Contact dermatitis

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Abstract | Contact dermatitis (CD) is among the most common inflammatory dermatological conditions and includes allergic CD, photoallergic CD, irritant CD, photoirritant CD (also called phototoxic CD) and protein CD. Occupational CD can be of any type and is the most prevalent occupational skin disease. Each CD type is characterized by different immunological mechanisms and/or requisite exposures. Clinical manifestations of CD vary widely and multiple subtypes may occur simultaneously. The diagnosis relies on clinical presentation, thorough exposure assessment and evaluation with techniques such as patch testing and skin-prick testing. Management is based on patient education, avoidance strategies of specific substances, and topical treatments; in severe or recalcitrant cases, which can negatively affect the quality of life of patients, systemic medications may be needed.

Allergen
A substance, usually a protein, that can stimulate the immune system and induce sensitization.

Irritant
A substance that has irritant properties that does not rely on the process of sensitization or immunological memory.

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Contact dermatitis (CD) is among the most common inflammatory dermatological conditions and is caused by the exposure to exogenous substances that elicit an immune response resulting in inflammation in the skin and/or mucous membranes[1,2]. Categories of CD include allergic CD (ACD), photoallergic CD (PACD), irritant CDD (ICD), photoirritant CD (PICD, or phototoxic CD) and protein CD (PCD) (TABLE 1). Contact urticaria has some overlap with PCD (BOX 1). Occupational CD encompasses all types of CD that relate to exposures in the work environment and is the most common occupational skin disease. ICD is caused by direct cellular toxicity leading to the inflammation and activation of the innate immune system, whereas ACD results from type IV delayed-type hypersensitivity involving both innate and acquired immune responses. After the initial exposure to an allergen that generates a pro-inflammatory skin environment (but no clinical signs or symptoms), ACD lesions develop during subsequent exposures following the activation of antigen-specific effector and memory T cells. Although exposure to the relevant allergen most commonly occurs through the topical contact route, other routes, such as ingested, airborne and parenteral, may be important in specific cases. Exposure to non-self materials is a requisite for developing all CD types; by contrast, such exogenous exposures can play a role in other inflammatory dermatoses, such as *Staphylococcus aureus* in atopic dermatitis (AD), but are not a prerequisite. In PACD and PICD, the addition of light exposure triggers the allergic or irritant reaction. CD may arise from readily identifiable, easily avoidable culprits and resolve after a limited time; in other cases, the course is chronic, diagnostically challenging and can lead to substantial negative effects on the quality of life (QoL). The diagnosis relies on clinical presentation, thorough exposure assessment and a patch test (for ACD and PACD), which is the gold standard for the identification of contact allergens, or a skin-prick or prick-prick test (for PCD); ICD is a diagnosis of exclusion. Contact allergy is identified by a positive patch test reaction (that may or may not be of current clinical relevance). The distinction between ACD and contact allergy is important — individuals who have contact allergy can develop ACD due to exposure to the contact allergens to which they are sensitized (indicated by a positive patch test reaction). However, someone with contact allergy does not necessarily develop ACD to that allergen. The field of CD is unique in the breadth of the investigative techniques utilized in clinical practice, the opportunity to cure disease without medication or surgery, and the integral role that patients play throughout the process of their care from diagnosis to disease resolution. Herein, we present a Primer on the epidemiology, mechanisms and pathophysiology of CD as well as on its diagnosis and screening, management approaches, effect on the quality of life of patients, and future outlook.

Epidemiology

Prevalence

Overall, the most common form of CD is ICD, accounting for 80% of cases[3]. Typically, ICD is caused by the cumulative effect of weak irritants such as soap and water. Other common irritants include degreasing agents, cosmetics, dust, foods and solvents[3]. Most studies on ACD are based on highly selected clinical populations presenting to specialized patch testing clinics and it is therefore difficult to estimate the incidence and prevalence

Table 1 | **Overview of the types of contact dermatitis**

Type of contact dermatitis	Primary immunological mechanisms	Examples of culprits	Evaluation technique examples
Allergic[a]	Type IV hypersensitivity reaction	Metals, fragrances, preservatives, dyes, adhesives, topical medications (for example, antibiotics), rubber accelerators and antioxidants	Patch testing, repeat open application test/use test
Photoallergic	Type IV hypersensitivity reaction; requires light exposure (primarily on the ultraviolet A spectrum)	Chemical sunscreens, NSAIDs, fragrances	Photopatch testing
Irritant	Direct cellular damage	Soaps and detergents, water, acids, alkalis, adhesives, solvents, oils	No routine testing available; it is a diagnosis of exclusion
Photoirritant (also called phototoxic)	Direct cellular damage; requires light exposure (primarily on the ultraviolet A spectrum)	Plants and fruits, medications	No routine testing available
Protein	Type I and type IV hypersensitivity reactions	High-molecular-weight proteins, especially food proteins such as in vegetables[373], spices[374], animal protein[375,376], wheat[377] and milk[378,379]; other substances include enzymes[380] and latex[381] and cross-reactivity has been described between several protein sources[382]	Short-term occluded patch testing (may be done on finger or palm), prick-prick testing, skin-prick testing

[a]Can often coexist with irritant contact dermatitis.

of ACD in the general population. Among 5,597 clinic patients specifically referred to members of the North American Contact Dermatitis Group (NACDG) for assessment of contact allergy, 66.6% had at least one positive reaction to a patch test and 50.2% had a final, primary diagnosis of ACD[4]. By contrast, among a randomly selected group of 3,119 people from five European countries, 27% of individuals had a positive patch test and therefore had contact allergy. The diagnosis of ACD was estimated at 8.2% based on the presence of contact allergy, a clinical history compatible with CD and a history of exposure to the allergen suspected to have caused the dermatitis[2]. A systematic review and meta-analysis of 20,107 individuals from the general population found a similar prevalence of contact allergy in ~20% of people[1]. This meta-analysis included 22 studies from Europe, 4 from North America and 2 from Asia. No studies from Africa or South America were identified. The prevalence of contact allergy was consistently ~20% across China, North America and Europe.

The prevalence of ACD in paediatric populations has frequently been underestimated, with the assumption that children have immature immune systems and limited exposure to allergens. However, ACD is increasingly recognized and studies have found positive patch test reaction rates of 54–65%, with higher relevant reaction rates than in adult populations. This difference is probably because proportionately fewer children are patch tested and only when there is a very high clinical suspicion for ACD[5–7].

Rates of photocontact allergy have been reported to vary from 5.7% in the United Kingdom to 49.5% in China[8]. These differences likely result from variations in skin type, ultraviolet (UV) light exposure, sunscreen and topical medication use, and photopatch testing utilization.

The prevalence of PCD worldwide is unknown; however, most cases seem to have an occupational origin, mainly in food handlers[9], and there is often a history of pre-existing dermatitis. PCD constituted 11% of all cases of occupational skin disease between 2005 and 2011 in Finland[10]. There is a paucity of data on the prevalence of PCD in other geographical areas.

Occupational CD. Occupational ICD is the most common type of occupational CD; however, the prevalence is not known and is likely to be far greater than reported. The workers most commonly affected by occupational CD include hairdressers, health-care workers, metal workers, blacksmiths, painters, construction workers and food processing workers[11]. Common occupational allergens include thiurams and carbamates (rubber accelerators), epoxy resin (which has various applications), formaldehyde (a preservative) and nickel (a metal)[11,12]. The NACDG reported that 10.2% of individuals evaluated at tertiary referral centres who received a patch test in 2015–2016 had occupationally related skin disease[4]. The European Surveillance System on Contact Allergies (ESSCA) found a similar rate of occupational CD, with a diagnosis in 10.3% of patients from non-specialized clinics and in 44.6% from specialized clinics[11]. Estimates from other surveillance studies in the United Kingdom suggest that the incidence of occupational CD is 13–34 cases per 100,000 workers[13,14].

There is less data on occupational CD in Asia, probably owing to the lack of an established system in reporting these diseases. However, a review found that occupational skin disease in industrial workers in Asia was more common than in Western countries, probably owing to the reduced emphasis on preventative measures[15]. Of note, the occupational dermatoses seen in health-care workers, food processing workers and domestic workers were similar.

A study from Australia found that, of 2,177 patients diagnosed with occupational skin disease, 44% had ICD and 33% had ACD[16]. There is a lack of data regarding the incidence in South America, with cases of occupational CD vastly underreported. However, a study from Brazil that assessed the sociodemographic profile of patients with occupational CD attending a tertiary centre from 2000 to 2014 found that occupational CD in this population was five times more likely to occur in men than in women; those working in the construction sector had the highest rates of occupational CD and, for women, the most common occupation was domestic work[17]. The incidence of occupational CD in the general population was not assessed. There are also insufficient data regarding occupational CD in Africa.

Risk factors

Risk factors for ACD can be acquired or innate. Acquired risk factors include underlying inflammatory skin diseases such as ICD and stasis dermatitis, which facilitate the development of ACD due to skin barrier damage. Innate risk factors include genetic susceptibility, such as mutations in the gene encoding filaggrin (a filament aggregating protein, which is important for epidermal differentiation and skin barrier function), and ethnicity, with some reports suggesting that those with darker skin types have a lower risk of ACD than individuals with lighter skin types owing to better barrier function (for example, more limited increases in transepidermal water loss after exposure to topical irritants)[18]. The prevalence of contact allergy and ACD is also greater among women than men, probably resulting from occupational and domestic exposures, rather than from any intrinsic differences of skin vulnerability between the sexes[19]. Additionally, on average, ACD starts at a younger age in women (20–29 years old) than in men (50–59 years old)[20]. Patients with AD have a reduced threshold to irritant exposure owing to factors such as increased transepidermal water loss and therefore have an increased risk of developing ICD[21]. However, the association between AD and ACD is much more complex and the results from different studies have been conflicting[22–24]. A recent large, single centre investigation over a 30-year time period found that contact allergy to topical products was more prevalent in those with AD than in those without AD[25]. However, this study also found that contact allergy to metals such as nickel and cobalt was less likely to occur in those with AD than in those without AD for reasons that remain unclear. Conversely, previous studies have suggested that filaggrin deficiency, as observed in AD, is a risk factor for nickel contact allergy owing to the reduction in nickel chelation in individuals with reduced filaggrin function[26–28]. Another systematic review and meta-analysis showed that, in patients with mild AD (in general population studies), the prevalence of contact allergy was higher than in controls, whereas a lower prevalence was observed in patients with more severe forms of AD who were referred for patch testing[29]. One explanation for these findings may be that patients with severe AD are referred for patch testing to rule out ACD when dermatitis is difficult to control or to evaluate alternative diagnoses prior to initiating systemic treatment.

The primary risk factor for PCD is workplace handling of food[30,31]. In a registry study from Finland over a 12-year period, occupations shown to be at risk for PCD included bakers, pastry cooks and confectionery makers as well as farmers, veterinary personnel, chefs, gardeners and hairdressers[10]. Occupation is also an important risk factor for the development of ICD and ACD. The highest risk occupations include hairdressers, health-care workers, beauticians, construction workers, metal workers and those in the foodservice industry[2,11,32]. Employees in these professions are frequently exposed to common irritants such as soaps, water, detergents, rubber, solvents, oils, and foodstuffs and such exposures can precede ACD[33] due to allergens such as hair dyes, metals, epoxies, acrylates and rubber accelerators.

Trends in allergens

Although the prevalence of contact allergy is generally comparable between Europe, North America and Asia, allergen trends vary between regions and over time (FIG. 1)[1,34]. Nickel is the leading contact allergen in most industrialized countries worldwide[35]. The prevalence of nickel contact allergy in the general European population is approximately 8–19% in adults[2]. Since the introduction of the European Union (EU) Nickel Directive in 1994, which came into force in 2000 and into full force in 2001, several European countries have reported significant decreases in nickel sensitivity, particularly in women aged 18–35 years (11.4% in 2006 compared with 19.8% in 1998 among participating Danish adults)[36] and in patients with dermatitis aged 18–30 years. The northern European countries have observed the greatest prevalence reductions, possibly due to the lack of enforcement of the EU Nickel Directive in some southern European countries[37]. However, the overall prevalence of nickel sensitization still remains high, particularly in women[35,38]. Similarly, the introduction of legislation regulating hexavalent chromium in cement and consumer leather goods in the EU has resulted in a decrease in the prevalence of chromium allergy[39].

Whereas the frequency of nickel sensitivity has decreased in Europe since the implementation of the EU Nickel Directive, nickel sensitivity remains an issue in the United States, where nickel release is unregulated. In a study of 44,908 patients patch tested in the United States included in the North American Contact Dermatitis Group (NACDG) screening series from 1994 to 2014, nickel contact allergy significantly increased over time from 14.3% in 1994–1996 to 20.1% in 2013–2014 (REF.[40]). However, the rate of positive reactions to nickel related to occupational exposure significantly decreased from 7.9% in 1994–1996 to 1.9% in 2013–2014. Other countries that have reported increasing rates of nickel sensitivity include Taiwan (from 14.3% in 1978–1990 to 23.0% in 1991–2003)[41], Singapore (from 13.9% in 1984–1985 to 19.9% in 2001–2003)[42] and China (from 15.4% in 1990 to 31.6% in 2006–2009)[43].

Box 1 | **Contact urticaria**

Contact urticaria (CU) clinically presents with a pruritic wheal, which typically appears within 60 minutes of exposure to the culprit urticant and resolves within 24 hours[386,387]. CU is divided into three subtypes: immunological CU (ICU), non-immunological CU (NICU) and mixed CU (also called CU of unknown origin)[388,389]. ICU involves an IgE-mediated reaction that requires prior sensitization (similarly to allergic contact dermatitis and photoallergic contact dermatitis), while NICU results from the direct release of urticants, such as histamine, without the need for prior sensitization. The mixed or undetermined subtype has a less well-defined mechanism. Common causes of ICU include plant or animal proteins, grains, and enzymes[387]. NICU can occur with exposure to substances such as nettles, cinnamon derivatives, benzoic acid and sorbic acid[386]. In some cases, ICU can present with systemic symptoms and even anaphylaxis. Evaluation with various testing methods, such as skin-prick test (for ICU) and open test/skin provocation test (for NICU) can be performed. In the case of ICU, testing for the presence of IgE-specific antibodies to the suspected culprits within the patient's serum can be obtained. Treatment includes the avoidance of identified causes, protective equipment (such as gloves for unavoidable occupational food exposures), antihistamines (for ICU), aspirin or NSAIDs (for NICU), management of acute symptoms (such as adrenaline for ICU with anaphylaxis), and other immunosuppressive options in cases of severe, recalcitrant CU[390].

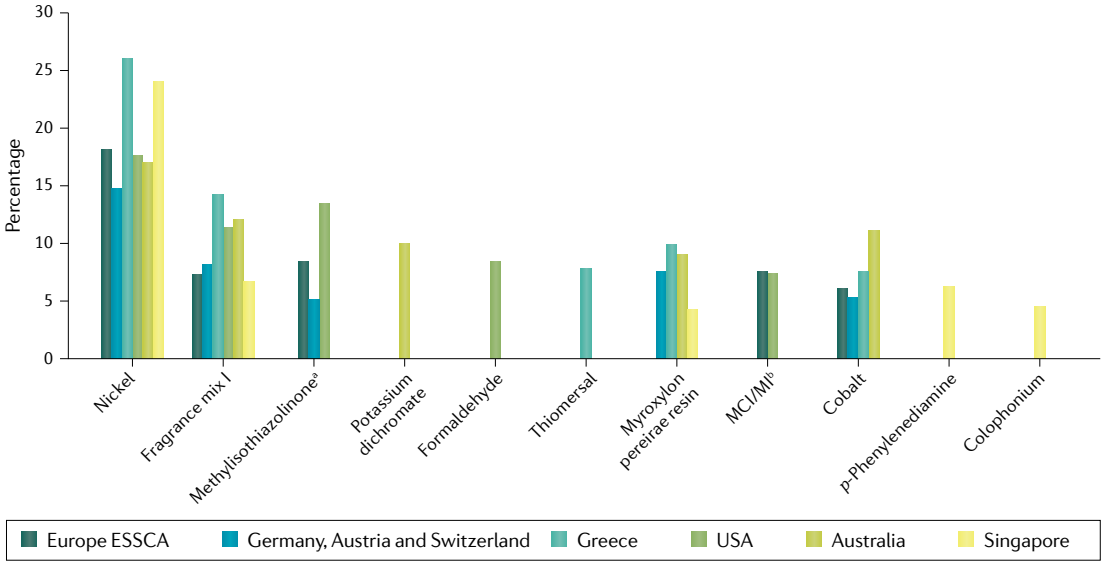

Fig. 1 | **Top sensitizers in various regions worldwide.** Prevalence of the most common allergens among various locations. Nickel is the most commonly identified contact allergen worldwide, followed by methylisothiazolinone or fragrance mix I, depending on the region. The presented data is based on studies from Europe (12 countries, time period 2013–2014)[44], Germany, Austria and Switzerland (2007–2018)[383], Greece (20104–2016)[384], North America (2015–2016)[4], Australia (2001–2010)[48] and Singapore (2009–2013)[385]. [a]Combined average of percentage of patients sensitized to methylisothiazolinone 0.02%, 0.05% or 0.2%. [b]Combined average of percentage of patients sensitized to methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) 0.01% or 0.02%. ESSCA, European Surveillance System on Contact Allergies.

p-Phenylenediamine (PPD), a component present in oxidative hair dyes, is an important contact allergen, particularly for hairdressers in their occupational setting. However, a recent analysis from 46 departments in 12 European countries showed an overall decline in PPD patch test positivity from 4.1% in 2004 to 3.2% in 2013–2014 (REF.[44]). This decline is probably due to the reduced use of PPD in oxidative hair dyes as it is being replaced with derivatives[45].

Other important trends include the recent epidemic of ACD to methylisothiazolinone (a preservative), which peaked in the first half of the 2010s before legislation was introduced in Europe to prohibit methylisothiazolinone in leave-on personal care products and to reduce the concentration in rinse-off products to 15 ppm (REF.[46]). A similar epidemic of ACD to methacrylates (specifically hydroxyethyl methacrylate (HEMA)) has occurred in recent years, previously associated with industrial exposures but now also with artificial nails, resulting in HEMA being added to the baseline patch test series worldwide[4,47,48]. Novel contact allergens will continue to be identified and new sources of known allergens will be discovered, necessitating the reporting of sentinel cases and the flexibility of baseline patch test series.

Mechanisms/pathophysiology

The development of CD relies on a chain of complex, interlinked and finely controlled processes. ICD, PICD, ACD, PACD and PCD engage different arms of the immune system and therefore have varied underlying mechanisms. ICD is mainly due to the toxicity of chemicals on skin cells, which triggers inflammation by the activation of the innate immune system[49,50]. By contrast, ACD is due to type IV delayed-type hypersensitivity responses[51–54] induced by the immunogenic properties of a subset of chemicals and requires the activation of both innate and acquired immunity. The mechanisms for PICD and PACD are similar to those of ICD and ACD, respectively, but require the addition of light exposure. All chemicals per se may induce ICD upon repeated exposure, with very large differences in the concentrations of individual irritants that are required to elicit a response[55]. By contrast, only a minority of chemicals, called haptens, may induce ACD[56,57] (see below). The skin inflammation that develops in sensitized individuals occurs with the recruitment and (re)activation of antigen-specific effector memory T cells in the skin. Finally, although the pathophysiology of PCD remains largely unclear, it is thought to be due to combined type I and type IV hypersensitivity reactions[58,59].

Irritant CD

The mechanisms by which chemicals cause skin irritation are poorly understood and vary from the disorganization of the lipid bilayers of cell membranes to the damage of epidermal barrier proteins such as keratins, claudins, involucrin and filaggrin[60,61]. Certain chemicals, such as acids, bases or detergents, trigger an intense cell necrosis, causing major disruption of the skin barrier; these chemicals are known as corrosives. Corrosive substances irreversibly damage the skin beyond repair, whereas irritant substances lead to a reversible local inflammatory reaction caused by the innate immune system of the affected tissues. Irritants have minimal and reversible effects on epidermal cells and may require repetitive applications before an ICD reaction occurs[62].

In both cases, the release of stress-associated molecular patterns (reactive oxygen species (ROS), ATP)

Hapten
A chemical that reacts with skin self-proteins through a process termed haptenization; haptens bind to self-proteins and generate hapten–self-protein complexes (or haptenated proteins) that will be processed in hapten–self-peptide complexes (or neo-antigens). These neo-antigens will then be presented in MHC to T cells.

and damage-associated molecular patterns (DAMPs; high-mobility group protein B1 (HMGB1), heat-shock proteins, IL-1α) by injured cells are sensed by receptors of the innate immune system on surrounding healthy cells (FIG. 2)[63,64]. The recognition of these ligands results in the release of a myriad of chemokines[49,65], derivatives of arachidonic acid metabolism[66] and proteases[67] within minutes or hours after contact. Irritants may also excite nociceptors, thereby producing acute pain and neurogenic inflammation through the release of vasoactive peptides such as substance P[68]. This release induces vasodilation and the infiltration of diverse leukocytes (neutrophils, eosinophils, basophils and/or inflammatory monocytes) from the blood into the skin[69,70], which further amplify the reaction. The resulting physiological signs of irritation include damage to the epidermis with spongiosis (characterized by intercellular oedema), microvesicle formation and/or necrosis (which can be detected by histology), and clinical manifestations such as erythema, induration (hardened skin) and oedema, which can be associated with painful and burning areas of skin. The inflammatory reaction resolves with the removal of the offending agent(s) and the elimination and replacement of injured or dead cells by skin repair processes.

Allergic CD

In contrast to ICD, ACD is induced in sensitized individuals after contact with certain chemicals, also referred to as haptens, or metals[56,57]. If haptens and metals are non-immunogenic by themselves, by binding to self-proteins, they generate neo-antigens that are eventually recognized by the immune system as "altered self"[52]. ACD is a type IV delayed-type hypersensitivity response that develops in two temporally dissociated phases: sensitization and elicitation. After permeation of the allergen into the skin and the formation of hapten–self-protein complexes[56,71] (see below), ACD requires the generation of a local inflammatory milieu in the skin for an efficient T cell priming in lymphoid organs by migratory skin dendritic cells (DCs)[72]. At this stage, individuals are sensitized and have a contact allergy, although they remain asymptomatic. Subsequent exposure to the chemical leads to the localization to the skin and reactivation of hapten-specific effector and memory T cells, which kill haptenized keratinocytes. This elicitation phase results in the development of local erythema and epidermal spongiosis, which is the most characteristic histological appearance of ACD lesions[51]. The persistence of a local and systemic T cell memory promotes the recurrence of the disease, also known as ACD flares, and the progressive worsening of skin inflammation upon hapten re-exposure (FIG. 2).

Initial sensitization: the formation of hapten–self-protein complexes. The mechanisms by which haptens react towards self-proteins have been extensively studied and include mainly interactions between electrophilic residues of the chemical and nucleophilic residues of certain protein amino acids, notably cysteine, lysine or tyrosine, as well as free radical reactions[56,57,73]. However, a majority of haptens are not per se electrophilic but gain protein reactivity via prior transformation: prehaptens are activated outside the skin via chemical or physical activators such as air oxidation or photo-activation, whereas prohaptens (such as urushiol, derived from the poison ivy plant, or PPD, a hair colouring chemical) are activated inside the skin via biotic activation by different detoxifying enzymes such as cytochrome P450 isoenzymes, alcohol and aldehyde dehydrogenases, monoamine oxidases, and others[74]. Of note, metal ions such as nickel, chromium and cobalt compose a specific category of allergens that react somewhat differently with self-proteins; these allergens generate non-covalent coordination chelation complexes with amino acids such as histidine[75].

