



# Skin Barrier Dysfunction in Contact Dermatitis and Atopic Dermatitis-Treatment Implications

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Published online: 3 August 2020

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This article is part of the Topical Collection on *Urticaria and Atopic Dermatitis*

**Keywords** Epidermal barrier · Cornified envelope · Contact dermatitis · Hand eczema · Atopic dermatitis

## Abstract

**Purpose of review** A variety of skin diseases are associated with impaired barrier function. The crucial pillars in therapy of previously mentioned conditions are avoidance of triggers, skin protection and individually adapted medical therapy. Until recently, besides of topical corticosteroids, the treatment options were limited. However, a variety of new therapies of skin barrier-related skin diseases became available over the last years. Our goal was to investigate new findings and treatment options in skin diseases with barrier dysfunction, emphasizing on contact dermatitis, hand eczema and atopic dermatitis.

**Recent findings** Besides of new relatively nonspecific anti-inflammatory therapies, such as topical calcineurin inhibitors, crisaborole and delgocitinib, also highly specific targeted treatments are currently under investigation, and some already available on the market. Worth mentioning is dupilumab, the first biologic drug approved for treatment of atopic dermatitis, but used also off-label for treatment of hand eczema. There are ongoing trials investigating tralokinumab and lebrikizumab for atopic dermatitis therapy. Anti-IL-31 monoclonal antibodies were reported to improve atopic dermatitis-related pruritus.

**Summary** This review focuses on new findings and treatment options for skin diseases with barrier dysfunction regarding their efficacy, safety profile and mechanism of action.

## Introduction

The skin is the biggest organ of the human body with a variety of functions. It is composed of three main layers: epidermis, dermis and subcutis. The outermost layer of the epidermis, the stratum corneum, serves as barrier for protection against the environment [1, 2]. The keratinocytes in the epidermis undergo a differentiation process: epidermal stem cells proliferate and form basal cells, further maturation and migration processes lead to spinous, granular and transitional cells, finally forming corneocytes. This process is known as "cornification" [2]. During cornification, cross-linked proteins and lipids embed the terminally differentiated corneocytes and form an insoluble blend [1]. An intact skin barrier is a strong fortress, preventing penetration of irritating substances and microorganisms from the outside; for this feature, it is known as the "outside-in barrier". Furthermore, it protects from increased water and heat loss, the so called "inside-out barrier" [3–6]. However,

internal and external factors can contribute to epidermal barrier dysfunction: genetic predisposition, exposure to irritants and allergens. Damage of the epidermal barrier function can lead to increased permeability and pathogen penetration, and also allergens can penetrate non-functional stratum corneum and lead to subsequent contact sensitization and allergy [4, 7]. Treatment of impaired skin barrier requires multimodal therapy. First, triggering factors should be identified and avoided [8]. Additionally, regular application of moisturizers, preferably without preservatives and fragrances, is vital for regeneration of damaged skin [4, 8]. Pharmacotherapy for restoration of fully functioning epidermal barrier has to be adapted to the underlying disease. However, it has to be considered that some treatments can cause further harm to the skin barrier when used for long term or lead to systemic absorption in case of large treatment areas or strongly impaired barrier [8].

## Skin barrier

The skin is composed of three layers: the epidermis, the dermis and the subcutis. The outermost layer of the skin, the epidermis, consists of different, specialized layers. Epidermal stem cell differentiation includes morphological changes and migration towards the surface. Beginning at the level of the basal cell layer (stratum basale), cuboidal basal cells differentiate into keratinocytes and re-shape into the spinous cell layer (stratum spinosum), subsequently forming a thin middle granular cell layer (stratum granulosum) and the cornified layer (stratum corneum). This process, known as cornification, describes the highly organized differentiation of keratinocytes to achieve protection against harmful agents. Continuous shedding of the stratum corneum requires an epidermal renewal cycle which takes approximately 30 days in healthy individuals [1, 2].

