



Contact Dermatitis: Classifications and Management

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Abstract

Contact dermatitis (CD) is a common inflammatory skin disease caused by exposure to contact allergens and irritants. It is also the most common reason of occupational dermatitis and contributes greatly to hand dermatitis and facial dermatitis. Besides the two major forms of contact dermatitis: allergic contact dermatitis and irritant contact dermatitis, other subtypes of CD have been recognized including immediate skin reactions, photoinduced contact dermatitis, systemic contact dermatitis, and non-eczematous contact dermatitis. CD is a great imitator which can mimic many kinds of skin diseases, such as atopic dermatitis, lichen planus, and angioedema. For the diagnosis of CD, a complete medical history, including occupational history, is very important. It can give a clue of CD and provide a list of suspected substances. Besides the well-known diagnostic test, patch testing, there are many other diagnostic tests can be used to help diagnosis of CD and identify the causative allergens, including photopatch test, skin tests for detecting of immediate contact reactions, serum allergen-specific IgE test, and qualitative and quantitative testing of allergen in the suspected materials patients exposed to and challenge test. Before the treatment, the suspected irritants or allergens should be avoided completely. This includes both the removal of the patient from the environment that contains those substances and the promotion of the metabolism and expulsion of the allergens that have been absorbed by the body. In addition, it is also important to restore the skin barrier and reduce skin inflammation through multiple treatments, such as emollients, topical corticosteroids, and antihistamines, as well as systemic corticosteroids and immunosuppressants. Early and appropriate treatments are important to prevent further deterioration and persistence of the skin condition.

Keywords Allergic contact dermatitis (ACD) · Atopic dermatitis · Irritant contact dermatitis (ICD) · Contact dermatitis (CD) · Subtypes · Systemic contact dermatitis (SCD) · Patch test · Management

Introduction

Contact dermatitis (CD) is an inflammatory skin disease caused by chemicals or metal ions that exert irritant (toxic) effects or by small reactive chemicals (contact allergens) that modify proteins and induce immune responses (predominantly by T-cell response) [1]. It is characterized by erythema, edema, oozing, crusting, vesicles, and intense pruritus [2]. There are different types of contact dermatitis known: allergic contact dermatitis (ACD), irritant contact dermatitis (ICD), immediate skin reactions, photoinduced contact dermatitis, systemic contact dermatitis (SCD), and non-eczematous contact dermatitis. CD can occur in any age, gender, and ethnic group. However,

there is wide variation in the prevalence of CD at a global level. A nationwide, cross-sectional study in Japan collected information on 67,448 cases from 170 clinics, and it revealed that around 3.92% (2643/67,448) outpatients and inpatients were affected by CD and the age distribution was somewhat evenly dispersed [3]. In China, CD was the tenth common skin disease in children aged 0–7 years and its prevalence was 0.5% (100/20,033) [4]. According to a survey carried out in 5 different European countries, CD was the third common skin disease in Europe, and the lifetime prevalence of CD in the general European population is 15% with a peak in the group of subjects aged 35–50 years. Moreover, women were more at risk of CD than men [5]. On the other hand, contact allergy is also a common condition in the general population. A meta-analysis including 28 studies has confirmed that at least 20% of general population is contact-allergic to common allergens, such as nickel, fragrances, and cobalt [6]. Compared with the prevalence of contact allergy, the relatively low prevalence of

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CD may be attributed to the low proportion of hospital visits for skin conditions and the misdiagnosis of CD as other skin diseases, such as atopic dermatitis (AD), lichen planus, or angioedema. The commonest mistake made by clinicians with regard to contact allergy is failing to consider the diagnosis. Although many cases of contact allergy arise from direct contact of the skin by the causative allergen and produce dermatitis at specific sites, there are many other different and subtle ways in which contact allergy can present such as airborne contact dermatitis or cannibal dermatitis. Without an awareness of these different manifestations, many cases of contact allergy will be missed or misdiagnosed [7]. The long-lasting contact of allergen may lead to a chronic course of CD with features of other skin diseases, which increases the difficulty of diagnosis. Moreover, CD could also significantly impair the quality of life in patients, cause productivity loss, and increase societal costs [8]. Therefore, this article reviewed the inducing factors, clinical manifestations, diagnosis, and treatment of different types of contact dermatitis.

Classifications of Contact Dermatitis

Besides the two major subtypes of contact dermatitis, ACD and ICD, other subtypes of CD have been also recognized based on the different causes and distinct clinical features including immediate skin reactions, which can be further classified as immunological contact urticaria (ICU), non-immunological contact urticaria (NICU), and protein contact dermatitis; photoinduced contact dermatitis, which can be also classified into phototoxic contact dermatitis (PTCD) and photoallergic contact dermatitis (PACD); SCD; and non-eczematous contact dermatitis, which includes many different manifestations such as erythema multiforme-like contact dermatitis and lichen planus-like contact dermatitis. Table 1 displays the core features and different treatment strategies for each subtype.

Based on the course of the inflammatory response of the skin and the duration of irritation, contact dermatitis can be also classified as acute, subacute, and chronic courses. Chronic ACD can mimic AD, and it needs to be differentiated from AD [9]. In addition, contact dermatitis is the common cause of dermatitis with special locations, such as hand dermatitis and facial dermatitis.

Mechanisms of Contact Dermatitis

Depending on the pathophysiology, contact dermatitis is caused by an allergic reaction after specifically recognizing an allergen or direct damage to the skin (non-allergic reaction).

The allergic reaction is an adaptive immune response toward allergens penetrating the skin. Most allergens are low

molecular weight chemicals, and some proteins can also act as allergens. The chemicals (haptens) have to bind to host proteins (carrier) to become full antigens. The whole allergic reaction progresses in two phases. During the initial sensitization phase, allergens are recognized and processed by dermal dendritic cells, and they are presented to T cells and B cells. Naive T cells clonally expand and become effector T cells (type IV hypersensitivity reaction). B cells produce allergen-specific IgE, which binds to the IgE receptors on the mast cells and basophils (type I hypersensitivity reaction). During the elicitation and effector phase, effector T cells can rapidly be activated by re-exposure to the sensitized allergen and a lot of cytokines are released by T cells. Then, some inflammatory cells are attracted, such as granulocytes and macrophages (type IV hypersensitivity reaction). The same allergens bind to receptor-bound specific IgE, and the cross-linking of two adjacent receptors on the mast cells and basophil cell membrane initiates the release of histamine, proteases, heparin, prostaglandin D₂, and platelet-activating factor. This is known as degranulation (type I hypersensitivity reaction). Finally, these inflammatory cells and mediators cause the clinical manifestations of contact dermatitis [10]. Among the subtypes of CD, the mechanisms of ACD, ICU, PACD, SCD, and non-eczematous contact dermatitis involve type IV or type I hypersensitivity reactions. Type II or type III hypersensitivity might be also involved in the development of CD since bullous reaction and purpura can be also seen.

In contrast to allergic reactions, direct damage to the skin is mainly mediated by innate immunity without the specific recognition of a foreign substance. Multiple pathways are considered to be involved, including skin barrier disruption, epidermal cellular damage, and the activation of innate immunity. For example, repeated washing of the hands removes the lipids from the stratum corneum, which increases transepidermal water loss and leads to skin barrier dysfunction, followed by dryness and fissure of the skin. Among the subtypes of CD, ICD, PTCD, NICU, and non-eczematous contact dermatitis are non-allergic skin reactions.

Clinical Features of Contact Dermatitis

The clinical features of CD vary depending on the irritants or allergens exposed, the duration of exposure, and the host's susceptibility. In general, the clinical findings of acute stage include erythema, papules, swelling, vesicles, and blisters. In the subacute and chronic stages, lichenification, fissuring, and scaling can be observed. In most cases, the lesions are localized to the site of contact, while patchy or diffuse lesions can also occur. In addition, there are some variants of contact dermatitis with atypical clinical features, such

Table 1 Core features and treatment strategies for subtypes of contact dermatitis

Subtypes	Core features	Further classifications	Treatment strategies
Allergic contact dermatitis	- Caused by allergic individuals repeatedly contacting sensitized allergens - Usually occurs at the contact site		- Identification of the causative allergens primarily topical or, if necessary, systemic corticosteroids
Irritant contact dermatitis	- The clinical characteristics are polymorphous - Erythema, scaling, edema, vesiculation, and erosions in acute cases - Erythema, lichenification, hyperkeratosis, and fissures in chronic cases	- Chemical burns - Irritant reactions - Acute irritant dermatitis - Late-onset acute irritant dermatitis - Subjective reaction - Cumulative irritant contact dermatitis - Traumatic irritant dermatitis - Abscess and acne-like dermatitis - Frictional dermatitis	- The treatment goal is to restore normal epidermal barrier function - TCSs are frequently used, but their efficacy has been controversial - Systemic corticosteroids, although potentially helpful in reducing acute inflammation, are not useful in the treatment of chronic irritant contact dermatitis
Immediate skin reactions	- Usually starts within 30–60 min following skin exposure and clears completely within 24 h	- Contact urticaria, including immunological contact urticaria (ICU) and non-immunological contact urticaria (NICU) - Protein contact dermatitis	- Antihistamines may reduce ICU; NSAIDs have been reported to reduce or prevent NICU - High-potency TCSs and topical tacrolimus may accelerate the healing process
Photocontact dermatitis	- Phototoxic contact dermatitis presents as minor symptoms (skin pricking/burning or minor sunburn) or typically as phytophotodermatitis, acute exaggerated sunburn, eventually with bullae, as photoonycholysis, or other less frequent patterns - The main presentation of photoallergic contact dermatitis is an acute or subacute eczema or, in severe cases, erythema multiforme-like lesions	- Phototoxic contact dermatitis (PTCD) - Photoallergic contact dermatitis (PACD)	- Avoid sunscreen and use sunscreen clothing instead - TCS is the first line of treatment, but TCIs are also available - Antihistamines and moisturizing are the basis of symptomatic treatment - Systemic corticosteroids and other immunosuppressants may be used in severe or refractory cases - Photosensitivity may be reduced by oral administration of hydroxychloroquine sulfate and beta-carotene
Systemic contact dermatitis	- The clinical features include flare-up of previous dermatitis or previously positive patch test sites, vesicular palmar and/or plantar dermatitis, flexural dermatitis, and the baboon syndrome or SDRIFE		- For most people with systemic contact dermatitis, the rash resolves spontaneously if they avoid re-exposure to allergens in various ways
Non-eczematous contact dermatitis	- The exact mechanisms of these eruptions are unknown - The cause can be confirmed by simple patch testing	- Erythema multiforme-like eruption - Pigmented purpuric eruption - Lichen planus-like eruption - Bullous eruption - Papular and nodular eruption - Granulomatous eruption - Pustular eruption - Scleroderma-like eruption - Pigmented contact dermatitis - Lymphomatoid contact dermatitis - Vascular-occlusive contact dermatitis	- Timely and thorough removal of allergens can reduce the severity of skin lesions in the early stage effectively

TCS topical corticosteroids, TCI topical calcineurin inhibitor, NSAID non-steroidal anti-inflammatory drug, SDRIFE symmetrical drug-related intertriginous and flexural exanthema.

as targeted erythema, purplish papules, and plaques and hyperpigmentation.

Allergic Contact Dermatitis

ACD, also called allergic eczematous contact dermatitis, dermatitis venenata, contact eczema, and industrial dermatitis, is a type IV allergic eczematous skin reaction caused by allergic individuals repeatedly contacting sensitized allergens [10].

It usually occurs at the contact site and is generally manifested as eczematous lesions. Mild ACD is shown as light erythema and slight edema, and papules ranging from the tip of a needle to the size of a rice grain can appear on the surface. The skin lesions of severe ACD include obvious erythema and swelling with dense papules, vesicles, and even bullae [11]. Erosions, oozing, and crusting can also develop. Pustules can be seen if secondary infection occurs. ACD at loose tissue sites, such as eyelids, lips, and genitals, can appear as diffuse swelling with unclear boundaries and loss of skin texture. For example, the clinical manifestation of ACD due to hair dye contact allergy is diffuse swelling of the eyelid and face, which closely resembles angioedema [12].

ACD generally occurs at the same site where the allergen contacts the skin (Fig. 1). Hand movements such as scratching may bring allergens to other sites; for example, nail polish can cause eyelid dermatitis [13]. After systemic absorption of the allergen, rashes may also appear on the distant parts of the body. Subjective symptoms are generally itching, but there can also be a sense of burning or pain. A few patients can also have a pale complexion, fever, nausea, and other systemic symptoms. Acute ACD usually recovers within a few days after the removal of allergens. However, if there is continuous exposure to the allergens, repeated episodes of skin lesions will turn into chronic hypertrophic lesions [10] and some may mimic AD [9]. In addition to eczematous reactions, ACD can also manifest itself as erythema multiforme, lichen planus, eruptive rashes, and pigment changes which are categorized as non-eczematous reactions (see below) [14].

Contact allergens can be found in many substances, such as dyes (Figs. 2 and 3), oils, resins, coal tar derivatives, and compounds used in textiles, rubber, cosmetics, and insecticides; products, tissues, and body fluids of animals, bacteria, parasites, and insects; and certain plants and medicine (Figs. 4, 5, 6, and 7) [15]. Surgical implants are a new source of allergens [16]. Many medical specialties need implanted devices to treat different diseases, such as orthopedics, cardiovascular, dentistry, and gynecology. However, some common surgical implants contain many metals with immunological activity, including orthopedic prostheses, plates, pins, nails, bolts, screws, fixators, cardiac/intravascular

devices, dental implants and restorations, and Essure contraceptive device. Released metal ions are processed by the immune system and elicit an immune reaction against the implanted metal alloy. Nickel, cobalt, and chromium remain the most common metals in implant failure due to metal sensitization.

