Best Practices, New Perspectives and The Perfect Emollient: Optimizing the Management of Contact Dermatitis

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Abstract

Contact dermatitis (CD) is caused by environmental agents, irritants and allergens, that penetrate the epidermis and lead to inflammation. An intact skin barrier prevents penetration and is important in maintaining healthy skin. Classical diagnosis of CD is made using the patch test, and traditional treatment strategies for CD promote skin barrier integrity and resolve the inflammatory component of the condition. This can be achieved by using emollient-based therapy, which is most important for skin barrier repair, and in addition to topical glucocorticosteroids, which are used in severe cases of CD and are most effective in reducing inflammation. Preventative measures, such as irritant and allergen avoidance in the workplace, also play a pivotal role in effective CD management. Moreover, CD management necessitates a holistic approach that incorporates prevention, barrier repair and inflammatory resolution to ensure optimized efficacy. It is also important to consider potential barriers to optimal management when evaluating individuals with CD, such as limited patient education or poor access to care. Finally, key literature and our own clinical practice experience have highlighted the value of patient preference, as well as safety, efficacy and simplicity, in building the perfect emollient.

Key words: Contact dermatitis, emollient, skin barrier

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The impact of a damaged skin barrier in contact dermatitis

The skin's role as a barrier to chemical, physical and microbial threats is an important function. Early models of the skin compared the outermost stratum corneum to a brick wall, with keratinocytes and intercellular lipid lamellae forming its respective bricks and mortar [1, 2]. However, while the stratum corneum was previously considered to be a dead, exfoliative structure without active function, its role in maintaining homeostasis in the skin is now apparent [2]. A simplified model of skin structure is shown in **Figure 1**: the epidermis has a columnar arrangement, with deeper layers characterized by a columnar structure, with flatter keratinocytes at the top of the epidermis [3, 4]. Keratinocytes are the site of a number of biochemical processes, including production of the structural proteins keratin, loricrin, involucrin, and filaggrin, as well as lipid synthesis, so play a pivotal role in the development and maintenance of the skin barrier [5, 6].

[Figure 1 near here]

Disruption of the skin barrier is at the centre of many inflammatory dermatoses, and contact dermatitis (CD) is no exception. The first step of CD pathogenesis is disruption of the skin barrier by mechanical stress, exposure to harmful chemicals, or prolonged contact with water or detergents, leaving the skin vulnerable to penetration by allergens, irritants, and pathogens. Langerhans cells (LCs) and T cells in the skin react to allergens, causing sensitization, inflammation, and exacerbation of dermatitis [7]. This allergic reaction is coupled with increased transepidermal water loss and cell proliferation in an attempt to remove any offending allergen from the skin [8].

The signs and symptoms of CD can vary depending on factors such as whether dermatitis is acute or chronic, the nature of the offending irritant or allergen, and the localization of the dermatitis. Symptoms include itch, burning sensation, pain, dry skin, papules, and vesicles, as

well as lichenification and fissure in chronic CD (**Table 1**) [9]. From a patient's perspective, itch is an important symptom that can impair quality of life and interfere with occupational activities. While itch associated with CD may not deemed as problematic by clinicians, especially when compared with the itch–scratch cycle in atopic dermatitis (AD), it is important CD treatment exhibit some anti-pruritic effects. Fissures associated with repeated contact with irritants are a consequence of thickening of the epidermis, which causes inelastic skin that easily cracks [10]. Fissures on the finger tips are common in CD and the associated pain may respond poorly to nonsteroidal anti-inflammatory drugs [11, 12].

Classification of CD

CD has traditionally been classified by the nature of the causative agent: an irritant (i.e. irritant CD, or ICD) that produces direct chemical toxicity, or an allergen (i.e. allergic CD, or ACD) that induces antigen-specific T cell activation by autoantigenicity [13]. In the past, irritation and allergy were considered to be separate mechanisms; more recently, a relationship between the two has been established, with ICD considered an excellent example of non-specific innate immunity while ACD is an example of specific adaptive immunity [14, 15].

Of note, the onset of ACD is also characterized by two distinct phases: sensitization and elicitation. Sensitization is observed following first exposure to a contact allergen, which non-specifically activates keratinocytes to release inflammatory cytokines, leading to an influx of activated LCs to the site of allergen contact. Some antigen-presenting LCs move to the lymph nodes, where they active antigen-specific T cells. The activated T cells proliferate to form Th1 and Th17, which are subsequently released into the circulation and migrate to the dermis. Elicitation is observed if the same contact allergen penetrates the skin for a second time, stimulating antigen-specific memory T cells, leading to the recruitment of inflammatory

cytokines and an allergic reaction [16]. The reaction observed in ACD contrasts significantly with the modulatory response thought to be elicited when healthy skin with an intact barrier is exposed to a contact allergen. The immune-mediated reaction in ACD also contrasts to ICD, which can occur in any individual without prior sensitization.