Several factors mitigate the formation of hapten–self-protein complexes upon chemical exposure. One important aspect is the size[76] and intrinsic lipophilic or electrophilic nature[77] of the allergen itself as well as different exposure metrics such as the dose, frequency[78], duration[79], and vehicle or formulation through which the compound is applied[80]. These parameters dictate the permeation of the compound through the different layers of the skin and thus the localization and quantity of hapten–self-protein complexes that are generated[81,82]. Alternatively, the formation of these complexes can also be influenced by factors such as the humidity of the skin[83], the genetic susceptibility of the skin barrier (for example, filaggrin or claudin deficiency) and a genetic deficiency in detoxification enzymes (for example, arylamine N-acetyltransferases 1 and 2 or glutathione-S-transferases)[84,85].

The activation of innate response: the generation of a pro-inflammatory milieu in the skin. It is important to note that hapten exposure does not necessarily lead to an efficient T cell sensitization. A genuine immunological tolerance can develop in exposed individuals through the activation of regulatory T (T_{reg}) cells and subsequent anergy, with the resulting deletion of antigen-specific T cells[86–88]. This concept has been illustrated in experimental models of ACD exposed to clinically relevant molecules, such as fragrances, dyes and drugs, which fail to induce a response in normal mice but trigger a strong reaction in T_{reg} cell-depleted animals[89,90].

Nevertheless, by creating a potent pro-inflammatory milieu into the skin, certain haptens endowed with a strong sensitizing potential generate the conditions necessary to circumvent tolerance mechanisms[91,92]. When this occurs, hapten exposure prompts the full migration and activation of skin DCs that have engulfed hapten–self-protein complexes and subsequent T cell priming in effector and memory subsets. Conversely, the mechanisms for sensitization by compounds with weak or very weak sensitizing properties remain obscure. Such compounds induce a substantial proliferation of T cells in the draining lymph nodes[93] but no differentiation into effector cells that can trigger skin inflammation, even upon repeated administration and at high hapten doses[86,89]. Hypotheses include specific genetic predispositions, as noted in individuals with a family history of sensitization to weak sensitizers, and possible associations with peculiar SNPs in genes encoding TNF, IL-16

Sensitization
The initial phase of contact allergy where the immune system is primed to the allergen after exposure, with subsequent immune memory that can recognize the allergen with re-exposure.

Elicitation
In a previously sensitized individual, re-exposure to an allergen can cause mobilization of the immune system (immunological memory).

Prehaptens
Haptens that need to be activated by exogenous triggers (such as UV light, air or others) before they can react with self-proteins.

Prohaptens
Haptens that need to be activated by endogenous mechanisms (via enzymes or other biological processes) before they can react with self-proteins.

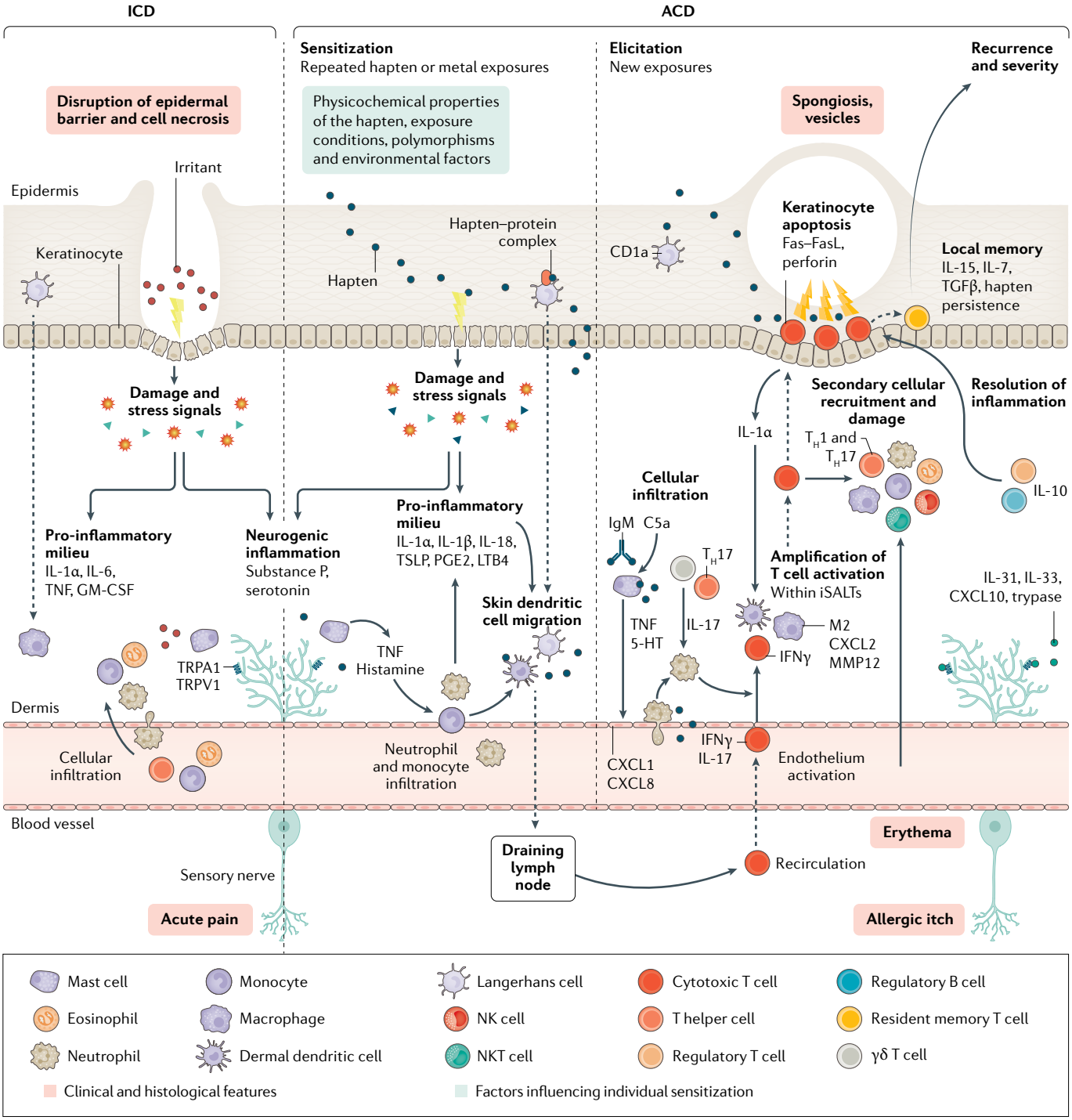

Fig. 2 | **Schematic representation of the pathophysiology of ICD and ACD.** Irritant contact dermatitis (ICD) develops due to toxic effects of chemicals on skin cells, which trigger an acute reaction through the release of damage and stress signals and subsequent innate immune cell infiltration. Irritants also excite nociceptors, thereby producing acute pain and neurogenic inflammation. In allergic contact dermatitis (ACD), after permeation of the allergen into the skin and the formation of hapten–self-protein complexes, the generation of the local inflammatory milieu into the skin induces T cell priming in lymphoid organs by migratory skin dendritic cells. The nature of skin dendritic cells responsible for T cell priming as well as the nature of hapten-specific T cell polarization and its MHC restriction varies depending on haptens and models. Subsequent contact with the chemical may lead to the mobilization and reactivation of hapten-specific effector and memory T cells into the skin through a complex and highly intricate inflammatory process in which neutrophils, IL-17-producing γδ and conventional αβ T cells, mast cells, or inducible skin-associated lymphoid tissue (iSALT)-forming M2 macrophages are key. Cytotoxic $CD8^+$ T cells then kill haptenized keratinocytes and potentiates the (re)activation of other inflammatory cells, which leads to the formation of local erythema, epidermal spongiosis and vesicles in severe cases. An intense itch–scratch cycle can also be initiated in response to the release of numerous pruritogens. Finally, the resolution of inflammation requires the recruitment and activation of forkhead box protein P3 ($FoxP3^+$) regulatory T cells and regulatory B cells. Importantly, resident memory T cells persist long term in the healed skin of ACD patients, where they may trigger flare-up reactions upon re-exposure. NK, natural killer; T_H, T helper.

or C-X-C motif chemokine 11 (CXCL11)[94]. Sensitization to weak allergens could also be promoted by the provision of an external adjuvant signal through the simultaneous administration of several allergens[95] and/or irritants[91], an underlying psychological stress[96], or a concomitant infection. Additionally, although skin or intestinal microbiota were shown to be dispensable for strong sensitizers, they may also play a role in the sensitization to weak haptens[97]. Such signals could maximize the immunogenic potential of skin DCs to prompt the priming of effector T cells.

The activation of innate immunity by strong sensitizers. Major progress has been made in recent years to understand how strong haptens activate innate immunity. Similar to irritants, innate responses are primarily triggered via the intrinsic pro-inflammatory or toxic properties of the causative allergen and involve the indirect or direct activation of pattern recognition receptors (PRR) (FIG. 3).

By accumulating within the cell, strong sensitizers, such as urushiol or experimental molecules like 2,4,6-trinitrochlorobenzene and oxazolone, stimulate the release of ROS and an increase in hyaluronidase activity[98,99]. These processes lead to the degradation of high-molecular-weight hyaluronic acid present in the extracellular matrix[100]. The resulting low-molecular-weight hyaluronic acid fragments act as DAMPs and, in combination with other molecules such as HMGB1 (REF.[101]) or human beta-defensins 2 or 3, activate Toll-like receptor (TLR) platforms. TLR2 and TLR4 activation triggers NF-κB signalling to stimulate the production of several inflammatory cytokines key in ACD, including TNF, IL-6, IL-12, IL-23, pro-IL-1β and pro-IL-18 (REFS[102,103]). The relative contribution of each cytokine varies depending on the specific haptens and models[104]. The production of active IL-1β or IL-18 requires the activation of caspase 1 using an NLRP3 inflammasome-dependent mechanism[103,105,106]. Similar to irritants, inflammasome activation is induced indirectly by cell damage and the release of ATP into the extracellular space[107]. Of note, an ITAM-coupled receptor–Syk–CARD9–BCL10-dependent signalling cascade was recently identified as a key pathway in hapten response[103]. One of the ITAM-coupled receptors involved in this signalling may be the C-type lectin receptor Mincle (Clec4e). This receptor is strongly up-regulated in response to skin damage and senses cholesterol sulfate,

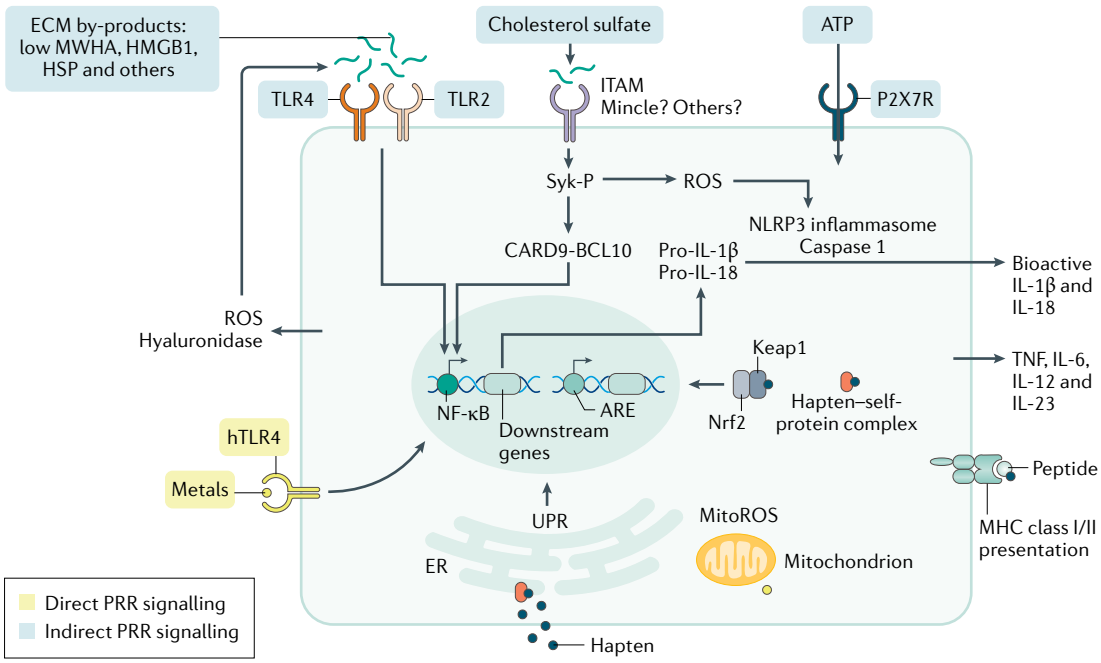

Fig. 3 | **Recognition of haptens and metal allergens by the innate immune system.** Haptens and metal allergens trigger innate immunity through the direct or indirect activation of pattern recognition receptors (PRRs). By accumulating within the cell, strong haptens induce cell death and/or the release of a multitude of damage-associated molecular patterns from injured cells. The production of reactive oxygen species (ROS) and an increase in hyaluronidase activity trigger the degradation of high-molecular-weight hyaluronic acid (MWHA) present in the extracellular matrix (ECM), which activates, in combination with other damage-associated molecular patterns (ATP, high-mobility group protein B1 (HMGB1), heat-shock proteins (HSP), etc), Toll-like receptors (TLR2 and TLR4) and purinergic receptors (P2X7R). This results in the production of key cytokines, including TNF, IL-6, IL-12, IL-23, IL-1β and IL-18, in an NF-kB-dependent or NLRP3 inflammasome-dependent manner. Complementary mechanisms to trigger inflammation include an ITAM-coupled receptor–Syk–CARD9–BCL10-dependent signalling cascade, induced possibly by cholesterol sulfate released from the damaged epidermis, as well as the unfolded protein response (UPR) pathway, activated in response to unfolded or misfolded proteins. Unlike organic haptens, metal allergens activate PRRs by binding directly to human TLR4 or via mitochondrial ROS (mitoROS). By promoting ROS and hapten detoxification, the cytosolic hapten sensor Keap1 and the transcription factor Nrf2 participate to maintain skin tolerance to chemical sensitizers. ER, endoplasmic reticulum.

a molecule present in the epithelial layer of barrier tissues at relatively high concentrations[108]. Finally, as strong haptens generate numbers of unfolded and/or misfolded proteins inside the cell, they also activate the unfolded protein response to trigger inflammation[109].

In contrast to organic haptens, metal allergens use slightly different mechanisms to generate the initial pro-inflammatory milieu, by direct binding to human (but not mouse) TLR4 for nickel, cobalt and palladium[110], or via an ATP signalling-independent NLRP3 inflammasome activation by mitochondrial ROS for chromium[111,112].

Thus, electrophilic and oxidative stress as well as cell damage are at the centre of hapten immune recognition and need to be tightly controlled. By promoting ROS and hapten detoxification, the cytosolic hapten sensor Keap1 and the transcription factor Nrf2 play a fundamental part in the maintenance of skin tolerance. This role was illustrated in Nrf2-deficient models, which mounted robust responses to weak allergens compared with their non-reactive wild-type counterparts[113]. Alternatively, Nrf2 could directly regulate the expression of key inflammatory genes to prevent or inhibit immune reactions to chemical allergens[114].

The activation of adaptive responses: the mobilization and contribution of skin DC subsets. To migrate into the draining lymph nodes, skin DCs integrate a multitude of inflammatory signals not only provided by the direct stimulation of their PRRs but also by the skin environment. Seminal studies have described the inflammatory dialogue existing between keratinocytes and Langerhans cells (LCs) to promote LC mobilization from the epidermis[106,115]. Recent works, using new genetic or imaging tools, have explored how, in the skin, resident and newly recruited immune cells cooperate to orchestrate the DC migration and maturation processes. In mice, possibly activated through Mas-related G protein-coupled receptor member b2 (or its human MRGPRX2 homologue)[116,117], skin mast cells produce TNF and histamine to activate DCs[118,119]. In parallel, mast cells, aided by skin macrophages, also induce the recruitment of neutrophils from the periphery[120], a crucial event amplifying DC activation and migration towards draining lymph nodes. Hence, the acute depletion of mast cells or neutrophils before sensitization substantially abrogates T cell priming[121].

Several DC subsets colonize the skin at homeostasis and are responsible for sensitization. LCs pave the epidermis, whereas conventional type 1 and type 2 DCs (cDC1 and cDC2) are present in the dermis. Plasmacytoid or monocyte-derived DCs can be recruited into the skin upon exposure and augment the pool of haptenated DCs[122]. In preclinical models, the contribution of skin DC subsets is dependent on the mouse strain and the hapten dose[52,123]. LCs, which express Langerin (also known as C-type lectin domain family 4 member K), mediate tolerance in response to weak and tolerogenic haptens[86] but, by contrast, are required for ACD responses induced by strong haptens, in particular at low hapten doses[123,124]. At higher concentrations, haptens further permeate in the skin and are taken up by dermal DCs (including Langerin$^+$ cDC1 and cDC2), which thereby complement (in normal mice) or compensate (in timed-inducible LC depletion models) LC activity[125–128]. However, these findings were challenged by specific models of constitutive and timed-inducible LC depletion, based on the use of human Langerin promoter, which demonstrated that LCs suppress responses to strong haptens in an IL-10-dependent manner[52]. Thus, skin DCs may be functionally redundant in ACD. Of note, plasmacytoid DCs have not been found to play a key role in hapten sensitization and the functional relevance of monocyte-derived DCs remains unknown[122,129].

The activation of adaptive responses: hapten-specific T cell activation. Hapten sensitization results in the full activation and proliferation of CD4$^+$ and CD8$^+$ T cells and B cells within 5–7 days in mice or 10–15 days in humans. A large diversity of T cell polarization was reported both in models and patients, with effector lymphocytes mainly producing type 1 (IFNγ, TNF), type 17 (IL-17) and type 22 (IL-22) cytokines but also type 2 (IL-4, IL-5, IL-9, IL-13) cytokines in response to certain chemicals[51,130,131]. The variability in T cell polarization seems to be related to the capacity of haptens to activate specific pathways of innate immunity. By binding to TLR4, nickel stimulates IL-23 production by human monocyte-derived DCs to promote IL-17-producing CD4$^+$ T cells[132]. Fluorescein isothiocyanate exposure leads to canonical type 2 polarization mediated by the release of keratinocyte-derived thymic stromal lymphopoietin (TSLP) and subsequent activation of TSLP-responsive LCs or dermal cDC2 cells[128,133,134]. A similar diversity of responses was also observed in the molecular signatures of positive patch test lesions induced by different allergens, with prominent type 1 and type 17 polarization induced by molecules such as nickel and mixed type 1–type 17–type 2 polarization in response to fragrances and rubber[135].

So far, it is largely unknown why some haptens could stimulate different pathways of innate immunity. An attractive hypothesis suggests that the capacity of haptens to stimulate specific pathways of innate immunity could be associated with their ability to preferentially bind certain amino acids (notably lysine or cysteine); however, so far, there is no formal demonstration of this mechanism.

It is noteworthy that some T lymphocytes activated in response to hapten exposure are not restricted to conventional MHC class I or class II molecules. Indeed, recent studies based on in vitro T cell clone technology have demonstrated that many small and extremely hydrophobic haptens, such as 2,4-dinitrochlorobenzene, cinnamaldehyde, benzoate or benzyl cinnamate, stimulate the production of inflammatory cytokines by T cells restricted for cell-surface glycoproteins CD1a, CD1b, CD1c or the antigen-presenting glycoprotein CD1d[136,137]. The molecular features of the hapten-induced CD1a–d response remain unclear but, by inserting within CD1 pockets, haptens could serve as classical epitopes, unmask reactive areas at the CD1a surface or promote

the presentation of endogenous self-lipids to stimulate TCR responses[136]. Although largely absent in mice (except for CD1d, which is responsible for the activation of NKT cells in mouse ACD[138–140]), the importance of CD1 reactivity may be underestimated in ACD development as recently illustrated by the transgenic overexpression of the human CD1a molecule in mice, which triggered a potent LC-dependent CD1a-restricted $CD4^+$ T cell response to urushiol[141].

Importantly, a variety of immune cells endowed with regulatory potential are activated in parallel of effector lymphocytes, including $ICOS^+$ forkhead box protein P3 $(FoxP3)^+$ T_{reg} cells, $CD5^+CD1d^{hi}$ regulatory B cells and invariant NKT cells, which limit the activation of skin DCs and the expansion, differentiation and egress of effector T cells from the draining lymph nodes[139,142,143]. Although partially understood, the regulatory mechanisms are multiple and involve direct cell–cell contact via gap junctions or Fas–FasL signalling, the secretion of inhibitory cytokines such as IL-10 and TGFβ, the regulation of ATP turnover by the 5'-nucleotidases CD73 and CD39 (also known as ectonucleoside triphosphate diphosphohydrolase 5) with the subsequent production of immunosuppressive adenosine, and possibly the deprivation of the IL-2 pool[144–149]. A majority of these mechanisms are also triggered when individuals are exposed to non-immunogenic doses of allergens. IL-10-producing $FoxP3^+$ T_{reg} cells notably maintain the tolerogenic state of skin DCs[88]. Tolerogenic DCs then produce adenosine[150] and/or TNF[151] to precipitate the anergy and deletion of T cell precursors[86] or to promote the generation of $CD8^+$ T_{reg} cells[88]. Hence, the production of a pro-inflammatory milieu provides the cues necessary to counterbalance T_{reg} cell suppression and leads to the priming of hapten-specific effector T cells. The mechanisms by which the milieu circumvents T_{reg} cell retro-control remain largely unknown but could involve cytokines such as IL-6, Il-1β and Il-15 (REF.[152]).

Hapten exposures following sensitization: the key role of cytotoxic $CD8^+$ T cells and neutrophils in the formation of ACD lesions. ACD lesions develop in sensitized individuals after a secondary contact with the causative allergen and typically show a polymorphic cellular infiltrate dominated by T cells and neutrophils[51]. $CD8^+$ T cells are localized both in the epidermis and dermis, whereas $CD4^+$ T cells are mainly found in the dermis, at least in mice[153]. Possible explanations for this differential localization include the increased expression of specific chemokine receptors as a response to the chemokines produced by the exposed keratinocytes and the cytotoxic properties that enable $CD8^+$ T cells to degrade the dermal–epidermal junction more efficiently than $CD4^+$ T cells. In patch test models, human $CD8^+$ T cells are the main epidermal T cells (M.V., unpublished data). Additionally, unconventional lymphocytes, such as γδ T cells[154], NKT cells[155] and innate lymphoid cells (including NK cells[156,157]), and other inflammatory cells, such as monocytes and macrophages[122], eosinophils[158], and mast cells[117], also accumulate in ACD lesions. Together, these cells participate in a complex and highly intricate inflammatory process that orchestrates the formation of the cutaneous findings of ACD.

Cytotoxic $CD8^+$ T cells are commonly considered the primary and key driver of ACD inflammation. Indeed, animals deficient in $CD8^+$ T cells are unable to develop a skin response to a multitude of experimental haptens[51,159]. The participation of effector $CD4^+$ T cells as a key driver of disease has also been suggested for some haptens[160–162]. In fact, T cells operate at three different levels to promote the formation of ACD lesions: they initiate the infiltration of blood leukocytes within the tissue (at hapten doses that classically fail to induce such recruitment in non-sensitized individuals)[163], kill haptenized keratinocytes, a major histological hallmark of ACD reaction[164,165] and potentiate the (re)activation of other inflammatory cells, which exaggerate the inflammation.