ACD to food is relatively rare [17]. Direct exposure to fruits, vegetables, and spices is the most common cause of ACD in response to food. Oleoresins in fruits and vegetables are the most frequent allergens causing ACD, with urushiol being the responsible allergen. Well known in the USA as an allergen in poison oak and poison ivy, it is also contained in mango sap, fruit skin, and leaf or the stem of the mango tree. Exposure to urushiol from mango most frequently leads to dermatitis of the perioral region. Urushiol is also contained in the seed of the female ginkgo tree, where it may cause perioral and perianal dermatitis upon ingestion. Food industry workers are at high risk of developing ACD. The most common foods causing ACD in cooks, caterers, chefs, and produce workers are spices, such as garlic, paprika, clove, Jamaica pepper, cinnamon, nutmeg, and ginger. Other common causes are bay laurel leaf and vanilla. Twenty out of approximately 60 spices and their essential oils can cause ACD [17, 18].

Airborne dermatitis is contact dermatitis caused by airborne substances, such as plants, pollen, perfumes, fragrance in cosmetics, formaldehyde, or isothiazolinones in water-based paints. It may be allergic or irritant. The clinical features are acute or chronic eczematous lesions of the uncovered skin.

Connubial contact dermatitis refers to contact dermatitis caused by exposure to contact allergens or irritants through connubial contact. It is not rare. Reactions related to close contact or sexual activity has been reported including poison ivy dermatitis, cosmetic dermatitis, contact urticaria, or even anaphylactoid reactions.

Irritant Contact Dermatitis

ICD, also known as cutaneous irritation, is an inflammatory skin response caused by external substances through non-immune mechanisms. It is the most common type of contact dermatitis and is considered a complex biological syndrome with different pathophysiological conditions, natural histories, and clinical manifestations. ICD is a complex reaction modulated by both intrinsic (genetic) and extrinsic (environmental) factors, both of which are important in the pathogenesis of ICD, especially of hand dermatitis. Age, sex, body region, and the presence of atopy affect the susceptibility to ICD. Furthermore, the nature of the irritant, amount of exposure, concentration, duration, repetition, and the presence of overlaying environmental and mechanical factors should be considered in the evaluation of ICD as it is not evident



Fig. 1 Allergic contact dermatitis of the child's palms caused by color clay

whether endogenous or exogenous factors make a stronger contribution to the development of ICD [19]. ICD has wide morphological changes, mainly manifested as skin erythema, edema, desquamation and keratinocyte vesiculation in the acute phase, and skin cracks, lichens, and hyperkeratosis in



Fig. 2 Allergic contact dermatitis of the scalp caused by hair dye



Fig. 3 Allergic contact dermatitis of the right upper arm caused by tattoo dyes

the chronic phase. Because these changes are non-specific, ICD is often difficult to distinguish from ACD and endogenous dermatitis. In addition, the clinical manifestations of ICD vary depending on the endogenous and exogenous factors that act on the skin [20, 21]. Table 2 shows the clinical classification of ICD [22].

Humans are exposed to many irritants in work and daily life. These irritants can be divided into physical factors (such as friction, oppression, stab wound, and dust), chemical factors (such as soap, detergent, acid, alkali, metal working fluid, organic solvents, petroleum products, oxidant, reductant, water, NaCl, and ethanol), and biological factors (such as part of the plant and animal products) [21, 22].

Chemical Burns

Chemical burns are serious skin lesions caused by substances, such as strong acids and alkalis [23]. Within a few minutes, painful erythema appears in the contact area of the skin, which then quickly leads to blisters and necrosis. Sometimes wheals occur. Pain is obvious. Cement, amine hardener, and other solid chronic irritation can also cause necrotizing damage [24]. The features of skin lesions are



Fig. 4 Allergic contact dermatitis of the left knee caused by Chinese traditional medicine plasters

distinctive in appearance and cannot be explained by common skin diseases. Caustic and calcareous burns are common in strong alkali burns, which can be very deep. Strong acid can make tissues solidify, form eschars, and can prevent deep tissue erosion [25]. The color of the eschars is diagnostic. For example, yellow scabs are nitric acid burns, black or brown black scabs are sulfuric acid burns, and white or gray yellow scabs are hydrochloric acid or carbonic acid burns. Organophosphorus can ignite spontaneously and causes

severe skin burns. Inhalation of burning smoke (phosphorus pentoxide powder) can cause pulmonary edema. The absorption of inorganic phosphorus from the wound surface can cause serious liver and kidney toxicity [26].

Irritant Reactions

An irritant reaction is a mild skin lesion that has not yet reached the dermatitis level. The lesions are singly manifested and are characterized by one or more of the following: (1) dryness and scaliness; (2) redness, at first red spots around hair follicles, later developing into erythema; (3) blisters; (4) pustules. This reaction is often induced by mild irritants, including water and its additives, such as salt, calcium chloride, and magnesium ion. Soap; detergents; surfactants; industrial lubricants; ammonia; ethanol; dimethyl sulfoxide; hydrogen peroxide; certain plants, such as garlic, onion, and pineapple; and animal body fluids can also cause this reaction [19]. The lesions are usually asymptomatic or accompanied by mild discomfort. This reaction is thought to be a prelude to dermatitis and is more common in people who have been repeatedly exposed to these substances. For example, hairdressers who often contact with water and detergent can have dryness, dandruffs, and chapped skin damage on the back of the hand. This disease has a good prognosis. Patients can be cured by discontinuing exposure to these substances and appropriate use of skin cream [27]. But some people develop irritant dermatitis with repeated and persistent irritation, and it is not clear how irritant reactions develop into dermatitis.

Acute Irritant Dermatitis

Acute irritant dermatitis refers to the acute skin damage caused by sufficient amounts and strong enough irritants which almost anyone with exposure can develop. The clinical manifestations vary greatly and are indistinguishable from ACD, and often misdiagnosed [20]. Diffuse dry

Fig. 5 Allergic contact dermatitis of the right knee and right wrist caused by flurbiprofen cataplasms





Fig. 6 Allergic contact dermatitis of the left upper arm and left underarm caused by iodophor



Fig. 7 Allergic contact dermatitis of the lower limbs caused by Chinese traditional medicine–medicated bath

erythema and desquamation are specific to acute irritant dermatitis, but edema, vesicles, and bullae can be also significant (Fig. 8) [19, 20]. After removal of the contact agent, acute irritant dermatitis tends to disappear quickly, but can also persist for several months in some cases. Common irritants include acid, alkali, ammonia, arsenic, calcium silicate, cement, cleaning agent, epoxy resin, formalin, croton oil, sawdust, silver, kerosene, dimethyl sulfoxide, capsaicin, lactic acid, nickel sulfate, potassium dichromate, paper, anthralin, retinoic acid, adhesive tapes, and nappies. Airborne irritation dermatitis can be induced by dust and steam, such as limestone dust [28–31]. There is a burning sensation on the skin and a slight itch. Certain chemicals can cause inflammation after 8 to 24 h of contact, which is called as delayed acute irritant dermatitis [32], making it more difficult to be distinguished from ACD, but patch test with the suspected agents is negative.

Chronic Irritant Contact Dermatitis

Chronic irritant contact dermatitis, also called cumulative irritant dermatitis, refers to chronic, eczematous lesions lasting for more than 6 weeks. Weeks or months

of exposure to water, detergent, chemical solvents, irritant food, and other known mild and moderate irritants is the main cause. It is more common on the hands. The rash appears as dry, scaly erythema and chapped skin, generally without blisters [33]. Patch test may be positive because it often coexists with contact allergy. People who are susceptible to this disease include butchers, cleaners, cooks, builders, dentists, fishermen, barbers, repairmen, horticulturists, nurses, and printers [34]. The common substances that cause chronic irritant contact dermatitis are soap, detergent, industrial cleaning agent, glue, paint, juice, plant juice, oxidizing and reducing agents, animal body fluids (tissues), insecticide, pesticide, cement, limestone, wood preservative, formalin, bleach, acid, and alkali [19, 33].

Subjective Reaction

Pain, itching, or burning sensation is caused by skin contact with certain substances, but no skin lesions or only fine scales are seen. The mechanism is unknown. It is common in women and mostly caused by cosmetics [35, 36].

Table 2 Clinical classification of ICD

Types	Onset	Clinical characteristic
Chemical burns	Emergency (usually single exposure) exposure to acid, alkaline, or caustic agents	Painful necrosis
Irritant reactions	Repeated exposure to water or solvent	Mild dryness, scaling or redness, no symptomatic, easily controlled by discontinuing exposure and skin cream
Acute irritant dermatitis	Emergency (usually single exposure), minutes or hours after exposure	Diffuse dry erythema and desquamation on exposed area or similar as ACD, with pain or burning sensation and itch
Late-onset acute irritant dermatitis	Late onset, 8–24 h or longer after exposure	Same as acute irritant dermatitis
Chronic irritant contact dermatitis	Slow onset, weeks to months after exposure	Chronic eczema with dry, scaly erythema and chapped skin, generally without blisters lasting for more than 6 weeks
Subjective reaction	Emergency, minutes after exposure	Burning or itching sensation without any lesions
Traumatic irritant dermatitis	Slow onset, weeks to months	Discoïd eczema-like
Abscess and acne-like dermatitis	Slow onset, weeks to months	Follicular papules or pustules
Frictional dermatitis	Slow onset	Chronic eczema
Others, such as alopecia areata, granuloma	Slow onset	Similar as the disease that is mimicked

Other Types

In addition to the above common types of skin damage caused by skin irritation, there are other types of irritation, such as follicular inflammatory eruptions, acne-like eruptions, miliary papule-like eruptions, alopecia areata, granuloma, and pigment changes.

The irritation potential of many chemicals is related to their dose, relative molecular weight, ionization, polarization, and lipid solubility. Usually there is a threshold concentration; however, the effective dose of irritant in skin tissue depends on the concentration, capacity, and duration of the irritant acting on the skin [22]. Different irritants, concentrations, and durations of exposition or AD criteria may have yielded different results [37]. Prolonged and high concentration exposure may lead to enhanced skin irritation [38]. Intermittent exposure to irritants produces a weaker irritating response to the skin than continuous exposure. Additive and synergistic effects may occur in skin irritation responses to simultaneous or continuous exposure to multiple irritants [39, 40]. On the other hand, simultaneous or continuous exposure to multiple irritants may also result in a reduced skin irritation response. For example, the cationic surfactant benzalkonium chloride inhibited the skin irritation of the anionic surfactant sodium dodecyl sulfonate (SDS) [41]. Since the result of skin irritation caused by simultaneous or continuous exposure to multiple irritants is difficult to predict, the mechanism of interaction between irritants needs further study. The irritation effect of the irritants increases with the decrease of environmental humidity, so in windy, dry winter, the irritation ability of the irritants increases and different irritation syndromes, such as pruritus and erythema

accompanied by wheals and desquamation, can occur. In addition, the irritants may have a stronger irritating effect at high temperatures [42]. Therefore, changing the temperature may be one of the important methods of preventing ICD. Common irritants include animal products, cosmetics, degreasing agents, detergents, dusts, foods, friction, low humidity, metalworking fluids, solvents, tear gases, topical medications, water, and wet work [19]. Table 3 provides the common causes of ICD based on region of involvement [19, 43].

It is generally believed that children under 8 years of age are more likely to develop skin irritation than adults. This may be related to immature skin structure and function, although some other factors may also play a role. Due to the



Fig. 8 Irritant contact dermatitis of the left foot caused by salicylic acid and phenol patch

Table 3 Common causes of ICD based on region of involvement

Region involved	Common causes
Diffuse or generalized	Clothing containing wool, burlap, polyester, or nylon
Eyelids	Propylene glycol, sunscreen and eye formulations
Face and other exposed areas	Compositae plant family, volatile substance (e.g., ammonia, formalin, natural resin, insecticides, and pesticides), powder (e.g., metallic oxide, cement, and cleaning agent), and particle (e.g., sawdust, wool, plastic, mineral particles)
Forehead	Topical medicine, cosmetics, and excessive face washing
Perioral dermatitis or contact cheilitis	Frequent licking, dry environments, chewing gum, contact with some foods, such as carrot, spinach, and citrus fruits
Neck	Violin players (fiddlers' neck)
Vulva	Feminine hygiene products and topical medicine
Buttocks	Prolonged contact with wet bathing suits (bikini bottom)
Nails	Organic solvents, weed killers, insecticides, and traumatic causes
Hands	Detergents, solvents, wet work, and friction (e.g., housewife, medical and dental workers, service workers)
Thighs	Toilet seat dermatitis due to lacquer or paint covering the seat or strong detergents used to clean the seat
Diaper area	Prolonged contact with urine or feces or both; contact with residual antiseptics, soaps, and detergents in diapers; and friction
Perineal	Prolonged contact with urine and feces for patients with incontinence
Feet	Excessive sweating, shoes and socks
Axillae	Shaving and use of depilatories

physiologic and pathophysiological differences in the skin of different ethnicities, the study of the influence of race on the occurrence of ICD has become an important issue in the field of dermatotoxicology. However, recent studies using objective bioengineering techniques have found that there is no statistically significant difference in ICD susceptibility between blacks and Caucasians, and there may be no fundamental difference in ICD susceptibility between Asians and Caucasians [44]. It is generally believed that women are more prone to skin irritation than men, but this difference may be due to different exposure [45]. It is believed that atopic diathesis is a risk factor for ICD [46].

