



Allergic contact dermatitis: From pathophysiology to development of new preventive strategies

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ABSTRACT

As the body's first line of defense, the skin is the organ most frequently exposed to chemicals present in personal hygiene products, household products, or materials used in the work environment. In this context, skin disorders account for more than 40 % of all occupational and work-related diseases, constituting a significant public health burden. Among skin disorders, allergic contact dermatitis (ACD) is the most prevalent occupational disease and the most common form of immunotoxicity in humans. ACD is a T-cell-mediated skin inflammation resulting from the priming and expansion of allergen-specific CD4⁺ and CD8⁺ T cells. The clinical condition is characterized by local skin rash, itchiness, redness, swelling, and lesions, being mainly diagnosed by the patch test. Upon ACD diagnosis, avoiding the exposure to the triggering allergen is the mainstay of treatment to prevent future flares. In cases where avoidance is not possible, the use of a standard of care interim treatments such as steroid creams or ointments, barrier creams, and moisturizers are strongly recommended to alleviate symptoms.

In this review, we sought to provide the reader with an overview of the pathophysiology of ACD as well as the currently available pharmacological treatment options. Furthermore, a comprehensive outline of several preventive strategies is also provided.

1. Introduction

Skin problems related to contact with chemicals is a continuous growing environmental and occupational health problem. Two main types of contact dermatitis are described considering the pathophysiological mechanism involved: irritant contact dermatitis (ICD), and allergic contact dermatitis (ACD) [1,2].

Irritant contact dermatitis (ICD) is the most common occupational skin disease, accounting for 80 % of all contact dermatitis cases. It can occur after a single exposure to an irritant or toxic substance (e.g. abrasives, cleaning, oxidizing, and reducing agents) and is characterized by skin damage resulting from a direct and local cytotoxic effect over the skin's cells [3]. Clinical manifestations of ICD include burning, stinging, smarting, and usually start within seconds after exposure. Additionally, the lesions range from erythema to vesiculation and caustic burn with necrosis, itching, and pain as fissures develop [3]. Of relevance, low-grade irritants can take longer to clinically express the condition. It

can be an acute reaction characterized by a single exposure to a material, such as chemical burns and ultraviolet light A-triggered phototoxic ICD, or a chronic type, resulting from cumulative and repetitive exposure to irritative substances such as solvents, soap, and detergents [3].

ACD accounts for 20 % of the cases of contact dermatitis. It is an adverse cutaneous inflammatory reaction caused by the direct contact of the skin with a specific exogenous allergen to which humans have previously been sensitized [4]. ACD represents the principal and most prevalent form of immunotoxicity found in humans [5,6]. It affects people of all ages, although it is uncommon in individuals older than 70 years [7]. After multiple exposures to the sensitizing agent, individuals develop the clinical manifestations, often characterized by intense pruritus, stinging and pain accompanied by well-demarcated erythema and oedema [3]. Many occupational activities such as hairdressers and beauty and wellness professionals are prone to develop this skin condition. Hands are the most common site of appearance and a correct diagnosis is essential for the treatment [8,9]. Indeed, exposure to a

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strong sensitizer results in sensitization in about a week or more, while exposure to a weak allergen may take months to years to promote sensitization [3].

With this review we sought to briefly recapitulate the pathophysiology of ACD and then focus on the currently available pharmacological treatment options, concluding with the indication of several preventive and future strategies.

2. Pathophysiology of ACD

ACD is a multifactorial disease in which genetic and environmental factors play a role. Genetic predisposition involves polymorphisms in genes that regulate xenobiotic metabolism and biotransformation, redox balance, inflammation, and skin barrier functions [10]. The most relevant risk factors include exposure at the workplace, age, and sex (most frequent in young females) [10,11]. ACD is a type IV hypersensitivity response caused by low molecular weight (LMW) reactive chemicals and metal ions such as nickel $[\text{Ni}]^{2+}$ and chromium $[\text{Cr}]^{3+}$ [12]. Its pathophysiology is characterized by two distinct phases, involving both innate and adaptive immune responses. First, the sensitization phase also referred to as the afferent or induction phase includes the events following the first contact with the allergen, in which the sensitizing chemical penetrates the *stratum corneum*, driving the development of effector T cells. Second, the elicitation phase also referred to as effector or challenge phase, where sensitized individuals are re-exposed to the sensitizing chemical, leading to clinical manifestation, usually within 24/72 h [10,13].

The vast majority of available mechanistic data on ACD has been obtained from the mouse model for ACD, the murine contact hypersensitivity model (CHS), in which skin inflammation is induced by hapten application onto the ears of mice. Studies with strong experimental contact sensitizers such as 2,4-dinitro-1-fluorobenzene (DNFB), dinitrochlorobenzene (DNCB), trinitrochlorobenzene (TNCB) and oxazolone, which are endowed with unique chemical and immunological properties but are not present in our daily environment, paved the way to a better comprehension of ACD pathophysiology. Although, recent studies performed in mice with common weak haptens demonstrated effector and regulatory mechanisms similar to those induced by those experimental contact allergens [14,15].

2.1. Sensitization phase

LMW reactive chemicals (< 1000 Da) are too small to be recognized by the immune system and must first react with a carrier protein to generate new antigenic determinants, a process termed haptenation [16, 17]. (Fig. 1). The majority of haptens displays lipophilic residues, which enable them to cross through the corneal barrier and electrophilic moieties, which account for the establishment of covalent bonds with the nucleophilic residues of endogenous cutaneous proteins [18]. The formation of such hapten–protein complexes is crucial for the activation of the innate immune system, and the efficient priming of T cells in the sensitization phase [19]. The covalent binding is the result of the classical nucleophilic-electrophilic reaction between electrophilic residues of the chemical and nucleophilic residues of some amino acids, such as cysteine (most common), lysine, methionine, tyrosine or histidine. Recent observations demonstrate that covalent binding is also produced via free radical reactions. Of note, sensitizing metal ions such as nickel and chromium react somewhat differently in that they generate non-covalent coordination protein–metal chelate complexes. Nevertheless, those complexes are sufficiently stable to stimulate acquired immunity [14]. Another signal for efficient sensitization is the generation of alarmins which include the release of danger signals such as reactive oxygen species (ROS), uric acid and ATP/ADP as well as damage-associated molecular patterns (DAMPs), such as hyaluronic acid fragments [20–22]. These DAMPs are then recognized by pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs) on skin dendritic cells (DCs) such as Langerhans cells (LCs) and dermal DCs, leading to their activation [23,24]. Interestingly, recruited T helper (Th) 1 cells have been found to release significant quantities of the DAMP molecule extracellular matrix A + fibronectin, which is an endogenous ligand of TLR4. This triggers a positive-feedback mechanism that further reinforces immune activation in ACD [19]. Furthermore, keratinocytes are also key players in the sensitization phase, as they contain enzymes that are required for the conversion of pro-haptens into biologically active haptens, thereby facilitating their binding to endogenous proteins and making them immunogenic. Keratinocytes also provide sets of alarmins and cytokines that generate a pro-inflammatory microenvironment in the skin, which is necessary for innate immune system activation. Hapten-proteins complexes are then engulfed and processed within LCs and dendritic