[Table 1 near here]

While typically divided between ICD and ACD, a number of other CD classifications exist (**Table 1**). For example, 'protein CD' has emerged in recent years as an additional subset of CD that warrants distinction from ICD and ACD. In ICD and ACD, irritants and haptens have a molecular weight of less than 1000 Da; however, larger proteins with a molecular weight much greater than 1000 Da can induce the same eczema pattern observed in ICD and ACD. Traditionally, protein CD has been grouped with contact urticaria (CU); however, immunological CU is an example of a typical Type I immune reaction, while ACD is a typical Type IV reaction, and 'protein CD' is likely to be an IgE-mediated eczematous reaction.

An additional key subcategory of CD is airborne CD (ABCD), where dermatitis arises due to airborne agents. While not as widely discussed as other subsets of dermatitis, ABCD is becoming increasingly prevalent, primarily due to rising global temperatures, which create a wider niche for insects and consequently new airborne allergens. For example, the processionary caterpillar *Thaumetopoea pityocampa* Schiff, which produces the irritant thaumetopoein, has spread into parts of northern Europe from the south of France, with populations of the caterpillar identified in Belgium, the Netherlands, Sweden and the UK [17]. ABCD is particularly prevalent in outdoor recreational settings and occupations associated with poor ventilation, such as factory environments [18]. Common causative agents that can induce ABCD include fibers, such as glasswool or rockwool, and dust

particles [19], as well as a range of other compounds (e.g. the preservative methylisothiazolinone (MI)has been reported as a causative agent of ABCD in painters [20]).

Other approaches to classification may be based on specific skin sites affected by CD, rather than the offending agent itself. Hand dermatitis, or hand eczema, is an example of this and is often considered individually. Efforts to classify different varieties of hand eczema have proven difficult, owing to its varied etiology, morphology, and symptoms [21].

Barrier impairment is as an integral risk factor for CD, with enhanced penetration of xenobiotics into the skin reducing the threshold for induction of CD by irritants and allergens. As a result, ACD is often preceded by ICD. Furthermore, potent allergens such as urushiol (poison ivy) may also be potent irritants, causing barrier disruption, irritation, and sensitization in a single contact.

Individuals with an impaired skin barrier, such as those with ichthyosis (dry, scaly skin) are particularly vulnerable to ICD, as are patients with AD, where dermatitis appears to develop because of genetic predisposition that leads to a reduced response threshold against allergens. Furthermore, many ICD patients appear to have a history of atopic conditions; a recent study in 152 adolescents with hand eczema found that 73% of patients had a history of AD [22], suggesting a possible relationship between the two dermatoses. Hand eczema in atopic patients (i.e. patients with a predisposition to AD, allergic rhinitis/conjunctivitis, allergic bronchial asthma, and food intolerance) is also referred to as atopic hand eczema, and may persist even after avoiding contact with irritant and allergens.

Occupational exposure to contact allergens is an important risk factor for CD. Hand eczema is the most important occupational skin disease, with an estimated 52% of hand eczema patients suffering due to occupational exposure [23]. In a survey evaluating the consequences

of hand eczema in occupational settings, Cvetkovski et al. found that higher proportions of sick leave were reported in patients working in food preparation when compared with other industries [24]. Individuals working in other occupational settings with high exposure to irritants, such as hairdressing, food preparation, and mechanics (who often also encounter mechanical stress), are also at particular risk of CD [25].

In addition to study of structural and biochemical disruption of the skin barrier, a number of investigations have sought to investigate the genetic basis of CD. In a landmark paper, Smith et al. were the first of many authors to report loss-of-function mutations in the structural protein filaggrin in ichthyosis [26]; studies published shortly afterwards reported that loss-of-function mutations were observed in approximately 30% of patients with AD in a number of European cohorts [27]. Further studies have identified the presence of distinct filaggrin mutations in Japanese and Chinese patient populations [28, 29, 30]. In addition, African-American patients with AD were found to have single nucleotide polymorphisms in claudin 1, a key protein in epithelial barrier function; such mutations were not commonly observed in European-American patients with AD [31].

While these studies provide a significant breakthrough in the understanding of AD, it has been proposed that filaggrin may not be the only functionally-relevant mutation in effect in AD. This suggestion is primarily based on the relative rarity of monogenic diseases and the proposed polygenetics of similar diseases, such as psoriasis [32]. Despite efforts to identify other gene changes that may predispose an individual to AD, no further mutations have yet been reported. Although possible polymorphisms have been identified, it is unclear whether these are functionally relevant [33]. While filaggrin mutations are not universally reported in AD, analyses of histology and filaggrin antibodies have revealed that expression of the protein is consistently lower in patients with AD [34]. However, it remains difficult to determine what other factors (e.g. the presence of other polymorphisms) may be responsible

for reduced filaggrin expression and, consequently, this is a topic that warrants further investigation.