Immediate Skin Reactions

Immediate skin reactions, including contact urticaria (CU) and protein contact dermatitis, are common in dermatological practice but may often be overlooked. In Finland, CU and protein contact dermatitis constituted 11% of all recognized cases of occupational skin diseases [47].

They usually start within 30–60 min following skin exposure and clear completely within 24 h; however, delayed-onset reactions may appear within 4–6 h. Inflammatory responses include wheal, flare, and temporary eczematoid erythema, which can be itching, tingling, or burning [48]. These reactions can be induced by non-immunological mechanism or type I immediate allergy. Milder reaction is mostly caused by cosmetics, fruits, or vegetables. Strong allergens may cause systemic reactions or death, such as

bronchial asthma, rhinoconjunctivitis, and gastrointestinal symptoms.

Contact Urticaria

CU was first described by Fisher. It is a rare skin manifestation with a frequency of <0.4% [49]. Clinically, CU is characterized by a typical triple response with wheal, flare, and itching on the skin at the site of contact to the eliciting agent. The lesion appears within 30 min after the exposure and disappears completely within hours (not over 24 h) without residual signs and symptoms. The triple response precipitates alone or together with an immediately induced erythema, which can also result if the exposure to the antigen persists. According to the underlying mechanism, CU is classified as NICU, ICU, and mixed/undetermined CU [50].

The pathogenesis of NICU is not clearly understood. It is mainly elicited by low molecular weight agents, such as cinnamal, sorbic acid, benzoic acid aldehyde, ammonium persulfate, and nicotinic acid esters. NICU does not involve immunological processes and does not require previous sensitization. For example, dimethyl sulfoxide (DMSO) can both damage blood vessels, making them leaky, and cause mast cell degranulation [1, 50–52].

ICU is a type I hypersensitivity reaction, mediated by allergen-specific IgE in a previously sensitized individual. It is mainly induced by proteins, which can be divided into four groups: group 1, plant-derived proteins (e.g., fruits, vegetables, spices, plants, and woods); group 2, animal-derived

proteins (e.g., epithelia, meat, various body fluids, dairy products, and seafood); group 3, grains (e.g., wheat, barley, oat, and cornstarch); and group 4, enzymes (e.g., α -amylase, glucoamylase, cellulase, xylanase, and proteases). Some chemicals can also cause ICU, such as preservatives (e.g., triclosan, 2-phenoxyethanol, formaldehyde), drugs (e.g., β -lactam antibiotics), metals (e.g., aluminum, chromium, cobalt, iridium salts, nickel, rhodium, platinum salt), and industrial chemicals (e.g., chloramine, isocyanates, methacrylates, persulfates). Allergens penetrate the epidermis and bind to IgE on mast cells. Then, mast cell degranulation and the release of histamine and other substances are induced. Other mediators may also be involved, such as prostaglandins, leukotrienes, and kinins [1, 50–52].

The clinical manifestation of NICU is restricted to the skin area in contact with the eliciting substance, while the urticaria of ICU may be limited to the contact areas, but sites other than the contact site may be affected. If systemic symptoms develop, such as wheezing, runny nose, watery eyes, lip swelling, hoarseness, difficulty in swallowing or nausea, vomiting, diarrhea, and cramps, contact urticaria syndrome (CUS), a subtype of ICU, should be considered and anaphylaxis may occur [50].

For the treatment of NICU, non-steroidal anti-inflammatory drugs (NSAIDs), such as oral or topical indomethacin and aspirin, can inhibit immediate contact reactions for more than 4 days, but the mechanism is unknown [43]. For the management of ICU, antihistamines are used for mild reactions, and if necessary, adrenaline is needed for those with life-threatening reactions [50]. Table 4 shows the differences between ICU and NICU.

Protein Contact Dermatitis

Protein contact dermatitis was first described in 1976 by Hjorth and Roed-Petersen. It describes a condition of some food handlers with hand and forearm eczema after contacting proteinaceous material [53]. The exact pathophysiological mechanism is still unclear. This reaction is mainly

considered a type I immediate hypersensitivity reaction caused by high molecular weight proteins penetrating into the skin. Some authors also think that protein contact dermatitis is induced by combined type I and type IV hypersensitivity reactions [54].

The most frequent clinical presentation of protein contact dermatitis is a chronic or recurrent eczema. The symptoms usually affect the hands, wrists, and forearms, and these areas are typically diffusely involved. Sometimes, only the fingertips are involved. In exceptional cases, the lesion can also appear on the face and belly, due to indirect contact with allergen [55, 56]. Among food handlers, chronic paronychia is not uncommon, with the proximal nail fold demonstrating severe swelling and itching. This pattern has also been recently described as occurring with latex allergy. Vesicular, urticarial, or edematous papules and plaques may occur within a few minutes after contact with the causative allergen. Pruritus, burning, stinging, and pain are not uncommon. Extracutaneous reactions, including angioedema, gastrointestinal symptoms, rhinoconjunctivitis, and bronchial asthma, may accompany the skin reactions if the allergen is ingested [54].

The diagnostic criteria of protein contact dermatitis include (i) a chronic recurrent dermatitis caused by contact with proteinaceous material, (ii) an acute urticarial or vesicular eruption occurring minutes after contact with the causative protein, (iii) immediate skin tests with suspected agents are usually positive, and (iv) patch tests with those are often negative [57].

Protein contact dermatitis plays an important role in occupational dermatology. Classically, the protein sources are divided into four main groups: group 1, fruits, vegetables, spices, plants, and woods; group 2, animal proteins; group 3, grains; and group 4, enzymes [58]. Other causes of protein contact dermatitis include latex, hydrolyzed protein hair mask, and cornstarch glove powder. Therefore, a wide variety of jobs can be affected, such as bakers, chefs, cooks, farmers, butchers, veterinarians, gardeners, and millers.

Table 4 Differences between ICU and NICU

	ICU	NICU
Predisposed population	People with atopic diathesis	Almost all exposed persons
Prior sensitization	Yes	No
Common causes	Proteins, chemicals	Chemicals
Pathogenesis	Type I hypersensitivity reaction	Unclear
Mediator	Histamine, prostaglandins, leukotrienes	Prostaglandins
The extant of lesions	Localized urticaria or generalized urticaria	Localized urticaria
Elicitation time	10–20 min	< 45 min
Systemic symptoms	Sometimes	No
Inhibitors	Antihistamines, adrenaline (necessary)	NSAIDs
Diagnosis	Skin prick test, specific IgE assay	Use test

NSAID non-steroidal anti-inflammatory drug

The clinical differential diagnosis of protein contact dermatitis includes ACD, CU, AD, and ICD (Table 5). In distinguishing protein contact dermatitis from other types of hand eczema, it is important to ask whether patients have associated immediate symptoms, such as burning, stinging, or itching. Of course, patients with protein contact dermatitis may have more than one condition, and preexisting irritant dermatitis or AD may be common [54].

As with other forms of allergic reactions, avoidance of the particular allergen is the first step and topical drugs, such as high-potency topical corticosteroids and topical tacrolimus, may decrease inflammation and accelerate the healing process [54].

Photocontact Dermatitis

Photocontact dermatitis (PCD) refers to skin inflammatory reaction caused by skin contact with photosensitive materials and sunlight (ultraviolet) or artificial light. The reaction can also be caused by systemic absorption of a compound followed by irradiation. PCD can be divided into two different types according to different pathogenesis. The reaction caused by non-immune mechanism is called phototoxic contact dermatitis (PTCD), while the reaction caused by immune mechanism is called photoallergic contact dermatitis (PACD), both of which are photosensitive. The source of photosensitive reaction is predominantly long-wave ultraviolet A (UVA) (320–400 nm) and may partially be medium-wave ultraviolet B (UVB) (290–320 nm) or visible light [59].

At present, there is no exact epidemiological data on the incidence of photoinduced contact dermatitis, which is often established based on the results of the photopatch test (PPT) in patients with photosensitive skin diseases. A retrospective chart review of all patients who underwent photopatch testing at Toronto Western Hospital between January 2001 and December 2010 showed that fifty-four patients (33.8%) had at least one photoallergic reaction [60]. In a study from

Athens, photocontact reactions were identified in 28/207 (13.52%) patients [61]. Gao et al. evaluated the results of PPT in 4957 Chinese patients, and a total of 3472 PACD reactions in 2454 subjects (49.5%) were recorded [62]. However, Bryden et al. conducted a trial on 1155 patients with suspected PCD at 17 centers across the UK, Ireland, and the Netherlands; 51 patients had photoallergy (PA) (4.4%), and 15 patients had combined PA and contact allergy (1.3%) [63]. Due to the influence of geographical location (sunshine), living habits, and labor production, the types and numbers of photopathogenic substances in different countries are not exactly the same, so there is no uniform catalogue of photopathogenic substances across the world [64]. The USA, Canada, Europe, and other countries have all established different catalogues of standard photopatch allergens, and the Chinese Center for Disease Control and Prevention has also established China's own standard catalogue by referring to foreign photopatch allergen series. The above data demonstrate that the incidence of PCD has a wide range of fluctuations, which may be closely related to the patient's skin type, geographical location, light intensity, standard catalogue range, and prevalence of the photopatch test [59].

The rash of PCD is mainly distributed in the light-exposed areas, such as the face, ears, the v-shaped area of the front of the neck, nape, below the cuffs of the two upper limbs, or the extensor side of the legs and feet. There is no lesion in non-light-exposed areas, such as behind the ear, over the eyebrow arch, in the nasolabial groove, and the sub-chin area, which can be distinguished from airborne contact dermatitis. Photoallergic rashes can expand, but most are confined to the exposed area. A clear line may appear between the exposed and non-exposed parts (e.g., at the textile boundary) [53, 60]. Rashes are sometimes asymmetrical due to uneven distribution of photosensitive material on the skin surface or asymmetric exposure. For example, if the driver is often irradiated on one side of his body, generally there is no skin lesion in the counterpart. However, there may not be skin

Table 5 Comparison of cutaneous allergic contact reactions

	Protein contact dermatitis	Allergic contact dermatitis	Contact urticaria
Clinical features	Eczematous dermatitis; sometimes accompanied by an initial wheal reaction	Eczematous dermatitis	Wheal and flare reaction
Pathogenesis	Type I hypersensitivity reaction mediated by allergen-specific IgE, with or without type IV hypersensitivity reaction	Type IV hypersensitivity reaction	ICU, type I hypersensitivity reaction mediated by allergen-specific IgE NICU, non-immunologic immediate reaction
Allergen size	High molecular weight	Low molecular weight	Low molecular weight or high molecular weight
Prick test	Positive	Negative	Positive
Scratch test	Positive	Negative	Positive
Specific IgE	Sometimes positive	Negative	Sometimes positive
Patch test	Negative or rarely positive	Positive	Negative

lesions in all the exposed parts, and the specific incidence depends on the distribution of photosensitive substances. If a photosensitive substance is present in shaving cream, skin damage occurs only in the shaving area, and photosensitivity may not be easily noted without attention [53].

PTCD

Phototoxic contact dermatitis patients exposed to phototoxic substances and irradiation of a moderate amount of ultraviolet light develop phototoxicity within a few hours of onset with clinical manifestations similar to severe sunburn. Anyone can develop phototoxicity if the light energy is strong enough and sufficient amounts of phototoxic substances are present on the skin surface. The appearance of rash is mainly erythema and often desquamation and pigmentation. Bullae can occur on the basis of erythema in severe cases. Phototoxic reactions induced by internal administration of phototoxic substances are not uncommon [43, 59]. Calka et al. reported a mother and her adult son, in whom phototoxic reaction developed on the sun-exposed body areas after ingestion of the plant of the Chenopodiaceae family [65]. A 53-year-old woman was seen with a phototoxic, edematous, erythematous eruption 3 days after commencing a celery soup diet (three bowls daily). The rash usually subsides spontaneously once exposure to photosensitizers or ultraviolet rays discontinued, leaving behind diffuse pigmentation after the dermatitis is healed [66]. The action spectrum of phototoxic contact dermatitis compounds is usually 280–430 nm, and certain dyes can also be found in the visible light region. Some common phototoxic reactions are given in Table 6 [43, 67–70].

PACD

PACD is less common than PTCD. It is more common in adult males due to their greater exposure to sunlight and light allergens. The clinical manifestations of PACD are the same as those of ACD. The rash may present as swollen erythema, wheals, pinhead-sized dense papules, blisters, and, in severe cases, exudation. But most skin lesions are eczematous, and chronic lichenification can occur [71]. The rash can spread to the covered area and even develop into erythroderma. Most patients feel itchy or burning pain. The onset was independent of age, skin color, or race. PACD has a long course and no systemic symptoms. Usually, patients can recover gradually after 2 weeks away from exposure to photosensitizers. Generally, there is no pigmentation after healing. The rash may recur after restoration of exposure to photosensitizers and UV rays. Individual patients continue to develop the disease and gradually evolve into a “continuous photosensitive response” with skin lesions that still do not heal even after the removal of exposure to allergens, but this mechanism is unknown. PACD should be distinguished from phototoxic reaction. The key points of identification are shown in the Table 7. The most valuable identification methods are patch test and photopatch test, and the photopatch test result of photoallergy is positive. The photopatch test result is positive in patients with PACD. Because some photoallergens are also phototoxic substances, and some phototoxic substances are also photoallergens, such as tar, it is often difficult to distinguish between them [72].

