, wheezing, and dyspnea that often improve during weekends and holidays [18]. The occurrence of localized contact dermatitis due to occupational exposure to cobalt in the hard metal industry has also been reported [19, 20].

However, contact with a hard metal powder in the workplace is a rare cause of SCD. In particular, there has been only one report of occupational cobalt-induced SCD [21]. The case was a 19-year-old male who had worked as a grinder for 1 month in a hard metal factory. The hard metals used in the factory contained cobalt. The patient developed erythema on his hands 2 weeks after starting the work, which thereafter progressed to a generalized eczematous eruption with itching [21]. Patch testing showed positive reactions for 1% cobalt chloride. After changing his workplace, his skin rush disappeared. In this case, the recurrent eczematous lesions of the hands were associated with a flare of systemic dermatitis and were highly suggestive of SCD triggered by cobalt inhalation. Dermatologists should, therefore, remind such patients to pay increased attention to avoid all kinds of cobalt exposure in their daily life and work.

2.3. Chromium and SCD. The element chromium was discovered by Vaquelin in 1798. It is ubiquitous in the environment and is widely used in the plating, leather tanning, pigmentation, dye production, metallurgy, and chemical industries and is found in cement as a byproduct of the cement manufacturing process itself [22, 23]. When exposed to skin, chromium salts can induce cutaneous irritation, which may progress to SCD in cases of chromium hypersensitivity [24]. Chromate-induced SCD is primarily exacerbated by skin contact with hexavalent and trivalent chromium compounds [25]; however, the ingestion of the allergen in the dichromate form has also been reported to cause exacerbations [26–29]. The oral ingestion of trivalent chromium, that is, chromium picolinate, for nutritional supplementation has been reported to cause SCD [30]. Recently, SCD resulting from the ingestion of chromium chloride in a multivitamin/multimineral tablet has been reported [31].

Metal allergy has also been associated with device failures following the insertion of intracoronary stents, hip and knee prostheses, and other implants. Gao et al. reported a case of SCD most likely caused by exposure to chromium after



(a) (b)

Figure 1: (a) A 49-year-old Japanese female with a diffuse edematous erythema with papules over her entire body. (b) The oral challenge test with zinc sulfate caused exacerbation of the preexisting eruptions on her palms, including itching edematous erythema.

a total knee arthroplasty, although this complication is very rare [32]. The majority of total joint prostheses are now made of cobalt-chromium alloys with a nickel content of less than 1% [33]. The occurrence of SCD is particularly uncommon following total knee arthroplasty because there is a polyethylene insert between the femoral and tibial components and no metal-on-metal contact exists.

2.4. Zinc and SCD. Zinc is an essential trace element involved in many physiological functions, including catalytic and structural roles in metalloenzymes, as well as regulatory roles in diverse cellular processes, such as synaptic signaling and gene expression. Zinc is widely used in dental restoration. The previously reported dental metal eruptions caused by zinc have included oral lichen planus [34], palmoplantar pustulosis [35], and a maculopapular rash [36]. It has also been reported to cause severe symptoms in cases of SCD. One case was a 49-year-old Japanese female who developed facial edema, blepharedema, and pruritic edematous erythema with papules over her entire body. Based on the results of a metal patch test, lymphocyte stimulating test (LST), and zinc challenge test, a diagnosis of zinc-allergic SCD was made (Figure 1) [37]. This case had four teeth that had been treated with metal fillings, which likely contained zinc. All of the patient's dental fillings were completely removed, and her diet was changed to a zinc-restricted diet. Two weeks later, the majority of the skin lesions, which had lasted for four months, subsided rapidly [37].

Saito et al. reported another severe case of SCD that developed because of the zinc contained in dental fillings, in which generalized flare-up reactions occurred from a zinc patch test [38]. In this case, one may suspect the amount of zinc that can be absorbed through the skin or oral mucosa compared with that obtained through dietary zinc intake to be small.

3. Diagnosis of Metal Sensitivity

Epicutaneous path testing has been used to diagnose metal sensitivity. It is the primary tool to diagnose allergens that cause allergic contact dermatitis. The main advantages of patch tests are that they can be completed without hospital surveillance since they rarely induce adverse reactions. Therefore, a patch test evaluation is the gold standard for detecting metal hypersensitivity. However, the accuracy of this method is strongly dependent on the experience of the observer, and distinguishing doubtful-positive from positive patch test reactions for different reagents remains difficult. Sometimes false-positive and negative reactions are observed in conditions of existing dermatitis. Some patch test substances, such as cobalt, nickel, copper, and chromium, sometimes cause false-positives and pustule formation [39, 40].

Oral metal challenges with nickel, cobalt, chrome, and zinc are sometimes performed and are diagnostic for metal allergies, especially SCD. However, flare-up reactions sometimes appear at previous sites of eczema, including hand eczema, and at patch test sites after an oral challenge [41].

In vitro tests, such as the LST, have some advantages over patch testing to diagnose allergic contact dermatitis. First, the LST does not cause flare-ups or exacerbation of symptoms in patients, is objective, and can be used in clinical situations where patch testing is not recommended [42]. However, the LST has not yet been sufficiently optimized or validated to be used as the sole routine diagnostic method for confirming a suspicion of a contact allergy. With regard to the diagnosis of nickel allergy, the task is made quite difficult because of the frequent overlap in test results between nickel-allergic and nonallergic subjects, which may be partly due to a nonspecific, mitogenic effect exerted by nickel [43].

It is useful to assess metal-induced cytokine profiles using the *in vitro* stimulation of primary peripheral blood

mononuclear cells (PBMCs) with metal salts alone. Stimulation with nickel, cobalt, and chromium leads to a specific pattern of cytokine secretion in PBMC cultures obtained from metal-allergic patients, which involves both Th1- and Th2-type cytokines [44–47]. Based on a blood analysis of 14 patients with SCD to nickel, IFN-γ and IL-5 seem to play an important role in the pathogenesis of SCD [48]. Studies of the relationship between zinc and cytokines showed that zinc increased monokine secretion more efficiently than other related divalent cations, including cobalt, nickel, and mercury [49]. Furthermore, zinc stimulation of the PBMCs obtained from SCD patients showed higher macrophage migration inhibitory factor (MIF) and TNF-α secretion compared to that found in healthy subjects [37]. MIF increases TNF-α production and is thought to play an important role in contact hypersensitivity responses [50]. MIF is secreted from both Th1- and Th2-type cells [51]. This suggests that the presence of zinc in the peripheral blood of zinc-allergic patients induces PBMCs to produce increased levels of MIF, which could lead to SCD.

In conclusion, the determination of Th1- and Th2-type cytokine production in PBMC cultures is a potentially promising *in vitro* method for diagnosing metal allergies, including SCD. Therefore, the analysis of PBMC cultures may be helpful in confirming the diagnosis of SCD caused by metal allergy in patients with positive patch testing.

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