The maintenance of epidermal structures is a result of the differentiation of keratinocytes from basal stem cells. The basal keratinocytes produce keratins. Keratins gather together and form keratin intermediate filaments (KIF), which extend from the nuclear lamina to the desmosomes. Subsequently, the keratinocytes are migrating to the spinous layer, where they lose their mitotic activity and start producing other proteins that are characteristic for cornification. In the stratum granulosum, further keratins and keratohyalin granules are produced, and lamellar bodies arise. Keratohyalin granules contain profilaggrin, keratin filaments and other intracellular components of the stratum corneum (SC), whereas lamellar bodies contain lipids, corneodesmosins and other extracellular components. At the junction between the stratum granulosum and stratum corneum, profilaggrin undergoes proteolytic processing and conglomerates with keratin filaments [3, 9]. Transglutaminase (TG), an

epidermal enzyme, catalyses cross-links to hold the proteins together. Three active TGs were identified which participate in cross-link formation in the epidermis: TG 1, TG 3 and TG 5. At the level of the cornified layer, keratinocytes acquire their characteristic flat appearance and are tightly connected by modified desmosomes, "corneodesmosomes". Furthermore, the lipid-containing lamellar bodies secrete their content (ceramides, cholesterol, fatty acids) into the intercellular space. At this point, keratinocytes become corneocytes [2, 3, 5]. The stratum corneum is formed by the corneocytes embedded in lipids, according to the "brick and mortar" model [10]. The epidermal protein mass consists to 90–95% of KIF and filaggrin (FLG). Further proteins of the cornified envelope are proline-rich-proteins, involucrin, loricrin and antimicrobial peptides (AMPs) (Fig. 1). AMPs are small molecules play an important role in skin protection against pathogens (bacteria, fungi and viruses), wound healing, cell migration and differentiation and angiogenesis. Upregulation is presented in case of epidermal barrier disruption or injury [11]. The further process of shedding off of corneocytes is called desquamation and is strictly controlled by specific proteases, which are enhanced by increased intracellular  $\text{Ca}^{2+}$  in the upper layers. The cornified envelope is highly hydrophobic and prevents epidermal water loss, as well as entry of infectious organisms, allergens and toxic substances [1, 3, 5, 12]. However, some degree of interchange between the epidermal barrier and the environment takes place. Permeability depends on the physiological state of the skin: small, hydrophilic particles use the transcellular pathway, whereas lipophilic agents diffuse intercellularly. Diffusion resistance depends on the amount of lipids as well as the thickness and cohesion of the stratum corneum [9]. Epidermal barrier disruption can be caused by internal factors, such as genetic abnormalities in genes coding for epidermal proteins and consequent alterations in the process of cornification. However, a dysfunctional immune response also plays an important role. Epidermal cells produce various cytokines essential for intercellular communication, affecting keratinocyte differentiation and proliferation. Lack of cytokine regulation can cause alterations in epidermal function and is involved in the development of several diseases (e.g. atopic dermatitis, psoriasis) [1]. But also external factors, such as contact with chemical and physical irritants, can be a causative factor. Barrier dysfunction facilitates penetration of allergens and development of

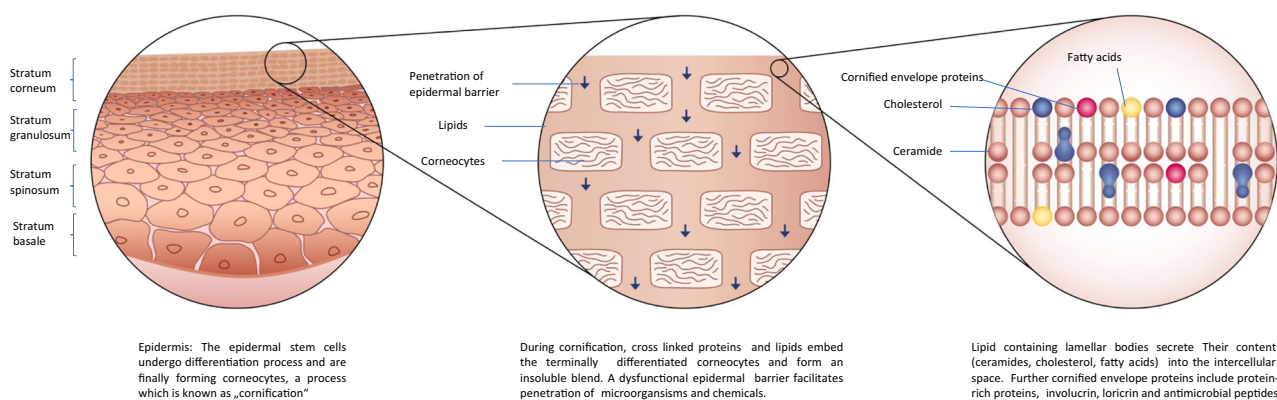


**Fig. 1.** Epidermal barrier.

contact allergy (CA), of which, approximately 20% of the adult population is affected [7, 13, 14].