A variety of phototoxic substances and contact photoallergens have been found. The important agents inducing phototoxic reactions include psoralen, 5-methoxypsoralen

Table 6 Common phototoxic contact dermatitis

PTCD	Alternative name	Clinical features	Causes	Light source
Phytophototoxic contact dermatitis	Dermatitis bullosa striata pratensis	Sunburn-like lesions on light-exposed area, linear erythema, vesicles, bullae followed with pigmentation	Direct contact with psoralen-containing plants, such as angelica, celery, lemon, and carrot	UVA
Berloque dermatitis	Perfume dermatitis	Erythema appears in areas on which perfume is applied, such as the sides of the neck, behind the ears, the face, the breast, and the shoulders; after these areas are exposed to light, pigmentation is left behind. Pigmentation can last for months	Menthol or 5-methoxypsoralen	UVA
Tar “Smart”		Workers engaged in tar work and is associated with UVA exposure in summer. A burning or stinging sensation occurs at the exposed site. Erythema and pigmentation are common	Coal tar or its derivatives, such as creosote	UVA
Photoonycholysis		Onycholysis	Phototoxic drugs, such as tetracycline or psoralen	Sunlight or ultraviolet light

Table 7 Differences between phototoxic and photoallergic contact dermatitis

Feature	Phototoxic	Photoallergic
Incidence	High	Low
Occurrence on first exposure	Yes	No
Onset after ultraviolet exposure	Minutes to days	Usually 24–48 h (6–72 h)
Chemical	Important	Not crucial
Radiation	Important	Not crucial
Site	Confine to exposed areas	Extensible
Cross-reaction	No	Yes
Clinical morphologic appearance	Sunburned-like reaction (erythematous and bullous, hyperpigmentation)	Eczematous
Pigmentation after healing	Common	Rare
Action spectrum	Absorption spectrum	Longer than the absorption spectrum
Required concentration and amount of illumination	High	Low
Minimal erythema dose	Reduced	Normal or reduced
Histology	Necrotic keratinocytes	Spongiotic dermatitis
Diagnosis	Clinical history and physical	Photopatch testing

(bergapten), 8-methoxypsoralen, and angelicin. They are found in many plants, such as parsley, celery, citrus, fennel, wild carrot, parsnip, figs, sweet citron, lemon, and rue. The most common causes of photoallergic dermatitis are sunscreens and topical medications, such as benzophenone-3 and para-aminobenzoic acid. Table 8 provides the common agents inducing phototoxic and photoallergic reactions [43, 71, 72].

Systemic Contact Dermatitis

SCD may occur when a person is re-exposed to the same sensitized contact allergen through oral administration, intramuscular injection, intravenous infusion, inhalation, or absorption through the skin or mucosa (Fig. 9). In the general population of Denmark and Germany, 15.2 to 25% of the population are sensitized to one or more haptens from the European standard screening series [73, 74]. Although there is no data on the sensitization of the general population in China, the positive rate of patch test can reach 40 to 80% in patients with dermatitis and eczema. Many of these allergens may re-enter the body through systemic pathways and activate the immune system, so theoretically the total number of individuals at risk for SCD is large [75].

The first to describe the appearance of SCD was British dermatologist Thomas Bateman, who described a bright red form of eczema caused by mercury exposure that was very similar to what we today call “baboon syndrome” [76]. In 1925, Schittenhelm and Stockinger carried out nickel sulfate patch tests among workers with nickel allergy and found that dermatitis was present in areas with previous nickel exposure, although no further nickel exposure was observed. This condition cannot be explained by classical contact dermatitis

mechanisms [77]. In the 1950s, Calnan [78] and Marcussen [79] found that many patients with nickel allergy developed eczema in areas without definite contact with nickel, especially folds of the skin and hands. They used the term “secondary rash” to describe this phenomenon and speculated that the blood spread of nickel was the cause of the rash. Wilson reported that five nurses who were allergic to streptomycin developed eczema and urticaria during subcutaneous streptomycin desensitization therapy. Patch test with 0.1% streptomycin solution was positive [80]. Since then, SCD has been reported in the literature, mostly caused by drugs, and Fisher once named it “systemic eczematous contact drug eruption” [81].

SCD has a variety of manifestations, with some relatively specific skin manifestations suggesting the possibility of SCD. For example, after systematic exposure to a substance, the recurrence of dermatitis at the site of previous contact or the site of positive patch test should be highly suspected as SCD. This is common in drug-induced SCD and is also common in some experimental oral challenge trials [75, 82].

Pruritic vesicular eczema of the hands (pompholyx), also a common form of SCD, usually manifests itself as deep blisters on the palm, lateral margins of the fingers and palm, or perinail. If the skin around the fingernail is involved, the nail deck may also appear as transverse grooves. Chronic eczema occurs when a blister rash recurs, but clusters of blisters can still be seen around the chronic lesions. SCD may sometimes present as recurrent dermatitis of the elbow or flexion of the knee, which is difficult to distinguish from AD [83].

Baboon syndrome is a relatively rare but distinctive SCD characterized by bright red to mauve-red rashes with a V-shaped distribution on the buttocks and inner thighs. This is common in mercury-induced SCD, sometimes

Table 8 Agents commonly inducing phototoxic and photoallergic reactions

Agents	Product
Phototoxic agents	
Plants	Cow parsley, celery, citrus, fennel, carrot, parsnip, fig, sweet citron, lemon, bergamot, lime, bitter orange, common rue, dill, wild chervil, mustard, burning bush, buttercup
Fragrance materials	
Coal tar derivative	Pitch Acridine Coal tar Anthracene Creosote
Drugs	8-Methoxypsoralen 4,5,8-Trimethylpsoralen Chloroquine Thiazole diuretics Tetracycline drugs Sulfonamides Phenothiazines Griseofulvin Colchicine Fluoroquinolones Amiodarone
Dyes	Eosin Peruvian balsam Halogenated salicylanilides Methylene blue Disperse blue 35
Photoallergic agents	
Sunscreens	p-Aminobenzoic acid (PABA) Benzophenones Salicylates Octocrylene Cinnamates
Fragrance materials	Cinnamic aldehyde Lavender Musk ambrette
Dyes	Para-phenylene diamine
Drugs	Benzocaine Chlorpromazine Promethazine NSAIDs (ketoprofen, piroxicam, etofenamate) Sulfanilamides Quinidine sulfate
Others	Olaquinox Thimerosal Pesticides

accompanied by systemic pustular eruptions. Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), emerging as a clinical manifestation similar to the baboon syndrome, is thought as the manifestation of drug-induced SCD. Unlike other types of drug eruptions that are more common in women, SDRIFE is more common in men and has a shorter incubation period ranging from hours to 2 days [82]. SDRIFE usually does not involve mucous membrane, and the face and metatarsalis are rarely involved. Like other mild drug eruptions, the rash heals

within 3 weeks after withdrawal. SDRIFE is most often induced by β -lactam antibiotics such as amoxicillin. Other drugs reported in the literature include roxithromycin, terbinafine, fluconazole, valacyclovir, oxycodone, and TNF inhibitors [84].

SCD may also present as non-specific, generalized maculae and maculopapules and can develop into erythroderma in severe cases. Other rare and special skin manifestations include urticaria rash, generalized eruptive pustular rash, erythema multiforme-like rash, purpura, and vasculitis rash.

Fig. 9 Systemic contact dermatitis of the flexion parts caused by oral administration of Chinese traditional medicine



SCD sometimes presents with extracutaneous systemic symptoms, such as headache, fever, fatigue, weakness, and gastrointestinal and respiratory symptoms. Oral haptens have been reported to cause nausea, vomiting, and diarrhea in patients sensitive to neomycin and chromite and, in some cases, joint pain. Patients who are sensitive to gold will develop low fever when gold preparation is used in the system. Leukocytosis and fever may occur in patients with mercury-induced SCD [75].

Common causes of SCD include drugs, metals, plants, and food, as well as in vivo implants. Most SCD is caused by drugs, which is common in the early stage of antibiotic discovery and use. At that time, antibiotics such as streptomycin and penicillin would be used both locally and systematically. When some individuals become sensitized with topical drugs through the skin, systematic use of antibiotics may induce SCD. External use medicine directly administered on the skin is the most common skin sensitization path, although some other sensitization paths are easy to be ignored, such as drug leakage to the epidermis during intravenous drug use, occupational exposure, eye drops coming into contact with the skin, anal suppositories, bladder medication, medication inside ear, intraperitoneal injection, or surgical wound medicine. All of these paths may cause sensitization.

Many drugs can induce SCD as reported in the literature, including acetyl salicylic acid, 5-aminosalicylic acid, butyl hydroxyanisole (BHA), butylated hydroxytoluene, codeine, diclofenac, erythromycin, 8-methoxypsoralen, nystatin, penicillin, phenobarbital, pseudoephedrine, resorcinol, double sulfur shimron, vitamin C, vitamin B6, neomycin, budesonide, and hydroxyl Lamictal [85]. A 50-year-old male developed erythematous rash on buttocks, anogenital area, and arms after the application of 5-aminosalicylic acid foam to treat hemorrhoids. He tested positive in the patch test to the foam at 10% concentration in petrolatum, and his rash resolved with discontinuation of this drug [86]. A 39-year-old female who was breastfeeding developed rash on her breast, left arm, chest, neck, and cheek after contact with bufexamac topically that she was applying to her infant child due to eczema. The patient tested positive in the patch test to bufexamac [87].

Drug-induced SCD is usually manifested as a recurrence of dermatitis at the site of previous contact with the allergic site or the site of positive patch test and is rarely manifested as SDRIFE, which is often induced by semi-synthetic penicillin [75].

Industrial production and modern lifestyles have led to a significant increase in skin exposure to various metals, as well as a significant increase in the incidence of metal allergies. A variety of metals have been found to cause SCD, and nickel is the most reported metal. Nickel exposure allergy has a 19% prevalence rate in the population [88].

Calnan [78] and Marcussen [79] classified nickel dermatitis as primary and secondary: primary skin rash refers to the rash that occurs at the site of initial contact sensitization and is triggered by direct skin contact with nickel; secondary rash refers to symmetrical, generalized rashes away from the direct contact site, with blisters of hand eczema, limb bending eczema, and eyelid eczema. SCD can be induced by oral challenge test in patients with nickel allergy. The most common manifestations are eczema of the hands and dermatitis at the site of previous contact, but also generalized dermatitis involving the buttocks, perineum, and flexion of the limbs and eyelids. There is a significant dose–response relationship between nickel intake and skin reaction, which rarely occurs when nickel intake is lower than 0.5 mg, while SCD occurs in most patients with nickel allergy when it is higher than 5.6 mg. We eat about 150 to 500 µg of nickel per day. Therefore, food does not induce SCD in most cases. However, many factors can affect the absorption of nickel in food, such as alcohol consumption, allergies, and medications taken at the same time. Some studies have found that the severity of eczema in patients with nickel allergy is improved when they are given a low-nickel diet. In addition, it has also been reported that SCD is induced by nickel release through stainless steel intravenous infusion needle, dialysis equipment, implant prosthesis, and intraoral orthotics.

Other metals that can cause SCD include cobalt, chromium, mercury, gold, and zinc. Patients with cobalt allergy who underwent oral challenge tests presented with recurrent rashes at the site of previous contact dermatitis and vesicular hand eczema. In patients with chromium allergy, dietary supplementation with chromium trivalent pyridinate

or chromium divalent chloride may induce SCD, presenting with recurrent dermatitis and recurrent blister eczema of the hands. Inhalation of mercury vapor from damaged thermometers is the most common route of mercury-induced SCD exposure, most presenting as diffuse bright red maculopapules (baboon syndrome) distributed on the croup and buttocks, and some as an acute generalized eruptive pustule-like rash [75]. Aside from its use in jewelry, gold can be ingested via medications and has been used in dentistry materials [89]. A 76-year-old female with history of earlobe swelling with gold earrings developed a pruritic generalized vesicular eruption associated with discomfort and low body temperature. The patient was patch test positive to gold sodium thiosulfate on day 3 (3+ positive). The patient had been ingesting a homeopathic medication named Aurocard®, which contained gold. Upon stopping the medication, her eczema cleared within 4 weeks and the patient remained asymptomatic 5 months later [90]. In a 52-year-old female with a history of delayed positive patch test to gold, an intramuscular introduction of gold as therapy for rheumatoid arthritis led to reactivation of her previously positive patch test [91]. The intravenous administration of gold salts may induce extensive dermatitis in patients with gold allergy. Contact dermatitis caused by zinc is not common, but there are still some reports of SCD caused by zinc in oral fillings, manifested as facial erythema edema, generalized papules, or edematous papules [92].

In plants and foods, Compositae are often used as herbal and pharmaceutical therapeutics, while Compositae extracts are also added to a variety of cosmetics, personal hygiene products (such as shampoos and soaps), and foods. Sesquiterpene lactones are the main allergens in Compositae and can cause ACD and SCD [93]. It has been reported that drinking chamomile tea induces SCD, in which a very small amount of sesquiterpene lactone can induce systemic allergic reaction.

Peruvian balsam is a common dietary cause for inducing SCD, and SCD is likely to occur in patients who are positive for the Peruvian balsam patch test when they ingest foods supplemented with Peruvian balsam [94]. Sorbic acid, a food additive, is one of the main allergens of perioral contact dermatitis caused by toothpaste. It has been reported that sorbic acid in processed foods can induce SCD, presenting as vesicular eczema [75]. Table 9 shows the reported causative agents of SCD including foods, metals, and drugs [89, 95, 96].