T cells are possibly reactivated by endothelial cells of postcapillary venules, which have captured the allergen[163]. By producing IFNγ and IL-17 (REFS[166,167]), they activate the endothelium to produce CXCL1, CXCL2 and CXCL8, which results in the early extravasation of neutrophils into the tissue parenchyma[163]. Neutrophils, in turn, release granules that contain multiple attractants or cytotoxic mediators (such leukotrienes B4, C-C motif chemokine 1 (CCL1), CCL2, CCL5, CXCL9, CXCL10, FasL, perforin and extracellular matrix-degrading enzymes[168]) that mediate tissue injury and promote the infiltration of blood leukocytes, including $CD8^+$ and $CD4^+$ T cells. If neutrophils are depleted at this stage, few T cells infiltrate the skin and the ACD reaction is minimal[121,169]. Thus, all the skin cells that amplify neutrophil recruitment, such as IL-17-producing dermal γδ T cells[170], $CD4^+$ T helper 17 (T_H17) cells[171], and TNF-producing and serotonin-producing mast cells[172], exaggerate the reaction. Mast cells are stimulated during this phase by C5a complement generated in response to hapten–IgM immune complexes through a specific process requiring the participation of NKT cells and B cell immunity established during the sensitization phase[173]. In the parenchyma, T cell activation is next amplified in different leukocytes-clustering structures, such as inducible skin-associated lymphoid tissues (iSALT), formed early during the elicitation phase of the ACD response around postcapillary venules[174]. iSALTs are composed of various types of leukocytes, including iSALT-driving perivascular macrophages, dermal DCs and T cells. Some clusters of inflammatory CX3C chemokine receptor 1 $(CX3CR1)^+$ monocytes and T cells are also formed after a few hours on top of iSALT, close to the hair follicle[175]. These clusters favour the infiltration of $CD8^+$–C-X-C chemokine receptor type 3 $(CXCR3)^+$ T cells into the epidermis, where they kill keratinocytes presenting allergen on their cell surface through perforin and Fas/FasL mechanisms[176]. Additionally, by producing IFNγ, IL-17 or IL-2 upon reactivation, $CD8^+$ T cells prime skin cells for killing by other cells, notably $CD4^+$ T_H1 cells[177], NKT cells[178], γδ T cells, NK cells[156], or inflammatory monocytes and macrophages[167,175,179]. Of note, several studies have reported the capacity of mouse and human liver NK cells to mediate antigen-dependent responses to haptens and metals[180–182]. Although

experimental evidence showed that the NK cell role is minor after classical skin sensitization[183], the adoptive transfer of those cells confers potent reactions with memory features[184] through a process requiring the participation of skin macrophages and the NLRP3 inflammasome[185].

Resolution of ACD inflammation and development of a local and systemic T cell memory. The resolution of an ACD reaction requires the removal of the offending allergen and the activation of numerous mechanisms of regulation, most notably the recruitment and activation of FoxP3$^+$ T_{reg} cells[186] and peritoneal CD22$^+$ B1a regulatory cells[187] as well as the engagement on epidermal cells and dermal mast cells of regulatory, non-MHC ligands such as programmed cell death 1 ligand 1 (PDL1)[188–190]. FoxP3$^+$ T_{reg} cells with high functional and phenotypic diversity are found in the inflamed skin[191,192]. They infiltrate the skin concomitantly with effector T cells, where they progressively inflect the course of skin inflammation in an IL-10-dependent and CTLA4-dependent manner[193–195]. In parallel, adoptive transfer experiments in mice have shown that they also regulate leukocyte influx into the skin by downregulating the expression of E-selectin and P-selectin[196] and strengthening junctions on the vascular endothelium[197]. Finally, some skin T_{reg} cells leave the inflamed skin to migrate back to the draining lymph nodes, where they probably participate to terminate the systemic immune response[186]. Beyond their essential function in preventing and regulating inflammation, recent work demonstrates that FoxP3$^+$ T_{reg} cells also partake in tissue repair[198]. It will be interesting to determine whether these cells help in the renewal of the spongiotic epidermis in ACD.

Importantly, upon the resolution of inflammation, effector T cells progressively differentiate into memory T cells. Several types of memory T cells are generated, bearing the same TCR[199], including the circulating effector and central memory T cells[200], as well as tissue-resident memory T cells (T_{RM})[199,201], which accumulate in the sites of prior reactions in response to keratinocyte-derived IL-15 and IL-7 (REF.[202]), autocrine production of TGFβ[203], and the persistence of the allergen in the epidermis[153]. The speed at which the allergen or irritants are eliminated from the skin remains poorly studied and understood and is associated with epidermal renewal. One month after skin contact, low amounts of hapten can still be detected[153]. T_{RM} cells are key in the recurrence of the pathology with allergen (re)exposure. They persist long term[153] and are responsible for the early and intense flare-up reactions, which tend to develop on previously affected but healed skin of patients with ACD[199]. By contrast, circulating memory T cells are responsible for delayed and mild flare-ups on previously non-involved skin[199,204]. Of note, T_{RM} cells express several inhibitory receptors, such as programmed cell death protein 1 (PD1) or T cell immunoglobulin and mucin domain-containing protein 3 (TIM3, also known as hepatitis A virus cellular receptor 2), which keep them in check by engaging their respective ligands expressed on keratinocytes or other skin cells to preserve skin integrity and avoid the development of severe and persisting inflammation[153].

PICD and PACD

PICD and PACD result from the combined action of light, especially in the UVA (wavelength of 320–400 nm), UVB (290–320 nm) and visible (400–700 nm) light regions, and photoreactive chromophores, referred to as photosensitizers[205,206].

When a photosensitizer absorbs a photon, it enters a transient activation state and elicits a chemical reaction by transferring the energy of the photon to another molecule[207]. A major target of this transfer is cellular oxygen, resulting in the increased production of ROS (for example, singlet oxygen, hydroxyl radicals and superoxide anions)[208] in target tissues, leading to photo-oxidative stress[209]. Excessive ROS production overwhelms the antioxidant defence systems and injures cells by inducing irreversible DNA and RNA damage as well as membrane and/or organelle alterations through lipid peroxidation and by inhibiting key cytoprotective enzymes, which precipitates cell death in surviving or healthy neighbouring cells and/or skin inflammation[210–212]. Alternatively, photosensitizers may also use light energy to form stable photoproducts with cell biomolecules; for example, the covalent binding of psoralen to DNA[213]. Ketoprofen (an anti-inflammatory drug) and its derivatives[214,215] were also reported to generate hapten complexes by binding to self-proteins, which leads to T cell sensitization and a subsequent PACD reaction after repeated exposure. Of note, haptens responsible for PACD can be the photosensitizer itself, which behaves in this case as a prehapten, or a novel hapten, a photohapten, created upon light energy transfer[216].

The sequential events leading to PICD and PACD are virtually the same as those of ICD and ACD, respectively, except for the requirement of light for dermatitis to occur[216]. Hence, by inducing photo-oxidative stress, photosensitizers may trigger innate inflammation through various mechanisms, including the activation of the transcription factor NF-κB[217], the assembly of the NLRP3 inflammasome complex[218], and the stimulation of redox-sensitive signal transduction pathways like c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK)[219]. Additionally, DAMPs (for example, calreticulin, uric acid, HMGB1) released locally in response to irradiation-induced and chemical-induced cell apoptosis and necrosis[220–222] play a major part in activating skin DCs and priming for efficient T cell sensitization against photosensitizers. However, the molecular mechanisms behind photo-damage and chemo-damage are highly complex and major progress remains to be made to improve our understanding of the development of such reactions. Recent observations using in vitro models of photodynamic therapy, which uses the properties of light and photosensitizers to kill neoplastic cells, suggest that the nature and extent of photo/chemo-damage depend on multiple factors, including the type of photosensitizer, its concentration, its subcellular localization, the amount of energy and the fluence (energy per unit area)

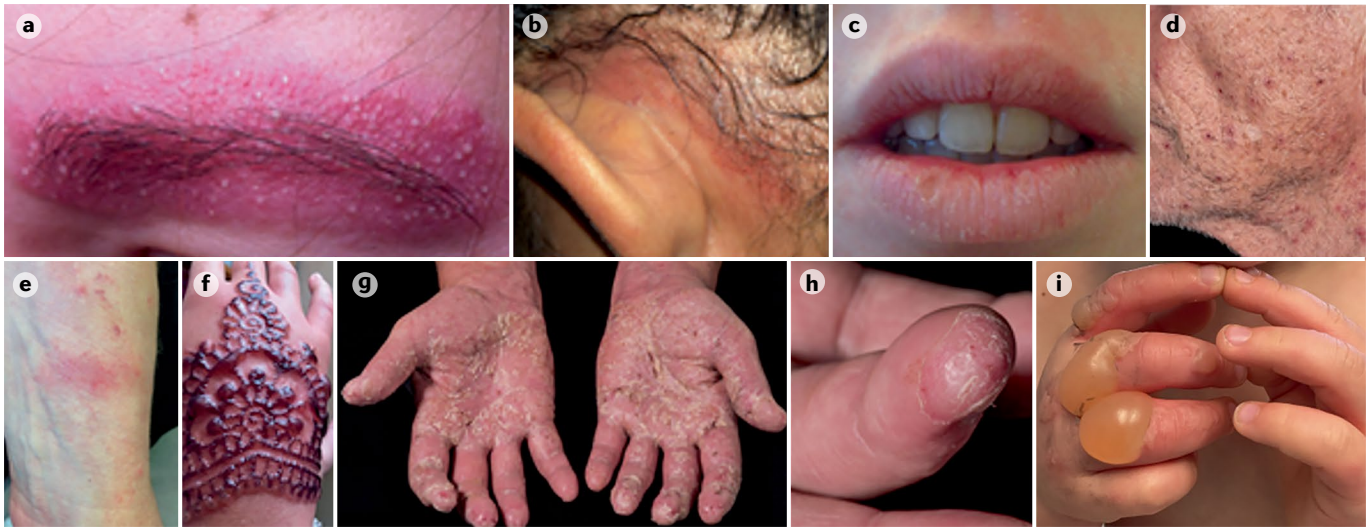

Fig. 4 | **Typical CD reactions to various chemicals.** Reaction caused by allergic contact dermatitis (CD) to hair dye products used on eyebrows (part **a**) and scalp (part **b**), fragrances in a lipstick (part **c**), shaving foam (part **d**), chromium found in a leather wristwatch strap (part **e**), *p*-phenylenediamine used in a semipermanent tattoo on the hand (part **f**), rubber chemicals in gloves (part **g**) and glues used in dental care (part **h**). Photoirritant CD reaction to citrus juice (part **i**). Part **i** adapted from REF.[8].

rate applied, and the characteristics of each cell type[223]. The thickness of the horny layer of the skin, the degree of melanin pigmentation and the immunological status of the affected person are additional factors that further influence photosensitivity reactions[224].

Diagnosis, screening and prevention

Clinical presentation

Clinical manifestations of CD vary by factors such as the specific allergen, irritant or protein culprit, route of exposure, degree of sensitivity, skin type, chronicity of the dermatitis and exposure to the offending agent, and others (FIG. 4). The skin reaction typically begins at sites that have been in either direct or indirect contact with the offending exogenous stressor. It is impossible to make a reliable clinical distinction between the CD subtypes on the basis of the morphology of skin lesions, although ACD has a tendency to form vesicles and even bullae and PCD often begins with wheal (a swollen erythematous area) and flare reactions that gradually become more eczematous. Generally, the morphology of acute CD is characterized by oedema, erythema and vesicles, whereas chronic dermatitis shows xerosis (dry skin), scales, hyperkeratosis and fissures (tears in the skin). Acute and chronic CD can be distinguished clinically but may overlap, such as during acute worsening of chronic lesions. In cases of hand dermatitis, specific clinical findings may aid in differentiating between CD subtypes. ICD tends to localize to the interdigital spaces and dorsal side of the hands and fingers but the involvement of these areas is not specific to or required for a diagnosis of ICD. Notably, ACD and ICD often present simultaneously on the hands; analyses of exposures and the results of patch testing can aid in the diagnosis.

Traditionally, ACD tends to spread outside of the skin area that had direct allergen contact if the allergen exposure persists or the amount of allergen exposure is substantial[225]. However, ICD may also spread in selected cases, such as from the hands to the forearms[226]. Systemic ACD is a less common subtype of ACD observed in a minority of cases where eczematous lesions classically manifest in flexural areas (among others) following systemic (for example, oral or parenteral) exposure to an allergen. A systemic ACD reaction can also be elicited by drugs, in particular antibiotics; this variant has been described as symmetrical drug-related intertriginous and flexural exanthema and typically involves the buttocks[227]. Examples of other clinical presentations of systemic ACD include vesicular hand dermatitis (also called pompholyx or dyshidrosis), vasculitis or erythema multiforme-like lesions, diffuse maculopapular lesions, eyelid oedema or dermatitis, flare of prior patch test reaction sites, and worsening of underlying eczematous dermatitis[228,229].

Airborne ACD results from contact allergens distributed through the air before deposition on the skin; reactions typically affect exposed sites of skin such as the face, hands and forearms. An airborne ACD can be caused by exposures to allergens, for example, in plants and preservatives added to paints. PACD can present with a similar distribution as airborne ACD, typically affecting sun-exposed areas (and often sparing shaded submental and retroauricular areas, for example) and arises following the exposure to ingredients found in, for example, cosmetics, sunscreens, and topical medications and requires light exposure[8]. Photoreactions arise at doses of sunlight that are commonly regarded as harmless in the absence of photosensitizers.

Consort (also known as connubial) ACD is an uncommon result of allergen exposure from a partner or close contact in the distribution of the exposure (for example, transfer of a product from the lips of a partner to the cheek of the person with ACD). Culprits implicated in consort ACD are commonly cosmetic products

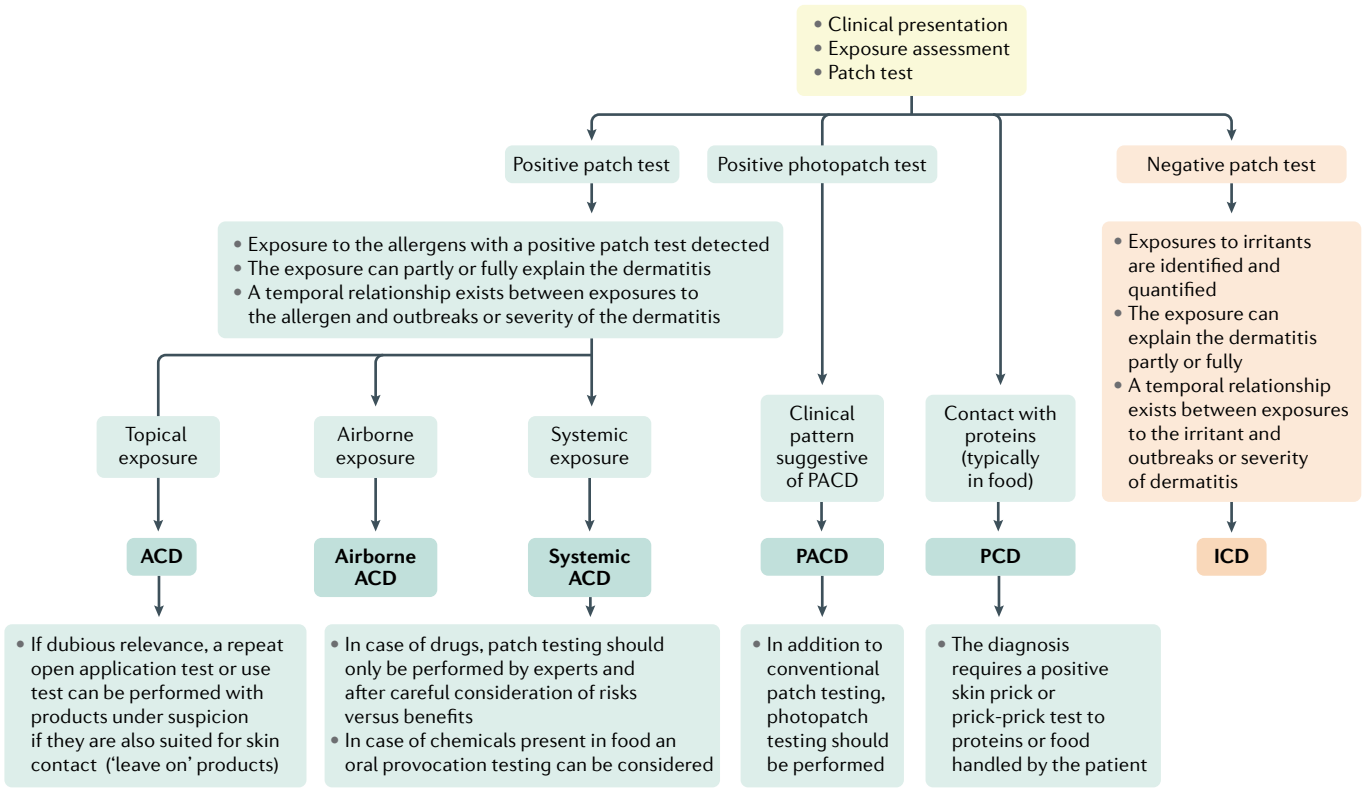

Fig. 5 | **Diagnostic algorithms for contact dermatitis.** General diagnostic algorithms for the evaluation of allergic contact dermatitis (ACD), airborne ACD, systemic ACD, photoallergic contact dermatitis (PACD), protein contact dermatitis (PCD) and irritant contact dermatitis (ICD).

such as lipsticks, moisturizers and aftershave as well as topical medications.

As other conditions, including cutaneous T cell lymphoma, pre-bullous bullous pemphigoid (a phase of bullous pemphigoid prior to the onset of bullous lesions), psoriasis and paraneoplastic phenomena, can mimic and/or coexist with ACD and cause recalcitrant dermatitis, when patients are not responding as expected to allergen avoidance strategies and other interventions (see Management), it is important to perform a skin biopsy and proceed with additional clinical investigations. However, there are no diagnostic histopathological findings on skin biopsy that are consistently observed in CD.

Diagnostic work-up

The diagnostic test for ACD and PACD is the patch test, whereas the prick test, prick-prick test and, sometimes, specific serum IgE levels are used for the diagnosis of PCD. In all cases, these investigations are combined with the clinical presentation and an exposure assessment to reach a diagnosis; exposure assessment is helpful to determine which substances should be used for testing and to devise an avoidance plan based on the identified culprits. The diagnosis of ICD and PICD relies solely on the clinical presentation, exposure assessment to irritants, and exclusion of ACD (FIG. 5). Skin biopsies are generally of limited value in diagnosing CD but can be helpful in certain cases to further evaluate the differential diagnosis.

Exposure assessment. The tools used to determine relevant exposures include taking a comprehensive history from the patient as well as the knowledge of exposures in different occupations, consumer settings and products. Ingredient labelling on different types of products is a major source of information, especially when it concerns cosmetics. However, even product labelling can provide incomplete information; prior studies have identified unlisted formaldehyde or formaldehyde-releasing preservatives in personal care products[230,231]. It is often much more difficult to obtain reliable information about the composition of other consumer products, including paints, glues, textiles and footwear, as well as of medical accessories as illustrated by the many recent cases of ACD to chemicals in glucose sensors[232]. If a material safety data sheet exists, this should be consulted but, importantly, it cannot be used to exclude the presence of an allergen[233].

Spot-tests can also help determine exposures and to evaluate products for the release of nickel, chromium, cobalt, formaldehyde and isothiazolinones. Spot-tests rely on a compound that, by binding to the substance of interest, forms a complex that changes the colour of the test solution. Thin-layer chromatography is a chemical method that can physically separate compounds present in a mixture or product and may be used for materials such as (extracts from) textiles; the thin-layer chromatography plates with the separated compounds may be used directly for patch testing[234]. The fraction that causes a reaction is then subjected to further chemical analysis

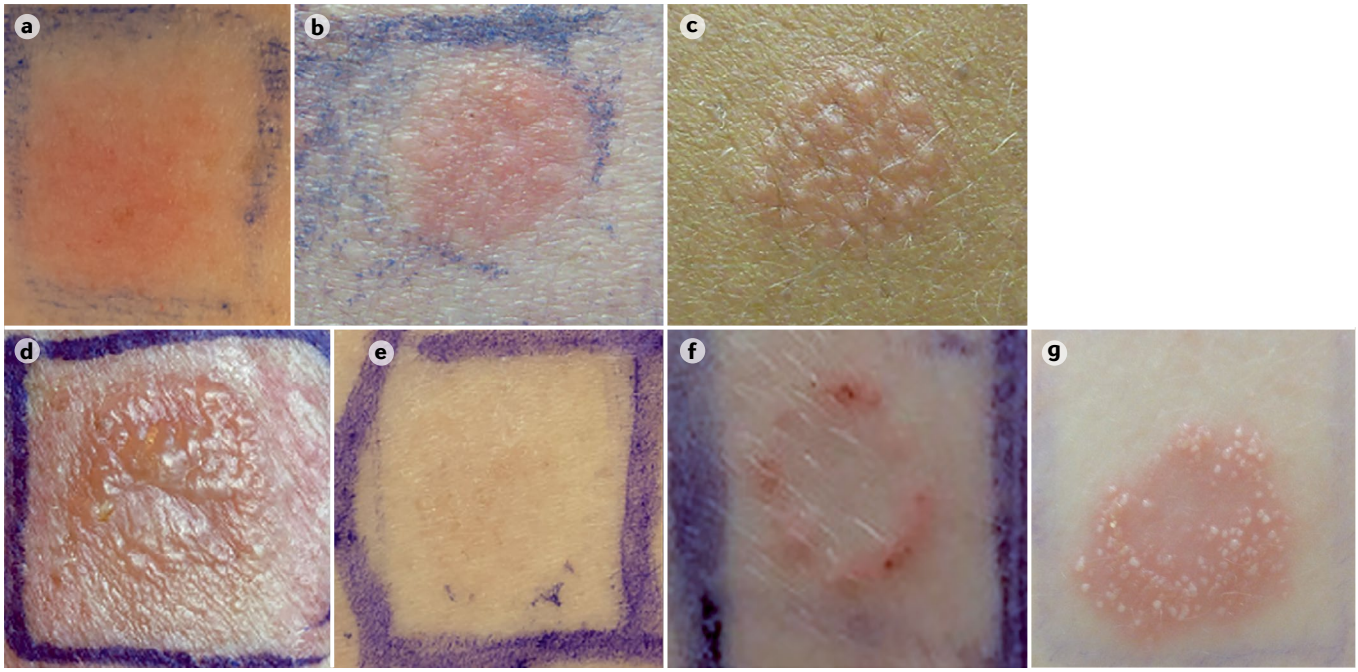

Fig. 6 | **Grading system for patch test reactions.** The photographs show examples of different grades of patch test reactions. Doubtful (?+) reaction showing macular erythema only and no infiltration (part **a**). Positive (+) reaction with homogenous erythema and infiltration in the test area (part **b**). Positive (++) reaction; in addition, vesicles are seen (part **c**). Positive (+++) bullous reaction (part **d**). Irritant reaction, with dry and shiny skin (part **e**). The edge effect may be interpreted differently depending on the test substance (parts **f** and **g**); it can be due to irritation or, in the case of corticosteroids, it may be interpreted as a positive reaction (corticosteroids have an anti-inflammatory effect more concentrated in the centre leading to an allergic reaction at the rim of the test site).

to determine the offending substance[235]. Exposure measurements of allergen directly on the skin can be done for nickel and cobalt[236] and have been developed for PPD from hair dyes as part of an experimental setup. This can be done by swabbing or rinsing the skin before and after some hours of normal work procedure and then subjecting the deposited material to relevant chemical analysis for detection of the allergen. These methods should be further developed to be integrated in the routine clinical work-up of individuals with suspected ACD. If airborne or systemic ACD is suspected from the clinical pattern, exposure assessment should entail the potential of airborne or systemic exposures, for example, by drugs (see below).