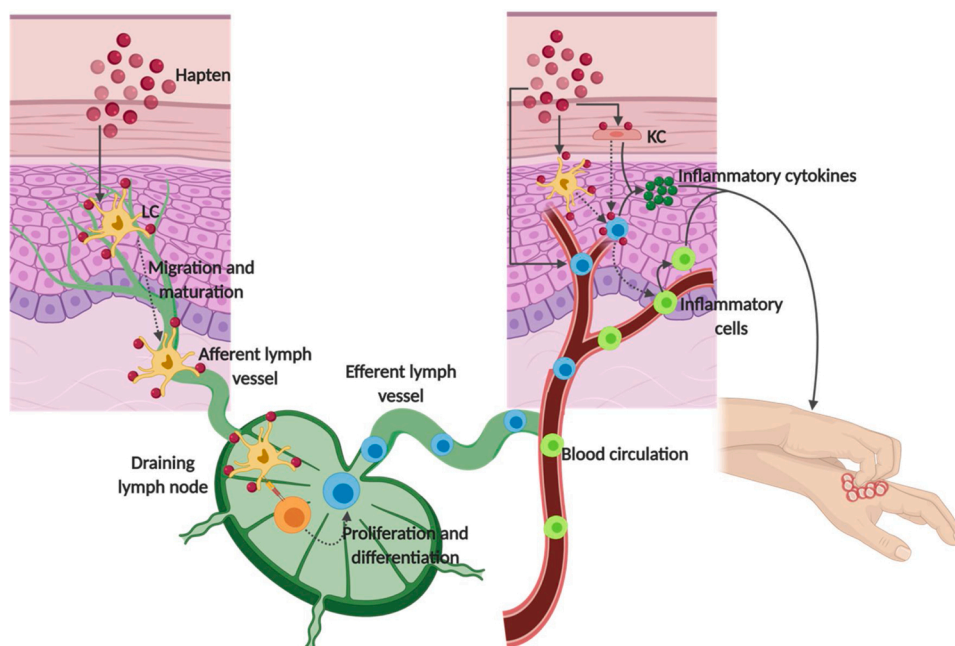


Fig. 1. Schematic representation of sensitization (left) and elicitation (right) phases in allergic contact dermatitis. During the sensitization phase (left), skin contact with a hapten leads to the formation of hapten-proteins complexes and the creation of an inflammatory microenvironment. Hapten-protein complexes are captured and processed by Langerhans cells (LC) and dermal dendritic cells, that mature and migrate to the skin-draining lymph nodes. There, dermal dendritic cells and LCs prime hapten-specific T-cells generating effector and memory T cells that expand and recirculate to the skin via blood vessels. recirculate. Renewed allergen exposure sparks off the elicitation or effector phase (right). Due to their lowered activation threshold, hapten-specific effector T-cells are triggered by various haptenized cells, including LC and keratinocytes (KC), to produce proinflammatory cytokines and chemokine, leading to a gradually developing eczematous reaction. (Adapted from [26]).

cells (DCs) being presented as haptened peptides in the groove of major histocompatibility complex (MHC) classes I and II molecules at the cell surface. These hapten-bearing antigen-presenting cells migrate from the skin into the para-cortical area of regional lymph nodes (LN) where they prime naïve CD8⁺ and CD4⁺ T lymphocytes, leading to differentiation of memory or effector T cells [24]. T cells proliferate and emigrate out of the LNs to the blood where they re-circulate between the lymphoid organs and the skin. Indeed, the development of ACD requires close cooperation of different cell types such as antigen-presenting cells (APCs), T, B, NK (natural killer) lymphocytes, keratinocytes, endothelial cells, mast cells, fibroblast and platelets, which communicate through numerous cytokines and chemokines [2,25]. Mast cells, which are an important source of tumor necrosis factor (TNF)- α , are responsible for neutrophil extravasation into inflamed tissue, through localization on the proximity of blood vessels and by secretion of the neutrophil-attracting chemokine (C-X-C motif) ligand 1 (CXCL1) and CXCL2. Furthermore, mast cell deficiency or depletion significantly impairs CHS development, also compromising T-cell recruitment to the skin [2].

In the sensitization phase, several cytokines and chemokines are secreted in the skin, namely IL-1 β , IL-1 α , IL-8, IL-18, IL-23, TNF- α and granulocyte-macrophage colony-stimulating factor (GM-CSF). IL-1 α , TNF- α and GM-CSF promote E-cadherin downregulation and upregulation of the expression of adhesion molecules ((cluster of differentiation (CD)54, α_6 integrin and CD44 variants), facilitating LC migration. Concomitantly, LCs also increase their expression of chemokine receptors such as C-C chemokine receptor type 4 (CCR4), CCR7 and C-X-C chemokine receptor type 4 (CXCR4), and produce matrix metalloproteinases, such as MMP-9, that facilitate LC migration through the dermis to the regional lymph nodes [11,19,26–29]. CCR7 ligands (chemokine ligand (CCL)19 and secondary lymphoid tissue chemokine (SLC/CCL21) are produced by both lymphatics and high endothelial cells, making CCR7 particularly important in guiding mature DCs to lymph node paracortical areas, where CCR7-expressing naïve T cells are also found [12,26,27]. LC maturation process is characterized by morphological, functional and phenotypical changes, namely the up-regulation of costimulatory (CD83, CD86, CD40, CD54/ICAM-1 and CD58) and antigen-presenting molecules (MHC-II) [27,30]. In the lymph node, LC presents the antigen to T lymphocytes through MHC and T cell receptor (TCR) interaction. Antigen bound to MHC-I or MHC-II are recognized by CD8⁺ and CD4⁺ T cells, respectively [27]. For efficient priming of naïve T lymphocytes, a triple signal coming from skin dendritic cells must be provided: signal 1, binding of TCR to MHC-antigen complex; signal 2, upregulation of co-stimulatory molecules and signal 3, secretion of cytokines and chemokines. In the absence of co-stimulatory signals, MHC/TCR interaction normally leads to anergy or deletion, promoting tolerogenic responses. Upon activation, T-cells produce IL-2, which is a highly potent T-cell growth factor, allowing appropriately stimulated T-cells to proliferate abundantly. Signal 3 - DCs cytokine profile, defines T cell polarization, with IL-12 leading to the formation of effector cells, while IL-10 promotes regulatory T cells generation. A microenvironment rich in IL-12, and interferon (IFN)- γ promotes the differentiation of Th1 and Tc1 cells, while IL-6, transforming growth factor (TGF)- β , IL-21, IL-23 and IL-1 β lead to Th17/22 polarization. In the presence of IL-4 and IL-10, which are induced by most respiratory sensitizers and some contact allergens, T cells will develop a Th2 phenotype [19,25]. Skin DCs also induce the expression of skin T cell homing receptors (e.g. cutaneous lymphocyte antigen, (CLA), CCR4 and CCR10) which preferably direct these lymphocytes to the tissue of origin of the corresponding DCs [19,25,27]. These cytokines also attract more immune cells to the challenging site (e.g. skin), strengthening the immune responses. The outcome is determined by the balance of both sensitizing and tolerizing pathways.