In vivo implant is a new cause of SCD. The increasing use in modern medicine of artificial joints, metal nails and plates for fracture treatment, pacemakers, metal stents, resin and metal dental prostheses, dentures, artificial heart valves, and hernia repair materials in the human body increases the risk of allergy to these materials and may cause SCD [16, 75]. Some scholars suggest that patients with suspected metal

Table 9 Reported causative agents of SCD

	Topical agents	Systemic agents
Foods, vegetables and plants	Aspartame	Balsam of Peru
	Balsam of Peru	Mango
	Compositae plants (chamomile, echinacea)	Garlic
	Garlic	Propylene glycol
	Propylene glycol	Propolis
Metals	Propolis	Sorbic acid
	Nickel	Sesquiterpene lactone
	Chromate	Nickel
	Cobalt	Chromate
	Gold	Cobalt
Medications	Mercury	Gold
	Zinc	Mercury
	Aminosalicylic acid	Amoxicillin
	Ampicillin	Cephalosporins
	Anesthetics (benzocaine, cinchocaine)	Corticosteroids
	Bufexamac	Erythromycin
	Diclofenac	Estrogen
	Hydroxyquinoline	Ethylenediamine
		Gentamicin
		Neomycin
		Nystatin

allergy should be evaluated by patch test before implantation of metal prosthesis.

SCD is easy to be misdiagnosed or missed due to its wide variety of manifestations, so it is necessary to ask the patient in detail about previous sensitization history and repeated local contact dermatitis history. For specific skin manifestations such as recurrent eczema-like dermatitis, recurrent blister hand eczema, and baboon syndrome, it is necessary to inquire in detail about substances that enter the body through various systematic ways and confirm it by patch test. For patients with recurrent generalized eczema with unknown causes, patch tests are routinely recommended to look for potential allergens. Oral challenge tests are the gold standard for the diagnosis of SCD, but they are difficult to operate in clinical practice and are more often used in research. The clinical manifestations of SCD are diverse and need to be distinguished from dermatitis and eczema diseases such as generalized eczema, pompholyx, and AD. Others also need to be differentiated from eruptive drug eruption, urticaria vasculitis, erythema multiforme, acute generalized eruptive pustulosis, and cutaneous small vasculitis [75].

Non-eczematous Contact Dermatitis

In addition to eczematous contact dermatitis, there are a variety of different types of manifestations commonly known as non-eczematous contact dermatitis. They play an important role in contact dermatitis. In the daily diagnosis and treatment process, the diagnosis of non-eczematous contact

dermatitis often needs to be assisted by a combination of the patient's detailed medical history and clinical examination technology, due to its atypical clinical manifestations.

Erythema Multiforme-like Contact Dermatitis

Erythema multiforme-like contact dermatitis usually occurs 1–14 days after the occurrence of contact dermatitis, with pruritus targeted erythema around the primary eczematous skin lesion or on the distant part of the skin, which lasts longer than the primary contact dermatitis. A case from Japan reported a wood-induced contact dermatitis with an erythema multiforme-like reaction. The patient was engaged in wood processing. The rash first appeared in his palms and spread throughout the body within 2 weeks, with fever, itching, and pain. A patch test was conducted using five kinds of wood commonly used in the patient's workplace. Large blisters were found 48 h after contact with santos rosewood, which showed positive reaction to wood. Topical clobetasol propionate ointment was applied for treatment, and the rash was relieved after daily shower to remove allergens [97]. Another study suggested that the occurrence of erythema multiforme-like contact dermatitis may be related to (R)-3,4-dimethoxydalbergione in *Machaerium scleroxylon* [98]. A study in Taiwan, China, reported a 22-year-old woman with extensive (hands, forearms, upper arms, and forehead) erythema multiforme-like lesions after local exposure to 1,2-ethanedithiol, a protective agent commonly used in chemical synthesis. The lesions were histologically consistent with erythema multiforme, and the patch test for 1,2-ethanedithiol was positive [99]. A report from Shandong, China, found that 8 patients with dimethyldithioester allergic contact dermatitis developed allergic contact dermatitis around 10 days after contact, of which 5 patients were complicated with epidermal necrolysis and 3 patients presented erythema multiforme-like contact dermatitis. Dimethyldithioester is an intermediate in the production of cimetidine. It is a hapten and a strong allergen with a strong sensitizing effect that can cause allergic contact dermatitis. Severe patients may present bullous epidermal necrolysis, accompanied by high fever, liver and kidney damage, and other symptoms. Dimethyldithioester mostly enters the body through the skin and mucosa, inducing allergic reaction. Individual patients have different degrees of reaction to dimethyldithioester sensitizer, thus showing different clinical manifestations [100].

Cobalt chloride is an allergen with a high allergy rate. It is mainly found in glass and porcelain pigments, alloys, dental fillings, metallic medical products, hair colorants, perspirants, and foam stabilizers for beer. It has been reported that it may cause erythema multiforme-like contact dermatitis and air-borne contact dermatitis [101].

Lichen Planus-like Contact Dermatitis

Lichen planus-like contact dermatitis is a contact-allergic reaction caused by a number of chemicals. Dark brown or purplish red papules or plaques with pruritus appear at the contact site. As a result of an allergic reaction, skin lesions may appear in the distant part of the contact site.

In stomatology, the main allergens of contact dermatitis are palladium, nickel, gold, and amalgam, and metal allergy is very common in patients with oral lichen planus-like lesions [102]. Allergy to metallic compounds in dental prostheses can cause lichen planus lesions in adjacent oral mucosa. In addition, a few cases of lichen planus contact dermatitis have been reported with manganese as a substitute for nickel in dental restorations [103]. Copper has also been reported to be associated with oral lichen planus. Unlike other common metals such as nickel and cobalt, copper has a low sensitization potential and rarely causes allergic contact dermatitis. Vergara et al. reported a case of lichen planus-like contact dermatitis associated with the presence of copper sulfate in dentures [104]. The presence of such positive results is generally considered to be irritating and non-specific and may be co-sensitized with other metals. It is recommended to include metal items in the evaluation of patients with stomatitis, especially those with dentures, to avoid delays in the diagnosis and treatment of such oral lesions. Allergies to acrylates are most common in the beauty and nail industry, where acrylates are found mainly in perfumes and rubber products [105]. Carr et al. reported a case of lichen planus-like contact dermatitis on the nails caused by acrylic salts [106]. The patient had previously suffered from nail dystrophy. For cosmetic purposes, the patient applied nail polish to modify nails. During the treatment, the patient intermittently wore false nails to relieve embarrassment. The patch test showed a strong positive reaction (+++) to 2-hydroxyethyl methacrylate. The presence of 2-hydroxyethyl methacrylate in the prosthetic nails worn by the patient resulted in no relief of symptoms, which manifested as lichen planus changes in the nail. Acrylate allergy is occasionally seen in patients with oral lichen planus-like contact dermatitis. Acrylates are included in a variety of coatings, plastics, dentures, hearing aids, paints, joint replacement materials, glass substitutes, acrylic nails, inks, and adhesives. Acrylates do not polymerize enough, and the remaining monomers are released, which sensitizes and triggers rash formation. Quist et al. reported a special case of acrylate allergy [107]. The patient developed fistulas after fracture surgery, so the placement of g-PMMA beads, which are composed of multiple polymethyl methacrylate copolymers, caused lichen planus-like contact dermatitis. It is also not uncommon for foodborne allergens to cause widespread lichen planus-like contact dermatitis throughout the body, such as drinking water in nickel pipes, and

these potential sensitivities sometimes are difficult to avoid. In addition, drugs can also cause lichen planus-like contact dermatitis. Kuroda and Hisanaga reported a case of lichen planus-like rash caused by a chlorpheniramine maleate topical agent [108]. Patch test for each component showed only positive reaction to chlorpheniramine maleate. This is the first case of lichen planus-like contact dermatitis associated with chlorpheniramine maleate. Topical extrinsic chlorpheniramine maleate is widely used over the counter in Japan and may be a neglected allergen.

Lymphomatoid Contact Dermatitis

Lymphomatoid contact dermatitis (LCD) is a pseudolymphoma, a skin hypersensitivity syndrome with clinical and histopathological characteristics similar to those of mycosis fungoides (MF). LCD is a rare and possibly underreported disease. Allergens that can lead to LCD are various, such as rubber chemicals, dyes, metals, and preservatives. Etiologically, it is associated with several haptens, such as phosphorus sesquisulfide, gold, nickel, dimethyl fumarate, methyl isothiazolinone, and azo dyes. LCD was first described in 1976 by Orbaneja et al. [109]. Four patients developed lymphoma-like lesions after carrying matchboxes. Histopathological and clinical features suggested the infiltration stage of MF. After inquiring about the medical history, it was believed that after the matchbox had contacted the skin of the thigh, the lesions spread to other parts and caused the corresponding clinical manifestations. The patch test showed a strong positive for the burnt-out area of the matchbox, and the sensitizer was suspected to be phosphorus sesquisulfide in the matchbox. The patient avoided further contact and was cured. In 2014, Knackstedt and Zug reported 23 cases of LCD, with the most common sites being thighs, head and neck, buttocks, and groin [110]. In most cases, symptoms can be improved by avoiding exposure to allergens. In addition to T-cell LCD, B-cell LCD caused by methylisothiazolinone has been reported abroad [111]. A case of lymphoma-like skin lesion caused by manicure materials has been reported abroad [112]. The patient presented with recurrent asymptomatic papulosis in the upper eyelids. Immunohistochemistry showed CD30+ cell infiltration in the dermis, and the final diagnosis was consistent with type A lymphoma-like papulosis. Patch tests showed that the disease was related to methacrylic acid in the nail material. Gatica-Ortega et al. reported a case of LCD associated with limonene hydroperoxide, which is widely used in cosmetics, households, and health industries [113]. Uzunçakmak et al. reported a case of recurrent erythema and plaque in the glans penis, which was initially considered “CD8-positive

mycosis fungoides” and “primary cutaneous CD8-positive epidermal cytotoxic T-cell lymphoma.” The diagnosis was inclined to LCD based on the histopathological characteristics and clinical manifestations of the patient. The patch test showed positive results for nickel sulfate and disperse blue 106. Disperse blue 106 mainly exists in textile dyes, indicating that textile dyes may be one of the trigger factors for genital allergic contact dermatitis manifested by eczematous or non-eczematous lesions [114].

Granulomatous Contact Dermatitis

The first case of granulomatous contact dermatitis (GCD), associated with gold in earrings, was reported in 1983 [115]. Several other metals and their salts have subsequently been reported to cause granulomatous anaphylaxis involving various allergens, such as beryllium in mining, fluorescent tube production and beryllium alloy production, aluminum as adjuvant in vaccines, hypoallergenic extracts, antiperspirants and tattoos, mercury, chromium, and cobalt in tattoos as pigments. Also, nickel and palladium have been reported as the cause of a granulomatous reaction [116]. The clinical presentation of GCD is a rather hard red nodule, and it shows a granulomatous skin reaction with epithelioid histiocytes surrounded by a dense infiltrate of lymphocytes in the histopathological finding [116, 117]. In addition, nickel was reported to be the cause of the granulomatous reaction due to its presence in the nickel-containing sternotomy sutures. GCD caused by wearing nickel-containing earrings has also been reported. For puncture operation in vivo, inert metals should be selected to avoid allergic reactions. For such cases, removal of allergens and removal of granulomatous lesions are the most effective means of permanently resolving the problem, whereas local and intramural steroid injections provide only temporary relief. Zirconium salts are commonly found in deodorants for axillary odors. Allergic granuloma reactions can occur 4–6 weeks after exposure. The rash is localized at the site of contact. Histopathological changes with epithelioid cells are sometimes difficult to distinguish from sarcoid [100].

Moreover, as a rare complication of diaper dermatitis, granuloma gluteale infantum (GGI) presents as multiple, oval, red–purple-colored granulomatous nodules and plaques on the gluteal area. It is thought as an irritant dermatitis with unknown pathogenesis. Occlusion, topical halogen steroids, candidiasis, and urine or feces irritation have been considered the contributing factors [118]. Therefore, removal of the precipitating factors is the key aspect of the treatment, and prevention of secondary infection and recovery of skin barrier function should be attempted by using gentle antiseptic cleansers and barrier creams [119].

Other Forms of Contact Dermatitis

There are many kinds of contact dermatitis, but the classification is confusing. Some are classified according to the location of the disease, such as hand dermatitis and facial dermatitis; some are classified by pathogenic substances, such as ring dermatitis, cosmetic dermatitis, and lacquer dermatitis; some classifications are divided by the pathogenesis, such as irritant dermatitis, contact urticaria, and phototoxic dermatitis; and some classifications are based on pathogenic pathways, such as occupational contact dermatitis. The boundary between the diseases is not completely clear; for example, facial dermatitis is often caused by cosmetics but can also be caused by other allergens. Cosmetic dermatitis occurs mostly on the face but can also occur in the hands and armpits. The above classification may not be reasonable, but it has certain practical value in clinical practice. Several types of common contact dermatitis are reviewed below.

Airborne Contact Dermatitis

Airborne contact dermatitis (“ABCD”) is an inflammation of the skin caused by volatile chemicals such as droplets, dust, or fibers [31].