After the association between filaggrin and AD was discovered, it was proposed that mutations to the gene may also be functionally relevant for CD. However, literature to date has yet to identify a significant association between filaggrin mutations and CD; rather, the severity of CD appears to depend more on an individual having an AD phenotype than a filaggrin genotype [35]. Research has also been undertaken to identify other genes that may predispose an individual to CD, and a number of candidate genes have been identified from different receptor pathways and processes associated with allergen-specific and non-allergen specific susceptibility [36]. Unfortunately, to date, no functionally relevant mutations or polymorphisms have been identified.

A number of other key genetic defects have been reported in atopic skin that are thought to leave patients at risk of ICD. A study by Jakasa et al. reported that the penetration profile of the irritant sodium lauryl sulfate (SLS) was different in skin with AD compared with healthy controls, suggesting that AD skin has distinct barrier characteristics compared with healthy skin [37]. In addition to filaggrin mutations, these alternative characteristics are thought to derive from defects in stratum corneum lipids. For example, total ceramide level, as well as the levels of five individual ceramide classes, were found to be significantly lower in affected sites of AD patients compared with healthy sites in healthy individuals, while some ceramide classes were expressed at significantly higher levels in AD patients compared with healthy controls [38]. As low ceramide levels have been associated with greater sensitivity to SLS-induced ICD [39], the compromised ceramide profile seen in AD patients is likely to predispose them to greater risk of ICD. Recent research has also suggested that ACD skin may display similar barrier abnormalities to AD, a finding that warrants further investigation [40].

Mechanistic and genetic studies have established the pivotal role of tight junctions (of which claudins are a central component) in the maintenance of skin barrier integrity; therefore, defects in the claudin family are also thought to contribute to the impaired barrier observed in AD [41, 42]. Results of an analysis by De Benedetto et al. were in-keeping with these observations [31]. The authors reported substantially reduced expression of claudin-1 and claudin-23 in patients with AD, along with significantly impaired barrier function. Taken together, these observations demonstrate the importance of claudins in the effective function of the skin barrier; therefore, the impairment observed in AD leaves patients at significant risk of outbreaks of ICD.

A holistic approach to optimize management – how do we treat CD and restore the skin barrier in practice?

Our understanding of the skin barrier has informed modern approaches to CD management, which promotes a holistic approach with three main facets: prevention and allergen avoidance; restoration of the skin barrier; and resolution of inflammation as necessary (**Figure 2**).

[Figure 2 near here]

Diagnosis of CD

Despite their etiological differences, there is significant overlap between the symptoms of ICD and ACD, making it difficult to distinguish between the dermatoses in a clinical setting and using skin histology. Furthermore, the same patient can suffer different types of CD concomitantly, so a correct dermatological approach is necessary before proceeding with classification. The patch test remains the clinical gold standard and the only test that is generally reliable enough to assess whether a patient is suffering from ACD [43]. While quick and easy to perform, the interpretation and scoring of patch test results can be challenging, to the extent that new approaches to testing are being explored. However, establishing a new consensus in the presence of such well-established methodology is challenging. If a patch test is insufficient to confirm a diagnosis of ACD, other available tests include open tests, semi-open (semi-occlusive) tests, and repeated open application tests (ROAT). Each, however, has its own advantages and disadvantages (**Table 2**).

[Table 2 near here]

An important key issue with allergen testing is that each individual test can lead to sensitization and induction of CD, or indeed reactivation of near-resolved sensitization. It is possible, therefore, that experienced patients may refuse repeated allergen testing.

Current treatments

What can we do about the inflammatory component of CD?

CD treatment guidelines recommend that once ICD or ACD has been diagnosed, the first step of treatment is to reduce inflammation. The traditional and most established means of tackling the inflammatory component of CD is topical glucocorticosteroids. A study by Fritsch et al. demonstrated that once-daily treatment with methylprednisolone aceponate (MPA) led to rapid relief of skin irritation after approximately 5 days and clearance of symptoms after 20 days; no significant increase in efficacy was observed in patients receiving a twice-daily dose [44]. The efficacy of once-daily application of corticosteroids was consistent with observations by Mensing and Lorenz, where approximately 40% of eczema patients treated with MPA were symptom-free after 12.5 days [45]. In addition, corticosteroids appear to exhibit a secondary anti-pruritic effect by reducing inflammation. MPA treatment has also been found to reduce itch intensity in patients with ACD after 5 days, which is thought to be an indirect consequence of resolving inflammation [46].