The sensitization step lasts 10–15 days in man and 5–7 days in the mouse [23] and although this first step has no clinical consequences in the majority of cases, some allergens may induce hapten-specific skin

inflammation, 5–15 days after the initial skin contact [14,31]. This phenomenon has been referred to as the primary ACD. As demonstrated by Mezard in a murine model, the pathophysiology of this primary (one-step ACD) is identical to the classical (two-step) ACD reaction. The afferent and efferent phases of primary ACD can be induced after a single contact with strong haptens like DNFB and FITC. These chemicals persist in the skin for a long period, allowing the recruitment and activation of the skin CD8⁺ T cells, which have been primed in the lymphoid organs a few days before [32,33]. Primary ACD is mediated by hapten-specific CD8⁺ T cells, which are primed in the draining auricular LN by skin migrating DC [32,33]. The results shown by Mezard and colleagues suggest that the inflammatory reaction induced by the pro-inflammatory properties of haptens, which is required for the recruitment of leukocytes in tissue, is still present 5 d after skin painting [32]. This model could be a useful tool for understanding the unknown mechanisms underneath the regulation of antigen-specific inflammatory responses once they have shown evidence that the regulation of the allergic response occurs despite the continuous presence of the hapten in the skin.

2.2. The elicitation phase

The elicitation phase occurs after the re-exposure of a sensitized individual to the same hapten. Haptens diffuse into the skin and are taken up by skin cells that then present MHC classes I and/or II/haptenated peptide complexes, to effector and memory T-lymphocytes developed during the sensitization phase (Fig. 1). Despite the crucial role of LCs in the sensitization phase, they are not required in the elicitation phase. As mentioned before, macrophages, keratinocytes and mast cells may also act as “non-professional” APCs amplifying the activation of hapten-specific effector T cells. Indeed, studies with UVB/topical corticosteroid-induced LC depletion or their selective ablation in experimental models did not result in a reduced allergic response [27].

The chemical-induced innate immune response triggers the release of IL-1 β , TNF- α , and IL-18 from keratinocytes and LCs. Keratinocytes also secrete T cell-attracting chemokines (e.g. CXCL9/10, CCL17, CCL20, and CCL27). T cells must cross the dermal microvasculature and the dermis to reach the keratinocytes modified by the allergen. Although some antigen-driven T cell-specific migration may occur, most T cells are recruited in a non-antigen specific way, attracted to the skin through the expression of chemokines and adhesion molecules by keratinocytes, DC, fibroblasts, mast cells and endothelial cells [27,34]. Activated T cells present the homing antigen CLA, very late antigen (VLA)-4 as well as chemokine receptors. CLA binds to E-selectin (expressed on stimulated endothelial cells) and VLA-4 binds to endothelial integrin vascular cell adhesion protein (VCAM)-1 initiating diapedesis [27]. Upon encounter of their specific antigen, specific T cell proliferates *in loco*, induced by mature DCs combined with the antigen [29]. Both CD4⁺ and CD8⁺, mediate skin inflammatory reaction, however, CD8⁺, which enter the skin first, are the main effector cells, whereas CD4⁺ assume a pathogenic and regulatory role [25,27]. After the chemical challenge, natural killer T cells are activated and produce IL-4, resulting in type-1 B lymphocytes (B1) activation and specific IgM production, which cleaves complement, thus forming C5a, which then promotes the release of vasoactive substances such as serotonin and TNF- α by mast cells and platelets. [25,27]. Furthermore, C5a also functions as a chemoattract for T cells and macrophages [25]. Th1 cells, carrying the receptors CXCR3 or CCR5 are mostly attracted by CXCL10 and CXCL9 together with CCL2 and CCL5, respectively. On the other hand, chemokines CCL20 and CCL27/CTACK (cutaneous T-cell attracting chemokine) preferentially attract CCR6⁺ and CCR10⁺ T cells, including Th1, and particularly Th17 and Th22. CCL17/TARC (Thymus and activation- regulated chemokine) mostly attract Th2 cells rich in CCR4. IL-8/CXCL8 produced in response to IL-17 and IL-22 will further attract neutrophils. The relative predominance of these subphenotypes of effector T cells in the area of contact with the sensitizer may account for the clinical and histologic variations in the ACD patterns. In the skin, infiltrating T cells release

INF- γ , IL-4, IL-17 and TNF- α . In response to INF- γ , keratinocytes upregulate adhesion molecules and cytokines/chemokines, which further increases the recruitment of T-cells, NK cells, macrophages, mast cells and/or eosinophils to the challenged site [19]. An inflammatory response is then mounted to eliminate antigen-modified keratinocytes, which undergo apoptosis, resulting in loss of cell cohesion, tissue destruction and desquamation. Desquamation removes the antigen and the inflammatory process decreases [27]. IL-17 makes keratinocytes particularly sensitive to the T cell killing by Th1 cells [35].

The inflammatory reaction persists for several days and then decreases following the activation of down-regulatory mechanisms [14].