Common skin diseases whose pathogenesis involves an impaired barrier function are contact dermatitis (CD) and atopic dermatitis (AD) [1].

## Contact dermatitis

The two main subgroups of contact dermatitis (CD) are irritant CD (ICD) and allergic CD (ACD) [15]. The term CD refers to a condition of cutaneous inflammation that can show an acute phase as well as a chronic course of disease. During acute phase, it is characterized by vesicles and erythema. The chronic phase is characterized by presence of lichenification, fissuring and dryness. The point prevalence is of up to 20% among the general population; also, many cases can be attributed to atopic predisposition [15, 16]. ACD involves sensitization to an allergen with a resulting dermatitis after renewed contact. The most commonly identified allergens are base metals, fragrances and preservatives. Particularly, patients with persistent dermatitis or dermatitis involving the hand or face should undergo patch testing [15, 17]. In a recent study, Koppes et al. tried to tag biomarkers for ACD. However, specific biomarkers could not be identified [16]. ICD is more frequent than ACD and typically caused by repeated contact to weak irritants (e.g. water, detergents) which lead to damage of the epidermal barrier and inflammation of the skin. But even one single exposure to strong irritants can cause ICD. However, the cause is often multifactorial [15, 18]. Shin et al. recently explored the different autofluorescence patterns of non-lesional skin in ACD and ICD skin since it contains many autofluorescent components (KRT, collagen, elastin, melanin). The difference between ACD and ICD was not significant. In ACD, the dermal infiltrate was more intense and deeper than in ICD. However, increased autofluorescence was found in ICD due to the scaling and reactive epidermal proliferation [19].

Emollients help restoring a functional epidermal barrier by hydration and retaining moisture by providing a seal, as suggested in the “outside in” approach [11]. Newer strategies are focusing on the “inside out” approach with active ingredients that penetrate the epidermis and stimulate production of intercellular lipids. Creams containing physiological epidermal constituents such as ceramides and cholesterol are recommended because it is assumed that they contribute to the restoration of lipid bilayers and mediate stimuli for epidermal barrier restoration. Though further studies regarding this topic are needed [4, 8, 20, 21]. Ceramide-containing formulations help to improve the skin barrier by skin hydration and reduction of transepidermal water loss (TEWL) [22]. TEWL plays an important role in the evaluation of barrier functionality [23]. Beside the “barrier repair creams”, “barrier protection creams” are also available. The latter provide a protective layer on the skin and are recommended as prophylactic agents [24]. Jordan et al. investigated the effect of combined therapy with hand protectant cream, cleanser and repair cream in subjects with occupational irritant contact dermatitis. The three-step approach was found to be effective in skin hydration and improved epidermal barrier function [25]. However, it is still not conclusively clarified if the effect of barrier creams is superior to that of vehicle [24]. Topical corticosteroids (TCS) are

effective to suppress inflammation, but their use is limited because they can cause reduction of epidermal thickness, increased TEWL, abnormal keratinocyte differentiation and changes in SC [8, 11, 26].

## Hand eczema

A frequent manifestation site of CD is the hand [15]. Hand eczema (HE) has a high prevalence of 10% among the general population, and the course of is often chronic [8]. HE has a high socioeconomic impact, mainly due to prolonged sick leave in case of occupational HE [27, 28]. Heede et al. demonstrated that the proportion of subjects receiving disability pension was increased among HE patients compared with the general population [27]. It is a clinically heterogeneous disease characterized by epidermal barrier dysfunction [4, 8]. Risk factors for development of HE include history of AD, skin occlusion by gloves, repeated contact to water and irritants [27, 28]. AD in childhood is the strongest individual risk factor for HE [29].