Patch test. The patch test is the gold standard for diagnosing contact allergy. However, the presence of contact allergy (sensitization to a substance) in an individual is not sufficient to establish the presence of ACD and an assessment of the allergen's current relevance and relationship to the clinical pattern, such as distribution and effects of dose and time of exposure, is also required for diagnosis[237]. The patch test is a clinical provocation test in which the contact allergens under suspicion are applied to small areas of skin (~0.5 cm^2), most commonly on the upper back, using chambers that are affixed to the patient's skin with tape. With this testing method, the allergen is applied on the skin under occlusion within the patch test chamber. The specific substance concentration varies by allergen; some allergens are available as finished products from different manufacturers, prepared with fixed concentrations and vehicles (often petrolatum or water and rarely alcohol). The optimal concentration has been determined to produce an allergic response with patch testing but without causing substantial irritation to the skin or other adverse effects. Exact dosing is also important for reliability, as an excessive dose can cause both false-positive test reactions and lead to active sensitization, whereas an insufficient dose can lead to false-negative test results[238]. The patches are left in place for 2 days before removal and a reading is performed according to an internationally agreed-upon, semi-quantitative scale (FIG. 6)[237]. This scale is used for all skin types but evaluation may be more challenging in darker skin types, for example, owing to less visible erythema. Optimally, three readings are performed after the removal of patches, including at day (D) 2, D3 or D4, and D7. If only one reading is performed, D4 should be used to ensure high sensitivity. If no late reading (D7) is done, 15% of positive test reactions may be missed[239]. Some allergens are especially prone to appearing late, for example, corticosteroids owing to their inherent anti-inflammatory properties, or metals, gallates, gentamycin and neomycin[240]. A positive corticosteroid patch test reaction may also only appear at the rim of the patch (FIG. 6f,g), where the anti-inflammatory action is minimal.

Patch testing in cases where systemic ACD to medications is suspected requires special expertise as the disease may be reactivated by patch testing. Although this occurrence is rare, severe reactions to medication can lead to substantial morbidity. Both the medical literature

and relevant guidelines[241] should be consulted prior to performing patch tests in such cases.

Some substances become allergens after exposure to light and can lead to PACD in sensitized individuals. In cases where these allergens are suspected, photopatch testing, a variant of traditional patch testing, can be performed. With photopatch testing, a group of known photo-allergens are exposed to UV light after a set time of occlusion on the skin. Specific guidelines exist for the selection of relevant substances and procedures[242].

Selection of test substances for patch testing. Around 5,000 substances have been identified as potential contact allergens[243]; as a result, the selection of substances to apply for each individual patient is a crucial step in the patch testing process. Baseline test series exist, which typically contain 30–100 test substances and match the exposures to allergens in a specific geographical area. Often, national CD groups further adjust or add test substances of local relevance. Generally, patients with suspected ACD are tested with the baseline series, which is also supplemented with specialized test series and individual allergens relevant to the patients' exposures such as occupation, hobbies and skin-care products. The choice of test substances is based on a meticulous and systematic exposure analysis drawing on all available types of information[244].

Products used by the patient may be included in the patch test procedure, especially products intended for prolonged skin contact such as moisturizers, gloves and textiles; wash-off cosmetics should be diluted prior to testing to avoid irritant skin reactions, which may be misinterpreted as allergic skin reactions. To minimize the risk of irritation, a semi-occlusion can be used by fixing the test material directly to the skin with special tape after allowing the substance to dry[237]. This procedure may be conducted in addition to the testing of the specific, potentially allergenic ingredients in the product. Products with a high or low pH should never be patch tested, as skin necrosis and scarring may occur. Products with unknown composition or those with strong allergens, such as acrylates or epoxy resins, should not be used for patch testing as these may cause active sensitization. Instead, these allergens should be evaluated through a standardized patch test substance series in which a safe test concentration has been established.

Skin-prick test. Skin-prick tests are used to evaluate immediate type I allergic immune reactions, which are classically caused by proteins or, rarely, by chemicals. The typical clinical reaction occurs as a contact urticarial reaction, which presents as immediate (within 1 hour), transient (lasting <24 hours) urticaria at the site of contact with the offending agent. However, vesicles and chronic dermatitis may occur, particularly in cases of repeated skin exposures to type I allergens.[245].

In cases of suspected PCD, skin-prick testing with standard solutions of food proteins can be performed but, more often, a variant called prick-prick testing with the food itself is used[30]. The skin-prick test is typically performed on the ventral forearm, where drops of allergen in solution are applied and pricked into the upper layers of the skin with a small lancet, whereby histamine and other mediators are released if the individual has been sensitized previously to the specific allergens tested. Negative (saline) and positive (histamine) controls should be tested as well. A positive reaction appears as a wheal and flare reaction after 15–20 minutes. When performing skin-prick testing, safety items such as a crash cart should be available in the clinic owing to the increased risk of type I hypersensitivity reactions and potential anaphylactic reactions. Standard panels of type I allergens exist, including of food, but they do not cover all relevant allergens; thus, patients may also be advised to bring fresh food they are exposed to while at work for testing. These foods are then used for prick-prick testing[246].

Diagnosis

Following a positive patch test to a substance, an analysis should be performed to pinpoint the sources of exposure to the allergen. Depending on the clinical presentation, a search for relevant exposures may focus on topical products used on the skin (the typical route of exposure in ACD), airborne products (particularly for certain allergens such as fragrances) and/or systemic products (for example, foods, medications, implants), which may be considered in clinical presentations suggestive of systemic ACD. When a current exposure relevant to the dermatitis is detected, a diagnosis of ACD can be made[237]. The use of a step-wise procedure for exposure assessment has been suggested[244] and has led to the diagnosis of ACD in half the cases.

The diagnosis of ICD can only be made after an exhaustive exposure analysis is performed and the relevant exposure to irritants at the sites of dermatitis is detected that can qualitatively and quantitatively explain the disease partly or fully. A time-relationship should be present between exposure and initiation or worsening of the disease. In many cases, patch testing is needed to exclude the diagnosis of ACD, as there are no unique clinical or histological signs that can be used to reliably differentiate between ICD and ACD. ACD also often co-exists with ICD[247]. In such cases, it is especially important to make an exhaustive exposure assessment and determine whether both diagnoses are relevant, for example, by different exposures and ideally by observations over time following exposure interventions. The proportion of ACD and ICD co-existence depends on the specific patient population studied and how strictly the diagnostic criteria are applied; rates range from 5%[248] to 50%[249].

The diagnosis of PCD is generally made when there is a typical clinical presentation (for example, eczematous hand dermatitis) along with a positive prick-prick test to a food item handled by the patient.

Criteria for establishing the occupational causation and aggravation of CD have been developed[250] (BOX 2). The essence of these seven criteria is implemented in most guidelines for diagnosing occupational CD today, usually with criteria 1–5 being more or less obligatory.

Box 2 | **The Mathias Criteria for establishing occupational causation and aggravation of CD**

At least 4 out of 7 criteria should be positive to conclude that the contact dermatitis (CD) is probably occupational[250].

1. Typical clinical presentation consistent with CD
2. Workplace exposure to potential cutaneous irritants or allergens supported by toxicological data or clinical experience
3. Anatomical distribution of dermatitis consistent with workplace exposure
4. Temporal relationship between exposure and onset of CD
5. Non-occupational exposures excluded as probable causes
6. Dermatitis improves away from work exposure
7. Patch or provocation tests identify a probable causal agent

Ancillary testing methods

Repeated open application test. In a repeated open application test (ROAT), patients simulate normal product use by applying a product intended for long-term skin contact (leave-on product) that is suspected of causing ACD directly to the skin. This test is employed to clarify the clinical relevance of a positive patch test in relation to the use of the product or in the case of a negative patch test when a strong suspicion concerning a particular product remains. If the ROAT is positive, the next step is normally to identify the causative allergen. ROATs have also been used for scientific purposes to establish thresholds of reaction to allergens under real-life conditions. Usually, the ROAT is performed in the elbow flexure or at the lower or upper arm, as these skin sites are easily accessible to the patient (who is going to perform the applications) with applications 2–3 times a day for at least 2 weeks (and for topical corticosteroids for up to 4 weeks). A scale has been developed for reading reactions[251]. The ROAT is more sensitive than patch testing, as positive test reactions may appear following 30 times lower doses per application[252]. If applications of an allergen are made on a skin site where an allergic reaction has previously appeared, a positive reaction will develop faster, in some cases within hours, and can be triggered by lower doses of allergen than on naive skin sites. This phenomenon is due to the formation of memory T cells present in the skin following an allergic reaction, which trigger a response upon re-exposure[201]. Of note, false negatives may also occur with the ROAT[253].

Oral provocation tests. These tests may be considered when systemic ACD to chemicals in food is suspected and, ideally, they should be performed in a dose–response manner with increasing concentrations of allergens and with a placebo control in a blinded way[254]. In general clinical practice, however, oral provocation tests are not routinely performed. In the case of drugs, oral provocation tests should only be performed by experts in a hospital setting and after careful consideration of potential complications from the provocation.

Screening and prevention

There are no screening programmes for CD for the general population, in part as the disease is either straightforward to identify or is more complex and requires a specialist to evaluate and diagnose.

Information about skin care, skin protection (for example, correct use of gloves) and reduction of irritant exposures have been shown to decrease the number of new cases of ICD in relevant occupations[255,256]; however, education needs to be intermittently repeated to be effective over time. In some regions, regulations have been instituted targeting important allergens in an effort to reduce contact sensitization rates[257]. Nickel release from metal items in close and prolonged contact with the skin has been successfully regulated in some areas of the world, reducing the proportion of young women developing ACD from nickel from approximately 20% to 10%[38]. Recently, the preservative methylisothiazolinone was banned from leave-on products in many countries and restricted to a low level of use in rinse-off products owing to an epidemic of ACD caused by this substance in consumer products; the number of individuals with ACD due to methylisothiazolinone has subsequently decreased[46]. Such interventions at the community level can also be very effective.

Management

Early diagnosis and treatment have been shown to improve the prognosis in patients with eczematous hand dermatitis[258]. Regulatory interventions aimed at reducing exposures to specific allergens not only have an effect on the number of new cases of ACD but also typically reduce the severity of disease in those already sensitized. At an individual level, it is important to understand which allergens one is sensitized to and how to avoid them.

The mainstay of CD management is to remove offending allergens for ACD, PACD and PCD and to remove offending irritants for ICD and PICD. This process involves a thorough evaluation of each case to understand key exposures and to develop avoidance strategies. Patient education is also essential for a successful outcome. The use of bland emollients that do not contain irritants and allergens to which the patient is sensitized and applications of topical anti-inflammatory treatments may be helpful for mild cases of CD. Systemic treatments may be added for moderate-to-severe CD (FIG. 7). When persistent CD remains, further evaluation for alternative diagnoses may be needed to rule out other causes.

Patient education

Equally important to defining irritants and what allergens an individual is sensitized to is educating patients about the mechanisms behind their CD and the approaches to avoidance strategies. To achieve a cure and remain CD free, patients must understand the key aspects of their disease, such as where their allergens and potential cross-reactors (typically, but not exclusively, substances with similar chemical structures) are found, what is the expected time course between allergen exposure and cutaneous and/or symptom manifestation, and how threshold effects are involved in the elicitation of ACD[259]. This process will also prevent unnecessarily extreme avoidance strategies that some patients may believe are required. For ACD, reactions typically occur 1–2 days after exposure and, even for the most sensitive

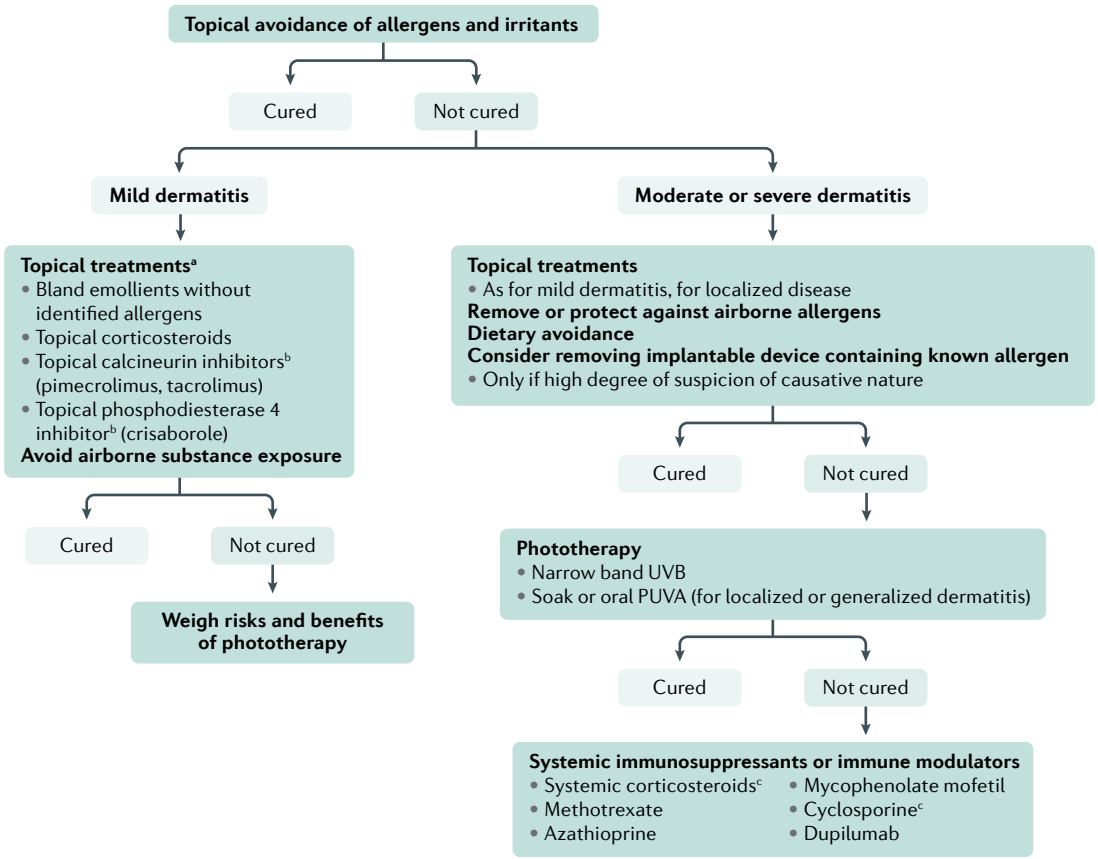

Fig. 7 | **Suggested algorithm for the treatment of allergic contact dermatitis.** Avoidance of documented allergens and irritants is typically the first-line management approach. If this fails to cure the dermatitis but the dermatitis is mild in nature, the addition of bland emollients without the individual's identified contact allergens and/or topical anti-inflammatory agents, as needed, can be added. If the mild dermatitis is still not cured, phototherapy could then be considered. For moderate-to-severe dermatitis, if localized, topical anti-inflammatory agents can also be used as needed. Additionally, dietary elimination trials of proven contact allergens can be considered for both recalcitrant localized disease and recalcitrant generalized disease. For persistent, moderate-to-severe disease despite the above measures, phototherapy and then systemic immunosuppressants/immune modulators can be considered. PUVA, psoralen plus UVA. [a]Inactive ingredients should be checked for the presence of the allergens. [b]These medications may be considered 'off-label' when being used for contact dermatitis. [c]Not a suitable long-term treatment option.

patient, there will be a lowest limit of allergen dose per unit area below which patients will not have an immune reaction despite prior sensitization. For example, most patients allergic to nickel tolerate stainless steel earrings containing nickel as, typically, nickel is not released from stainless steel in a high enough dose per unit area to cause a reaction even in someone sensitized to it[35,260].

As ICD can cause an impaired skin barrier, which predisposes to ACD, and ICD and ACD often coexist, it is important to avoid situations that can lead to ICD. Examples include avoiding repetitive wetting and drying of the skin, minimizing friction and rough fabrics against the skin, avoiding direct skin contact with solvents, oils and detergents by appropriate personal protective equipment, using cool or lukewarm water instead of hot water when washing, using soap substitutes rather than soap, wearing gloves for a prolonged period of time only when necessary and frequently using bland emollients to enhance skin barrier function. At times, topical corticosteroids can also help minimize inflammation caused by ICD. Recalcitrant ICD in the occupational setting may require systemic treatments (FIG. 7) and, sometimes, a period away from work or even a job change.

Acute ICD from acids or alkalis, which typically occurs in the occupational setting, can cause severe burns and ulcerations. Such patients need to be managed emergently and, depending upon the extent of skin and mucous membrane involvement, may need care similar to that of a burn patient[3].

Algorithm for treatment

For many patients with defined contact allergens, irritants, protein contact allergens and photocontact allergens, topical avoidance alone is curative[261]. When the initial avoidance changes are not successful, a follow-up visit (for example, after 6–8 weeks) should be scheduled to perform an additional exposure review and provide further education about the patient's allergens and irritants. In some cases, there may be inadvertent exposures, a need for further encouragement (for example, if not all of the adjustments initially recommended have been made) and/or occult exposures that were not thought of at the initial discussion. When CD persists, medical

management can be approached in a step-wise manner starting with treatments that have the fewest side effects and progressing, as necessary, to those with more frequent and potentially severe adverse effects.

Topical treatments. Topical corticosteroids are used as a mainstay of treatment of inflammation in all types of CD. Although calcineurin inhibitors (tacrolimus and pimecrolimus) and topical phosphodiesterase inhibitors (crisaborole) are off-label use for ACD, these agents are known to be effective steroid-sparing agents for the treatment of AD[262]. Topical tacrolimus has been used to treat nickel-induced ACD[263] and tacrolimus pretreatment significantly decreased inflammation in patients sensitized to diphenylcyclopropenone[264]. A barrier cream containing glutathione and iron sulfate blocked the elicitation of allergy to hexavalent chromium in patients previously sensitized to potassium dichromate[265]. In the selection of topical treatments, knowledge of the inactive ingredients in the vehicle is essential, as an individual's contact allergens may be present; incidental use of a topical medication containing contact allergens may lead to recalcitrant dermatitis. ACD secondary to the topical corticosteroid active ingredient itself can also occur but it is less common than ACD to the inactive ingredients of the vehicle.

Phototherapy. For recalcitrant CD not responding to topical treatments, phototherapy (primarily narrow-band UVB or psoralen plus UVA (PUVA)) can be used. Factors that may limit the possibility of phototherapy use include distance to a treatment centre (although home units can be arranged) and a history of skin cancer, which is more relevant with PUVA. UV light induces apoptotic cell death in activated T cells, increases T_{reg} cell activity and numbers, and decreases the responsiveness of antigen-presenting cells[266]. Narrow-band UVB phototherapy involves 2–3 treatments weekly for at least 4–6 weeks with progressively higher doses of UV light to suppress immune reactions[266]. Once remission is achieved, patients can be treated with decreasing weekly doses (for example, once or twice per week for several months) and then treatment is stopped. PUVA is a type of photochemotherapy in which psoralen, a photosensitizing chemical, is administered orally or topically (in a soak form) and intercalates with DNA; when exposed to UVA, gene expression is modified[266]. Although psoralen is associated with PICD reactions, its photosensitizing properties can also be employed in a controlled setting as a treatment option, using UVA with progressively incremented lengths of exposure time. Once remission is achieved, patients can be treated with decreasing weekly doses as with other forms of UV treatments[266–268].

Systemic therapy. There are various systemic treatments for patients with recalcitrant ACD, including off-label uses and medications on the horizon[269] (FIG. 7). Current systemic treatments for recalcitrant CD include systemic corticosteroids and cyclosporine (neither is preferred as a long-term option), methotrexate, azathioprine, mycophenolate mofetil, and dupilumab. Future potential treatments include JAK inhibitors[270] and other biological therapies blocking the various inflammatory cascades present in CD[269]. Individual patients may also have specific contraindications to the use of a particular systemic treatment; newer treatment options, such as dupilumab, offer an alternative adverse effect profile and can also be beneficial for other potential co-morbidities (for example, atopic dermatitis and asthma).

Topical allergens

It is important to provide patients written information detailing each allergen to which they have reacted on patch testing. Both digital and hard copy information materials should be easily accessible in clinics. Information sheets for distribution to patients can be found on various websites and in textbooks (Supplementary Table 1).

When reviewing allergens with patients, it is also helpful to group a patient's allergens into general categories, such as metals, rubber allergens, textile dyes, preservatives and fragrances, and to review the functions of each allergen and potential exposure sources[271]. Certain allergens may belong to multiple categories and within seemingly unrelated exposures there may lie a cross-reactor (for example, colophony, a plant resin, is a fragrance cross-reactor); a lack of understanding of these complexities can lead to unresolved CD. Furthermore, given the evolving nature of product development and applications for chemical compounds, clinicians and scientists continue to identify new clinical scenarios to consider for specific allergens and, conversely, as a result of the education process, patients may identify exposures to allergens that may not be obvious to the treating physician. Patients must also understand how to read ingredient lists, looking for cross-reactors or alternative chemical names for their allergens, and recognize that terms such as "hypoallergenic", "dermatologist tested", "for babies" and "dermatologist recommended" are meaningless from a contact allergy perspective. Additionally, fragrance chemicals are permitted in "fragrance-free" products as long as the fragrance is not solely used to impart an odour to a product[272]. Furthermore, many patients believe that "all-natural" products are safe, but many natural products contain botanical derivatives that are common ACD offenders[273]. Additionally, certain barrier strategies are not universally effective; for example, certain allergens, such as methacrylates, can penetrate commonly used glove materials (for example, nitrile)[274]. Moreover, the very gloves used to protect the skin often contain rubber additives that can be culprits in causing or perpetuating ACD[32].

In addition to advising patients on what products and other exposures to avoid, the identification of alternative topical products that would be safe to use based on the individual patient's contact allergens is also a key part of the process. Useful resources that are currently available include the contact allergen management programme (CAMP; www.contactderm.org) and Skin Safe Products (www.skinsafeproducts.com), which offer patients a listing of numerous products such as soaps, shampoos, lotions, and prescription and over-the-counter medications without their identified contact allergens. Both resources have programmes that enable patients

to easily shop for products using a computer or cell phone. Depending on the identified contact allergens, alternatives for products such as clothing, gloves and other miscellaneous items may also be important for successful avoidance (Supplementary Table 2) and a list of alternatives for items ranging from earplugs to household glues is available[275]. Patients may also utilize various tests (Supplementary Table 3) to determine if products/items are allergenic for them, although false-negative results can occur. Despite efforts to educate patients, it can be difficult for them to remember the outcomes of patch testing[276].

Systemic allergens

Although ACD is primarily caused by topical sensitization followed by topical re-exposure, ingested, inhaled or implanted allergens may lead to a recalcitrant, systemic ACD[228,260,277]. For the ingested route, potential contact allergens, such as metals, fragrances and preservatives, are present in foods and beverages (Supplementary Table 4). Point system low-cobalt[278] and low-nickel[279] diets have been suggested, on the assumption that only ~1% of individuals will react to low daily levels of dietary consumption[260,280]. A study found that 47% of patients allergic to fragrance improved on a low balsam of Peru diet[281]. Several potential allergens may be added to various foods; a review of common sources of many of these additives and alternative options for allergic patients is available[282].

In an effort to minimize the morbidity associated with systemic medications in patients with substantial, clinically bothersome dermatitis not responding to topical allergen avoidance, some authors have found that dietary trials may be helpful; in these trials, the ingested sources of identified contact allergens are eliminated from the patient's diet before gradual reintroduction after approximately 6–8 weeks. Avoided foods or beverages can be reintroduced initially in small quantities and one at a time in 5–7-day intervals. Food diaries are helpful to track whether certain exposures reproducibly cause symptoms up to 2 days after ingestion. If even small quantities consistently cause symptoms, these should be completely eliminated from the diet. If patients do not experience any improvement within 1 month of initiating such dietary changes, it is recommended that they resume their regular diet.

In a relatively similar process to aeroallergen immunotherapy, tolerance to systemic nickel dermatitis was induced by administering minute amounts of nickel granules to ingest daily, gradually increasing the dosage until reaching a maintenance dosage 2–3 times per week for 1 year[283]. Patients who continued on this maintenance dose ingested nickel in their diet without restriction and remission of dermatitis was maintained in 67% of patients. However, this nickel oral hyposensitization treatment is not currently widely available. Chelating therapy, such as disulfiram, while previously used for systemic contact allergy to nickel[284,285], is associated with liver and nervous system toxicities and is therefore not a recommended treatment[286].