2.3. Regulation/resolution phase

The resolution phase of ACD involves several different mechanisms, including the clearance of the hapten from the skin, by increased blood flow, hapten metabolism by cells of the inflammatory infiltrate and the activation of CD4⁺ regulatory T cells (Tregs). Although the precise phenotype and site of action remain to be fully elucidated, Treg cells have been associated with the control of the priming/expansion of specific CD8⁺ T cells in lymphoid organs and the activation of CD8⁺ T cells in the skin. [36].

3. Incidence and prevalence

ACD and ICD have a significant impact on healthcare costs and industry productivity due to absence to work [37]. Indeed, it represents one of the most common occupational skin diseases in many countries [38]. For instance, in Europe, it is estimated that the annual incidence of occupational contact dermatitis ranges from 0.5 to 1 case per 1000 workers [39]. Furthermore, ACD also accounts for 30 % of all cases of occupational diseases in industrialized nations [4] and 4–7% of all dermatological consultations [40].

The prevalence of ACD has been increasing worldwide for the past few decades [41], currently affecting 15–20 % of the general population worldwide with 5–10 % developing clinical symptoms at least once a year [1].

4. Chemical nature of skin allergens

Innovation and ever-changing consumer practices influence the

emergence or the re-emergence of sensitizing chemicals. Indeed, daily exposure to fragrance allergens results mainly from the use of household products [42] (Fig. 3). Currently, there are more than 4000 substances known as potential chemical sensitizers [43,44], and every year, several new contact allergens are identified, constantly expanding the horizon of known causes of ACD [45]. Recently, impurities from the synthesis process of several compounds used in consumer products have been described as the actual sensitizers [46]. This brings to the foreground the need for improvements on the purification methods in the production chain [46]. According to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS), “a skin sensitizer is a substance that will lead to an allergic response following skin contact” [47]. As previously detailed in Fig. 2, a set of characteristics determine whether a chemical can function as a contact sensitizer: (1) ability to penetrate the skin, (2) reactivity with carrier endogenous protein to form a hapten-protein complex, (3) induction of epidermal and dermal inflammation, (4) dendritic cell activation, migration to lymph nodes and recognition as antigenic by T cells [43]. Some sensitizers are not inherently reactive and need to be activated/metabolized either by oxidation (pre-haptens) or enzymatically (pro-haptens) [31].

The knowledge resulting from several years of research culminated in the development of the so-called adverse outcome pathway (AOP) (OECD 2012b; OECD 2012a) [48] for skin sensitization in 2012, which represents a mechanistic basis for the integration of skin sensitization-related information. Importantly, the recent developments that led to the development of integrated approaches for the testing and assessment of skin allergens were based on this AOP (Fig. 2).

Common skin allergens include transition metals (nickel, chromium, and cobalt), fragrances, preservatives, multiple topical drugs, hair dyes, acrylates, rubber chemicals, epoxy resins, and plant defense-related substances [46]. Metals are common triggers of ACD in both occupational and non-occupational settings. Nickel (nickel sulphate) has been recognized as one of the major causes of contact dermatitis among women with high socioeconomic costs associated [49,50]. Despite the 1994 EU restriction regarding its use in consumer products [11,49], the prevalence of nickel-induced dermatitis remains relatively high [49]. Nickel can be easily found in stainless steel cookware, ear piercing, jewellery, and clasps or buttons on clothing and also in pacemakers, as they can release nickel from its battery components [46]. For instance, acidic environments may increase the release of nickel from stainless steel (e.g. tomato sauce in stainless steel pan). Allergy to chromium

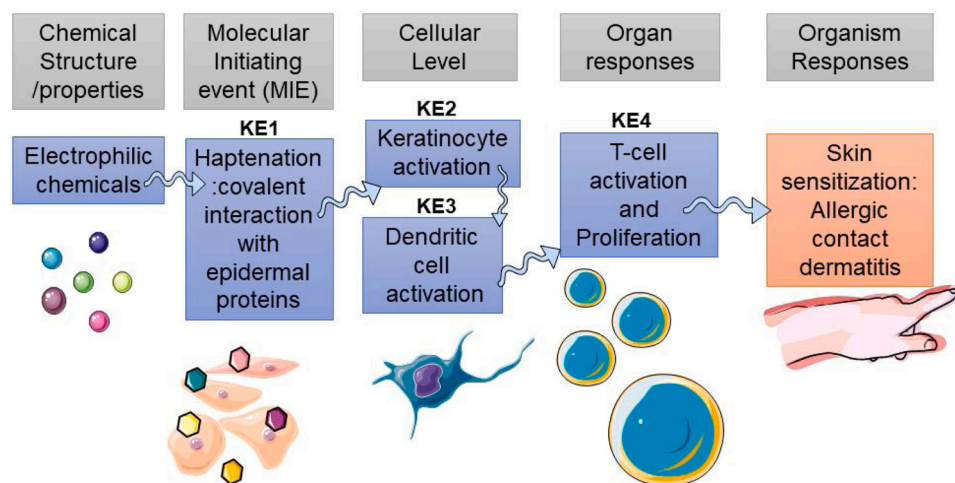
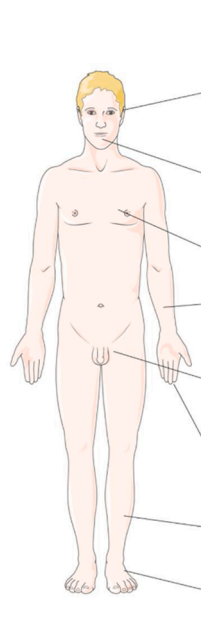


Fig. 2. Schematic representation of the adverse outcome pathway (AOP) for skin sensitization showing the complex biology underlying disease processes. Four different key events (KE) of the AOP have been identified and associated with the development of skin sensitization, namely: KE1, also known as the molecular initiating event - covalent binding of a xenobiotic hapten to skin protein, forming the protein-hapten complexes and subsequent penetration of the allergen through the stratum corneum into the viable layers of the underlying epidermis; KE2 - activation of keratinocytes, resulting in cytokine secretion (e. g. interleukin (IL)-1 α , IL-18, and tumour necrosis factor- α); KE3 - Langerhans cell (LC) activation (migration and maturation), directly or by the hapten-carrier protein complex and KE4 - presentation of the allergen by matured LCs to antigen-responsive T lymphocytes in the draining lymph nodes, resulting in the formation of primed effector and memory specific T lymphocytes that will lead to inflammation and the development of the symptoms of the disease, upon a later contact with the same allergen.