Molin et al. identified patterns of barrier protein expression in HE skin compared with healthy controls. Using mass spectrometry, the authors identified 185 candidate proteins differentially regulated compared with healthy skin. FLG, filaggrin 2 and hornerin were downregulated whereas desquamation-related enzymes, such as cystatin E/M, kallikrein-related peptidase 5 and 7 were upregulated. Additionally, upregulation of the antimicrobial peptides S100A7 and S100A8/A9 was observed. [30].

Skin barrier dysfunction is a major pathogenetic factor in HE. Heede et al. found an increased risk for HE among FLG mutation carriers [27]. About 10% of the European and 3–6% of the Asian population but only 1% of the African population are affected by FLG mutations [31]. FLG contributes on the one hand to mechanical and structural integrity of the epidermal barrier, and on the other hand, its degradation products are involved into the process of skin hydration and maintenance of acidic milieu. The latter is essential for the activity of enzymes, which are responsible for lipid synthesis, desquamation and skin inflammation. Besides genetic factors, which result in impaired skin barrier, environmental determinants play an important role as well. Contact to irritants and water can lead to a disturbed epidermal barrier. Especially among high-risk occupations, such as hairdressers, kitchen staff, cleaners and craftsmen, an increased risk for development of HE was found [27]. In a recent study TEWL was investigated after occlusion of the skin of the hands for either 72 consecutive hours or 8 h per day for 7 days. In healthy skin, TEWL was not influenced by occlusion, whereas it was increased in skin previously irritated by sodium lauryl sulphate. [32] Therefore, it can be concluded that especially in diseased skin occlusion should be avoided or reduced to a short amount of time. If protective gloves are required for a time period of more than 10 min, cotton gloves can be worn underneath [8]. Wang et al. found downregulated expression of caspase-14, elevated TEWL and PH in lesional skin of CHE patients [33].

A cornerstone in the management of HE is avoidance of irritants and allergens [8]. Protection of the skin involves the use of protective gloves to avoid contact to irritants and allergens. They should be chosen according to individual allergies and the irritant spectrum. However, occlusion for longer

time periods can cause further damage to the skin barrier. In this case, it is highly recommended to wear cotton gloves underneath protective gloves [8]. Hand eczema is associated with increased contact sensitization rates, especially in case of persistent HE. Patch testing should be performed in all HE patients with HE persisting for 3 months or longer [8, 20, 34]. Patient education and training is essential part of HE therapy [35]. Corti et al. developed a systematic educational program on skin care and protection for patients with hand eczema. Hand eczema symptoms improved significantly as a result of patient education and pharmacological treatment after 3 months [36]. In Germany, employer's liability insurances offer skin protection seminars for patients with occupational HE [37]. However, for subjects with non-occupational hand eczema, these training programs are not available. A recent study investigated the effectiveness of sending text messages to affected individuals to remind them of their medication and address preventive behaviour. It was found that subjects who received the message presented a better adherence to therapy and an increased use of moisturizers. [15]

Emollients contribute to the restoration of the epidermal barrier by hydration, and retaining moisture by providing a protective seal, as suggested by the "outside in" approach [11]. Christoffers et al. reviewed recent literature regarding the effect of different interventions for hand eczema. They found topical corticosteroids and UV therapy to be the standard treatments; however, it remains unclear if one therapy is superior over another. Comparing efficacy of narrow band UVB and PUVA therapy, little to no difference could be found [38••]. In a recent study of Kumari et al., the vitamin A derivative alitretinoin was found to be effective in restoration of the epidermal barrier after treatment for a duration of up to 27 weeks with 30 mg of alitretinoin daily. The authors demonstrated that alitretinoin contributes to normalisation of regulation of epidermal barrier genes and proteins, such as FLG, claudin 1, loricrin and cytokeratin 10 [39]. Dupilumab, a new biologic treatment approach for treatment of AD, was reported to be effective in off label use in HE. However, further studies will be needed [40, 41]. Recent data confirmed that the topical Janus kinase/signal transducers and activators of transcription (JAK-STAT) inhibitor delgocitinib might be a potential new treatment option for hand eczema. Delgocitinib reduces inflammation in hand eczema by inhibiting several cytokine-mediated signalling cascades, JAK1, JAK2, JAK3 and tyrosine kinase [42•].