In a very small subset of patients sensitized to a material used in an implanted device, such as orthopaedic and dental implants, endovascular devices, pacemakers, and intrauterine devices, dermatitis can occur with manifestations ranging from involvement immediately above the device to a more generalized dermatitis[287–289] or even at a site or sites distant from the implanted device[229,290–294] or causing systemic symptoms without cutaneous signs[295,296]. For suspected cases of implant-related ACD, depending upon the location of the implant, the risks involved with its removal and the temporal connection of symptoms with the device placement, the removal of the implant can be considered, with or without replacement with a non-allergenic substitute or by using a device coating[289,295–297]. However, one of the proposed major criteria for the evaluation of an implant-related ACD is complete recovery after removal of the offending implant[298]. The decision to remove an implanted device should be weighed carefully as the removal of a device containing one of the identified contact allergens does not guarantee the resolution of dermatitis. Thus, other approaches, such as the exploration of alternative causes or other contributing factors that can be more easily addressed, may be beneficial. Additionally, if removal is not feasible or recommended, treatment with oral immunosuppressants can be considered to modify the patient's immune response to the device[299].

Airborne and photo-allergens

Allergens reported to cause airborne dermatitis include plants, acrylates, epoxies, rubber additives, isothiazolinones, benzalkonium chloride and other preservatives, and metals[300]. These exposures may occur in the occupational and non-occupational settings. For airborne allergens, treatment approaches include minimizing direct exposure, reducing time outdoors and removing offending plants from inside and near the home (for plant allergens)[300], or repainting the walls (for contact allergy induced by allergens emitted from wall paint)[301]. Other strategies include increasing ventilation and wearing masks, booties, aprons and/or goggles for indoor exposure, especially if occupational[300]. A barrier cream was shown to prevent airborne propolis CD in one case report[302].

If the above measures fail, phototherapy[303] or systemic therapies[300] can be instituted (FIG. 7). Weekly dosing of azathioprine[304] and methotrexate[305] have been studied for the treatment of airborne parthenium ACD. Compared to azathioprine, methotrexate clears dermatitis in significantly fewer weeks[305]. Cyclosporine has also been used to treat airborne ACD[306].

The management of PACD includes allergen avoidance, strict sun avoidance, photo-protective clothing and sunscreen use. Topical corticosteroids or calcineurin inhibitors can be used to relieve inflammation in uncomplicated cases[8,307]. Often, airborne plant allergens can cause chronic dermatitis of exposed skin. For severe and recalcitrant cases, systemic agents can be used with airborne and other forms of ACD (FIG. 7).

Occupational allergens

The treatment of airborne occupational ACD involves increasing ventilation and wearing protective equipment when appropriate (Supplementary Table 2),

which should be supplied by the employer; however, protective equipment can also be associated with ACD, ICD and other reactions[308]. The evaluation of air samples for the presence of allergens may also be beneficial in developing intervention strategies and workplace modifications.

Multidisciplinary interventions have been used successfully in Europe and Canada for workers with occupational CD[309–312] and studies from the Middle East and Asia have emphasized the need for multispecialty involvement[313–316]. Since occupational irritants often coexist with occupational allergens, it is important to also minimize the exposure to both when managing occupational CD[317]. Recommendations to alternate work and non-work days or switching, at least for a short time period (for example, weeks), to duties not involving wet work or glove wearing may help improve certain occupational CD before returning to regularly scheduled duties[318]. Some patients may also require several weeks away from work in cases of particularly severe or widespread dermatitis.

Patients with severe and persistent occupational CD despite job modifications may require a job change. Unfortunately, sometimes even a change in occupation may not cure a chronic occupational CD[318], which can require long-term systemic treatment.

As with all types of ACD, treatment of PCD involves the avoidance of allergens. However, this may not be practical for some patients particularly as, most often, PCD occurs in the occupational setting. High-dose topical corticosteroids can decrease inflammation but may not be successful in treating PCD and can lead to adverse effects, particularly with chronic use (FIG. 7). Tacrolimus 0.1% ointment was reported to successfully treat patients with PCD from chicken and halibut[319].

Quality of life

Patients with dermatitis (with the most common groups broadly defined as atopic, contact and seborrhoeic) have been estimated to have the highest global disease burden of all skin conditions as measured in disability-adjusted life years[320]. Evidence suggests that ACD, in particular, has a substantial effect on patients' QoL. Data for patients with occupational CD (which includes both ACD and ICD) using both generic and dermatology-specific indices demonstrate a reduced QoL. Methodological variation as well as heterogeneous definitions of occupational CD make comparisons difficult[321]. In addition to the effects of CD symptoms, the negative impacts on QOL can also be measured by the concurring psychosocial, functional and often socioeconomic impairment, particularly with occupational CD[322]. Importantly, the subjective QoL impairment in ACD can outweigh objective assessments of severity and is therefore crucial in evaluating the overall disease burden[323,324].

Tools to measure dermatological QoL, including the DLQI and the Skindex, have been employed to evaluate the effect of ACD in adults[325]; none have been validated in children to date but are currently under development. Many studies employing these tools find that patients with ACD report a worse QoL than those with psoriasis[324,326,327]; it is notable that ACD, an exogenous (usually curable) inflammatory disease connotes worse QoL than a chronic, incurable skin condition. ACD patients experience impairment in multiple categories; those with hand dermatitis and occupational disease generally note more frequent functional impairment[322,324,328]. Patients with ACD most often report that the symptoms of itch, sleep disturbance[329] and skin sensitivity[330] negatively affect their QoL; cracking, sloughing, flaking and peeling of the skin are particularly bothersome[331].

Emotional impact significantly impairs QoL and is striking in ACD patients[328,330]. Embarrassment, most often associated with facial dermatitis[324], and depression are notable[332], although the prevalence of depression among those with ACD is currently unknown. An ACD-specific QoL instrument, divided into three domains, highlights more nuanced drivers of emotional impairment. The physical domain includes symptoms or signs of itching, cracking, sloughing or flaking, burning or stinging, irritation, and pain. The emotional domain includes feelings of frustration with disease persistence and chronicity ("never goes away"), annoyance, embarrassment, unpredictability ("out of control") and worry about exposures to triggers. Finally, the functional domain includes limitations due to difficulties in concentrating or focusing, constant thoughts about the skin condition, effects on sleep, and effects on social life. Addressing and targeting the disease-specific emotional needs of patients with ACD enables a more personalized approach and improved care[330].

Patch testing and subsequent allergen avoidance remain the mainstay for diagnosis and management of ACD and have demonstrated great benefit to patients, both in terms of disability and QoL[324,331,333–336]. Some studies have shown significant QoL improvement in all patients who have undergone patch testing, irrespective of result[324,335]. Others demonstrate improvement only in patients who have a positive patch test[333,334] or a more marked benefit among this cohort than in tested controls[336]. In another study, emotional wellbeing was noted as the domain most impacted and most responsive to change with intervention (patch testing and allergen avoidance)[331]. Certain factors have also been correlated with greater improvement after patch testing, including a lower number of positive reactions and an improved ability to recall allergens[336].

Outlook

Monitoring sensitization trends

The field of CD is constantly evolving and rapidly expanding. Changes in chemical applications within products, consumer exposure trends, and industrial practices contribute to novel allergens and sensitization patterns. Between 2008 and 2015, approximately 17 newly described allergens were reported each year, with one-third found in cosmetics[337]. These realities necessitate regular updates to patch test baseline series; for example, propolis and HEMA were recently added to the European Baseline Series in place of primin and clioquinol because of infrequent positive and relevant reactions to the latter two[338].

Updating the patch test procedure

The primary diagnostic tool in ACD remains the patch test, which was first described by Josef Jadassohn in 1895. Since then, patch testing and its principles have generally remained the same and it is still the gold standard diagnostic test with a reasonable degree of reproducibility. One of the greatest challenges in reading patch tests is differentiating irritant from allergic reactions. Many allergens, such as cocamidopropyl betaine, carbamate mix and benzalkonium chloride, are marked irritants as well as allergens[339–342]. Some authors have also proposed the inclusion of sodium lauryl sulfate as a marker of increased skin reactivitiy[343,344]. A concurrent sodium lauryl sulfate reaction and macular erythematous reactions to other allergens that are known to have strong irritant properties could lead to the interpretation of these reactions as irritant in nature rather than weakly allergic. Future developments in patch testing should make use of advances in dermatopharmacokinetics to determine methods for the identification of allergenicity and for the reduction of irritancy and false-positive reactions. It has been suggested that patch test removal can occur at 24 hours in the majority of cases, without losing positive results, rather than the current international standard of 48 hours[345–348]. Further investigations are needed to evaluate whether patch test occlusion can indeed be performed for a shorter duration, which would be more convenient for patients[349].

Preventing sensitization

The prevalence of contact allergy in approximately one-quarter of the general population calls for more stringent ways to prevent sensitization[2]. Concerted efforts need to be made by industry to reduce the exposure to allergens, even weak ones, whenever possible. For example, health-care workers become sensitized to weak allergens in hand cleansers, which they are required to use as part of their occupation[350]. These efforts must also weigh the necessity for certain ingredients such as preservatives to prevent infectious contaminants within products.

Intervening early

Although the early diagnosis and management of CD has been shown to improve patient outcomes[351], there is limited information in the literature regarding the screening of patients in high-risk industries for hand dermatitis. The Hand Dermatitis Screening Tool has recently been developed and tested in health-care workers and may serve as a useful screening tool, especially in the prevention of ICD[352]. Patients with newly diagnosed occupational CD have been found to have inadequate knowledge of both skin care and treatment, which was more pronounced in males and older individuals[353]. Workers in high-risk occupations should be educated on skin care through, for example, hand hygiene programmes, which have been shown to reduce the prevalence and severity of hand dermatitis. Repeating programmes at regular intervals is also essential as effectiveness is attenuated over time[350,354,355].

There is often a substantial time delay between the onset of symptoms and the individual seeking medical attention, particularly in occupational CD, which may be seen as 'part of the job'. A delay in presentation as well as other factors, including smoking and stress, have been shown to be associated with a poorer prognosis[258,318,356]. An Australian study reported the mean duration of occupational CD symptoms before presentation to a physician as 120 weeks[357]. Other studies show that nearly a quarter of patients have waited over 1 year to see a physician[358] and that patients may wait an average of over 2 years before seeing a dermatologist[258].

Advancing through technology

Technological advances in proteomics have enabled the identification of contact allergen-induced changes in protein profiles. Further genomic and proteomic studies are required to gain a deeper understanding as to how contact sensitization occurs, to aid diagnosis through the development of biomarkers and to identify novel drug targets. Biomarkers would be particularly useful to differentiate between ACD, ICD and other types of eczematous dermatoses[359]. The development of in vitro assays for the detection of contact allergens would be a positive step towards the replacement of current animal testing. Research and development of alternative, 3D skin constructs for product testing is ongoing[360]. Other advances might include the detection of the uptake of haptens in the skin to determine how allergens are distributed. A recent proof-of-concept study showed that imaged mass spectrometry can be used for the visualization of nickel, including its penetration and distribution in human skin[361].

Adopting new treatment approaches

There is emerging evidence that biologics may play a role in the treatment of ACD. Dupilumab is a monoclonal antibody that has been approved for use in AD and several other conditions such as asthma[362]. New evidence is emerging to also support the use of dupilumab in patients with recalcitrant ACD[363,364]. The first report observed a dampened patch test response in a patient on dupilimab[365]. A case series showed a potential beneficial effect in ACD caused by sesquiterpene lactones[366]. Another study described a patient with refractory ACD to nickel secondary to numerous endovascular stents and clips who was successfully managed with dupilumab[367]. Furthermore, a case series of three patients successfully treated with a 90% sustained clinical improvement after 6–13 months of dupilumab treatment is encouraging[368]. Despite this, a number of patients with AD on dupilumab were reported who underwent patch testing with subsequent positive results, suggesting that not all ACD reactions are necessarily suppressed by the medication[369]. Further clinical studies are required to investigate the use of dupilumab and other biologics in ACD[366].

Previously, the innate immune system was thought to only play a part in the initial sensitization phase of ACD. However, recent advances have shown that it is likely to be responsible for several aspects of the elicitation phase, thereby providing a diverse variety of therapeutic targets[174,370,371], including the interactions between macrophages, T cells, NK cells and other signalling molecules. T cells are the primary mediators

of inflammation in ACD and the chemokine receptor (CKR) system is a crucial regulator of T cell movement. There are several different chemokines and CKR systems involved in the various stages of ACD, with specific chemokines appearing to be hapten dependent and patient specific. The CKR systems, particularly the CXCR3 signalling pathway (and its endogenous chemokines CXCL9, CXCL10 and CXCL11), seem to be selectively up-regulated in ACD but not in ICD and are therefore attractive potential therapeutic targets[372].

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1. Alinaghi, F., Bennike, N. H., Egeberg, A., Thyssen, J. P. & Johansen, J. D. Prevalence of contact allergy in the general population: A systematic review and meta-analysis. *Contact Dermatitis* **80**, 77–85 (2019). **This review and meta-analysis provides extensive information on contact allergy prevalence in the general population, including data from 28 studies between 2007 and 2017, and over 20,000 individuals from multiple continents who underwent patch testing.**
2. Diepgen, T. L. et al. Prevalence of contact allergy in the general population in different European regions. *Br. J. Dermatol.* **174**, 319–329 (2016).
3. Bains, S. N., Nash, P. & Fonacier, L. Irritant contact dermatitis. *Clin. Rev. Allergy Immunol.* **56**, 99–109 (2019).
4. DeKoven, J. G. et al. North American Contact dermatitis group patch test results: 2015-2016. *Dermatitis* **29**, 297–309 (2018).
5. Zug, K. A. et al. Patch testing in children from 2005 to 2012: results from the North American contact dermatitis group. *Dermatitis* **25**, 345–355 (2014).
6. Goldenberg, A. et al. Pediatric contact dermatitis registry inaugural case data. *Dermatitis* **27**, 293–302 (2016).
7. Ortiz Salvador, J. M. et al. Pediatric allergic contact dermatitis: clinical and epidemiological study in a Tertiary Hospital. *Actas Dermosifiliogr.* **108**, 571–578 (2017).
8. Hinton, A. N. & Goldminz, A. M. Feeling the burn: phototoxicity and photoallergy. *Dermatol. Clin.* **38**, 165–175 (2020).
9. Pongpairoj, K. et al. Proposed ICDRG classification of the clinical presentation of contact allergy. *Dermatitis* **27**, 248–258 (2016).
10. Pesonen, M., Koskela, K. & Aalto-Korte, K. Contact urticaria and protein contact dermatitis in the Finnish register of occupational diseases in a period of 12 years. *Contact Dermatitis* **83**, 1–7 (2020).
11. Pesonen, M. et al. Patch test results of the European baseline series among patients with occupational contact dermatitis across Europe-analyses of the European Surveillance System on Contact Allergy network, 2002-2010. *Contact Dermatitis* **72**, 154–163 (2015).
12. Wiszniewska, M. & Walusiak-Skorupa, J. Recent trends in occupational contact dermatitis. *Curr. Allergy Asthma Rep.* **15**, 43 (2015).
13. Meyer, J. D., Chen, Y., Holt, D. L., Beck, M. H. & Cherry, N. M. Occupational contact dermatitis in the UK: a surveillance report from EPIDERM and OPRA. *Occup. Med.* **50**, 265–273 (2000).
14. Turner, S. et al. The incidence of occupational skin disease as reported to The Health and Occupation Reporting (THOR) network between 2002 and 2005. *Br. J. Dermatol.* **157**, 713–722 (2007).
15. Bhatia, R. & Sharma, V. K. Occupational dermatoses: An Asian perspective. *Indian J. Dermatol. Venereol. Leprol.* **83**, 525–535 (2017).
16. Cahill, J. L. et al. Occupational skin disease in Victoria, Australia. *Australas. J. Dermatol.* **57**, 108–114 (2016).
17. Melo, M., Villarinho, A. & Leite, I. D. C. Sociodemographic and clinical profile of patients with occupational contact dermatitis seen at a work-related dermatology service, 2000 - 2014. *Bras. Dermatol.* **94**, 147–156 (2019).
18. Peiser, M. et al. Allergic contact dermatitis: epidemiology, molecular mechanisms, in vitro methods and regulatory aspects. *Cell. Mol. Life Sci.* **69**, 763–781 (2012).
19. Nassau, S. & Fonacier, L. Allergic contact dermatitis. *Med. Clin. North Am.* **104**, 61–76 (2020).
20. Cashman, M. W., Reutemann, P. A. & Ehrlich, A. Contact dermatitis in the United States: epidemiology, economic impact, and workplace prevention. *Dermatol. Clin.* **30**, 87–98 (2012).
21. Agner, T. Noninvasive measuring methods for the investigation of irritant patch test reactions. A study of patients with hand eczema, atopic dermatitis and controls. *Acta Derm. Venereol. Suppl.* **173**, 1–26 (1992).
22. Thyssen, J. P., McFadden, J. P. & Kimber, I. The multiple factors affecting the association between atopic dermatitis and contact sensitization. *Allergy* **69**, 28–36 (2014).
23. Milam, E. C., Jacob, S. E. & Cohen, D. E. Contact dermatitis in the patient with atopic dermatitis. *J. Allergy Clin. Immunol. Pract.* **7**, 18–26 (2019).
24. Uehara, M. & Sawai, T. A longitudinal study of contact sensitivity in patients with atopic dermatitis. *Arch. Dermatol.* **125**, 366–368 (1989).
25. Teo, Y., McFadden, J. P., White, I. R., Lynch, M. & Banerjee, P. Allergic contact dermatitis in atopic individuals: results of a 30-year retrospective study. *Contact Dermatitis* **81**, 409–416 (2019).
26. Hegewald, J., Uter, W., Pfahlberg, A., Geier, J. & Schnuch, A. A multifactorial analysis of concurrent patch-test reactions to nickel, cobalt, and chromate. *Allergy* **60**, 372–378 (2005).
27. Malajian, D. & Belsito, D. V. Cutaneous delayed-type hypersensitivity in patients with atopic dermatitis. *J. Am. Acad. Dermatol.* **69**, 232–237 (2013).
28. Ross-Hansen, K. et al. Filaggrin is a predominant member of the denaturation-resistant nickel-binding proteome of human epidermis. *J. Invest. Dermatol.* **134**, 1164–1166 (2014).
29. Hamann, C. R. et al. Association between atopic dermatitis and contact sensitization: a systematic review and meta-analysis. *J. Am. Acad. Dermatol.* **77**, 70–78 (2017).
30. Vester, L., Thyssen, J. P., Menné, T. & Johansen, J. D. Occupational food-related hand dermatoses seen over a 10-year period. *Contact Dermatitis* **66**, 264–270 (2012).
31. Barbaud, A., Poreaux, C., Penven, E. & Waton, J. Occupational protein contact dermatitis. *Eur. J. Dermatol.* **25**, 527–534 (2015).
32. Lertphanichkul, C. & Scheinman, P. L. Occupational allergic contact dermatitis (OACD) in a cohort of 458 consecutive dermatitis patients; A case series of 17 patients with OACD. *J. Am. Acad. Dermatol.* **84**, 798–804 (2020).
33. Johnston, G. A. et al. British Association of Dermatologists' guidelines for the management of contact dermatitis 2017. *Br. J. Dermatol.* **176**, 317–329 (2017).
34. Goldminz, A. M. & Scheinman, P. L. Comparison of nickel sulfate 2.5% and nickel sulfate 5% for detecting nickel contact allergy. *Dermatitis* **29**, 321–323 (2018).
35. Ahlström, M., Thyssen, J. & Wennervalft, M. Nickel allergy and allergic contact dermatitis: a clinical review of immunology, epidemiology, exposure, and treatment. *Contact Dermatitis* **81**, 227–241 (2019).
36. Thyssen, J. P., Linneberg, A., Menné, T., Nielsen, N. H. & Johansen, J. D. The association between hand eczema and nickel allergy has weakened among young women in the general population following the Danish nickel regulation: results from two cross-sectional studies. *Contact Dermatitis* **61**, 342–348 (2009).
37. Uter, W. et al. ESSCA results with nickel, cobalt and chromium, 2009-2012. *Contact Dermatitis* **75**, 117–121 (2016).
38. Ahlström, M. G., Thyssen, J. P., Menné, T. & Johansen, J. D. Prevalence of nickel allergy in Europe following the EU Nickel Directive - a review. *Contact Dermatitis* **77**, 193–200 (2017). **This review investigates the prevalence of nickel allergy in Europe following the highly effective EU Nickel Directive, an important public health initiative that has successfully reduced rates of nickel contact allergy among the European population.**
39. Bregnbak, D. et al. Chromium allergy and dermatitis: Prevalence and main findings. *Contact Dermatitis* **73**, 261–280 (2015).
40. Warshaw, E. M. et al. Epidemiology of nickel sensitivity: Retrospective cross-sectional analysis of North American Contact Dermatitis Group data 1994-2014. *J. Am. Acad. Dermatol.* **80**, 701–713 (2019).
41. Cheng, T. Y., Tseng, Y. H., Sun, C. C. & Chu, C. Y. Contact sensitization to metals in Taiwan. *Contact Dermatitis* **59**, 353–360 (2008).
42. Goon, A. T. & Goh, C. L. Metal allergy in Singapore. *Contact Dermatitis* **52**, 130–132 (2005).
43. Dou, X., Zhao, Y., Ni, C., Zhu, X. & Liu, L. Prevalence of contact allergy at a dermatology clinic in China from 1990-2009. *Dermatitis* **22**, 324–331 (2011).
44. Uter, W. et al. European Surveillance System on Contact Allergies (ESSCA): results with the European baseline series, 2013/14. *J. Eur. Acad. Dermatol. Venereol.* **31**, 1516–1525 (2017).
45. Kirchlechner, S., Hübner, A. & Uter, W. Survey of sensitizing components of oxidative hair dyes (retail and professional products) in Germany. *J. Dtsch. Dermatol. Ges.* **14**, 707–715 (2016).
46. Uter, W. et al. The epidemic of methylisothiazolinone contact allergy in Europe: follow-up on changing exposures. *J. Eur. Acad. Dermatol. Venereol.* **34**, 333–339 (2020). **This survey study assessed changes in isothiazolinone contact allergy following regulations implemented for isothiazolinones in skin-care products, another important example of an effective public health initiative in the area of contact dermatitis.**
47. Rolls, S. et al. Recommendation to include hydroxyethyl (meth)acrylate in the British baseline patch test series. *Br. J. Dermatol.* **181**, 811–817 (2019).
48. Toholka, R. et al. The first Australian Baseline Series: Recommendations for patch testing in suspected contact dermatitis. *Australas. J. Dermatol.* **56**, 107–115 (2015).
49. Lee, H. Y., Stieger, M., Yawalkar, N. & Kakeda, M. Cytokines and chemokines in irritant contact dermatitis. *Mediators Inflamm.* **2013**, 916497 (2013).
50. Nosbaum, A., Vocanson, M., Rozieres, A., Hennino, A. & Nicolas, J. F. Allergic and irritant contact dermatitis. *EJD* **19**, 325–332 (2009).
51. Vocanson, M., Hennino, A., Rozieres, A., Poyet, G. & Nicolas, J. F. Effector and regulatory mechanisms in allergic contact dermatitis. *Allergy* **64**, 1699–1714 (2009).
52. Kaplan, D. H., Igyarto, B. Z. & Gaspari, A. A. Early immune events in the induction of allergic contact dermatitis. *Nat. Rev. Immunol.* **12**, 114–124 (2012).
53. Honda, T., Egawa, G., Grabbe, S. & Kabashima, K. Update of immune events in the murine contact hypersensitivity model: toward the understanding of allergic contact dermatitis. *J. Invest. Dermatol.* **133**, 303–315 (2013).
54. Martin S. F., Rustemeyer T., Thyssen J. P. Recent advances in understanding and managing contact dermatitis. *F1000Res*. 2018;https://doi.org/10.12688/f1000research.13499.1
55. Basketter, D. A., Kan-King-Yu, D., Dierkes, P. & Jowsey, I. R. Does irritation potency contribute to the skin sensitization potency of contact allergens? *Cutan. Ocul. Toxicol.* **26**, 279–286 (2007).
56. Lepoittevin, J. & Leblond, I. Hapten-peptide T cell receptor interactions: molecular basis for the recognition of haptens by T lymphocytes. *EJD* **7**, 151–154 (1997).
57. Karlberg, A. T., Bergstrom, M. A., Borje, A., Luthman, K. & Nilsson, J. L. Allergic contact dermatitis–formation, structural requirements, and reactivity of skin sensitizers. *Chem. Res. Toxicol.* **21**, 53–69 (2008).
58. Barbaud, A. Mechanism and diagnosis of protein contact dermatitis. *Curr. Opin. Allergy Clin. Immunol.* **20**, 117–121 (2020).
59. Hannuksela, M. *Protein Contact Dermatitis* 345–348 (Springer, 2006).
60. Fartasch, M. Ultrastructure of the epidermal barrier after irritation. *Microsc. Res. Tech.* **37**, 193–199 (1997).
61. Angelova-Fischer, I. Irritants and skin barrier function. *Curr. Probl. Dermatol.* **49**, 80–89 (2016).
62. Eskes, C. et al. Regulatory assessment of in vitro skin corrosion and irritation data within the European framework: Workshop recommendations. *Regul. Toxicol. Pharmacol.* **62**, 393–403 (2012).