Clinical manifestations can be divided into three categories: (1) airborne irritation dermatitis, which is irritant dermatitis caused by volatile chemicals or dust. It is more common in exposed areas of the skin, such as the face, eyelids, and upper limbs. This disease is the result of superimposed irritation of many physical and chemical factors. These factors include sunlight, wind, and excessively dry or humid air along with the effects of the substance itself. The substances causing the disease include: 1) volatile substances, such as acid, alkali, ammonia, cleaning agents, formalin, industrial solvents, carbon-free paper, epoxy resin; 2) powders, such as aluminum, metal oxide, detergent, cement, and anhydrous calcium silicate; and 3) particles, such as sawdust, wool, dry plastic, plant particles, and ore particles [43, 120]. (2) Airborne mechanical contact dermatitis, which is caused by the mechanical friction of fibrous substances such as fiberglass, asbestos, and grain particles. Chang et al. reported a typical case of fiberglass contact dermatitis [43]. And (3) airborne allergic contact dermatitis. Allergens can be in the form of dust, powder, pollen, sprays, or other volatile substances such as volatile oils from trees, fragrances, and medicines. Plant-derived allergens are the most common cause of airborne ACD worldwide. Classic airborne ACD occurs from the Compositae (Asteraceae) family of plants, which contains more than 32,000 species. The common Compositae plants in North America include absinthe, aster, arnica, artichoke, chamomile, chrysanthemum, etc.

Airborne ACD to Compositae can be caused by outdoor plants as well as edible Compositae plants; the latter include

absinthe, artichoke, cardoon, chamomile, chicory, dandelion, and lettuce [121].

Flares from Compositae exposure typically occur in spring and summer, although symptoms can persist year-round in severe cases. Airborne allergic contact dermatitis occurs when allergen particles suspended in the air deposit on the skin, such as eyelids, under the collar of the neck, below the cuff of the forearm, or the lower extremity. Such chronic patients should be distinguished from photosensitive dermatitis. A clinical clue that favors a diagnosis of airborne ACD is involvement of relatively light-protected areas (upper eyelids, submandibular area, post-auricular folds), which are typically spared in photodermatoses.

Oral Contact Dermatitis

Of all the tissues and organs, the lips and oral cavity probably receive the most irritation from various external substances every day because of food, beverage, medicine, and anything put into the mouth. Common irritants are foods, drugs, oral cleaning products, and dental materials. Some specific groups of patients are unknowingly experiencing sensitization. In the department of dermatology outpatient clinic, we often encounter oral contact dermatitis patients. For some patients, the cause of the disease can be quickly identified, and the symptoms can be improved after timely and appropriate treatment. However, it is also not uncommon to see cases of repeated incidence of the disease and delay in recovery.

Oral contact dermatitis can be divided into oral irritant contact dermatitis (OICD) and oral allergic contact dermatitis (OACD). Clinically, OICD is more common than OACD. Compared with the skin, oral mucosa needs a higher concentration of allergens to induce allergic reactions. The reason is related to the constant secretion of saliva and rich blood supply of buccal mucosa, which makes it easier to tolerate external irritants. The proteins contained in the cuticle are more likely to combine with some common compounds into allergens, so the red lip margin is more likely to have contact-allergic reaction than the oral mucosa. After the oral mucosa and lips are exposed to allergens at the same time, only cheilitis usually occurs, and the oral mucosa may not have the same reaction. On the contrary, if the mouth is sensitive, then the skin is likely to have similar symptoms, so the patient can be in the presence of contact stomatitis at the same time, accompanied by cheilitis and perioral dermatitis [122].

Common oral and lip irritants are mechanical factors. Improper installation of denture and irregular surface of dental filling are common in stomatology department. In dry autumn and winter, it is easy to cause cracks when the lip corner of patients is pulled by using disposable oristocopy. Players of musical instruments with more than 5 years of

playing experience and more than 10 h of practice per week are more likely to develop irritant contact cheilitis (ICC). Chemical irritation factors include excessive concentrations of some toothpastes, mouthwash detergents, and bleaches. During dental procedures, the oral cavity of the patient may accidentally come into contact with the etching agents of phosphoric acid, lactic acid, and citric acid, which are used to treat the dental surface, or improper operation may cause superficial mucosal irritation. For people with poor oral hygiene, the mucosa will be continuously irritated by the proliferation of bacteria on the surface due to long-term absence of denture cleaning [123]. Nicotine stomatitis also occurs in smokers. Frequent use of e-cigarettes by smokers can lead to inflammation in the corner of the lip [124, 125]. Finally, physical factors, such as overheated food and drinks, and excessively spicy seasonings, can also cause irritation.

Allergens of allergic contact stomatitis (ACS) and cheilitis are various, which can be divided into several types: (1) stomatological materials. The supporting materials of active denture include a kind of thermosetting base resin, which is still used in rural areas of China. Because there are different degrees of residual methyl methacrylate, ACS will occur in individual patients clinically. Latex, which is found in rubber gloves and some dental tools, and metallic fillers such as nickel, cobalt, platinum, and mercury are also common allergens [126]. (2) Oral cleansing products and medicines. Toothpaste, mouthwash detergents (sodium lauryl sulfate, etc.), antiseptic/antibacterial agents (sodium benzoate, methyl paraben, chlorhexidine, triclosan, etc.), flavoring agents (cinnamon oil, menthol/oil, etc.), and bleaching agents (silicon dioxide, pyrophosphate, etc.) may become allergens [127–129]. (3) Food and cosmetics. Allergen ingredients, such as spice blends, Peruvian balsam, gallic acid esters, and propolis, are found in many foods, condiments, and lipsticks [122]. In some cases, allergic contact cheilitis (ACC) can also occur in a few patients due to their contact with metal or wood of musical instruments [130].

The occurrence of irritant contact stomatitis (ICS) and ICC is related to the irritation, permeability, concentration, duration, frequency of exposure, and individual differences in the patient's inflammatory response. Subjective symptoms may be more obvious than objective signs. Patients may report taste loss, numbness, burning, and pain in the affected area, but itching is uncommon. The objective lesions of mucous membrane may result in only mild erythema, or obvious erythema, with or without edema. In the presence of obvious edema, the mucosa has a smooth, waxy, lustrous appearance. As the lips are often active, blisters, if present, often burst quickly and form erosion. Therefore, blisters of oral mucosa may not be seen in patients in outpatient department. For erosion in the buccal mucosa, consideration should be made to determine whether it is related to chewing irritating food [122].

OACD is mainly due to type I and type IV mediated hypersensitivity, and the latter is more common than the former. Type I allergy is mediated by IgE, which can cause blisters and ulcers in the mouth. Latex is one of the most common allergens in this type of reaction and is found mainly in gloves and tools used in stomatology. Oral metallic materials such as nickel, cobalt, and platinum can cause contact urticaria and respiratory reactions. Mouthwash containing chlorhexidine can induce severe local and systemic allergic reactions when applied directly to the oral mucosa. Although the severity of type I allergy is different from person to person, clinical doctors, especially dental doctors, should have this awareness and make emergency plans. People with pollen allergy should be aware that ingestion of unprocessed fruits, vegetables, and nuts can rapidly lead to IgE-mediated "oral allergy syndrome." This is due to exposure of oral mucosa and throat to allergen elements similar to pollen. The main symptoms are obvious pruritus or paresthesia in the mouth and throat, edema of mucous membrane, hoarseness, vomiting, diarrhea, and even coma in a few cases [131, 132].

Type IV allergy of clinical symptoms can either be limited or can be diffuse lesions, often involving the lips and the surrounding tissues. No matter what the cause is, it may be clinically manifested as erythema, dryness, desquamation, scab, edema, chapped skin, and angular cheilitis, which may be accompanied by obvious itching, pain, or burning sensation [133]. The mucous membrane may appear as edema, flushing and other mild abnormalities, and limited mild erythema. Some chronic lesions are characterized by white spots or lichen planus lesions, and the lingual papilla may disappear. Severe patients develop blisters, erosions, and ulcers. These objective manifestations and subjective feelings are often confusing in the process of diagnosis due to the lack of clinical specificity.

Erythroderma/Exfoliative Dermatitis

Exposure to trichloroethylene and bromomethane may cause exfoliative dermatitis, presenting as localized or diffuse erythema, with or without papules and blisters, followed by skin exfoliation, lasting several weeks. A middle-aged male patient suffered exfoliative dermatitis after applying realgar externally. Eating mango or contacting with home decoration materials can also induce exfoliative dermatitis. A 58-year-old female patient mistakenly applied body wash as body moisturizer and presented with a widespread exfoliative erythroderma-like eruption [134]. A 47-year-old male patient developed chills due to the eruption of white mercury vapor during the heating process of gold amalgam, followed by dizziness, chest tightness, shortness of breath, gingival swelling and pain, and erosion of oral mucosa. Symptoms improved after symptomatic treatment.

Exfoliative dermatitis occurred after re-exposure to large amounts of mercury vapor 1 month later. The urine mercury was 887 µg/g Cr. Mercuric toxic dermatitis is one of the common clinical manifestations of acute and subacute mercury poisoning. It is closely related to the form, route, exposure amount, and exposure time of mercury entering the body, but not all patients with mercury poisoning develop it. Urine mercury in this patient significantly exceeds the standard. The first contact with mercury vapor shows non-specific symptoms such as fatigue and chills, but the body is sensitized. After the second contact, a local violent inflammatory reaction occurs, which is consistent with the characteristics of allergic reaction. The rash occurs within 24 h of re-exposure to mercury. After discontinuing exposure to mercury, skin lesions are further developed, showing diversified and widespread manifestations, which are not restricted by toxic dose and have no obvious dose–effect relationship; therefore, it is consistent with the characteristics of allergic disease [135].

A 66-year-old man presented with erythroderma and patch tests showed an allergy to nickel. After examining his medical history, he recalled that 25 years ago, he had placed a resetting metal screw in his right elbow as a result of a car accident. The patient sought surgical removal of the screw from his elbow. After the screw's removal, a dimethylglyoxime test showed a pink color change on the cotton tip used to rub the metal, which indicated that nickel was leaking from the screw. His skin problem resolved completely within 2 to 3 months [136]. *Parthenium hysterophorus* is a member of the Compositae family, which was accidentally introduced to India in 1956 in a wheat shipment from the USA. Since then, it has spread all over the country and has become the commonest cause of plant dermatitis in India. Erythroderma is a rare manifestation of *Parthenium* dermatitis [137]. A 75-year-old male patient developed exfoliative dermatitis after aromatherapy with valiya narayana thailam — an ayurvedic oil [138].

Hand Dermatitis

With the progress of modern industrialization, new irritants and sensitizers appear constantly. As one of the most frequently exposed parts, the incidence of hand contact dermatitis has increased in recent years. The data indicate that hand contact dermatitis is the most common type of hand eczema and is also a common occupational skin disease. Hand dermatitis is a common condition with a lifetime prevalence of 20% [139]. Most hand dermatitis is the result of the accumulation of many factors with an etiology that is hard to determine, so the treatment is very difficult. The clinical manifestations of mild cases are pruritus, dryness, chapping, and desquamate. The clinical manifestations of severe cases include erythema, blisters, exudation, keratinization,

hypertrophy with hyper- or hypopigmentation. Although certain types of skin diseases may also occur on the hands, such as AD, exfoliative dermatitis, and psoriasis, hand dermatitis commonly refers to dermatitis of the hands alone or dermatitis originally occurring on the hands before extending to other parts of the skin, such as the upper limbs.

According to the different pathogenesis, hand contact dermatitis (HCD) can be classified into ICD, ACD, and immediate skin reaction [140]. In clinical work, it is very important to identify the etiology for the prevention and treatment of HCD, so etiological classification is preferred.

Hand Irritant Contact Dermatitis Hand irritant contact dermatitis is the most common occupational skin disease. Patients generally have definite contact history of hand irritants, and the severity of skin lesions is positively correlated with exposure time and dose. Although the patch test may not identify the associated irritant contact substance, it is still necessary to perform the patch test to exclude allergic contact dermatitis [43, 140]. Severe irritant dermatitis, such as chemical burns caused by strong acids and alkalis, is relatively easy to identify and will not be repeated here. This article mainly describes the ICD caused by other irritants. Common irritants are water, detergents, soaps, organic solvents, food, household cleaners, soil, cement, and plants [43]. For example, alkalis can cause hand ICD, such as soaps, detergents, and cleansers. Acids, including hydrocarbons, petroleum and oils, are the common cause of hand ICD. The repetitive handling of some objects or materials, such as fabrics, paper, cardboard, metal objects, steering wheels, and gloves, can lead to frictional dermatitis, a subtype of ICD. Some solvents can damage the skin barrier and cause ICD, such as gasoline. Organic materials, such as food, may also cause ICD. In addition, wet work and warm, dry air can be irritants as well [21].

Hand irritant contact dermatitis is more often seen in young and middle-aged women, especially housewives and matrons, therefore, it is also known as housewife dermatitis. The disease starts slowly and goes unnoticed until it develops into obvious erythema, scales, and rhagades, accompanied by different degrees of pruritus. Repeated contact with water, detergent, paper, powder, vegetables, raw meat, and so on can cause this disease. Hand irritant contact dermatitis is characterized by erythema, edema, and rhagades, but blisters are rarely seen [27, 43].

Asteatosis Asteatosis can be caused by the weather factor, the mechanical frictions of clothing, and certain external preparations such as detergent. The main symptoms are dry skin, small scales, and fine chapping. Sometimes pruritus is obvious, and the rash can become eczematous, which eventually leads to asteatotic eczema [43].

A dry and low-temperature environment can cause skin moisture evaporation, resulting in dry skin. Washing too often can also make the skin sebum layer fall off. Even taking on and off gloves too often can cause dry skin and inflammation due to frictions from gloves damaging the skin and rubbing off sebum. This disease usually occurs in winter in elderly and people with mysophobia. For example, in order to clean hands, some people repeatedly wash their hands or even use alcohol to wipe their hands, resulting in asteatosis.