Side effects of corticosteroid use are an important consideration and a key concern for patients. To address this, a therapeutic index has been developed to assist in balancing the efficacy of a given corticosteroid against potential unwanted effects (**Figure 3**) [47]. Some researchers challenge use of the therapeutic index because the effects of corticosteroids, both positive and negative, depend on their affinity of steroid receptors, meaning potent corticosteroids can cause severe side effects, whereas less potent corticosteroids cause fewer side effects. Because side effects are dose-dependent, corticosteroids with high efficacy and a

high risk of unwanted side effects should be used at lower doses, or for a shorter period of time.

[Figure 3 near here]

Although not licensed for CD, calcineurin inhibitors are occasionally used to resolve AD, but are a considerably less effective treatment option for AD than fast-acting, short-term corticosteroids [48]. However, a study investigating pimecrolimus demonstrated a degree of skin barrier repair activity, performing better than betamethasone [49]. In a clinical setting, calcineurin inhibitors have been shown to be particularly useful as a treatment for chronic CD of the eyelid; the use of corticosteroids is limited in dermatitis of thin and sensitive skin areas, owing to its association with adverse events such as skin-thinning [50]. However, further independent trials are necessary to increase the level of evidence for topical calcineurin inhibitors to treat hand eczema.

How can we restore the skin barrier?

As our understanding of the role of the skin barrier in CD has improved, approaches to CD treatment have increasingly incorporated repair of the damaged skin barrier as a major element. Restoration of skin barrier function can be achieved by the use of creams and ointments, also called moisturizers and emollients [51]. The terms ‘moisturizers’ and ‘emollients’ are often used interchangeably, but moisturizers typically contain humectants that bind water molecules to hydrate the stratum corneum [51]. In contrast, emollients form a semi-occlusive layer on the surface of the stratum corneum that helps prevent water from evaporating from the skin surface, allowing it to penetrate the stratum corneum and increase skin hydration (**Table 3**) [52]. In addition, emollients produce a protective layer that reduces the penetration of harmful chemicals into the skin [53]: emollient preparations rich in lipids (non-polar) should reduce the penetration of water-soluble chemicals, while creams rich in

water (polar) should reduce the penetration of lipophilic chemicals. Furthermore, some emollients have been shown to interact with, and significantly impact the physiology of the skin barrier [51]; in doing so, emollients are able to restore barrier function, which can indirectly relieve the itch and inflammation associated with both ICD and ACD. This was reflected in research by Lodén, who found that use of a moisturizing cream accelerated the rate of recovery in surfactant-damaged skin and reduced SLS-induced irritation in normal skin [54]. Use of an emollient alone, without a corticosteroid cream, is usually sufficient to treat mild cases of CD. While there are no specific criteria for defining 'mild' cases of CD, these patients can typically be identified based on the extent and intensity of their CD, supported by their physician's personal experience and expertise.

In addition to symptom relief, emollients offer a valuable tool in CD prevention. Daily use of emollients is thought to improve the integrity of the skin barrier in CD patients [54]. As such, use of an emollient should be part of a normal skincare routine in any individual who has a problem with their skin barrier, regardless of its cause, to reduce symptoms of CD and ensure that risk of sensitization is minimized. The preventative effect of emollient therapy has been evaluated in AD, with an investigation by Simpson et al. showing that daily emollient use led to a statistically significant reduction in the cumulative incidence of AD in children with a family history of atopic disease [55]; similar high-quality studies will further support the value of non-steroidal products in CD prevention.

It should be noted that excessive use of emollients is not recommended in certain cases. For example, if an individual is at risk of occupational exposure, use of the cream during their working day may increase allergen penetration: in instances of ABCD due to fibers or sharp dust particles, moisturizing creams are contraindicated as they may exacerbate irritation [19]. For these individuals, it is recommended that an emollient is used first thing in the morning, at lunchtime and late in the evening.

Efforts to adopt a holistic approach to CD management may mean that a corticosteroid and emollient are prescribed together in future, targeting inflammation and repairing the skin barrier simultaneously. Whilst this has yet to be investigated in a clinical trial setting, further research is warranted to ascertain the safety and efficacy of such an approach in CD management.

In addition to optimizing treatments and treatment strategies, it is important to consider other factors, such as age, in CD management. Children are sensitized as easily as adults, but usually have limited exposure to allergens. ACD is therefore less common in children than in adults, but rates of sensitization in children have increased in recent years [56]. A review by Simonsen et al. found that the prevalence of positive patch test reactions and ACD in selected groups of Danish children was 26.6–95.6% [57]. Despite the significant range in reported ACD prevalence, these rates were significantly higher than figures presented from similar studies in 1982 to 1998, where positive patch tests were reported in 14.5–70.0% of cases [57, 58]. This may be as a consequence of increased exposure to allergens, including fragrances, cosmetics, food, medicines and preservatives. Significantly, ACD acquired in childhood can have important repercussions on daily life for patients and may affect their choice of occupation in later life [56].