Anatomic location	Source of sensitization	Most common allergens
Scalp and neckline	Styling products, fragrance, essential oils, jewellery, dyes	nickel sulphate; cobalt chloride; copper sulphate; Chromium;
Periorbital, face, lips	Cosmetics, beauty preparations, fragrance, hair products, jewellery, topical medicine transfer, lip and oral hygiene products	fragrances (fragrance mix, balsam of Peru, colophony, cinnamyl alcohol, eugenol); preservatives; acrylates;
Chest and abdomen	Sun exposure, sunscreens, belts, tattoos, jewellery	hair dyes (3-aminophenol, 4-aminophenol, p-toluenediamine); rubber chemicals (paraphenylenediamine dihydrochloride, carba mix, mercaptobenzothiazole); epoxy resins; adhesives; essential oils;
Arms and wrists	Jewellery, watches, tattoos	vehicles (formaldehyde, propolis, paraben mix); antimicrobials (neomycin sulphate, fusidic acid)
Anogenital region	Contraceptives, personal hygiene sprays, perfumes, powders, baby wipes, personal lubricants	
Hands	Nail polish, rubber gloves, cosmetics and personal care products	
Legs	Plants, topical preparations, adhesives, cosmetics	
Ankles and feet	Shoe materials or chemicals including rubber, adhesives and chromates, jewellery	

Fig. 3. Anatomic relevance and source of sensitization for the most common allergens. Adapted from [55].

(CrVI) is also very common given that the metal is frequently used in the tanning process of leather is present in products such as shoes and couches [51,52]. It can also be found in cement, facial cosmetics, and some bar soaps (Fig. 3) [53]. Other metals are known to cause skin reactions include aluminium and cobalt chloride, which are frequently present in hair dyes and antiperspirant, and gold (gold sodium thiosulfate), often found in jewellery and dental prostheses [54].

Personal hygiene products such as creams, lotions, oils, shampoos, conditioners, and deodorants have multiple fragrances, which can be complex mixtures of up to 2000 substances, many of them behaving as contact allergens. Terpenes, such as linalool, citronellol, geraniol, coumarin, hexyl cinnamal, limonene, and L-carvone, a constituent of mint flavour commonly used in toothpaste, are among the most frequent cosmetics ingredient triggering ACD [11,56].

Preservatives are natural or synthetic biocidal chemicals that inhibit the growth of microorganisms and prevent the putrefaction of foods. They are widely used in numerous personal care products to prevent contamination and/or oxidation. Indeed, many preservatives are antioxidant molecules capable of suppressing oxidation phenomena and the formation of free radicals [57]. Nearly 25 % of the cosmetic products in the USA and Europe contain at least one of the five common formaldehyde-releasing preservatives (e. g. imidazolidinyl urea) [58]. Formaldehyde is considered the ninth most common allergen inducing ACD, representing 7% of positive patch test reactions. Another frequent allergen is quaternium-15, a formaldehyde releaser that is present in cosmetic products such as self-tanners, shampoos, nail polishes, sunscreens, and in industrial products like polishes, paints, and waxes [59]. Other preservatives with sensitizing potential include sodium benzoate, the most common preservative in rinse-off products, and phenoxyethanol, a compound frequently present in leave-on and makeup [60]. Isothiazolinones are another group of preservatives present in personal care, household, and commercial products [61]. They are components of “slime”, a very popular toy among children, which may account for the growing incidence of ACD in this age group [62]. Methylisothiazolinone (MI) within the group of isothiazolinones, is a powerful synthetic biocide and accounts for the European scale-up ACD problem [63,64]. It has been used as a stand-alone preservative (up to 100 ppm) in cosmetics [61], although, since February 2017, its use on leave-on cosmetics has been banned. Though, and despite the changes in cosmetic regulation, there’s still an increase in ACD reports after MI exposure,

demonstrating its presence in nowadays products [63].

Prolonged use of anaesthetics such as pramoxine, diphenhydramine or amide, and topical steroids contribute to a large number of contact allergies in the spectrum of patch test diagnoses [65]. Povidone iodine-containing solution, a well-known disinfectant and antiseptic, can also cause allergic reactions [66]. Anti-haemorrhoidal creams are also reported and associated with perianal dermatitis and pruritus [66].

Hair dyes are among the substances most frequently reported for causing ACD [67]. For instance, p-phenylenediamine (PPD) is a hair dye ingredient with a wild spread use between hairdressers’ professionals and is reported as a causative agent of severe allergic reactions. It can also appear associated with resorcinol in black “henna tattoos” frequently causing pruritic papules in some individuals. Plastic and rubber materials can also cause skin sensitization [68].

Acrylates are found in medical devices like dental implants and prosthesis, bone cement, wound dressings, surgical glues, aesthetics, eyelash, hair extensions, and other industrial products like plastics, glues, adhesives, paints, printing inks, and fibreglass [45,69]. Chemicals such as 2-hydroxyethyl methacrylate (HEMA), 2-hydroxypropyl methacrylate (HPMA) and ethylene glycol dimethacrylate recently became very popular due to their use in artificial nail lacquers and other related products [70,71]. Although acrylate use in industrial settings is controlled by legislation, cosmetics usage remains unregulated [71]. In the context of medical devices, methyl and methacrylate are often present in transcutaneous electrical nerve stimulation electrodes, glucose sensors, insulin pumps, and wearables, being responsible for skin sensitization reactions [46].

Epoxy resins are a family of monomeric or oligomeric materials usually added to diluents and hardeners, being indispensable in painting, mechanics, construction and chemical industries and thus strongly increasing the risk of sensitization in these workers classes [72]. The most-reported rubber associated materials causing ACD are derivatives of p-phenylenediamine which is used as colouring antioxidants, and thiurams and dithiocarbamates. Mercaptobenzothiazole is a well-known causative agent of ACD being identified in rubber products, shoes, gloves, and car tires [46]. Some emulsifiers and surfactants commonly found in topical products can also cause contact allergy. Examples include salicylates used as fragrance (benzyl salicylate), as UV-filters in sunscreens (octyl salicylate and homosalate), or as other cosmetic ingredients (methyl and phenyl salicylate) [46]. There are also reports

acknowledging that some plants such as *Ginkgo biloba* and species from the genus *Toxicodendron*, particularly poison ivy can cause skin sensitization [46,73].