Irritant Reaction The symptoms are dryness, roughness, and rhagades, but no eczematous lesions, and the course of disease is prolonged. It is found on the backs of the hands of people who work with detergents, such as barbers, laundrymen, and repairmen. Chapped hands are generally considered to be irritant reactions [43].

Irritant Dermatitis Acute stage skin lesions mainly show erythema, edema, and small papules, and chronic stage skin lesions can include hypertrophy and lichenification. It usually occurs on the back of the hand and on the skin of the fingers under the ring. It can also occur on the palm [43, 141].

Pulpitis Clinical findings include dryness, chapped skin, and sometimes ache of finger pulp. It starts with one finger and expands to ten fingers. It is more common in young women with unclear mechanism and may be related to contact with water, detergent, and mechanical friction. This disease is more common in teachers, librarians, and photocopiers and may be the result of repeated contact with dry paper, chalk, and other items, coupled with friction effects [142]. Such patients are not uncommon in dermatology clinics. Treatment is very difficult, and easy to relapse.

Hand Allergic Contact Dermatitis Many contact allergens can cause hand allergic contact dermatitis. Common allergens include nickel, chromium, hair dye, p-phenylenediamine, and spices [43]. In women who are allergic to nickel from wearing piercing earrings, ACD may occur quickly when

the hands touch the electroplating solution during the first electroplating work. Marked itching, rapid emergence of erythema, blisters, and exudate are all the characteristics of this disease. In health care workers, hairdressers, cleaning personnel, kitchen workers, craftsmen, construction workers, laboratory workers, and homemakers, glove ACD is a very important dermatitis. One study examining the prevalence of glove-related dermatitis in an Italian hospital found that roughly 1 in 4 health care workers experienced cutaneous symptoms in response to habitual glove use and nearly 11% had positive patch tests to rubber allergens. In laboratory workers, 37% reported symptoms of hand dermatitis, whereas 7% had positive patch tests to rubber allergens. Workers in the food-processing industry were noted to have a significantly higher incidence of ACD to rubber accelerators compared with a control group. Within the cleaning industry, 10 to 28% of workers experience hand dermatitis, and the leading allergens include thiurams, a group of rubber accelerators found in rubber gloves [139]. ACD may be hard to distinguish from ICD, AD, or hand hyperkeratotic eczema.

Hand allergic contact dermatitis generally has a clear history of exposure. The morphology of skin lesions is complex and varied, including erythema, papules, scales, blisters, keratinization, and rhagades (Fig. 10). In general, erythema and blisters are the characteristics of acute eczema, while hyperkeratosis and fissures are the characteristics of chronic eczema. Subjective symptoms may include varying degrees of itching, pain and burning. The course of disease at different stages may present different lesions, and there is no corresponding relationship between the morphology of lesions and the etiology. Therefore, it is not recommended to classify the lesions only according to morphological characteristics [140]. In clinical work, it is very important to identify the etiology of hand eczema. Therefore, etiological classification should be given priority in the diagnosis of patients.

Hand Immediate Skin Reactions Contact urticaria/protein contact dermatitis is characterized by the rapid occurrence of

Fig. 10 Hand allergic contact dermatitis caused by cement



urticaria, such as wheals and skin scratches after hand contact with proteins (food proteins, latex, or biological materials), followed by scratching and eczematoid lesions, which are more common among workers in health care, agriculture and food-processing industries. Prick test and serum-specific IgE test can help with diagnosis [140].

Facial Dermatitis

Facial dermatitis refers to contact dermatitis mainly occurring on the face. Skin lesions can occur in other areas, such as the hands and neck, but they mainly occur on the face.

Facial Allergic Contact Dermatitis Facial allergic contact dermatitis is not uncommon and can be caused by cosmetics, external drugs, occupational contacts, and some daily necessities. For example, hair dye allergy often causes dermatitis in the upper eyelid (Fig. 11), hairline edge, and both ears. Eyeglass frames often cause dermatitis in the temporal and infraorbital regions. Cosmetics often cause dermatitis on both cheeks. Topical medications, such as acne medications, often cause dermatitis at the site of use. Airborne substances can cause contact dermatitis on the face and neck, such as industrial dust [143]. ACD of the face most commonly occurs as a result of either allergens applied directly to the



Fig. 11 Allergic contact dermatitis of the face caused by hair dye

face, such as moisturizers, soaps, and makeup, or allergens rinsing down over the face, such as shampoo and conditioner. Also, allergens can be transferred to the face indirectly from airborne or hand-to-face exposure. Its main characteristic is the occurrence of dermatitis after using cosmetics for several days or years. The main clinical manifestations are cheek erythema and pruritus. Inflammation is usually mild, and skin lesions can subside completely after the withdrawal of cosmetics, but relapse can be easy. It is worth noting that cosmetic dermatitis is often not suspected for the majority of patients in the first incidence.

A teenager with AD presented with a 12-month history of recurrent, pruritic, round, and polygonal patches on her face. Patch tests using the European standard series (including nickel, chromium, and cobalt chloride), a plastic and glue series of allergens, polyester components, and personal and environmental products in contact with the patient were conducted. For the patient and 3 of 14 healthy volunteers, positive reactions were observed to the patient's mobile phone touchscreen (TS), an extract solution from the TS, and a non-TS phone of another brand. Accordingly, the patient's dermatitis disappeared when contact with mobile phone screens was avoided [144].

Facial Irritant Contact Dermatitis Facial irritant dermatitis is also not uncommon. Common substances that cause facial allergic contact dermatitis can also cause irritant dermatitis on the face. Common pathogenic substances include external drugs, such as topical drugs for the treatment of acne, chloasma (Fig. 12), seborrheic dermatitis, flat wart, and cosmetics, such as face cream and soap. In addition, it is common to see facial irritant dermatitis caused by applying plant juice or human milk on the face for cosmetic purpose [43].

Facial Immediate Skin Reactions Plant juice applied to the face, such as watermelon juice, may cause contact urticaria on the face. Airborne allergens, such as pollen, can also cause seasonal facial dermatitis on the face, manifested as erythema, slight desquamation, and pruritus. The mechanism is IgE-mediated allergy caused by the substance [43].

Facial Photosensitive Reaction Overall, sunscreens are a relatively minor part of allergic reactions caused by cosmetics (Fig. 13). However, sunscreen use is increasing rapidly all over the world due to the media attention given to the carcinogenic and photoaging effects of solar radiation. In comparison, allergic reactions to these agents are still quite uncommon. The true incidence of sunscreen allergy is hard to estimate because many cases of photoallergic reactions are difficult to differentiate from the primary photosensitive dermatoses for which the sunscreen is being used. Topical sunscreens can cause photoallergic dermatitis on the face,

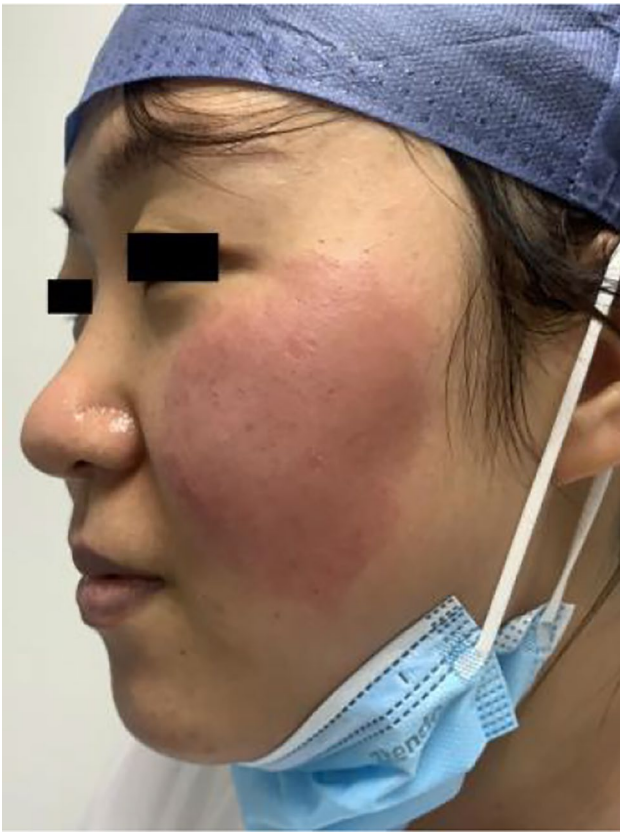


Fig. 12 Facial irritant contact dermatitis of the left cheek caused by hydroquinone cream

which is difficult to distinguish from contact dermatitis alone. A person allergic to rosin developed photoallergy after being exposed to the sun with a sticking plaster for facial surgery [43].

In a patient with a primary photosensitive dermatosis, a lack of expected response to treatment or a dramatic worsening after starting sunscreen use should prompt a search for a possible allergen in the sunscreen. In general, all cases of suspected cosmetic dermatitis, especially those that show photoaggravation or exclusive photolocalization, should have sunscreen dermatitis in the differential diagnosis.

Sunscreen allergy most frequently manifests as dermatitis. Although this is usually subacute or chronic, acute and vesicubullous dermatitis is not infrequent. The severity of the reaction depends on the allergen, e.g., benzophenones are in general known to cause more severe reactions than cinnamates. Most commonly, the reaction is photoallergic. The treated and sun-exposed parts are affected, whereas areas with sunscreen application that are unexposed to sun are spared. Clinically, this is seen as sparing of upper eyelids or submental area or a sharp cutoff at the edge of the clothes [13, 145]. If the reaction is asymmetrical, it may be due to



Fig. 13 Allergic contact dermatitis of the face caused by sunscreen

sunlight exposure from a window or due to connubial dermatitis caused by rubbed-off sunscreen from a close contact. Benzophenones are rarely reported in contact urticaria and anaphylaxis. Erythema multiforme-like reaction has also been reported to this group of sunscreen agents.

Seasonal Facial Dermatitis This disease is more common in spring, due to dry air and spring wind dehydrating the facial skin and reducing facial protection. It is more common in women. Some cases are facial irritant dermatitis caused by dry, windy environment and excessive washing, while other cases are immediate allergic reactions caused by pollen in the air.

Patterns of Facial Allergic Contact Dermatitis to Cosmetics The four general patterns of facial allergic contact dermatitis are as follows: lateral face, central face, unilateral predominance, and full face [13]. Lateral facial dermatitis involving the pre-auricular areas, post-auricular area, jawlines, and/or lateral neck is most commonly due to shampoo and/or conditioner rinsing down over these areas. Other diseases that can present in this distribution include irritant dermatitis, AD (particularly keratosis pilaris), and seborrhea. Central facial dermatitis involving the cheeks, nose,

chin, and forehead, most commonly due to ACD from facial cleansing materials, mask or moisturizers, wrinkle creams, topical medications, and makeup. The primary differential diagnosis includes irritant dermatitis, seborrhea, and rosacea. Sparing of the lateral face is largely due to the fact that patients are more assiduous about applying the above substances to the central face than to the lateral face. Generalized facial dermatitis should consider combined exposure to airborne contactant, facial cleansing milk, makeup foundation, or medicine. Unilateral facial dermatitis is strongly argued for an ectopic source, primarily transferred from the hands. Relevant sources are nail cosmetics, moisturizers, and soaps. Connubial or consort contact dermatitis owing to hair dyes, fragrances, and topical medication used by the partner may also occur on one side of the face [13].

Approaches to the Patients with Possible Contact Dermatitis

Medical History

A complete medical history, including occupational history, is important. Obtaining a thorough occupational history will help to give a clue of contact dermatitis and enable optimal results of targeted patch testing. Some questions should be included for occupational contact dermatitis, for example, “What is your current job title?,” “How many years have you been working at your current job?,” “What is your work task?,” “What are the materials you contact at work?,” “Can you provide the material safety data sheets (“MSDSs”) of these substances if applicable?,” “What protective wear or uniforms do you wear at work?,” “What is your work schedule?,” “Do your symptoms improve during days off or during vacations?,” “How many of your coworkers in the same situation have the similar skin symptoms?,” “Have you been unable to work at your usual job due to your skin problem?,” and “Have you filed a workers’ compensation claim?” [21].

History should be focused based on the distribution of the suspected contact dermatitis. For example, in oral contact dermatitis, a good understanding of dietary habits is necessary. All kinds of foods may induce contact cheilitis in heterogeneous individuals, such as betel nut, mustard, garlic, spices, flavorings, and wine [17, 146, 147]. Attention should be paid to inquire about the dietary characteristics of patients. Some ACD is accidental and related to certain daily actions of patients, such as the repeated touching of lips with nail polish, the habitual biting of metal on necklaces, or even the biting of a nickel pin while fixing hair can cause sensitization [122]. The gender and age of patients will also give us some hints. Women prefer to use lipstick, and cheilitis caused by applying ointment or lipstick is more common in women [148, 149]. Lip licking and biting are more common

in children, while oral ulcers in infants are more likely to be caused by infectious diseases. In a patient with cheilitis, or periodontitis, a combination with the deficiency of vitamin D, vitamin B, zinc, and iron should be considered, while at the same time excluding the possibility of aureus or candida infection [150, 151]. Oral administration of isotretinoin in acne patients and oral administration of vitamin A in psoriasis patients often result in lip desquamation [122]. Diabetes and AIDS patients with stomatitis or cheilitis are often associated with candida. Sick or poorly nourished children may develop staphylococcal and streptococcal infections, and face atopic and seborrheic dermatitis may also be associated with inflammation of the lip corner. Patients who have had gastrointestinal surgery can suffer from zinc and vitamin B6 deficiencies, leading to chronic stomatitis and glossitis [152]. If the patient has burning pain, numbness, dry mouth, and abnormal taste in the tongue and lips, but no objective clinical signs and irritant and allergic factors are found, the possibility of “burning mouth syndrome” related to neuropsychiatric factors should be considered [153, 154].