Furthermore, the nature of the CD reaction does not differ between children and adults. While certain patterns of dermatitis are observed and are more typical of CD in children, the same eczema symptoms are seen regardless of age, and approaches to management should therefore be similar. The most common allergens in children are cosmetic ingredients, topical medicaments, and footwear, which exhibit distinctive dermatitis patterns in characteristic areas of the skin: CD due to cosmetic ingredients is typically seen in the face, hands or joints; CD due to topical medicaments is typically seen in the ear or anogenital region; and as would be expected, CD due to footwear is typically limited to the feet [59]. Allergens in children

with suspected ACD are determined using patch testing [43]; when using the patch test in children, it is proposed that the baseline series of test allergens is reduced to 9, rather than the 30 used in adults [43], due to body space limitations and risk of active sensitization, as per the European Academy of Allergy and Clinical Inmunology recommendations [59]. This series includes the most common allergens affecting children, including nickel sulfate, fragrance mix I and II, and the preservatives methylchloroisothiazolinone (MCI), and MI. However, some significant allergens are excluded from the series, including Balsam of Peru and cobalt chloride, which are important to consider [43, 56].

In addition to a patient's age, it is important to consider the site of CD when looking to optimize management of the condition. In a study investigating the effect of two soaps of varying pH on the skin barrier of the hand and forearm, the authors reported that use of a soap at pH 7.5 led to significantly more skin barrier disruption on the back of an individual's hand than on their inner arm [Unpublished; data on file]. The fingertips and dorsal hand are particularly vulnerable to CD, possibly due to a greater level of allergen/irritant exposure or washing than other parts of the body [60, 61]. It is therefore important to identify the most suitable formulation for a particular area of the body to ensure varied sensitivities in different skin zones can be managed appropriately.

Preventative strategies

Approaches to CD prevention typically take the form of avoidance of an allergen/irritant altogether (or indeed its source), or avoidance of penetration, as well as avoidance of allergen sensitization in cases of ACD. However, this can be challenging to achieve in practice. Patients often encounter difficulty when reading ingredient lists on labels of cosmetic products due to the small font size and long chemical names [62], making it difficult for them to actively avoid an offending agent. Providing patients with better education on how to

identify causative allergens is of great importance, as the patients themselves are primarily responsible for facilitating effective allergen avoidance.

Prevention strategies can also be implemented on a larger scale. Primary prevention is based on regulation of allergen exposure either by legislation or regulations on the handling of allergens, with a view to reducing exposure to allergens and thus the occurrence of CD [63]. Notably, primary prevention measures can be implemented among the general population or on a smaller scale within specialist working groups. Educating those at risk of CD, such as individuals at risk of occupational exposure or those with atopic tendency, is a central element of primary prevention and should be emphasized repeatedly. In recent years, the value of Personal Protection Equipment (PPE) has become increasingly apparent. PPE typically takes the form of hypoallergenic protective gloves and clothing. It is important to note that while gloves usually protect against irritants, they have the potential to be harmful, occasionally inducing hyperhydration or a Type IV reaction, in which case thin cotton liners can be worn underneath [63]. However, the negative effect of occlusion is thought to be limited [64]. Whilst the principle of using PPE is well-followed in the workplace, it is important that such good habits continue at home. For example, gloves should be worn for activities such as washing up, decorating, food preparation, and gardening, as well as during colder weather.

However, individuals looking to make use of PPE should be aware that provisions differ from country to country, and indeed from employer to employer, who may or may not cover the associated cost of PPE. It is also important to note that making time for preventative care can mean that an individual works at a slower pace than their colleagues. Furthermore, the stress associated with a limited job choice or a potential loss of income means that it is vital to provide patients with appropriate levels of support to ensure that this can be minimized.

To better understand how avoidance and other preventative strategies can be implemented in ACD, it is important to consider which allergens/irritants are most prevalent. Pollen is an important Type I allergen to consider in atopic eczema, but the most significant groups of Type IV allergens causing CD are fragrances, preservatives, and metals.

Fragrance

Fragrance ingredients are a frequent cause of ACD, to the extent that the EU Cosmetics Directive states that 26 known fragrance allergens must be declared on a product's ingredient list [65]. In the clinic, fragrance allergy is typically assessed using patch tests to one of two fragrance mixes, which contains a mixture of the strongest fragrance allergens. However, patients can also be allergic to other ingredients in cosmetics products, such as colorants and sunscreens, which must also be included in any allergy assessment.