63. Patel, S. Danger-associated molecular patterns (DAMPs): the derivatives and triggers of inflammation. *Curr. Allergy Asthma Rep.* **18**, 63 (2018).
64. Gibbs, S. In vitro irritation models and immune reactions. *Skin. Pharmacol. Physiol.* **22**, 103–113 (2009).
65. Kumari, V., Babina, M., Hazzan, T. & Worm, M. Thymic stromal lymphopoietin induction by skin irritation is independent of tumour necrosis factor-alpha, but supported by interleukin-1. *Br. J. Dermatol.* **172**, 951–960 (2015).
66. Kendall, A. C., Pilkington, S. M., Sassano, G., Rhodes, L. E. & Nicolaou, A. N-Acyl ethanolamide and eicosanoid involvement in irritant dermatitis. *Br. J. Dermatol.* **175**, 163–171 (2016).
67. Clemmensen, A. et al. Genome-wide expression analysis of human in vivo irritated epidermis: differential profiles induced by sodium lauryl sulfate and nonanoic acid. *J. Invest. Dermatol.* **130**, 2201–2210 (2010).
68. Fulzele, S. V., Babu, R. J., Ahaghotu, E. & Singh, M. Estimation of proinflammatory biomarkers of skin irritation by dermal microdialysis following exposure with irritant chemicals. *Toxicology* **237**, 77–88 (2007).
69. Calhoun, K. N., Luckett-Chastain, L. R., Frempah, B. & Gallucci, R. M. Associations Between Immune Phenotype and Inflammation in Murine Models of Irritant Contact Dermatitis. *Toxicol. Sci.* **168**, 179–189 (2019).
70. Willis, C. M., Stephens, C. J. & Wilkinson, J. D. Differential patterns of epidermal leukocyte infiltration in patch test reactions to structurally unrelated chemical irritants. *J. Invest. Dermatol.* **101**, 364–370 (1993).
71. Landsteiner, K. & Jacobs, J. Studies on the sensitization of animals with simple chemical compounds. Ii. *J. Exp. Med.* **64**, 625–639 (1936).
72. Esser, P. R. & Martin, S. F. Pathomechanisms of contact sensitization. *Curr. Allergy Asthma Rep.* **17**, 83 (2017).
73. Aptula, A. O. & Roberts, D. W. Mechanistic applicability domains for nonanimal-based prediction of toxicological end points: general principles and application to reactive toxicity. *Chem. Res. Toxicol.* **19**, 1097–1105 (2006).
74. Karlberg, A. T. et al. Activation of non-sensitizing or low-sensitizing fragrance substances into potent sensitizers - prehaptens and prohaptens. *Contact Dermatitis* **69**, 323–334 (2013).
75. Schmidt, M. & Goebeler, M. Immunology of metal allergies. *J. Dtsch. Dermatol. Ges.* **13**, 653–660 (2015).
76. Fitzpatrick, J. M., Roberts, D. W. & Patlewicz, G. What determines skin sensitization potency: Myths, maybes and realities. The 500 molecular weight cut-off: An updated analysis. *J. Appl. Toxicol.* **37**, 105–116 (2017).
77. Fitzpatrick, J. M., Roberts, D. W. & Patlewicz, G. Is skin penetration a determining factor in skin sensitization potential and potency? Refuting the notion of a LogKow threshold for skin sensitization. *J. Appl. Toxicol.* **37**, 117–127 (2017).
78. Paramasivan, P. et al. Repeated low-dose skin exposure is an effective sensitizing stimulus, a factor to be taken into account in predicting sensitization risk. *Br. J. Dermatol.* **162**, 594–597 (2010).
79. van Och, F. M., Vandebriel, R. J., De Jong, W. H. & van Loveren, H. Effect of prolonged exposure to low antigen concentration for sensitization. *Toxicology* **184**, 23–30 (2003).
80. Sekiguchi, K. et al. Enhancement of mouse contact hypersensitivity appears with a short chain triacylglycerol but not with a long chain one. *Toxicology* **412**, 48–54 (2019).
81. Pickard, C. et al. The cutaneous biochemical redox barrier: a component of the innate immune defenses against sensitization by highly reactive environmental xenobiotics. *J. Immunol.* **183**, 7576–7584 (2009).
82. Aleksic, M. et al. Mass spectrometric identification of covalent adducts of the skin allergen 2,4-dinitro-1-chlorobenzene and model skin proteins. *Toxicol. Vitr.* **22**, 1169–1176 (2008).
83. Doi, T., Mizukawa, Y., Shimoda, Y., Yamazaki, Y. & Shiohara, T. Importance of water content of the stratum corneum in mouse models for contact hypersensitivity. *J. Invest. Dermatol.* **137**, 151–158 (2017).
84. Friedmann, P. S., Sanchez-Elsner, T. & Schnuch, A. Genetic factors in susceptibility to contact sensitivity. *Contact Dermatitis.***72**, 263–274 (2015).
85. Schnuch, A., Westphal, G., Mossner, R., Uter, W. & Reich, K. Genetic factors in contact allergy–review and future goals. *Contact Dermatitis* **64**, 2–23 (2011).
86. Gomez de Aguero, M. et al. Langerhans cells protect from allergic contact dermatitis in mice by tolerizing $CD8^+$ T cells and activating $Foxp3^+$ regulatory T cells. *J. Clin. Invest.* **122**, 1700–1711 (2012).
87. Cavani, A. et al. Human CD25+regulatory T cells maintain immune tolerance to nickel in healthy, nonallergic individuals. *J. Immunol.* **171**, 5760–5768 (2003).
88. Luckey, U. et al. Crosstalk of regulatory T cells and tolerogenic dendritic cells prevents contact allergy in subjects with low zone tolerance. *J. Allergy Clin. Immunol.* **130**, 781–797.e711 (2012).
89. Vocanson, M. et al. $CD8^+$ T cells are effector cells of contact dermatitis to common skin allergens in mice. *J. Invest. Dermatol.* **126**, 815–820 (2006).
90. Rozieres, A. et al. $CD8^+$ T cells mediate skin allergy to amoxicillin in a mouse model. *Allergy* **65**, 996–1003 (2010).
91. Watanabe, H. et al. Danger signaling through the inflammasome acts as a master switch between tolerance and sensitization. *J. Immunol.* **180**, 5826–5832 (2008).
92. Riemann, H. et al. IL-12 breaks dinitrothiocyanobenzene (DNTB)-mediated tolerance and converts the tolerogen DNTB into an immunogen. *J. Immunol.* **175**, 5866–5874 (2005).
93. Kimber, I., Dearman, R. J., Basketter, D. A., Ryan, C. A. & Gerberick, G. F. The local lymph node assay: past, present and future. *Contact Dermatitis* **47**, 315–328 (2002).
94. Wang, Y. & Dai, S. Structural basis of metal hypersensitivity. *Immunol. Res.* **55**, 83–90 (2013).
95. Bonefeld, C. M. et al. Immunological, chemical and clinical aspects of exposure to mixtures of contact allergens. *Contact Dermatitis* **77**, 133–142 (2017).
96. Saint-Mezard, P. et al. Psychological stress exerts an adjuvant effect on skin dendritic cell functions in vivo. *J. Immunol.* **171**, 4073–4080 (2003).
97. Martin, S. F. et al. Toll-like receptor and IL-12 signaling control susceptibility to contact hypersensitivity. *J. Exp. Med.* **205**, 2151–2162 (2008).
98. Esser, P. R. et al. Contact sensitizers induce skin inflammation via ROS production and hyaluronic acid degradation. *PLoS ONE* **7**, e41340 (2012).
99. Migdal, C. et al. Sensitization effect of thimerosal is mediated in vitro via reactive oxygen species and calcium signaling. *Toxicology* **274**, 1–9 (2010).
100. Muto, J. et al. Hyaluronan digestion controls DC migration from the skin. *J. Clin. Invest.* **124**, 1309–1319 (2014).
101. Galbiati, V., Papale, A., Galli, C. L., Marinovich, M. & Corsini, E. Role of ROS and HMGB1 in contact allergen-induced IL-18 production in human keratinocytes. *J. Invest. Dermatol.* **134**, 2719–2727 (2014).
102. Klekotka, P. A., Yang, L. & Yokoyama, W. M. Contrasting roles of the IL-1 and IL-18 receptors in MyD88-dependent contact hypersensitivity. *J. Invest. Dermatol.* **130**, 184–191 (2010).
103. Yasukawa, S. et al. An ITAM-Syk-CARD9 signalling axis triggers contact hypersensitivity by stimulating IL-1 production in dendritic cells. *Nat. Commun.* **5**, 3755 (2014).
104. Enk A. H. in *Immune Mechanisms in Allergic Cotact Dermatitis*. 76-80 (Springer, 2005).
105. Sutterwala, F. S. et al. Critical role for NALP3/CIAS1/Cryopyrin in innate and adaptive immunity through its regulation of caspase-1. *Immunity* **24**, 317–327 (2006).
106. Antonopoulos, C. et al. IL-18 is a key proximal mediator of contact hypersensitivity and allergen-induced Langerhans cell migration in murine epidermis. *J. Leukoc. Biol.* **83**, 361–367 (2008).
107. Weber, F. C. et al. Lack of the purinergic receptor P2X(7) results in resistance to contact hypersensitivity. *J. Exp. Med.* **207**, 2609–2619 (2010).
108. Kostarnoy, A. V. et al. Receptor Mincle promotes skin allergies and is capable of recognizing cholesterol sulfate. *Proc. Natl Acad. Sci. USA* **114**, E2758–E2765 (2017).
109. Luis, A. et al. Oxidative stress-dependent activation of the eIF2alpha-ATF4 unfolded protein response branch by skin sensitizer 1-fluoro-2,4-dinitrobenzene modulates dendritic-like cell maturation and inflammatory status in a biphasic manner [corrected]. *Free Radic. Biol. Med.* **77**, 217–229 (2014).
110. Schmidt, M. et al. Crucial role for human Toll-like receptor 4 in the development of contact allergy to nickel. *Nat. Immunol.* **11**, 814–819 (2010).
111. Adam, C. et al. Allergy-inducing chromium compounds trigger potent innate immune stimulation Via ROS-dependent inflammasome Activation. *J. Invest. Dermatol.* **137**, 367–376 (2017).
112. Li, X. & Zhong, F. Nickel induces interleukin-1beta secretion via the NLRP3-ASC-caspase-1 pathway. *Inflammation* **37**, 457–466 (2014).
113. El Ali, Z. et al. Allergic skin inflammation induced by chemical sensitizers is controlled by the transcription factor Nrf2. *Toxicol. Sci.* **134**, 39–48 (2013).
114. Helou, D. G., Martin, S. F., Pallardy, M., Chollet-Martin, S. & Kerdine-Römer, S. Nrf2 involvement in chemical-induced skin innate immunity. *Front. Immunol.* **10**, 1004 (2019).
115. Eaton, L. H., Roberts, R. A., Kimber, I., Dearman, R. J. & Metryka, A. Skin sensitization induced Langerhans' cell mobilization: variable requirements for tumour necrosis factor-alpha. *Immunology* **144**, 139–148 (2015).
116. Peng, B. et al. Thimerosal induces skin pseudo-allergic reaction via Mas-related G-protein coupled receptor B2. *J. Dermatol. Sci.* **95**, 99–106 (2019).
117. Meixiong, J. et al. Activation of mast-cell-expressed Mas-related G-protein-coupled receptors drives non-histaminergic itch. *Immunity* **50**, 1163–1171.e5 (2019).
118. Dudeck, A. et al. Mast cells are key promoters of contact allergy that mediate the adjuvant effects of haptens. *Immunity* **34**, 973–984 (2011).
119. Dudeck, J. et al. Mast-cell-derived TNF amplifies $CD8^+$ dendritic cell functionality and $CD8^+$ T cell priming. *Cell Rep.* **13**, 399–411 (2015).
120. Biedermann, T. et al. Mast cells control neutrophil recruitment during T cell-mediated delayed-type hypersensitivity reactions through tumor necrosis factor and macrophage inflammatory protein 2. *J. Exp. Med.* **192**, 1441–1452 (2000).
121. Weber, F. C. et al. Neutrophils are required for both the sensitization and elicitation phase of contact hypersensitivity. *J. Exp. Med.* **212**, 15–22 (2015).
122. Tamoutounour, S. et al. Origins and functional specialization of macrophages and of conventional and monocyte-derived dendritic cells in mouse skin. *Immunity* **39**, 925–938 (2013).
123. Clausen, B. E. & Stoitzner, P. Functional specialization of skin dendritic cell subsets in regulating T cell responses. *Front. Immunol.* **6**, 534 (2015).
124. Bacci, S., Alard, P., Dai, R., Nakamura, T. & Streilein, J. W. High and low doses of haptens dictate whether dermal or epidermal antigen-presenting cells promote contact hypersensitivity. *Eur. J. Immunol.* **27**, 442–448 (1997).
125. Edelson, B. T. et al. Peripheral $CD103^+$ dendritic cells form a unified subset developmentally related to $CD8\alpha^+$ conventional dendritic cells. *J. Exp. Med.* **207**, 823–836 (2010).
126. Honda, T. et al. Compensatory role of Langerhans cells and langerin-positive dermal dendritic cells in the sensitization phase of murine contact hypersensitivity. *J. Allergy Clin. Immunol.* **125**, 1154–1156.e2 (2010).
127. Noordegraaf, M., Flacher, V., Stoitzner, P. & Clausen, B. E. Functional redundancy of Langerhans cells and $Langerin^+$ dermal dendritic cells in contact hypersensitivity. *J. Invest. Dermatol.* **130**, 2752–2759 (2010).
128. Cho, Y., Kwon, D. & Kang, S. J. The Cooperative Role of $CD326^+$ and $CD11b^+$ dendritic cell subsets for a hapten-induced Th2 differentiation. *J. Immunol.* **199**, 3137–3146 (2017).
129. Le Borgne, M. et al. Dendritic cells rapidly recruited into epithelial tissues via CCR6/CCL20 are responsible for $CD8^+$ T cell crosspriming in vivo. *Immunity* **24**, 191–201 (2006).
130. Micosse, C. et al. Human "TH9" cells are a subpopulation of PPAR-γ^+ TH2 cells. *Sci. Immunol.* **4**, eaat5943 (2019).
131. Gibson, A. et al. In Vitro Priming of Naive T-cells with p-Phenylenediamine and Bandrowski's Base. *Chem. Res. Toxicol.* **28**, 2069–2077 (2015).
132. Bechara, R., Antonios, D., Azouri, H. & Pallardy, M. Nickel sulfate promotes IL-17A producing $CD4^+$ T cells by an IL-23-dependent mechanism regulated by TLR4 and Jak-STAT pathways. *J. Invest. Dermatol.* **137**, 2140–2148 (2017).
133. Connor, L. M. et al. Th2 responses are primed by skin dendritic cells with distinct transcriptional profiles. *J. Exp. Med.* **214**, 125–142 (2017).
134. Larson, R. P. et al. Dibutyl phthalate-induced thymic stromal lymphopoietin is required for Th2 contact hypersensitivity responses. *J. Immunol.* **184**, 2974–2984 (2010).
135. Dhingra, N. et al. Molecular profiling of contact dermatitis skin identifies allergen-dependent differences