Taken together, it is of utmost importance for individuals to disclose which allergens can elicit ACD so they can better assess their localization in the working place and comply with avoidance [8]. Indeed, avoiding exposure to contact allergens is the only way to fully prevent the development of ACD. This knowledge, combined with the patient history and examination are important tools that will guide the healthcare provider to appropriate clinical suspicion, patch testing, research, and management options [41,74].

5. Management and therapeutic strategies in ACD

ACD is a heterogeneous disease associated with many different aetiologies and morphologies, which makes treatment challenging and often requiring the use of different therapeutic approaches [75]. Currently, the definitive treatment of ACD relies on the identification and subsequent removal of any potential causal agent, otherwise, there's an increased risk for chronic or recurrent dermatitis [76]. Although, when allergen removal is not possible, protective measures are needed to prevent skin contact with sensitizing agents, which requires patient cooperation [77]. Dietary measures can also be helpful in cases of ACD to an orally-ingested contact allergen (as evidenced by patient history, patch testing, exclusion diet, and diagnostic provocation). Low-nickel diets may improve symptoms in individuals allergic to nickel, with chelating agents also been described as helpful [77]. Other treatment options would be tolerance induction, although, immunotherapy approaches have shown to conduce to limited results [77].

Currently, about 40 registered clinical trials are addressing the treatment and/or prevention of allergic contact dermatitis: 23 located in North America (2 in Canada, 1 in Mexico and 20 in the United States), 12 in Europe, 1 in the Middle East, and 1 in South Asia [78]. Of those, 28 studies are already completed, and 3 are still recruiting [78]. Additionally, and according to the World Intellectual Property Organization (WIPO), 616 patents for allergic contact dermatitis were reported, focused on the treatment strategies and in ACD prevention [79]. These data clearly highlight the scientific and commercial interest in discovering new therapeutic strategies to manage ACD.

5.1. Pharmacological interventions

The use of topical corticosteroids is the first line of treatment for ACD conducting to good results in monotherapy. Although inhibiting the repair of the stratum corneum, corticosteroids are very effective in the short term. The efficacy of topical treatment with class II or III corticosteroids such as betamethasone dipropionate, fluocinonide and mometasone furoate in acute ACD is undisputed due to their anti-inflammatory properties. Corticosteroid selection should account for lesions localization, as well as the severity and acuteness of dermatitis, whilst bearing the therapeutic index in mind. Indeed, due to the risk of severe complications such as osteoporosis and type 2 diabetes, systemic corticosteroids should be avoided. Other treatments to control inflammation include cyclosporine, azathioprine, methotrexate, psoralen, and UVA, measures that are used as second approaches, upon resistance to corticosteroids. When a delicate area such as skin folds or eyelids are affected, topical calcineurin inhibitors such as tacrolimus or phosphodiesterase 4 (PDE4) inhibitors may also be effective [68,76]. As with other inflammatory dermatoses, the galenic formulation in which the active substance is incorporated must be tailored to the severity of dermatitis. Acute dermatitis is generally moist and needs to be treated with a hydrophilic preparation (gel, lotion, cream), whereas chronic disease is more likely to require a water-in-oil-based preparation (ointment) [80,81].

So far, no biologics have been proven to be useful in the treatment of ACD and oral tolerance induction has not been successful. Therefore,

preventive strategies constitute a unique and effective way for the management of ACD [2,82].

5.2. Preventive strategies

5.2.1. Education, legislation, moderation and avoidance

As previously stated, ACD remains without a cure and once an individual is sensitized, it develops clinical manifestations upon re-exposure to the same chemical. Therefore, most guidelines recommend ceasing exposure to the triggering chemical and there's a need to develop preventive strategies such as educational activities, lifestyle changes as well as promoting the use of hand and body protection approaches [77,83,84]. Currently, it is possible to act at 3 different levels to reduce the burden of this disease in professionals. Therefore, primary prevention aims to avoid the onset of disease in individuals and to reduce the incidence of new cases at a population level. Secondary prevention aims to detect the disease at an early or pre-symptomatic stage (for instance, by health surveillance) so that corrective interventions can be managed. Tertiary prevention aims to mitigate the effects of established disease. Indeed, prevention is a multidisciplinary approach encompassing modern occupational medicine policies and practices that include the provision of information and training, as well as control measures with occupational health activities carried out in collaboration between employers and workers. Primary prevention is the most effective approach and it can be achieved by elimination, replacement, or reduction of the allergenic substances by substitution, namely by replacing the allergen with a less reactive/potent chemical [81,85]. Patient health education, which includes verbal and/or written advice or formal nurse-led training, is also essential.

These programs are responsible for alerting and identifying activities in which individuals are more prone to be exposed to allergens and irritants, helping them to acknowledge the early symptoms and signs, reinforcing safety precautions [85]. However, the outcome of these interventions varies, with some having no demonstrable effect. Another preventive intervention is personal hygiene and personal protection, for instance washing hands with mild soap and water or with alcohol to remove allergen and irritants from the skin, as well as regular washing or cleaning of protective clothes [85]. Personal protection such as gloves are meant to be used during the contact with irritants and allergens, although, occlusive gloves themselves are a substantial factor in the promotion of occupational allergic hand dermatitis [84,86–88]. Replacement of powdered natural rubber latex gloves with low-protein nonpowdered gloves reduces ACD symptoms and severity in sensitized individuals. Furthermore, the use of boots, masks, and aprons can also decrease the exposure and protect the skin against contact with sensitizers [83,89]. If ACD persists even after removal of the chemical agent (including changing workplace) redeployment to a low exposure area as well as the introduction of exposure controls may improve or resolve disease in some cases. Another relevant strategy is reducing wet work hours, a well-known risk factor for developing ACD [85,90]. Furthermore, motivation, administrative control, and regulation signs and labels should be placed in the containers and products [11,89]. Secondary prevention of ACD includes diagnosis and surveillance whereas tertiary prevention consists of the treatment, management, and rehabilitation [91].

Preventive strategies depend largely on surveillance and must be complemented with clinical epidemiological data, which will allow the generation of important preventive regulations and legislation [11]. Interestingly, there are currently a plethora of new tools for the identification and characterization of skin sensitizing chemicals as well as for the conduct of effective risk assessments [44]. Chemical testing for ACD and appropriate hazard labelling are currently required worldwide by regulatory authorities to minimize exposures. Furthermore, toxicologists have the responsibility to identify and characterize the skin sensitization potential of chemicals as well as to estimate human health risk [43].