The identification of fragrance allergens in consumer products is typically determined over three steps: baseline patch testing, analysis of fragrance components using thin layer chromatography, and analysis of fragrance chemical alerts by mass spectrometry [66]. Consequently, new allergens can be identified and prevalence assessed in epidemiological studies. Such epidemiological evidence is vital to influence legislation.

In addition to well-established fragrance allergens, oxidized fragrances, which need to oxidize before they become allergenic, are emerging as important contact allergens. As pure compounds, oxidized fragrances rarely lead to positive patch test reactions, but have been shown to autoxidize following air exposure at room temperature, forming different oxidation products with strong sensitization potential. Examples of oxidized fragrances are the hydroperoxides limonene and linalool. The prevalence of limonene and linalool hydroperoxide sensitivity has been demonstrated in epidemiological data from Australia, Denmark, Singapore, Spain, Sweden and UK, where positive patch test reactions to limonene

and linalool ranged between 5.0–5.2% and 4.9–6.9%, respectively, of tested individuals [67, 68, 69, 70, 71].

Preservatives

All preservatives can induce contact allergy because they are reactive chemicals. Analysis of the prevalence of preservative sensitivity through patch testing showed parabens to be among the safest preservatives available, whereas the isothiazolinones (e.g. MI/MCI) and formaldehyde elicited the highest proportion of positive patch test reactions [72].

Notably, the prevalence of sensitivity to MI/MCI has risen significantly since 2006 [72]. First used in cosmetics in the 1970s, MCI was soon reported to be a strong allergen, but the less allergenic MI was deemed to be relatively safe and, thus, was increasingly used alone as a highly effective preservative. However, since 2012, allergy to MI has increased markedly, leading to an epidemic of allergy to the preservative [73, 74, 75]. In response, The European Commission has implemented a recommendation to ban MI from leave-on cosmetic products and to keep concentrations of MI below 15 ppm in rinse-off products [76], but to make the recommendation mandatory by law may take several years.

In recent years, dimethyl fumarate has also emerged as a key allergenic preservative; used frequently in items manufactured in China, dimethyl fumarate has led to an epidemic of so-called furniture-related dermatitis in Finland and the UK [77], and shoe contact dermatitis in Spain, after the preservative was used in shoebox packaging [78].

Metals

Metal CD, sensitization to metal ions, is common in the general population, although the use of metals is now well-regulated in Europe. For example, sensitization to chromate was very common in previous years, particularly in workers in contact with cement. However,

European Union legislation that prohibited use or supply of cement containing >2 ppm of chromate led to a significant decline in the incidence of ACD attributed to chromate in the UK [79]. Similarly, nickel, which is one of the most common causes of ACD, is not allowed to be released in concentrations greater than 0.5 μg nickel/cm^2/week when used in consumer items [80]. This guidance, published in 2011, has led to a reduction in nickel allergy in Denmark, Sweden, and Germany [80]; however, a study in Spain found that the prevalence of nickel allergy was as high as 40.1% in females aged between 41–60 years, compared with 10.5% of males in the same age range [81]. This further highlights a clear need for primary prevention, working collaboratively in local and international networks alike.

Occupational allergens

It is important to consider the distinct set of allergens that are of great significance in occupational settings. For example, ‘wet work’ is a significant risk factor for ICD and can occur when the hands are in contact with water, including water-diluted detergents, or where the wearing of gloves for prolonged periods results in hands becoming moist from perspiration [82]. In recent years, epoxy compounds have been among the main causes of occupational ACD, and are used frequently by construction workers or cosmetic professionals [83].

How can we define the perfect emollient?

The number of emollients currently available to treat CD can be overwhelming, so it is important to consider the components and formulations that make an emollient most effective.

Our improved knowledge of the function and role of the skin barrier in CD has provided a strong basis to develop and optimize emollient treatments. The ingredients commonly seen in emollient preparations today are very much built on our understanding of the skin barrier and how it can be enhanced (**Table 3**).

The ideal emollient

When considering CD, an ideal emollient must first and foremost be safe and effective. In light of this, ingredients such as dexpanthenol are particularly valuable: dexpanthenol is found in a number of cosmetic products, owing to its hygroscopic properties, which are thought to be attributable to the compound's moisturizing effects. Moreover, dexpanthenol has also demonstrated hydrating and barrier-repairing effects on atopic skin, providing a clinically observable anti-irritative effect [84, 85, 86]. An investigation into the effect of dexpanthenol on the skin barrier revealed that the excipient increases the molecular mobility of several lipid and protein segments of the stratum corneum to generate the properties of a hydrated skin in dehydrated conditions, thus improving skin barrier function [87]. The effect of dexpanthenol on filaggrin expression is a topic that warrants further research.