## Atopic dermatitis

AD is a common, inflammatory skin disease, characterized by xerosis, pruritus and dermatitis [43••]. Epidermal barrier dysfunction and abnormal immune response via T-helper 2 cells (TH2) are typical findings in AD subjects [5, 6]. Transepidermal water loss (TEWL) is increased in AD skin [2, 5, 6, 47, 48]. During the past years, the treatment of AD rapidly involved and novel topical as well as systemic agents became available or are in development.

In 50% of moderate to severe AD cases, FLG mutations can be found [31]. Mutations in FLG present not only a risk factor for development of AD, but it is also a disease modifier. Subjects with AD related to filaggrin mutations present higher long-term medication costs and more frequent hospitalisations [44•]. In

the Barrier Enhancement for Eczema Prevention (BEEP) trial, it was found that daily use of emollients during the first year of life can help to prevent AD [45]. Also, AD is characterized as natural moisturizing factor (NMF) deficient diseases. Urea was effective in skin hydration since it is part of the skin's NMF source and regulates genes involved in the formation of the epidermal barrier [46].

A few years ago, topical calcineurin inhibitors (TCI) (tacrolimus, pimecrolimus) have been introduced for treatment of AD [49]. Comparing the effect of tacrolimus ointment 0.1% and betamethasone valerate 0.1% cream, the latter was found to significantly reduce skin barrier function after being used twice daily for 4 weeks, whereas tacrolimus 0.1% ointment, used with the same regimen, improved barrier function [50]. Chittock et al. compared the effect of betamethasone valerate 0.1% cream to tacrolimus 0.1% ointment applied twice weekly. Betamethasone valerate 0.1% preserved the epidermal barrier function, though the skin surface pH increased significantly with associated loss of SC cohesion. On the contrary, integrity of SC was improved by tacrolimus 0.1%, and protease activities were significantly reduced [51]. For many years, only unspecific anti-inflammatory drugs were available for therapy of AD. However, latest discoveries in the pathogenesis of AD have made the development of more specific, yet broad acting agents, possible. Crisaborole, a phosphodiesterase-4 inhibitor, leads to decreased cytokine production (e.g. IL-2, IL-4, IL-31) by inhibiting the degradation of cyclic adenosine monophosphate (cAMP) [52]. Crisaborole ointment 2% was found to be an efficient in reduction of disease severity and pruritus severity compared with vehicle. Due to its favourable safety profile, it is an option for short-term and long-term management of children and adults with mild to moderate atopic dermatitis [53–55].

Increased TH2 activity, which is typical for AD, enhances IL-4 and IL-13 production. This causes downregulation of FLG, keratin, ceramides and cell adhesion molecule production. Dupilumab, a new monoclonal antibody approach in AD therapy, modulates signalling by IL-4 and IL-13 receptor blockage and is found to ameliorate AD significantly and contribute to restoration of epidermal barrier [5, 56–58].

In recent studies, further treatment options for AD are being investigated. The AD subset depends on patient characteristics such as atopic status, ethnicity, FLG mutations and age. This variable phenotype might require individualized therapeutic approaches or dual cytokine targeting. Promising results for treatment of AD have been suggested in studies with broader acting agents such as JAK inhibitors, but also targeted treatments antagonizing Th2-pathway immune components are in centre of interest. Improvement of AD-related pruritus was reported in studies investigating anti-IL-31 monoclonal antibodies. Furthermore, anti-IL-13 monoclonal antibodies (tralokinumab, lebrikizumab) are showing favourable data in AD trials [59••].

The relationship between AD and contact allergies is controversial. While some studies found increased contact sensitization rates in AD subjects [6, 47], negative correlation has also been described [60]. Rundle et al. found an increased tendency for nickel sensitization in AD subjects which might be explained by the nickel binding capacity of FLG, which can be abnormal due to mutations in AD patients [20, 47].