5.2.2. Barrier creams, emollients skin protection creams and moisturizers

A barrier cream is a topical preparation that, upon application, provides a thin layer functioning as a barrier, helping to reduce the skin contact with contaminants, as well as facilitating their removal [84]. An optimal barrier cream should be able to block completely the contact between the allergen and the skin, functioning like a glove [52]. Barrier creams can also contain active ingredients, which may trap or transform sensitizers and irritants [84,92,93]. Although the effects of barrier creams on the improvement of irritant hand dermatitis in hairdressers have been extensively documented, an international survey revealed that the majority of international experts are sceptical about their specific properties [84,86]. However, under experimental conditions, barrier creams showed protective effects against acute irritation caused by solvents [84,93,94] and some studies show that the use of moisturizers and skin barrier repair creams can significantly increase the disease-free time interval [1,40]. Also, repair creams were shown to improve skin condition in workers with damaged skin and after-work creams appear to confer some degree of protection against developing ICD [84,95]. Furthermore, controlled clinical trials showed a decreased incidence and prevalence of ACD with the use of soap substitutes as well as after-work creams. The use of these products should be therefore encouraged and made readily available in the workplace [40].

Water-resistant barrier creams contain hydrophobic substances such as silicone, which protects against water-soluble acids, alkali, and dyes. On the other hand, oil or solvent resistant barrier creams protect against dust, oils, greases, and solvents, but their clinical effectiveness in preventing ACD is controversial and unsupported by clinical studies [91,96]. Furthermore, barrier creams should be used on normal skin as they cause aggravation of dermatitis if applied to inflamed skin [97,98]. Among the ingredients used in topical formulations, there is robust evidence that the topical skin protectant quaternium-18- bentonite can prevent urushiol-induced ACD and that the chelating agent diethylenetriamine penta acetic acid can prevent nickel, chromium, and copper dermatitis [80]. In contrast, multiple studies have shown that pentoxifylline is not effective in preventing nickel allergy [92,99,100]. Although barrier creams are usually recommended for use before work and at least two to three times during work time, the optimal frequency of application remains to be clearly defined [80,85]. Overall, it is important to emphasize that there is also a very small body of evidence, with a few good quality studies that pre-work or barrier creams improve clinical indicators of skin condition [80,85].

Moisturizers and emollients used alone or in combination with barrier creams may result in a clinically important protective effect, either in the long- or short-term, for the primary prevention of the disease. Moisturizers improve the hydration of *stratum corneum* by the use of humectants such as glycerine, urea, sorbitol, pyrrolidone carboxylic acid, and the emollients petrolatum, lanolin, mineral oil, silicone, and waxes. They are also used for regenerative skincare, during and after work, and should be applied regularly during work time after hand washing and after work at home to support the regenerative capacities of the skin [88,99,101]. Regardless of their protective role in preventing chemicals absorption, in some cases emollients may act as conduits for chemicals. Indeed, some ingredients present in emollients, can also act as haptens, mainly preservatives (e.g. imidazolidinyl urea, formaldehyde and methylisothiazolinone) and fragrances but also emulsifiers and humectants [102–104]. Therefore, primary care practitioners should consider the excipients in emollients, which can cause new onset rashes or aggravate existing skin conditions.

Barrier creams and gloves combined with adequate moisturizers are widely recommended as the most important mean of personal protection in professions where the skin is at risk [84]. However, studies addressing the use of gloves to prevent the development of occupational contact dermatitis are limited and the observed benefits were not exclusively endorsed to wearing gloves, since they were only one part of a comprehensive prevention strategy [84].

5.3. Future perspectives: Topical formulations containing antioxidants, chelators, and quenchers for the prevention of ACD

The field of allergic contact dermatitis is constantly evolving and expanding with the introduction of new chemicals, revival of old allergens, industrial practices and new consumer behaviours, due to the complexity of ACD a multi-layered strategy for treatment seems necessary. The future strategies could control ROS and interfere with mechanisms of inflammation, enforcement of immune regulation, and reduction, removal or suppression of effector and memory T cells. The continuous and growing understanding of pathomechanisms could lead to developing of combination strategies. Biomarkers are another area of ongoing research and will hopefully lead to the global technologies such as genomic and proteomic profiling of contact allergen-regulated gene and protein expression will identify additional relevant signalling pathways that can be explored to refine our molecular understanding of allergic contact dermatitis, and help in the development of drugs for targeted treatments and *in vitro* assays for contact allergen identification. Identification of suitable profiles for modern molecular diagnostics [2]. Furthermore, global technologies such as genomic and proteomic profiling of contact allergen-regulated gene and protein expression could lead to identify additional relevant signalling pathways that can be explored to refine our molecular understanding of allergic contact dermatitis, and help in the development of drugs for targeted treatments and *in vitro* assays for contact allergen identification [105].

The majority of studies are focused on the early cellular and molecular events in which the protein-haptenation stands as a crucial step for the development and elicitation of contact allergy [106]. Presently, a plethora of molecules and protocols are under investigation, while some patents and products aiming at the prevention and management of ACD are already available on the market [46,107,108]. For years, it has been suggested that ROS play an important role in the stimulation and maintenance of both irritant and allergic contact dermatitis [109]. As a result of exposure of the skin to different irritants and allergens, ROS are upregulated and, among other events, can disrupt the epidermal barrier, induce the release of various cytokines, activate different intracellular signalling pathways, and upregulate cellular surface molecules, thus contributing for the development of ACD [2,43,110]. Consequently, it can be hypothesized that the application of antioxidants into the skin may decrease the allergenic risk of chemicals. Accordingly, Gafvert and colleagues investigated the effect of ascorbic acid and α -tocopherol on reactions to the allergens limonene-2-hydroperoxide, chlorothalonil, and cobalt chloride, using the guinea pig model. The results demonstrated that the antioxidants may prevent the contact allergy inflicted by limonene-2-hydroperoxide, either in the sensitization phase or at elicitation. However, the antioxidants had no effect on cobalt allergy or on the allergenic effect of haptens that form antigens via nucleophilic-electrophilic reactions. A moderate protective effect of ascorbic acid and α -tocopherol on nickel-induced human ACD was also described [106,111]. Reinforcing the potential of antioxidants to reduce the allergic reactions to some allergens, Coenraads and colleagues investigated, in a proof-of-principle study, whether pre-treatment of the skin with ascorbic acid reduces the elicitation reaction to a PPD-containing hair dye in sensitized subjects. The results demonstrated that pre-treatment with ascorbic acid had an attenuating effect on the elicitation reaction by PPD in 7 of 12 subjects [108]. These results were corroborated by a parallel study conducted by Basketter and colleagues [112]. In 28 volunteers with a proven history of contact allergy to PPD, the pre-treatment of skin sites with ascorbic acid led to a reduction in the intensity, or even ablation, of the cutaneous allergic reaction in ~75 % of cases as compared with untreated skin. The authors conclude that the treatment of the skin adjacent to the hair-bearing area with antioxidants could form part of a strategy to reduce the burden of ACD caused by hair dyeing [112].