Ceramides are also among the important ingredients found in emollients. In physiological terms, stratum corneum lipids, ceramides, cholesterol, and free fatty acids occur in a 1:1:1 ratio in healthy skin; ceramide-dominant emulsions, which comprise a 3:1:1 ratio of these physiological lipids, have been used to repair the skin barrier for several years [88]. However,

more than 360 species of skin ceramide have now been identified and given the number of options available, it is important to determine which ceramides are the most effective. For example, ceramides with high molecular weight may penetrate the skin less readily than shorter molecules. There remains a need to further document the effects of different ceramides, or identify alternative ingredients that specifically stimulate ceramide production.

Indeed, an ideal emollient would stimulate filaggrin and ceramide production, rather than simply provide a means to replace or overcome the subsequent protein/lipid deficiency. While certain ingredients have been shown to stimulate filaggrin and ceramide in cell culture studies [Unpublished; personal communication], it is important to note that cell culture does not provide a perfect surrogate for the skin; thus, results from such studies should not be considered to provide definitive evidence for any given treatment effect.

Provided an emollient is safe and effective, other elements could also be incorporated into a preparation to further promote healthy skin. For example, maintenance of microbial eubiosis of the bacteria colonizing the surface of healthy skin, and indeed the association of certain bacterial species with dermatitis [89], could support the inclusion of an antimicrobial peptide in emollient preparations. Furthermore, while such ingredients may be of some benefit, emollient preparations should be as simple as possible, incorporating ingredients that significantly improve skin barrier function. A similar approach should be adopted when considering pH: while some products claim that they have a positive effect on skin pH, an ideal emollient should look to support the natural buffering capacity of the skin to maintain a normal pH, with minimal interference where possible.

In addition to active ingredients, preservatives are often an essential component of emollient preparations, particularly in products with a high water content such as creams and other lighter formulations. While preservatives have the potential to be allergenic, increasingly, a

mixture of preservatives can be used in skincare products, providing a viable alternative to one preservative used alone at a higher concentration.

Product formulation is a particularly important consideration in the context of patient compliance; while lipid-rich ointments are typically the most effective option for chronic skin diseases, foams and sprays are often preferred by the patient, as they provide a more pleasant, non-greasy preparation that is easier to apply [90]. However, it is essential that the efficacy of an emollient is not compromised by a formulation perceived by the patient to be more pleasant. In addition, different galenic formulations are required to treat different levels of allergen/irritant exposure as well as for different areas of skin, which have varying lipid content. For example, ointments are typically used to treat relatively thick skin, such as the palms of the hand and soles of the foot, while lighter cream and gels are preferred for the facial area and flexures [4, 91].

What are the barriers to optimal CD management?

Consideration of the patient perspective is key in effectively managing CD. However, a patient's understanding of the need to repair and protect their skin as part of their daily lifestyle can be poor, leaving them ill-equipped to properly manage and prevent their CD. Increasing dermatitis severity has been correlated with quality of life deficits, such as physical discomfort, sleep disturbance, and negative self-perception, as well as greater expenditure on lotions and emollients to resolve outbreaks of dermatitis. The same study also reported that patients with dermatitis do not access the expert medical care that could support them to better control of their condition [92]. It is therefore essential that patients are adequately supported to understand the need to repair and protect their skin as part of day-to-day care, and fully understand the implications of a positive patch test result.

In addition to patient education, providing better support for healthcare professionals across the multidisciplinary team will be key to addressing some significant barriers to optimizing CD management. Pharmacists, for example, should be better educated on CD as a condition and its management, to supplement their well-established understanding of the impact of different ingredients, while general practitioners, who can be confused by the number of emollients currently available, should be provided with a simple rationale and more streamlined options for treatment. Dermatologists could also benefit from further support in assessing the current treatment landscape for CD and overcoming the difficulties commonly associated with the condition.

Expert panel consensus recommendation to managing CD

The maintenance of an intact skin barrier forms the basis of current treatment strategies to manage CD. Skin barrier protection can encompass preventative measures, which can take the form of simple allergen avoidance, use of an emollient to ensure maintenance of skin barrier integrity, patient education or utilisation of PPE particularly in occupational settings. Equally, active treatment interventions can work to restore the skin barrier; emollient-based therapy, for example, is a key component of CD management and should be included as part of a patient's normal daily dermatitis care to restore and prevent skin barrier damage. Corticosteroids remain the main tool for resolution of the inflammatory component of dermatitis, but emollient treatment is often sufficient to resolve mild symptoms of CD. Taken together, an optimized approach to CD management must be holistic, and incorporate all three strategies (prevent skin barrier damage and allergen avoidance, reduce inflammation and restore skin barrier) to allow for effective CD resolution, as well as prevention where possible.

It is important to distinguish between different types of CD, specifically ICD and ACD, as identification of an offending allergen can inform avoidance strategies. The patch test remains the gold standard for distinguishing between ICD and ACD. However, other tests may be required to overcome the limitations of patch testing, such as its occlusive effect and occasional difficulties in interpretation.