**Table 1. Characteristics of contact dermatitis, hand eczema and atopic dermatitis**

|                    | Pathogenesis                                                                                                                                         | Feature                                                                                                                                                                                                            | Diagnosis and therapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|--------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Contact dermatitis |                                                                                                                                                      |                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| ACD                | Contact sensitisation: Most commonly identified allergens are bare metals, fragrances and preservatives [15]                                         | No characteristic biomarkers identified [16]<br>Dermal infiltrate more intense and deeper than in ICD [19]                                                                                                         | PT if contact allergy suspected. PT always indicated after 3 months disease duration [15]<br>Avoidance of offending allergen [15]<br>Emollients provide hydration and “sealing” of epidermis [11]                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| ICD                | Irritant damage: Repeated exposure to weak irritants water, detergents [18]<br>Single exposure to strong irritants [18]<br>Often multifactorial [15] | Increased autofluorescence due to scaling and reactive epidermal proliferation [19]                                                                                                                                | Active ingredients containing creams: ceramide containing formula leads to improved skin hydration and reduction of TEWL [22]<br>Barrier protection cream: provision of protective layer, recommended as prophylactic agent [24]<br>Combination of hand protectant cream, cleanser and repair cream found to be effective in skin hydration and improved barrier function in irritant contact dermatitis, unclear if skin protection cream superior to vehicle [24]<br>Topical corticosteroids: effective to suppress inflammation but limited use due to epidermal thinning, increased TEWL, abnormal keratinocyte differentiation and changes in stratum corneum [26] |
| Hand eczema        | Contact to irritants, allergens, occlusion, history of AD [28]<br>History of AD in childhood strongest individual risk factor [29]                   | Downregulation of FLG, FLG 2, hornerin, upregulation of desquamation-related enzymes (cystatin E/M, kallikrein-related peptidase 5 and 7) and antimicrobial peptides (S100A7, S100A8/A9) [30]<br>FLG mutation [27] | Patient education and training regarding skin protection and care [36, 37]<br>Avoidance of irritants and allergens (e.g. wearing of cotton gloves underneath plastic gloves if being worn for more than 10 min, avoidance of skin occlusion) [8]<br>If disease duration over 3 months patch testing recommended to rule out underlying contact sensitisation [8, 20]<br>Emollients contribute to restoration of the epidermal barrier and hydration by providing a “protective seal” [11]<br>Topical steroids and UV therapy were found to be standard therapy, superiority of one to another remains unclear. Comparing efficacy of narrow band UVB and PUVA therapy   |

Table 1. (Continued)

|    | Pathogenesis                                                                                                                                                        | Feature                                                         | Diagnosis and therapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| AD | <p>Abnormal immune response via T-helper 2 cells [5]</p> <p>FLG mutations as disease modifier with higher long term medication costs and hospitalisations [44•]</p> | <p>FLG mutations in 50% of moderate to severe AD cases [31]</p> | <p>little to no difference could be found [38••]</p> <p>Alitretinon 30 mg/day effective in restoration of epidermal barrier after 27 weeks [39]</p> <p>Dupilumab reported effective in off-label use [40]</p> <p>Increased TEWL [48]</p> <p>Primary prevention: daily use of emollients during first year of life effective for high risk children [45]</p> <p>Urea containing emollients since AD is a natural moisturizer deficient disease [46]</p> <p>Topical calcineurin inhibitors as follows:</p> <ul style="list-style-type: none"> <li>• Tacrolimus 0.1% superior to low potency corticosteroids, pimecrolimus 1% and tacrolimus 0.03%, equivocal results when comparing tacrolimus 0.1% to moderate to potent corticosteroids. No evidence was found regarding skin atrophy or increased risk of malignancies [49]</li> <li>• Comparing the effect of tacrolimus ointment 0.1% and betamethasone valerate 0.1% cream, the latter was found to reduce barrier function (BF) after 4 weeks whereas tacrolimus 0.1% improved BF [50]</li> <li>• Tacrolimus 0.1% improved stratum corneum (SC) integrity and reduced protease activity, whereas betamethasone valerate 0.1% caused increased surface pH and loss of SC adhesion.</li> </ul> <p>However, BF maintained preserved Crisaborole 2% ointment as an option for long-term management for patients with mild to moderate AD due to favourable safety profile [53••]</p> <p>Dupilumab, a IL-4 and IL-13 monoclonal antibody is found to ameliorate AD significantly [57]</p> <p>Various clinical trials of specific (e.g. IL-17C antagonist, IL-22 inhibitor) and nonspecific agents (e.g. JAK</p> |