in immune response. *J. Allergy Clin. Immunol.* **134**, 362–372 (2014).
This study identified differential up-regulation of specific T cell axes in response to varied contact allergens, with important implications for both understanding disease mechanisms and treatment approaches.
136. Nicolai, S. et al. Human T cell response to CD1a and contact dermatitis allergens in botanical extracts and commercial skin care products. *Sci. Immunol.* **5**, eaax5430 (2020).
137. Betts, R. J. et al. Contact sensitizers trigger human CD1-autoreactive T-cell responses. *Eur. J. Immunol.* **47**, 1171–1180 (2017).
138. Nieuwenhuis, E. E. et al. CD1d and CD1d-restricted iNKT-cells play a pivotal role in contact hypersensitivity. *Exp. Dermatol.* **14**, 250–258 (2005).
139. Goubier, A. et al. Invariant NKT cells suppress $CD8^+$ T-cell-mediated allergic contact dermatitis independently of regulatory $CD4^+$ T cells. *J. Invest. Dermatol.* **133**, 980–987 (2013).
140. Shimizuhira, C. et al. Natural killer T cells are essential for the development of contact hypersensitivity in BALB/c mice. *J. Invest. Dermatol.* **134**, 2709–2718 (2014).
141. Kim, J. H. et al. CD1a on Langerhans cells controls inflammatory skin disease. *Nat. Immunol.* **17**, 1159–1166 (2016).
These investigators used both mouse models and human tissues to study the CD1a recognition of urushiol, the subsequent inflammatory responses and the effects of CD1a blocking antibodies, with evidence supporting CD1a as a potential therapeutic target in cCD.
142. Wang, K. et al. TLR4 supports the expansion of $FasL^+CD5^+CD1d^{hi}$ regulatory B cells, which decreases in contact hypersensitivity. *Mol. Immunol.* **87**, 188–199 (2017).
143. Vocanson, M. et al. Inducible costimulator (ICOS) is a marker for highly suppressive antigen-specific T cells sharing features of TH17/TH1 and regulatory T cells. *J. Allergy Clin. Immunol.* **126**, 280–289, 289.e1-7 (2010).
144. Ring, S., Enk, A. H. & Mahnke, K. Regulatory T cells from IL-10-deficient mice fail to suppress contact hypersensitivity reactions due to lack of adenosine production. *J. Invest. Dermatol.* **131**, 1494–1502 (2011).
145. Mahnke, K. et al. Down-regulation of CD62L shedding in T cells by $CD39^+$ regulatory T cells leads to defective sensitization in contact hypersensitivity reactions. *J. Invest. Dermatol.* **137**, 106–114 (2017).
146. El Beidaq, A. et al. In vivo expansion of endogenous regulatory T cell populations induces long-term suppression of contact hypersensitivity. *J. Immunol.* **197**, 1567–1576 (2016).
147. Gorbachev, A. V. & Fairchild, R. L. $CD4^+CD25^+$ regulatory T cells utilize FasL as a mechanism to restrict DC priming functions in cutaneous immune responses. *Eur. J. Immunol.* **40**, 2006–2015 (2010).
148. Ring, S., Karakhanova, S., Johnson, T., Enk, A. H. & Mahnke, K. Gap junctions between regulatory T cells and dendritic cells prevent sensitization of $CD8^+$ T cells. *J. Allergy Clin. Immunol.* **125**, 237–246.e1-7 (2010).
149. Kish, D. D., Gorbachev, A. V. & Fairchild, R. L. $CD8^+$ T cells produce IL-2, which is required for $CD4^+CD25^+$ T cell regulation of effector CD8+T cell development for contact hypersensitivity responses. *J. Leukoc. Biol.* **78**, 725–735 (2005).
150. Silva-Vilches, C. et al. Production of extracellular adenosine by $CD73^+$ dendritic cells is crucial for induction of tolerance in contact hypersensitivity reactions. *J. Invest. Dermatol.* **139**, 541–551 (2019).
151. Luckey, U. et al. T cell killing by tolerogenic dendritic cells protects mice from allergy. *J. Clin. Invest.* **121**, 3860–3871 (2011).
152. Nish, S. A. et al. T cell-intrinsic role of IL-6 signaling in primary and memory responses. *eLife* **3**, e01949 (2014).
153. Gamradt, P. et al. Inhibitory checkpoint receptors control $CD8^+$ resident memory T cells to prevent skin allergy. *J. Allergy Clin. Immunol.* **143**, 2147–2157 (2019).
154. Dyring-Andersen, B. et al. $CD4^+$ T cells producing interleukin (IL)-17, IL-22 and interferon-gamma are major effector T cells in nickel allergy. *Contact Dermatitis* **68**, 339–347 (2013).
155. Gober, M. D., Fishelevich, R., Zhao, Y., Unutmaz, D. & Gaspari, A. A. Human natural killer T cells infiltrate into the skin at elicitation sites of allergic contact dermatitis. *J. Invest. Dermatol.* **128**, 1460–1469 (2008).
156. Carbone, T. et al. CD56highCD16-CD62L- NK cells accumulate in allergic contact dermatitis and contribute to the expression of allergic responses. *J. Immunol.* **184**, 1102–1110 (2010).
157. Rafei-Shamsabadi, D. A. et al. Lack of type 2 innate lymphoid cells promotes a type I-driven enhanced immune response in contact hypersensitivity. *J. Invest. Dermatol.* **138**, 1962–1972 (2018).
158. Simon, D., Aeberhard, C., Erdemoglu, Y. & Simon, H. U. Th17 cells and tissue remodeling in atopic and contact dermatitis. *Allergy* **69**, 125–131 (2014).
159. Kawano, M. et al. $NKG2D^+$ IFN-γ^+ $CD8^+$ T cells are responsible for palladium allergy. *PLoS One* **9**, e86810 (2014).
160. Kish, D. D. et al. Neutrophil cathepsin G regulates dendritic cell production of IL-12 during development of CD4 T cell responses to antigens in the skin. *J. Immunol.* **202**, 1045–1056 (2019).
161. Takeshita, K., Yamasaki, T., Akira, S., Gantner, F. & Bacon, K. B. Essential role of MHC II-independent $CD4^+$ T cells, IL-4 and STAT6 in contact hypersensitivity induced by fluorescein isothiocyanate in the mouse. *Int. Immunol.* **16**, 685–695 (2004).
162. Gautam, S. C., Matriano, J. A., Chikkala, N. F., Edinger, M. G. & Tubbs, R. R. L3T4 ($CD4^+$) cells that mediate contact sensitivity to trinitrochlorobenzene express I-A determinants. *Cell Immunol.* **135**, 27–41 (1991).
163. Kish, D. D., Volokh, N., Baldwin, W. M. 3rd & Fairchild, R. L. Hapten application to the skin induces an inflammatory program directing hapten-primed effector CD8 T cell interaction with hapten-presenting endothelial cells. *J. Immunol.* **186**, 2117–2126 (2011).
164. Trautmann, A. et al. T cell-mediated Fas-induced keratinocyte apoptosis plays a key pathogenetic role in eczematous dermatitis. *J. Clin. Invest.* **106**, 25–35 (2000).
165. Akiba, H. et al. Skin inflammation during contact hypersensitivity is mediated by early recruitment of CD8+T cytotoxic 1 cells inducing keratinocyte apoptosis. *J. Immunol.* **168**, 3079–3087 (2002).
166. He, D. et al. and IFN-gamma mediate the elicitation of contact hypersensitivity responses by different mechanisms and both are required for optimal responses. *J. Immunol.* **183**, 1463–1470 (2009).
167. Chong, S. Z. et al. CD8 T cells regulate allergic contact dermatitis by modulating CCR2-dependent TNF/iNOS-expressing Ly6C+CD11b+monocytic cells. *J. Invest. Dermatol.* **134**, 666–676 (2014).
168. Kish, D. D., Gorbachev, A. V., Parameswaran, N., Gupta, N. & Fairchild, R. L. Neutrophil expression of Fas ligand and perforin directs effector CD8 T cell infiltration into antigen-challenged skin. *J. Immunol.* **189**, 2191–2202 (2012).
169. Engeman, T., Gorbachev, A. V., Kish, D. D. & Fairchild, R. L. The intensity of neutrophil infiltration controls the number of antigen-primed CD8 T cells recruited into cutaneous antigen challenge sites. *J. Leukoc. Biol.* **76**, 941–949 (2004).
170. Jiang, X. et al. Dermal gammadelta T cells do not freely re-circulate out of skin and produce IL-17 to promote neutrophil infiltration during primary contact hypersensitivity. *PLoS One* **12**, e0169397 (2017).
171. Nakae, S. et al. Antigen-specific T cell sensitization is impaired in IL-17-deficient mice, causing suppression of allergic cellular and humoral responses. *Immunity* **17**, 375–387 (2002).
172. Dey, N., Szczepanik, M., Lau, K., Majewska-Szczepanik, M. & Askenase, P. W. Stimulatory lipids accumulate in the mouse liver within 30 min of contact sensitization to facilitate the activation of Naive iNKT cells in a CD1d-dependent fashion. *Scand. J. Immunol.* **74**, 52–61 (2011).
173. Campos, R. A. et al. Cutaneous immunization rapidly activates liver invariant Valpha14 NKT cells stimulating B-1 B cells to initiate T cell recruitment for elicitation of contact sensitivity. *J. Exp. Med.* **198**, 1785–1796 (2003).
174. Natsuaki, Y. et al. Perivascular leukocyte clusters are essential for efficient activation of effector T cells in the skin. *Nat. Immunol.* **15**, 1064–1069 (2014).
175. Liu, Z. et al. Visualization of T cell-regulated monocyte clusters mediating keratinocyte death in acquired cutaneous immunity. *J. Invest. Dermatol.* **138**, 1328–1337 (2018).
176. Kehren, J. et al. Cytotoxicity is mandatory for $CD8^+$ T cell-mediated contact hypersensitivity. *J. Exp. Med.* **189**, 779–786 (1999).
177. Pennino, D. et al. IL-17 amplifies human contact hypersensitivity by licensing hapten nonspecific Th1 cells to kill autologous keratinocytes. *J. Immunol.* **184**, 4880–4888 (2010).
178. Balato, A. et al. CD1d-dependent, iNKT-cell cytotoxicity against keratinocytes in allergic contact dermatitis. *Exp. Dermatol.* **21**, 915–920 (2012).
179. Suzuki, K., Meguro, K., Nakagomi, D. & Nakajima, H. Roles of alternatively activated M2 macrophages in allergic contact dermatitis. *Allergol. Int.* **66**, 392–397 (2017).
180. O'Leary, J. G., Goodarzi, M., Drayton, D. L. & von Andrian, U. H. T cell- and B cell-independent adaptive immunity mediated by natural killer cells. *Nat. Immunol.* **7**, 507–516 (2006).
181. Zhang, L. H., Shin, J. H., Haggadone, M. D. & Sunwoo, J. B. The aryl hydrocarbon receptor is required for the maintenance of liver-resident natural killer cells. *J. Exp. Med.* **213**, 2249–2257 (2016).
182. Stary, V. et al. A discrete subset of epigenetically primed human NK cells mediates antigen-specific immune responses. *Sci. Immunol.* **5**, eaba6232 (2020).
183. Rouzaire, P. et al. Natural killer cells and T cells induce different types of skin reactions during recall responses to haptens. *Eur. J. Immunol.* **42**, 80–88 (2012).
184. Paust, S. et al. Critical role for the chemokine receptor CXCR6 in NK cell-mediated antigen-specific memory of haptens and viruses. *Nat. Immunol.* **11**, 1127–1135 (2010).
185. van den Boorn, J. G. et al. Inflammasome-dependent induction of adaptive NK cell memory. *Immunity* **44**, 1406–1421 (2016).
186. Tomura, M. et al. Activated regulatory T cells are the major T cell type emigrating from the skin during a cutaneous immune response in mice. *J. Clin. Invest.* **120**, 883–893 (2010).
187. Nakashima, H. et al. CD22 expression mediates the regulatory functions of peritoneal B-1a cells during the remission phase of contact hypersensitivity reactions. *J. Immunol.* **184**, 4637–4645 (2010).
188. Hitzler, M. et al. Human Langerhans cells control Th cells via programmed death-ligand 1 in response to bacterial stimuli and nickel-induced contact allergy. *PLoS One* **7**, e46776 (2012).
189. Ritprajak, P., Hashiguchi, M., Tsushima, F., Chalermsarp, N. & Azuma, M. Keratinocyte-associated B7-H1 directly regulates cutaneous effector CD8+T cell responses. *J. Immunol.* **184**, 4918–4925 (2010).
190. Hirano, T. PD-L1 on mast cells suppresses effector $CD8^+$ T-cell activation in the skin in murine contact hypersensitivity. *J. Allergy Clin. Immunol.*, https://doi.org/10.1016/j.jaci.2020.12.654 (2021).
191. Ikebuchi, R. et al. Functional phenotypic diversity of regulatory T cells remaining in inflamed skin. *Front. Immunol.* **10**, 1098 (2019).
192. Braun, A. et al. Integrin αE(CD103) Is Involved in Regulatory T-Cell Function in Allergic Contact Hypersensitivity. *J. Invest. Dermatol.* **135**, 2982–2991 (2015).
193. Lehtimäki, S. et al. The temporal and spatial dynamics of Foxp3+Treg cell-mediated suppression during contact hypersensitivity responses in a murine model. *J. Invest. Dermatol.* **132**, 2744–2751 (2012).
194. Christensen, A. D., Skov, S., Kvist, P. H. & Haase, C. Depletion of regulatory T cells in a hapten-induced inflammation model results in prolonged and increased inflammation driven by T cells. *Clin. Exp. Immunol.* **179**, 485–499 (2015).
195. Ikebuchi, R. et al. A rare subset of skin-tropic regulatory T cells expressing Il10/Gzmb inhibits the cutaneous immune response. *Sci. Rep.* **6**, 35002 (2016).
196. Ring, S., Oliver, S. J., Cronstein, B. N., Enk, A. H. & Mahnke, K. $CD4^+CD25^+$ regulatory T cells suppress contact hypersensitivity reactions through a CD39, adenosine-dependent mechanism. *J. Allergy Clin. Immunol.* **123**, 1287–1296.e2 (2009).
197. Ring, S. et al. Regulatory T cells prevent neutrophilic infiltration of skin during contact hypersensitivity reactions by strengthening the endothelial barrier. *J. Invest. Dermatol.*, https://doi.org/10.1016/j.jid.2021.01.027 (2021).
198. Campbell, C. & Rudensky, A. Roles of regulatory T cells in tissue pathophysiology and metabolism. *Cell Metab.* **31**, 18–25 (2020).
199. Gaide, O. et al. Common clonal origin of central and resident memory T cells following skin immunization. *Nat. Med.* **21**, 647–653 (2015).
Using studies of both mouse models and human tissue, this group identified the generation of both central memory T cells in the lymph nodes and resident memory T cells in the skin in response to cutaneous immunization.

200. Mbitikon-Kobo, F. M. et al. Characterization of a CD44/CD122int memory CD8 T cell subset generated under sterile inflammatory conditions. *J. Immunol.* **182**, 3846–3854 (2009).
201. Schmidt, J. D. et al. Rapid allergen-induced interleukin-17 and interferon-γ secretion by skin-resident memory $CD8^+$ T cells. *Contact Dermatitis* **76**, 218–227 (2017).
202. Adachi, T. et al. Hair follicle-derived IL-7 and IL-15 mediate skin-resident memory T cell homeostasis and lymphoma. *Nat. Med.* **21**, 1272–1279 (2015).
203. Hirai, T. et al. Competition for active TGFβ cytokine allows for selective retention of antigen-specific tissue- resident memory T cells in the epidermal niche. *Immunity* **54**, 84–98 (2021).
204. Jensen, C. D., Johansen, J. D., Menné, T. & Andersen, K. E. Increased retest reactivity by both patch and use test with methyldibromoglutaronitrile in sensitized individuals. *Acta Derm. Venereol.* **86**, 8–12 (2006).
205. Nahhas, A. F., Oberlin, D. M., Braunberger, T. L. & Lim, H. W. Recent developments in the diagnosis and management of photosensitive disorders. *Am. J. Clin. Dermatol.* **19**, 707–731 (2018).
206. Greenspoon, J., Ahluwalia, R., Juma, N. & Rosen, C. F. Allergic and photoallergic contact dermatitis: a 10-year experience. *Dermatitis* **24**, 29–32 (2013).
207. Maverakis, E. et al. Light, including ultraviolet. *J. Autoimmun.* **34**, J247–257 (2010).
208. Zaheer, M. R. et al. Molecular mechanisms of drug photodegradation and photosensitization. *Curr. Pharm. Des.* **22**, 768–782 (2016).
209. Nathan, C. & Ding, A. SnapShot: reactive oxygen intermediates (ROI). *Cell* **140**, 951–951.e2 (2010).
210. de Jager, T. L., Cockrell, A. E., Du & Plessis, S. S. Ultraviolet light induced generation of reactive oxygen species. *Adv. Exp. Med. Biol.* **996**, 15–23 (2017).
211. Schieber, M. & Chandel, N. S. ROS function in redox signaling and oxidative stress. *Curr. Biol.* **24**, R453–462 (2014).
212. Nathan, C. & Cunningham-Bussel, A. Beyond oxidative stress: an immunologist's guide to reactive oxygen species. *Nat. Rev. Immunol.* **13**, 349–361 (2013).
213. Pathak, M. A. & Fitzpatrick, T. B. The evolution of photochemotherapy with psoralens and UVA (PUVA): 2000 BC to 1992 AD. *J. Photochem. Photobiol. B.* **14**, 3–22 (1992).
214. Devleeschouwer, V., Roelandts, R., Garmyn, M. & Goossens, A. Allergic and photoallergic contact dermatitis from ketoprofen: results of (photo) patch testing and follow-up of 42 patients. *Contact Dermatitis* **58**, 159–166 (2008).
215. Asensio, T., Sanchís, M. E., Sánchez, P., Vega, J. M. & García, J. C. Photocontact dermatitis because of oral dexketoprofen. *Contact Dermatitis* **58**, 59–60 (2008).
216. Tokura, Y. Drug photoallergy. *J. Cutan. Immunol. Allergy* **1**, 48–57 (2018).
217. Abeyama, K. et al. A role for NF-kappaB-dependent gene transactivation in sunburn. *J. Clin. Invest.* **105**, 1751–1759 (2000).
218. Hasegawa, T., Nakashima, M. & Suzuki, Y. Nuclear DNA damage-triggered NLRP3 inflammasome activation promotes UVB-induced inflammatory responses in human keratinocytes. *Biochem. Biophys. Res. Commun.* **477**, 329–335 (2016).
219. Hotamisligil, G. S. & Davis, R. J. Cell signaling and stress responses. *Cold Spring Harb. Perspect. Biol.* **8**, a006072 (2016).
220. Leighton, S., Kok, L. F., Halliday, G. M. & Byrne, S. N. Inhibition of UV-induced uric acid production using allopurinol prevents suppression of the contact hypersensitivity response. *Exp. Dermatol.* **22**, 189–194 (2013).
221. Garg, A. D. et al. A novel pathway combining calreticulin exposure and ATP secretion in immunogenic cancer cell death. *EMBO J.* **31**, 1062–1079 (2012).
222. Kurita, M. et al. Induction of keratinocyte apoptosis by photosensitizing chemicals plus UVA. *J. Dermatol. Sci.* **45**, 105–112 (2007).
223. Dos Santos, A. F. et al. Distinct photo-oxidation-induced cell death pathways lead to selective killing of human breast cancer cells. *Cell Death Dis.* **11**, 1070 (2020).
224. Vassileva, S. G., Mateev, G. & Parish, L. C. Antimicrobial photosensitive reactions. *Arch. Intern. Med.* **158**, 1993–2000 (1998).
225. Calnan, C. D. & Wells, G. C. Suspender dermatitis and nickel sensitivity. *Br. Med. J.* **1**, 1265–1268 (1956).
226. Williams, J., Cahill, J. & Nixon, R. Occupational autoeczematization or atopic eczema precipitated by occupational contact dermatitis? *Contact Dermatitis* **56**, 21–26 (2007).
227. Häusermann, P., Harr, T. & Bircher, A. J. Baboon syndrome resulting from systemic drugs: is there strife between SDRIFE and allergic contact dermatitis syndrome? *Contact Dermatitis* **51**, 297–310 (2004).
228. Veien, N. K. Systemic contact dermatitis. *Int. J. Dermatol.* **50**, 1445–1456 (2011).
229. Cressey, B. D. & Scheinman, P. L. Periocular dermatitis from systemic exposure to nickel in a palatal expander and dental braces. *Dermatitis* **23**, 179 (2012).
230. Ham, J. E., Siegel, P. D. & Maibach, H. Undeclared formaldehyde levels in patient consumer products: formaldehyde test kit utility. *Cutan. Ocul. Toxicol.* **38**, 112–117 (2019).
231. Nikle, A., Ericson, M. & Warshaw, E. Formaldehyde release from personal care products: chromotropic acid method analysis. *Dermatitis* **30**, 67–73 (2019).
232. Herman, A. et al. Allergic contact dermatitis caused by isobornyl acrylate in Freestyle® Libre, a newly introduced glucose sensor. *Contact Dermatitis* **77**, 367–373 (2017).
233. Friis, U. F., Menné, T., Flyvholm, M. A., Bonde, J. P. & Johansen, J. D. Difficulties in using Material Safety Data Sheets to analyse occupational exposures to contact allergens. *Contact Dermatitis* **72**, 147–153 (2015).
234. Bruze, M., Frick, M. & Persson, L. Patch testing with thin-layer chromatograms. *Contact Dermatitis* **48**, 278–279 (2003).
235. Lammintausta, K. et al. An epidemic of furniture-related dermatitis: searching for a cause. *Br. J. Dermatol.* **162**, 108–116 (2010).
236. Erfani, B., Midander, K., Lidén, C. & Julander, A. Development, validation and testing of a skin sampling method for assessment of metal exposure. *Contact Dermatitis* **77**, 17–24 (2017).
237. Johansen, J. D. et al. European Society of Contact Dermatitis guideline for diagnostic patch testing - recommendations on best practice. *Contact Dermatitis* **73**, 195–221 (2015).
The European Society of Contact Dermatitis guidelines represent a comprehensive set of recommendations for patch testing in clinical practice.
238. Bruze, M., Isaksson, M., Gruvberger, B. & Frick-Engfeldt, M. Recommendation of appropriate amounts of petrolatum preparation to be applied at patch testing. *Contact Dermatitis* **56**, 281–285 (2007).
239. van Amerongen, C. C. A., Ofenloch, R., Dittmar, D. & Schuttelaar, M. L. A. New positive patch test reactions on day 7 — the additional value of the day 7 patch test reading. *Contact Dermatitis* **81**, 280–287 (2019).
240. Davis, M. D. et al. Delayed patch test reading after 5 days: the Mayo Clinic experience. *J. Am. Acad. Dermatol.* **59**, 225–233 (2008).
241. Santiago, F., Gonçalo, M., Vieira, R., Coelho, S. & Figueiredo, A. Epicutaneous patch testing in drug hypersensitivity syndrome (DRESS). *Contact Dermatitis* **62**, 47–53 (2010).
242. Gonçalo, M. et al. Photopatch testing: recommendations for a European photopatch test baseline series. *Contact Dermatitis.***68**, 239–243 (2013).
243. DeGroot A. C. *Patch testing: test concentrations and vehicles for 4900 chemicals* (Elsevier, 2018).
244. Friis, U. F., Menné, T., Flyvholm, M. A., Bonde, J. P. & Johansen, J. D. Occupational allergic contact dermatitis diagnosed by a systematic stepwise exposure assessment of allergens in the work environment. *Contact Dermatitis* **69**, 153–163 (2013).
245. Hjorth, N. & Roed-Petersen, J. Occupational protein contact dermatitis in food handlers. *Contact Dermatitis* **2**, 28–42 (1976).
246. Vester, L., Thyssen, J. P., Menné, T. & Johansen, J. D. Consequences of occupational food-related hand dermatoses with a focus on protein contact dermatitis. *Contact Dermatitis* **67**, 328–333 (2012).
247. Friis, U. F. et al. Occupational irritant contact dermatitis diagnosed by analysis of contact irritants and allergens in the work environment. *Contact Dermatitis* **71**, 364–370 (2014).
248. Agner, T. et al. Classification of hand eczema. *J. Eur. Acad. Dermatol. Venereol.* **29**, 2417–2422 (2015).
249. Diepgen, T. L. et al. Hand eczema classification: a cross-sectional, multicentre study of the aetiology and morphology of hand eczema. *Br. J. Dermatol.* **160**, 353–358 (2009).
250. Mathias, C. G. Contact dermatitis and workers' compensation: criteria for establishing occupational causation and aggravation. *J. Am. Acad. Dermatol.* **20**, 842–848 (1989).
The 'Mathias Critera' continue to serve as the basis for the evaluation of occupational CD.
251. Johansen, J. D. et al. The repeated open application test: suggestions for a scale of evaluation. *Contact Dermatitis* **39**, 95–96 (1998).
252. Fischer, L. A., Voelund, A., Andersen, K. E., Menné, T. & Johansen, J. D. The dose-response relationship between the patch test and ROAT and the potential use for regulatory purposes. *Contact Dermatitis* **61**, 201–208 (2009).
253. Goldminz, A. M., Wald, M. S. & Scheinman, P. L. Positive occluded patch test in the face of negative repeat open application test. *Dermatitis* **29**, 162–163 (2018).
254. Hindsén, M., Bruze, M. & Christensen, O. B. Flare-up reactions after oral challenge with nickel in relation to challenge dose and intensity and time of previous patch test reactions. *J. Am. Acad. Dermatol.* **44**, 616–623 (2001).
255. Bregnhøj, A., Menné, T., Johansen, J. D. & Søsted, H. Prevention of hand eczema among Danish hairdressing apprentices: an intervention study. *Occup. Env. Med.* **69**, 310–316 (2012).
256. Held, E., Mygind, K., Wolff, C., Gyntelberg, F. & Agner, T. Prevention of work related skin problems: an intervention study in wet work employees. *Occup. Env. Med.* **59**, 556–561 (2002).
257. Schwensen, J. F., Bregnbak, D. & Johansen, J. D. Recent trends in epidemiology, sensitization and legal requirements of selected relevant contact allergens. *Expert Rev. Clin. Immunol.* **12**, 289–300 (2016).
258. Hald, M., Agner, T., Blands, J. & Johansen, J. D. Delay in medical attention to hand eczema: a follow-up study. *Brit. J. Dermatol.* **161**, 1294–1300 (2009).
259. Silvestri, D. L. & Barmettler, S. Pruritus ani as a manifestation of systemic contact dermatitis: resolution with dietary nickel restriction. *Dermatitis* **22**, 50–55 (2011).
260. Thyssen, J. P. & Menné, T. Metal allergy–a review on exposures, penetration, genetics, prevalence, and clinical implications. *Chem. Res. Toxicol.* **23**, 309–318 (2010).
261. Jacob, S. E. & Castanedo-Tardan, M. P. Pharmacotherapy for allergic contact dermatitis. *Expert Opin. Pharmacother.* **8**, 2757–2774 (2007).
262. Wollenberg, A. et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. *J. Eur. Acad. Dermatol. Venereol.* **32**, 657–682 (2018).
263. Saripalli, Y. V., Gadzia, J. E. & Belsito, D. V. Tacrolimus ointment 0.1% in the treatment of nickel-induced allergic contact dermatitis. *J. Am. Acad. Dermatol.* **49**, 477–482 (2003).
264. Mose, K. F. et al. Anti-inflammatory potency testing of topical corticosteroids and calcineurin inhibitors in human volunteers sensitized to diphenylcyclopropenone. *Br. J. Clin. Pharmacol.* **84**, 1719–1728 (2018).
265. Lejding, T. et al. Skin application of glutathione and iron sulfate can inhibit elicitation of allergic contact dermatitis from hexavalent chromium. *Contact Dermatitis* **82**, 45–53 (2020).
266. Kemény, L., Varga, E. & Novak, Z. Advances in phototherapy for psoriasis and atopic dermatitis. *Expert Rev. Clin. Immunol.* **15**, 1205–1214 (2019).
267. Schempp, C. M., Müller, H., Czech, W., Schöpf, E. & Simon, J. C. Treatment of chronic palmoplantar eczema with local bath-PUVA therapy. *J. Am. Acad. Dermatol.* **36**, 733–737 (1997).
268. Sezer, E. & Etikan, I. Local narrowband UVB phototherapy vs. local PUVA in the treatment of chronic hand eczema. *Photodermatol. Photoimmunol. Photomed.* **23**, 10–14 (2007).
269. Sung, C. T., McGowan, M. A., Machler, B. C. & Jacob, S. E. Systemic treatments for allergic contact dermatitis. *Dermatitis* **30**, 46–53 (2019).
270. Cinats, A., Heck, E. & Robertson, L. Janus kinase inhibitors: a review of their emerging applications in dermatology. *Skin. Ther. Lett.* **23**, 5–9 (2018).
271. Mowad, C. M. et al. Allergic contact dermatitis: patient management and education. *J. Am. Acad. Dermatol.* **74**, 1043–1054 (2016).
272. Scheinman, P. L. The foul side of fragrance-free products: what every clinician should know about managing patients with fragrance allergy. *J. Am. Acad. Dermatol.* **41**, 1020–1024 (1999).
273. Rubin, C. B. & Brod, B. Natural does not mean safe — the dirt on clean beauty products. **155**, 1344–1345 (2019).
274. Lönnroth, E. C., Wellendorf, H. & Ruyter, E. Permeability of different types of medical protective gloves to acrylic monomers. *Eur. J. Oral. Sci.* **111**, 440–446 (2003).
275. Scheman, A. et al. Alternatives for Allergens in the 2018 American Contact dermatitis society core series:

report by the American Contact Alternatives Group. *Dermatitis* **30**, 87–105 (2019).
276. Dizdarevic, A. et al. Intervention study to evaluate the importance of information given to patients with contact allergy: a randomized, investigator-blinded clinical trial. *Br. J. Dermatol.* **184**, 43–49 (2020).
277. Dou, X., Liu, L. L. & Zhu, X. J. Nickel-elicited systemic contact dermatitis. *Contact Dermatitis* **48**, 126–129 (2003).
278. Stuckert, J. & Nedorost, S. Low-cobalt diet for dyshidrotic eczema patients. *Contact Dermatitis* **59**, 361–365 (2008).
279. Mislankar, M. & Zirwas, M. J. Low-nickel diet scoring system for systemic nickel allergy. *Dermatitis* **24**, 190–195 (2013).
280. Jensen, C. S., Menné, T. & Johansen, J. D. Systemic contact dermatitis after oral exposure to nickel: a review with a modified meta-analysis. *Contact Dermatitis* **54**, 79–86 (2006).
281. Salam, T. N. & Fowler, J. F. Jr. Balsam-related systemic contact dermatitis. *J. Am. Acad. Dermatol.* **45**, 377–381 (2001).
282. Scheman, A., Cha, C., Jacob, S. E. & Nedorost, S. Food avoidance diets for systemic, lip, and oral contact allergy: an american contact alternatives group article. *Dermatitis* **23**, 248–257 (2012).
283. Tammaro, A., De Marco, G., Persechino, S., Narcisi, A. & Camplone, G. Allergy to nickel: first results on patients administered with an oral hyposensitization therapy. *Int. J. Immunopathol. Pharmacol.* **22**, 837–840 (2009).
284. Christensen, J. D. Disulfiram treatment of three patients with nickel dermatitis. *Contact Dermatitis* **8**, 105–108 (1982).
285. Kaaber, K., Menné, T., Veien, N. & Hougaard, P. Treatment of nickel dermatitis with Antabuse; a double blind study. *Contact Dermatitis* **9**, 297–299 (1983).
286. Peddawad, D., Nagendra, S., Chatterjee, R., Faldu, H. & Chheda, A. Fulminant encephalopathy with unusual brain imaging in disulfiram toxicity. *Neurology* **90**, 518–519 (2018).
287. Davis, M. D., Mowad, C. M. & Scheinman, P. Orthopedic prostheses: is there any point in patch testing? *Dermatitis* **15**, 210–212 (2004).
288. Schalock, P. C. & Thyssen, J. P. Metal hypersensitivity reactions to implants: opinions and practices of patch testing dermatologists. *Dermatitis* **24**, 313–320 (2013).
289. Resor, C. D. & et al. Systemic allergic contact dermatitis due to a GORE CARDIOFORM septal occluder device. A case report and literature review. *J. Am. Coll. Cardiol. Case Rep.* **2**, 1867–1871 (2020).
290. Aquino, M. & Mucci, T. Systemic contact dermatitis and allergy to biomedical devices. *Curr. Allergy Asthma Rep.* **13**, 518–527 (2013).
291. Bibas, N., Lassere, J., Paul, C., Aquilina, C. & Giordano-Labadie, F. Nickel-induced systemic contact dermatitis and intratubal implants: the baboon syndrome revisited. *Dermatitis* **24**, 35–36 (2013).
292. Lindsey, R. W. & Harper, A. Unusual complications related to spinal implants. *JBJS Case Connect.* **8**, e10 (2018).
293. Jia, Z., Tu, J., Wang, K., Jiang, G. & Wang, W. Allergic reaction following implantation of a nitinol alloy inferior vena cava filter. *J. Vasc. Interv. Radiol.* **26**, 1375–1377 (2015).
294. Pigatto, P. D. et al. Systemic allergic contact dermatitis associated with allergy to intraoral metals.*Dermatol. Online J.* **20**, 13030/qt74632201 (2014).
295. Andrews, I. D. & Scheinman, P. Systemic hypersensitivity reaction (without cutaneous manifestations) to an implantable cardioverter-defibrillator. *Dermatitis* **22**, 161–164 (2011).
296. Sharma, V. et al. Surgical explantation of atrial septal closure devices for refractory nickel allergy symptoms. *J. Thorac. Cardiovasc. Surg.* **160**, 502–509.e1 (2020).
297. Schalock, P. C. et al. Hypersensitivity reactions to metallic implants - diagnostic algorithm and suggested patch test series for clinical use. *Contact Dermatitis* **66**, 4–19 (2012).
298. Schalock, P. C. et al. Patch testing for evaluation of hypersensitivity to implanted metal devices: a perspective from the American Contact Dermatitis Society. *Dermatitis* **27**, 241–247 (2016).
299. Lai, D. W., Saver, J. L., Araujo, J. A., Reidl, M. & Tobis, J. Pericarditis associated with nickel hypersensitivity to the Amplatzer occluder device: a case report. *Catheter. Cardiovasc. Interv.* **66**, 424–426 (2005).
300. Kimyon, R. S. & Warshaw, E. M. Airborne allergic contact dermatitis: management and responsible allergens on the American Contact Dermatitis Society core series. *Dermatitis* **30**, 106–115 (2019).
301. Gruye, L. E., Yanovsky, R. L. & Goldminz, A. M. Preventing relapses of airborne allergic contact dermatitis to isothiazolinones in wall paint by painting over with an isothiazolinone-free paint. *Contact Dermatitis* **82**, 130–131 (2020).
302. Walls, A. C. & Silvestri, D. L. Prevention of airborne propolis-induced allergic contact dermatitis with barrier cream. *Dermatitis* **23**, 128–129 (2012).
303. Dogra, S., Parsad, D. & Handa, S. Narrowband ultraviolet B in airborne contact dermatitis: a ray of hope! *Br. J. Dermatol.* **150**, 373–374 (2004).
304. Verma, K. K., Sethuraman, G. & Kalavani, M. Weekly azathioprine pulse versus daily azathioprine in the treatment of Parthenium dermatitis: A non-inferiority randomized controlled study. *Indian J. Dermatol. Venereol. Leprol.* **81**, 251–256 (2015).
305. De, D., Sarangal, R. & Handa, S. The comparative efficacy and safety of azathioprine vs methotrexate as steroid-sparing agent in the treatment of airborne-contact dermatitis due to Parthenium. *Indian J. Dermatol. Venereol. Leprol.* **79**, 240–241 (2013).
306. Lakshmi, C., Srinivas, C. R. & Jayaraman, A. Ciclosporin in parthenium dermatitis–a report of 2 cases. *Contact Dermatitis* **59**, 245–248 (2008).
307. Snyder, M., Turrentine, J. E. & Cruz, P. D. Jr. Photocontact dermatitis and its clinical mimics: an overview for the allergist. *Clin. Rev. Allergy Immunol.* **56**, 32–40 (2019).
308. Yu, J. et al. Occupational dermatitis to facial personal protective equipment in healthcare workers: a systematic review. *J. Am. Acad. Dermatol.* **84**, 486–494 (2020).
309. Weisshaar, E. et al. Multicentre study 'rehabilitation of occupational skin diseases -optimization and quality assurance of inpatient management (ROQ)'-results from 12-month follow-up. *Contact Dermatitis* **68**, 169–174 (2013).
310. van Gils, R. F. et al. Process evaluation of an integrated, multidisciplinary intervention programme for hand eczema. *Contact Dermatitis* **66**, 254–263 (2012).
311. van Gils, R. F. et al. The effectiveness of integrated care for patients with hand eczema: results of a randomized, controlled trial. *Contact Dermatitis* **66**, 197–204 (2012).
312. Gomez, P., Kudla, I. & Wozniak, G. The impact of a multidisciplinary team and a dedicated return-to-work coordinator for workers with work-related skin disease. *Dermatitis* **22**, 308–309 (2011).
313. Kurt, O. K. & Basaran, N. Occupational exposure to metals and solvents: allergy and airway diseases. *Curr. Allergy Asthma Rep.* **20**, 38 (2020).
314. Lazarov, A., Rabin, B., Fraidlin, N. & Abraham, D. Medical and psychosocial outcome of patients with occupational contact dermatitis in Israel. *J. Eur. Acad. Dermatol. Venereol.* **20**, 1061–1065 (2006).
315. Ng, W. T. & Koh, D. Occupational contact dermatitis in manual cloud seeding operations. *Singap. Med. J.* **52**, e85–87 (2011).
316. Yan, Y. et al. Consensus of Chinese experts on protection of skin and mucous membrane barrier for health-care workers fighting against coronavirus disease 2019. *Dermatol. Ther.* **33**, e13310 (2020).
317. Holness, D. L. Occupational skin allergies: testing and treatment (the case of occupational allergic contact dermatitis). *Curr. Allergy Asthma Rep.* **14**, 410 (2014).
318. Holness, D. L. Occupational dermatosis. *Curr. Allergy Asthma Rep.* **19**, 42 (2019).
319. Mercader, P., de la Cuadra-Oyanguren, J., Rodríguez-Serna, M., Pitarch-Bort, G. & Fortea-Baixauli, J. M. Treatment of protein contact dermatitis with topical tacrolimus. *Acta Derm. Venereol.* **85**, 555–556 (2005).
320. Karimkhani, C. et al. Global skin disease morbidity and mortality: an update from the global burden of disease study 2013. *JAMA Dermatol.* **153**, 406–412 (2017).
321. Lau, M. Y., Burgess, J. A., Nixon, R., Dharmage, S. C. & Matheson, M. C. A review of the impact of occupational contact dermatitis on quality of life. *J. Allergy* **2011**, 964509 (2011).
322. Holness, D. L. et al. Hand and upper extremity function in workers with hand dermatitis. *Dermatitis* **24**, 131–136 (2013).
323. Anderson, R. T. & Rajagopalan, R. Development and validation of a quality of life instrument for cutaneous diseases. *J. Am. Acad. Dermatol.* **37**, 41–50 (1997).
324. Boonchai, W., Charoenpipatsin, N., Winayanuwattikun, W., Phaitoonwattanakij, S. & Sukakul, T. Assessment of the quality of life (QoL) of patients with dermatitis and the impact of patch testing on QoL: A study of 519 patients diagnosed with dermatitis. *Contact Dermatitis* **83**, 182–188 (2020).
325. Ramirez, F., Chren, M. M. & Botto, N. A review of the impact of patch testing on quality of life in allergic contact dermatitis. *J. Am. Acad. Dermatol.* **76**, 1000–1004 (2017).
326. Bhatia, R., Sharma, V. K., Ramam, M., Sethuraman, G. & Yadav, C. P. Clinical profile and quality of life of patients with occupational contact dermatitis from New Delhi, India. *Contact Dermatitis* **73**, 172–181 (2015).
327. Nagpal, N., Gordon-Elliott, J. & Lipner, S. Comparison of quality of life and illness perception among patients with acne, eczema, and psoriasis. *Dermatol. Online J.* **25**, 13030/qt3fk3f989 (2019).
328. Kadyk, D. L., McCarter, K., Achen, F. & Belsito, D. V. Quality of life in patients with allergic contact dermatitis. *J. Am. Acad. Dermatol.* **49**, 1037–1048 (2003).
329. Anderson, R. T. & Rajagopalan, R. Effects of allergic dermatosis on health-related quality of life. *Curr. Allergy Asthma Rep.* **1**, 309–315 (2001).
330. Botto, N. et al. Validating a quality-of-life instrument for allergic contact dermatitis. *Dermatitis* **30**, 300–305 (2019).
This is the first quality of life instrument validated for use in allergic CD.
331. Raffi, J., Elaine Allen, I. & Botto, N. Validating responsiveness of a quality-of-life instrument for allergic contact dermatitis. *Dermatitis* **31**, 209–214 (2020).
332. Boehm, D. et al. Anxiety, depression and impaired health-related quality of life in patients with occupational hand eczema. *Contact Dermatitis* **67**, 184–192 (2012).
333. Rajagopalan, R. et al. An economic evaluation of patch testing in the diagnosis and management of allergic contact dermatitis. *Am. J. Contact Dermatitis* **9**, 149–154 (1998).
334. Thomson, K. F., Wilkinson, S. M., Sommer, S. & Pollock, B. Eczema: quality of life by body site and the effect of patch testing. *Br. J. Dermatol.* **146**, 627–630 (2002).
335. Woo, P. N., Hay, I. C. & Ormerod, A. D. An audit of the value of patch testing and its effect on quality of life. *Contact Dermatitis.***48**, 244–247 (2003).
336. Korkmaz, P. & Boyvat, A. Effect of patch testing on the course of allergic contact dermatitis and prognostic factors that influence outcomes. *Dermatitis* **30**, 135–141 (2019).
337. De Groot, A. C. New contact allergens: 2008 to 2015. *Dermatitis* **26**, 199–215 (2015).
338. Wilkinson, M. et al. The European baseline series and recommended additions: 2019. *Contact Dermatitis* **80**, 1–4 (2019).
339. Uter, W., Lessmann, H., Geier, J. & Schnuch, A. Is the irritant benzalkonium chloride a contact allergen? A contribution to the ongoing debate from a clinical perspective. *Contact Dermatitis* **58**, 359–363 (2008).
340. Basketter, D. A., Marriott, M., Gilmour, N. J. & White, I. R. Strong irritants masquerading as skin allergens: The case of benzalkonium chloride. *Contact Dermatitis* **50**, 213–217 (2004).
341. Schnuch, A., Lessmann, H., Geier, J. & Uter, W. Is cocamidopropyl betaine a contact allergen? Analysis of network data and short review of the literature. *Contact Dermatitis* **64**, 203–211 (2011).
342. Rietschel R. L., Fowler J. F. & Fisher A. A. in *Contact Dermatitis* 7th edn Ch. "Rubber" (eds Fowler, J. F. & Zirwas, M. J.) (Contact Dermatitis Institute, 2019).
343. Geier, J., Uter, W., Pirker, C. & Frosch, P. J. Patch testing with the irritant sodium lauryl sulfate (SLS) is useful in interpreting weak reactions to contact allergens as allergic or irritant. *Contact Dermatitis* **48**, 99–107 (2003).
344. Löffler, H., Becker, D., Brasch, J. & Geier, J. Simultaneous sodium lauryl sulphate testing improves the diagnostic validity of allergic patch tests. Results from a prospective multicentre study of the German Contact Dermatitis Research Group (Deutsche Kontaktallergie-Gruppe, DKG). *Br. J. Dermatol.* **152**, 709–719 (2005).
345. Goh, C. L., Wong, W. K. & Ng, S. K. Comparison between 1-day and 2-day occlusion times in patch testing. *Contact Dermatitis.***31**, 48–50 (1994).
346. Rudzki, E., Zakrzewski, Z., Prokopczyk, G. & Kozłowska, A. Patch tests with potassium dichromate removed after 24 and 48 hours. *Contact Dermatitis* **2**, 309–310 (1976).
347. Brasch, J. et al. Reproducibility of patch tests. A multicenter study of synchronous left-versus right-sided patch tests by the German Contact Dermatitis Research Group. *J. Am. Acad. Dermatol.* **31**, 584–591 (1994).

348. Machácková, J. & Seda, O. Reproducibility of patch tests. *J. Am. Acad. Dermatol.* **25**, 732–733 (1991).
349. Ale, S. I. & Maibach, H. I. 24-Hour versus 48-hour occlusion in patch testing. *Exog. Dermatol.* **2**, 270–276 (2003).
350. Higgins, C. L., Palmer, A. M., Cahill, J. L. & Nixon, R. L. Occupational skin disease among Australian healthcare workers: a retrospective analysis from an occupational dermatology clinic, 1993-2014. *Contact Dermatitis* **75**, 213–222 (2016).
351. Halbert, A. R., Gebauer, K. A. & Wall, L. M. Prognosis of occupational chromate dermatitis. *Contact Dermatitis* **27**, 214–219 (1992).
352. Nichol, K., Copes, R., Kersey, K., Eriksson, J. & Holness, D. L. Screening for hand dermatitis in healthcare workers: comparing workplace screening with dermatologist photo screening. *Contact Dermatitis* **80**, 374–381 (2019).
353. Fisker, M. H., Ebbehøj, N. E., Jungersted, J. M. & Agner, T. What do patients with occupational hand eczema know about skin care? *Contact Dermatitis* **69**, 93–98 (2013).
354. Graversgaard, C., Agner, T., Jemec, G. B. E., Thomsen, S. F. & Ibler, K. S. A long-term follow-up study of the Hand Eczema Trial (HET): a randomized clinical trial of a secondary preventive programme introduced to Danish healthcare workers. *Contact Dermatitis* **78**, 329–334 (2018).
355. Clemmensen, K. K. B., Randbøll, I., Ryborg, M. F., Ebbehøj, N. E. & Agner, T. Evidence-based training as primary prevention of hand eczema in a population of hospital cleaning workers. *Contact Dermatitis* **72**, 47–54 (2015).
356. Olesen, C. M., Agner, T., Ebbehøj, N. E. & Carøe, T. K. Factors influencing prognosis for occupational hand eczema: new trends. *Br. J. Dermatol.* **181**, 1280–1286 (2019).
357. Keegel, T. et al. Incidence and prevalence rates for occupational contact dermatitis in an Australian suburban area. *Contact Dermatitis* **52**, 254–259 (2005).
358. Nurmohamed, S., Bodley, T., Thompson, A. & Holness, D. L. Health care utilization characteristics in patch test patients. *Dermatitis* **25**, 268–272 (2014).
359. Koppes, S. A. et al. Current knowledge on biomarkers for contact sensitization and allergic contact dermatitis. *Contact Dermatitis* **77**, 1–16 (2017).
360. Wei, Z. et al. Two-dimensional cellular and three-dimensional bio-printed skin models to screen topical-use compounds for irritation potential. *Front. Bioeng. Biotechnol.* **8**, 109 (2020).
361. Malmberg, P., Guttenberg, T., Ericson, M. & Hagvall, L. Imaging mass spectrometry for novel insights into contact allergy - a proof-of-concept study on nickel. *Contact Dermatitis* **78**, 109–116 (2018).
362. Hamilton, J. D., Ungar, B. & Guttman-Yassky, E. Drug evaluation review: dupilumab in atopic dermatitis. *Immunotherapy* **7**, 1043–1058 (2015).
363. Machler, B. C. et al. Dupilumab use in allergic contact dermatitis. *J. Am. Acad. Dermatol.* **80**, 280–281.e281 (2019).
364. Maloney, N. J. et al. Dupilumab in dermatology: potential for uses beyond atopic dermatitis. *J. Drugs Dermatol.* **18**, S1545961619P1053X (2019).
365. Puza, C. J. & Atwater, A. R. Positive patch test reaction in a patient taking dupilumab. *Dermatitis* **29**, 89–89 (2018).
366. Ruge, I. F., Skov, L., Zachariae, C. & Thyssen, J. P. Dupilumab treatment in two patients with severe allergic contact dermatitis caused by sesquiterpene lactones. *Contact Dermatitis* **83**, 137–139 (2020).
367. Joshi, S. R. & Khan, D. A. Effective use of dupilumab in managing systemic allergic contact dermatitis. *Dermatitis* **29**, 282–284 (2018).
368. Goldminz, A. M. & Scheinman, P. L. A case series of dupilumab-treated allergic contact dermatitis patients. *Dermatol. Ther.* **31**, 8–10 (2018).
369. Raffi, J. The impact of dupilumab on patch testing and the prevalence of comorbid allergic contact dermatitis in recalcitrant atopic dermatitis: a retrospective chart review. *J. Am. Acad. Dermatol.* **82**, 132–138 (2020).
370. Tuckermann, J. P. et al. Macrophages and neutrophils are the targets for immune suppression by glucocorticoids in contact allergy. *J. Clin. Invest.* **117**, 1381–1390 (2007).
371. Suwanpradid, J. et al. Arginase1 deficiency in monocytes/macrophages upregulates inducible nitric oxide synthase to promote cutaneous contact hypersensitivity. *J. Immunol.* **199**, 1827–1834 (2017).
372. Smith, J. S., Rajagopal, S. & Atwater, A. R. Chemokine signaling in allergic contact dermatitis: toward targeted therapies. *Dermatitis* **29**, 179–186 (2018).
For many years, allergen avoidance, topical corticosteroids, phototherapy and traditional, systemic immunosuppressants have been the mainstay for the treatment of CD; targeted therapies represent a new and exciting approach to benefit patients with recalcitrant disease.
373. Alonso, M. D. et al. Occupational protein contact dermatitis from lettuce. *Contact Dermatitis* **29**, 109–110 (1993).
374. Hafner, J., Riess, C. E. & Wüthrich, B. Protein contact dermatitis from paprika and curry in a cook. *Contact Dermatitis* **26**, 51–52 (1992).
375. Iliev, D. & Wüthrich, B. Occupational protein contact dermatitis with type I allergy to different kinds of meat and vegetables. *Int. Arch. Occup. Env. Health* **71**, 289–292 (1998).
376. Kumar, A. & Freeman, S. Protein contact dermatitis in food workers. Case report of a meat sorter and summary of seven other cases. *Australas. J. Dermatol.* **40**, 138–140 (1999).
377. Laurière, M. et al. Hydrolysed wheat proteins present in cosmetics can induce immediate hypersensitivities. *Contact Dermatitis.***54**, 283–289 (2006).
378. Crippa, M., Sala, E. & Alessio, L. Occupational protein contact dermatitis from milk proteins. *Contact Dermatitis* **51**, 42 (2004).
379. Doyen, V. et al. Protein contact dermatitis and food allergy to mare milk. *Ann. Allergy Asthma Immunol.* **110**, 390–391 (2013).
380. Kanerva, L., Vanhanen, M. & Tupasela, O. Occupational contact urticaria from cellulase enzyme. *Contact Dermatitis* **38**, 176–177 (1998).
381. Nettis, E., Colanardi, M. C. & Ferrannini, A. Type I latex allergy in health care workers with latex-induced contact urticaria syndrome: a follow-up study. *Allergy* **59**, 718–723 (2004).
382. Crisi, G. & Belsito, D. V. Contact urticaria from latex in a patient with immediate hypersensitivity to banana, avocado and peach. *Contact Dermatitis* **28**, 247–248 (1993).
383. Uter, W., Gefeller, O., Mahler, V. & Geier, J. Trends and current spectrum of contact allergy in Central Europe: results of the information network of departments of dermatology (IVDK) 2007-2018. *Br. J. Dermatol.* **183**, 857–865 (2020).
384. Tagka, A. et al. Prevalence of contact dermatitis in the Greek population: a retrospective observational study. *Contact Dermatitis* **81**, 460–462 (2019).
385. Ochi, H., Cheng, S. W., Leow, Y. H. & Goon, A. T. Contact allergy trends in Singapore - a retrospective study of patch test data from 2009 to 2013. *Contact Dermatitis* **76**, 49–50 (2017).
386. Süβ, H. et al. Contact urticaria: frequency, elicitors and cofactors in three cohorts (Information Network of Departments of Dermatology; Network of Anaphylaxis; and Department of Dermatology, University Hospital Erlangen, Germany). *Contact Dermatitis* **81**, 341–353 (2019).
387. Amaro, C. & Goossens, A. Immunological occupational contact urticaria and contact dermatitis from proteins: a review. *Contact Dermatitis* **58**, 67–75 (2008).
388. Saluja, S. S., Davis, C. L., Chong, T. A. & Powell, D. L. Contact urticaria to nickel: a series of 11 patients who were prick test positive and patch test negative to nickel sulfate 2.5% and 5.0. *Dermatitis* **27**, 282–287 (2016).
389. Verhulst, L. & Goossens, A. Cosmetic components causing contact urticaria: a review and update. *Contact Dermatitis* **75**, 333–344 (2016).
390. Bhatia, R., Alikhan, A. & Maibach, H. I. Contact urticaria: present scenario. *Indian J. Dermatol.* **54**, 264–268 (2009).

Author contributions

Introduction (A.M.G.); Epidemiology (K.D. and R.L.N.); Mechanisms/pathophysiology (M.V. and J.M.); Diagnosis, screening and prevention (J.P.T. and J.D.J.); Management (P.L.S.); Quality of life (N.C.B.); Outlook (K.D. and R.L.N.); Overview of Primer (A.M.G.).

Competing interests

P.L.S. is a member of the American Academy of Dermatology and the American Contact Dermatitis Society and has held leadership and committee positions for both of these organizations. P.L.S. is a consultant for Ella-Ola brands. N.C.B. is a member of the American Academy of Dermatology and the American Contact Dermatitis Society and has held leadership and committee positions for both of these organizations. A.M.G. is a member of the American Academy of Dermatology and the American Contact Dermatitis Society and has held leadership and/or committee positions for both of these organizations. A.M.G. is an investigator with research grants from Regeneron and The Human Skin Disease Research Center. A.M.G.'s spouse owns stock in Johnson and Johnson. All other authors declare no competing interests.

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Supplementary information

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