Improving the education available to both those at risk of CD (particularly in occupation settings and patients with AD) and members of the multidisciplinary team will be key to addressing unmet needs in CD, which generally stem from a poor understanding of the need to maintain skin barrier integrity as part of CD prevention.

Finally, an ideal emollient would demonstrate significant clinical efficacy and safety, provide a cosmetically-acceptable and cost-effective option for patients, and would consist of select, optimal ingredients which effectively reinforce the skin barrier. Similarly, its formulation should provide an easy-to-apply option for patients, without compromising treatment efficacy. Indeed, selecting a suitable galenic formulation is key to ensuring patient compliance; this will encourage daily use of an emollient as part of CD prevention, allowing for restoration and maintenance of an intact skin barrier.

Conflicts of Interest

Martin Metz is or was a speaker and/or consultant for Beiersdorf, Bayer AG, Novartis AG and Laboratoires Pierre Fabre.

Ana Gimenez-Arnau has been a medical advisor for Uriach, Almirall, Genentech, Novartis AG, GlaxoSmithKline plc and Bayer AG, has received research grants supported by Bayer AG/Intendis, Uriach and Novartis AG, and has engaged in educational activities sponsored by Uriach, Novartis AG, Genentech Inc, Menarini Pharma, Leo Pharma, GlaxoSmithKline plc, MSD and Almirall.

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Tables

Table 1: Clinical forms of contact dermatitis (adapted from Brasch et al.) [9]

Clinical forms of dermatitis	
Form of dermatitis	**Description**
Irritant contact dermatitis (ICD)	• Lesions prevalently restricted to the site of toxic agent/irritant exposure • Clearly demarcated in the acute stage, spreading in the chronic stage • Broad spectrum of erythema to necrosis • Presentation strongly dependent on acuteness and toxic agent • Relatively minor spreading
Allergic contact dermatitis (ACD)	• Specific immunological sensitization to contact allergens • Generally unclearly demarcated • Area and configuration of the dermatitis are suggestive of the triggering agent • Spreading reactions, moving outwards from the primary site of exposure, are typical
Airborne contact dermatitis (ABCD)	• Dermatitis on exposed areas of the body, particularly the face and neck, and other skin areas not protected by clothes, due to airborne allergens • Lesions are scratch marks and tiny papules of uniform shape and morphology (typically observed in the flexures or extensor aspects of the limbs or trunk)
Protein contact dermatitis	• Itching, erythema, urticarial swelling or small vesicles appear within a few minutes of contact with the causal agent • Cannot be differentiated on clinical grounds from ICD or ACD

Table 2: An overview of diagnostic tests used in dermatitis [43, 93, 94]

Diagnostic test	**Advantages**	**Disadvantages**
Patch test	• Quick and easy to deliver • Much more specific and detailed than alternative allergy tests	• Interpretation of results can be difficult – specific training is necessary • If application does not follow ESCD guideline recommendations, complications can appear, such as depigmentation, hyperpigmentation, scars and secondary infection
Open test	• Useful when unknown or little studied substances need to be tested	• Not as specific or detailed as patch test
Semi-open (semi-occlusive) test	• Useful modification for products that have irritation potential	• Not as specific or detailed as patch test
ROAT	• Useful when reaction has occurred after repeated exposure • Helpful supplementary test when patch test results are inconclusive	• Longer timeframe required compared with alternative diagnostic tests • Not as specific or detailed as patch test
ESCD = European Society of Contact Dermatitis; ROAT = repeated open application tests		

Table 3: Rationale for including emollient ingredients (adapted from Proksch and Lachapelle, 2005 and Proksch, 2008) [4, 95]

Ingredient	**Role**
Lipids (e.g. mineral, vegetable oil)	Act as a substitute for lost natural skin lipids
Physiological lipids (e.g. ceramides, cholesterol)	Play a role in epidermal differentiation through signalling; play a role in structural elements of the stratum corneum
Humectants (e.g. glycerol, natural moisturizing factor components)	Restore stratum corneum water content and barrier function
Anti-pruritics (e.g. glycine)	Break the itch–scratch cycle
Cell/lipid metabolism support (e.g. dexpanthenol)	Support fibroblast proliferation/protein synthesis/lipid synthesis; support normal epidermal differentiation
Antimicrobial peptides, prebiotics	Restore eubiosis of the skin microflora

Figure captions (please find figures uploaded separately from text, as per author instructions)

Figure 1: Structure of the skin (adapted from Proksch and Lachapelle, 2005) [4]

Figure 2: Considerations for optimal CD management

Figure 3: Therapeutic index for topical glucocorticosteroids (adapted from Luger et al., 2014) [49]