**Table 1.** (Continued)

| Pathogenesis                                                                                                                                                                                                                | Feature | Diagnosis and therapy                                                                                                                                                                |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                                             |         | inhibitors, a dual JAK-SYK inhibitor, histamine H4R antagonist) revealed favourable outcomes, and a new treatment paradigm is expected to become available in the near future [59••] |
| <i>ACD</i> allergic contact dermatitis, <i>AD</i> atopic dermatitis, <i>FLG</i> filaggrin, <i>FLG 2</i> filaggrin 2, <i>ICD</i> irritant contact dermatitis, <i>PT</i> patch testing, <i>TEWL</i> transepidermal water loss |         |                                                                                                                                                                                      |

Use of emollients and topical drugs on inflamed skin may facilitate penetration of allergens and cause contact allergy. However, the TH2 dominant immune response in AD subjects seems to decrease the risk for contact sensitizations compared with healthy controls [6]. Surprisingly, Hamann et al. found similar contact sensitization rates in subjects with and without AD by reviewing 74 manuscripts, published between 1964 and 2016. While the prevalence of contact sensitization was found to be increased among AD patients in general population studies, in a pooled analysis, no significant difference could be established. Increased sensitization rates for chromium and compositae mix was found in a sub-analysis. Chromium sensitization might be explained by the increased penetration rate in FLG deficient skin. Though, the reason for increased compositae sensitization remains unclear [60].

## Conclusions

Skin barrier defects can be caused by endogenous and exogenous factors. Among the latter, irritant damage and contact sensitization play an important role [15]. Mutations in the FLG gene are a major endogenous risk factor for skin barrier defects. FLG gene mutations are typical findings in AD and HE patients [27].

Multimodal therapy is required for the restoration of the skin barrier. First of all, the triggering factors must be identified. Patch testing should be considered for the detection of contact sensitization [15]. Avoidance of contact allergens and irritants is crucial for successful therapy. Therefore, protective gloves should be worn during skin damaging activities. However, it should be considered that occlusion by gloves for longer periods of time can cause further skin impairment. In this case, the use of cotton gloves worn underneath protective gloves should be considered [8, 17]. Regular use of emollients and moisturizers has to be regarded as basic therapy [4, 8, 15]. They provide moisture to the epidermal barrier, and some contain active ingredients which might even stimulate production of intercellular lipids [21]. Further studies regarding this topic are needed. Topical corticosteroids (TCS) are effective in suppressing inflammation, though, if used for longer periods of time, can cause epidermal thinning and increased TEWL, which indicates barrier impairment [11, 28]. In AD therapy, topical calcineurin inhibitors were found effective for the restoration of the

epidermal barrier function. Tacrolimus 0.1% was superior to betamethasone valerate 0.1% in daily as well as in twice weekly use, regarding the restoration of the epidermal barrier [50, 51]. In the last years, various systemic therapies have become available for skin diseases with impaired barrier function. Worth mentioning in particular is alitretinoin, a vitamin A derivate, which is an effective drug for treatment of chronic HE resistant to topical potent corticosteroids and contributes to improvement of epidermal barrier function [39]. New treatments for hand eczema are currently under investigation, among them delgocitinib, a pan-JAK inhibitor which has already shown positive first results. New systemic therapeutic approaches, such as JAK inhibitors and Th2-pathway immune component antagonizing agents, seem to be effective in restoration of the skin barrier [59, 61, 62]. However, clinical trials are still pending. Dupilumab was the first of the new treatment options for AD that became available (Table 1) [56, 57, 63].

Complex treatment regimens of skin barrier defects require profound patient training, and some educational programs are already available [17, 35, 36]. However, additional ways to increase patient information and awareness should be established.

## Compliance with ethical standards

### Conflict of interest

Sonja Molin and Thomas Herzinger have received honoraria as advisor and/or speaker and/or participated in clinical trials from Leo Pharma, Pfizer and GlaxoSmithKline. Hannah Aviv declares that she has no conflict of interest.

### Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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