Other antioxidants that are under investigation and have shown promising results are N-acetylcysteine (NAC) and glutathione [113].

NAC and glutathione are commonly used as thiol antioxidants and have been described to block nuclear factor κ B (NF- κ B) dependent signalling mechanisms [114]. In this context, Senaldi demonstrated that NAC was able to block the irritant as well as the allergic reaction evoked by TNCB in mice [115]. Additionally, glutathione-containing emollients inactivate methylchloroisothiazolinone/methylisothiazolinone, two chemicals known to cause chemical burns and skin sensitization [116]. Interestingly, a recent work addressed the capacity of formulas containing glutathione and iron sulphate to inhibit the elicitation of ACD in Chromium (VI)-allergic individuals. The authors observed a significant reduction in reactivity to the Chromium(VI) preparations on skin previously treated, compared with untreated skin [117]. Certain naturally occurring flavonoids, such as luteolin and quercetin also demonstrated relevant antioxidant, anti-inflammatory and mast cell blocking activities [118,119]. Antioxidants protective effect could be of practical therapeutic value and can be a possibility for the treatment of patients who become sensitized to haptens that form full antigens via radical mechanisms [106].

Metal-chelators such as sodium diethyldithiocarbamate, dimethylglyoxime and salts of ethyldiamine tetra-acetate (EDTA) have also been investigated as ACD preventive agents. Creams containing 7.2 % EDTA were shown to reduce the number and severity of the reactions to the application of 5% nickel sulphate in patch tests [120]. Similarly, a preparation containing 10 % of EDTA also demonstrated to effectively chelate nickel sulphate at 0,01 % (244 ppm), 0,1% (244 ppm) and 1% (2440 ppm). Although the methodology adopted in these studies cannot be compared with the real daily work situation, it is suggested that the barrier cream should be applied shortly before work and could be used as a barrier cream for nickel-allergic patients [120].

Interestingly, Stefan and colleagues re-evaluated the skin-protective capacities of an oil-in-water emulsion of 10 % diethylenetriaminepentaacetic acid (DTPA) in a randomized and double-blind study involving nickel-sensitized patients [52]. The same authors also extended the range of metal allergens examined to the less frequent metal allergens cobalt, copper, palladium, and chromium. The results demonstrated that the DTPA-containing cream also clearly abrogates positive patch test reactions in, cobalt- and copper-sensitized subjects, with a considerable amount of nickel ions remaining in an unbound form. The authors proposed that application of protective creams containing chelating agents fits into a comprehensive concept for patients sensitized to metals, who cannot thoroughly avoid allergen contact and who cannot wear protective gloves [52]. The authors conclude that this therapeutic options can be a reasonable solution to patients sensitized to nickel and cobalt, however if the protective cream was applicable regular frequent and correctly [52,93].

Currently, there are some products available on the market claiming to restore the skin barrier and concomitantly preventing contact dermatitis towards some skin allergens. Dermatologists' recommendation and advice to patients on the use of a barrier cream should always be based on knowledge of a proven effect of the barrier cream in properly designed and conducted studies [121]. For instance, the product NIK-I-BLOK® claims to have chelating effects over nickel. Indeed, NIK-I-BLOK® is a skin barrier cream that uses the active ingredient DTPA to capture free nickel ions, thus blocking their permeation through the skin. The cream's ingredients work effectively to protect the skin, preventing allergic reactions towards nickel, such as eczema, dryness, blisters, redness and itching.

Skintifique, another barrier cream available is marketed as an extremely safe and pure composition to be used to prevent skin rash by scavenging metals like nickel, chromium and cobalt at the skin surface. Through a patented method called "the capturifique technology" named by manufactures, that is not described in detail but claimed to capture particles of pollution and metals at the surface of the skin preventing them from penetrating the epidermis. The protective effect of one application is said to last up 14 h, but the cream must be reapplied after each washing of the skin [121]. They also claimed that in more than 70

% of the conducted tests the volunteers did not experience any adverse skin reaction upon exposure to the objects.

Interestingly, the Bariéderm cream, usually used as a repairing cream is currently on clinical trials for evaluation of the efficiency and tolerability in protecting individuals with hand dermatitis, either due to allergy or irritation. On this trial, with the primary propose of treatment, the patients are asked to apply the barrier cream twice a day on their hands for 3 weeks.

6. Conclusion

About 20 % of the general population has developed ACD to common haptens such as fragrances, preservatives, and metals, making this skin condition one of the most relevant occupational diseases. ACD represents not only an economic burden but also affects different areas of lifestyle, health, and psychological wellbeing. Indeed, in severe cases it may interfere with the ability to perform household chores, may involve the need to take prolonged sick leave, to change occupation, and the necessity to pursue time-consuming treatments. In clinically relevant cases, the disease can be resolved by avoiding future skin exposure. Although, it can take months and, in some cases, due to professional reasons, it is not possible to fully eliminate or avoid the triggering chemical. Regardless of the current treatment options, continuous research is mandatory towards dose optimization, treatment regimens, and potential drug combinations as well as the development of new therapeutic strategies. Indeed, and despite the ongoing pre-clinical and clinical studies for prevention and management of contact dermatitis with new molecules on the horizon, there's still room for improvement. For instance, most of the current knowledge about preventive strategies are derived from studies undertaken in experimental settings, where outcomes were measured after only short intervention periods. Also, there is a need to extend the current studies to a broadened list of chemicals.

Currently, in our view, the great challenge is to develop topical preparations that effectively prevent the disease during a re-exposure.

Author contributions

G.B., M.T.C., and B.M.N. designed and structured the manuscript. GB., IF., A.S., MC., and AIS. performed the literature search and wrote the first draft of the manuscript. GB., M.T.C., I.F., and B.M.N. revised and edited the final version of the manuscript. All authors read and approved the final manuscript.

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Declaration of Competing Interest

The authors report no declarations of interest.

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