Distribution Clues for Contact Dermatitis

There are well-established distribution clues suggesting contact dermatitis [155]. The infraumbilical dermatitis seen in nickel allergy related to a patient’s belt buckle is pathognomonic for ACD. Eyelid dermatitis is another example of a well-defined patient subset, although the differential diagnosis can be broad and contributing factors to consider in addition to ACD include AD, seborrheic dermatitis, psoriasis, ICD, rosacea/periorcular dermatitis, and connective tissue disease. Components of nail cosmetics, hair care products, facial moisturizers/cleansers, eye makeups, and jewelry are important to consider. Potential airborne contactants should also be considered. This is particularly important in the occupational setting. Contact dermatitis should be always considered in chronic hand eczema. While there is a great deal of overlap in the morphology among the various causes of hand eczema, some manifestations are more suggestive of ACD. For example, dermatitis affecting the dorsal hand and wrist is suggestive of an underlying ACD related to gloves. Edema and microvesicles affecting the fingertips have also been suggested as a clue to ACD.

Clinically, the diagnosis of acute contact stomatitis or cheilitis is relatively simple, but it is a great challenge to make the diagnosis and identify the allergens of chronic prolonged stomatitis or cheilitis, especially when non-specific lesions, such as erythema and erosion, are the main manifestations. The oral mucosa, lip redness, the corners of the mouth, and the skin mucosa in other parts of the body should be examined carefully and comprehensively. Irritation or allergic reaction caused by dental fillings or implant materials usually has a clear border between the lesion area and the

surrounding area without contact with materials. Extensive skin lesions and lesions in other parts of the mouth rarely occur. Contact stomatitis can cause erosion, but oral erosion can also be seen in immune bullous skin disease and lupus erythematosus; therefore, the doctor should pay attention to the examination of skin lesions in other parts of the body [122]. Mercury and gold in dental metallic materials are the most likely to induce oral lichen planus [126]. If the patient's lip corner is chronically dry, cracked, and scaly, toothpaste, mouthwash cleaner, moisturizer, preservative, and bleach should be considered possible allergens.

Differential Diagnosis

The skin manifestation of contact dermatitis is non-specific, and differential diagnosis is necessary. For example, hand contact dermatitis should not only be distinguished from psoriasis, tinea manuum, lichen planus, palmoplantar keratoderma, herpes simplex on the hands, fixed drug eruption, and other diseases, but also be distinguished from other types of hand eczema, including atopic hand eczema, in which patients generally have a history of AD or allergic diseases and have no history of exposure to irritants or allergic substances, and endogenous vesicular/keratinized eczema of the hands with unknown etiology and no history of exposure to irritants or allergenic substances. It should be noted that the hands are the common site of adult AD and contact dermatitis, which can superimpose each other.

AD is an immunologic disease and may be found within the triad of AD, allergic rhinitis, and asthma. Investigating a patient's medical history is helpful when considering AD and asking about childhood skin eruptions in the antecubital fossae or popliteal fossae (common locations for childhood AD) can aid in eliciting a positive history of atopy. Patients with AD report having "sensitive skin," and they tend to avoid irritants out of necessity [140].

AD may occur on the skin in many areas, including the hands. Hyperlinear palms, which are palms with increased skin markings, may be found in the setting of AD (but not exclusively to AD). AD on the hands can present in many patterns. Typically, AD appears as eczematous, scaly pruritic papules, and plaques on the dorsum and palmar aspect of the hands, including the fingertips and wrists. Painful fissuring can occur, and retracted cuticles may occur with chronic disease. Chronic AD may be hyperkeratotic, and some patients tend to manipulate the thicker scale. A pruritic vesicular or pustular hand dermatitis may occur in the setting of AD, sometimes controversially referred to as "pompholyx" or "dyshidrosis." Diagnosis of AD is made clinically or sometimes with skin biopsy. Skin biopsies taken from the hand may not be very helpful in diagnosis. Even skilled dermatopathologists cannot often differentiate ICD, ACD, or

AD. Therefore, clinical context is of the utmost importance in diagnosis of hand dermatitis [43].

Diagnostic Tests

There are six types of diagnostic tests for contact dermatitis: patch test, photopatch test, skin test for detecting immediate contact reaction, in vitro allergen test, qualitative and quantitative tests of allergen in the suspected materials patients contacted, and challenge tests.

Patch Test

Patch test is the most classical and reliable method for the detection of contact allergens and is easy to operate. Patch test can often reveal unexpected causes of contact dermatitis. The reliability of patch test has been fully proved, but it is often ignored by most physicians. For the individual patient, both negative and positive patch test results are important, because they may affect their life in many ways [156]. Patch test is also of great value in exploring the role of contact sensitization factors in the pathogenesis and treatment of skin diseases. For example, in the treatment of psoriasis and chronic eczema, contact dermatitis induced by external medication, especially corticosteroids, is one of the important reasons for the persistence of many cases. Contact dermatitis induced by topical antifungal agents is also common and is easily confused with the aggravation of the fungal infection [43]. Finally, patch test is of great significance for finding the substitutes. After finding out the allergen, it is necessary to guide the patients to choose the substitute without that allergen or take corresponding protective measures.

The European Society of Contact Dermatitis (ESCD) published recommendations for the best practice of patch testing in 2015 which recommended patch testing be considered in patients with suspected contact dermatitis (acute or chronic, including dermatitis related to occupational exposures), other types of (chronic) dermatitis (eczema) not improving with treatment and skin, and mucous membrane eruptions (including delayed-type drug eruptions) in which delayed-type hypersensitivity is suspected [156].

Patch test can be performed by using the Finnish chamber, IQ chamber, or TRUE Test system with commercial allergens including standard allergens, screening allergens, and backup allergens. Specifically, standard allergens refer to a series of allergens recognized by authoritative institutions and are usually the most common ones in the country or region. Screening allergens are the combinations of allergens that point to a particular population or class of substances. A backup allergen refers to an allergen that has a low positive rate and is not required for regular patch testing. It is only used when there is a high degree of suspicion.

The allergens can be self-made. For example, if an object is suspected to be a sensitizer, the original or diluted object may be applied to the skin. It should be noted that self-made allergens should be carefully selected and not all items can be applied. In addition, if dilution is required, attention should be paid to the vehicle and concentration. Common vehicles include petrolatum and water. The patch test of the vehicle itself should be carried out at the same time to avoid false positive due to stromal allergy. Improper concentration or matrix selection of self-made allergens may result in misjudgment of results [155, 157].

Several factors impact the timing of patch test placement. If possible, it is advisable to avoid patch testing during acute or severe flares of dermatitis, which is largely why patch testing is not often performed during the initial visit in the general clinic setting. Performing patch testing during acute and/or severe dermatitis can result in false-positive reactions which have been termed “angry back” and “excited skin” reactions. The angry back reaction is a generalized, erythematous, dermatitic reaction on the back where patch testing materials were placed [158]. This background noise may be so severe that the test is uninterpretable. The excited skin reaction was described by Mitchell in 1975 and denotes the finding of multiple false-positive patch test reactions [159, 160]. These positive test reactions are not reproducible on subsequent patch testing. In addition to testing during acute and/or severe episodes of dermatitis, patch test substances and location of allergen placement may contribute to the excited skin reaction [155].

The patch test should be conducted on a part that is less affected by daily activities, where it is easy to apply, and where it can be easily absorbed by the skin. The upper back is usually used as the patch test site. Care should be taken to avoid local skin lesions, pigmentation, or vascular diseases that may affect the interpretation of results. If more allergens are needed for patch test, the lower back, upper arm, and forearm can be used as patch test sites. In the cosmetic safety test, the patch test site should be the back or forearm flexion. In the diagnosis of cosmetic dermatosis, studies have shown that the facial skin is more positive than the forearm and

back. The reason may be related to the different anatomical and physiological characteristics of the cuticle thickness, sebum membrane, and skin barrier function of different parts of the skin. For highly suspected patients with negative back patch test results, we can consider carrying out patch test on the face to improve the positive detection rate with the consent of the patient [157].

To correctly interpret the results of the patch test, irritate response and allergy must be distinguished. Attention should be also paid to the possibility of cross-reaction. The erythema of the allergic reaction is bulged, palpable, and with unclear boundary and could be extended outside the spot detector or along the lymphatic vessels in the shape of a thin red line. Papules and blisters may accompany. The itching is obvious and the skin lesion can last for 4 days or longer. The skin lesion could be further aggravated after the removal of the spot tester. The expression of erythema and blister of irritant reaction can be identical with that of allergic reaction. However, pustules, necrosis, purpura, and ulcer can only be seen in irritation, and tiny epidermal wrinkles are characteristic. The boundary of erythema is sharp in consistence with the size and shape of the chamber used. Pruritus is infrequent, with possible pain or burning sensation. After removing the test material, the skin lesions can gradually decrease and mostly subside by the 4th day [155]. The International Contact Dermatitis Research Group (ICDRG) recommended the recording of patch test results as follows: the weak positive allergic reaction featuring erythema, infiltration, and possible papules or vesicles; the strong positive allergic reaction featuring erythema, infiltration, papules, and blisters; and the extreme positive allergic reaction featuring erythema, edema, infiltration, coalescing vesicles, and bullae. They are reported as “+,” “++,” and “+++,” respectively. The clinical presence of only mild erythema cannot be distinguished between an allergic and an irritant reaction, and it is reported as “?+.” Moreover, irritant reactions are common when conducting a patch test, and they are recorded as “IR.” It is very important to irritant reactions from allergic reactions. Table 10 shows the identifications of allergic and irritant reaction patch response.

Table 10 Identification of allergic and irritant reaction patch response

Allergic reaction	Irritant reaction
Erythema raised, palpable and vesicular bullae	It can be completely the same as allergy, but it differs from allergy in that pustules, necrosis, purpura, and ulcers can be seen, and tiny wrinkles on the epidermis are also characteristic
The boundary is not clear and can be expanded outside the spot tester	Boundary is very clear
It can spread along lymphatic vessels in fine red lines	No
Significant itch	Rare itch, pain, and burning may occur
The rash lasts for 4 days or longer	Skin lesions usually subside by the 4th day
When the allergen concentration changes in gradient, the reaction degree also changes in gradient	The reaction does not change in gradient and can suddenly disappear at a certain concentration

Sodium lauryl sulfate (SLS) is an anionic surfactant often used to study skin irritation. SLS penetration increases when the skin barrier function is impaired [161]. Some scholars have added SLS in the patch test to understand the skin sensitivity of subjects. Patients with increased skin sensitivity have a stronger response to SLS. If the SLS patch test is positive, it indicates that the skin sensitivity of that patient has increased and the incidence of irritation will be increased. Therefore, the weak erythema reaction of allergens is more likely to be judged as an irritation response. If the SLS patch test results were negative, the weak erythema reaction of the marketed allergen was more supportive of allergy [162]. It should be noted that the weak erythema response of the marketed allergens should not be judged as an irritation response just because of the positive SLS patch test, and it should be analyzed by integrating multiple factors. For example, the skin reaction of SLS has obvious seasonality. The skin reaction in winter and spring is stronger, while the skin reaction in summer and autumn is weaker [163].

A 48-h closed patch test is usually used clinically, and an open patch test is required if the subject to be tested has considerable irritation. Photopatch test should be used when photosensitive diseases are suspected [164].

The order of common allergens for different diseases is different, and the allergen-positive rates of allergic diseases of different body parts, times, seasons, regions, and populations are also different. Nickel sulfate, potassium dichromate, thiomersal, formaldehyde, p-phenylenediamine, and perfume mixtures have always had a high positive rate because they are widely used in various kinds of articles or there is no low allergenic substitute. In many regions of the world, relevant institutions regularly collect and analyze the patch test result data, list the allergens with high positive rates as the local standard allergens, and include some highly positive allergens targeted at specific populations into the screening allergen series. In addition to commonly known hair dye series, fragrance series, rubber series, plant series, and glucocorticoid series, such as budesonide, betamethasone pentanoic acid salt, and triamcinolone acetonide, there are other common allergens in drug series, such as chloramphenicol, kanamycin, sulfa, Nitrofurazone, bacitracin, and miconazole [165–167]. Some patients were positive for multiple allergens during the patch test, indicating the presence of multiple allergens and the relatively difficulty in escaping from the sensitizing environment.

Skin Test for Immediate Skin Reactions

The skin tests used to detect immediate contact reaction include scratch test, prick test, closed scratch test, application test, and friction test. This type of test is easy to operate, sensitive, and very applicable, but it may trigger a systemic reaction.

Skin scratch test is performed on the back or forearm skin. After skin disinfection, 5-mm scratches without bleeding are made with an injection needle or a special blade [168]. Then, a small amount of liquid allergen is dripped on the scratch. Allergens should be dissolved with normal saline and then added. The results are observed after 15–20 min. Histamine hydrochloride (10 mg/mL) serves as the positive control and normal saline as the negative control. The reaction is positive when the diameter of erythema induced by allergen is larger than that of histamine. The advantage of scratch test is that it is safe and does not easily cause systemic reaction. If systemic reaction occurs, the allergen can be immediately washed away. The scratch test is mainly used to detect IgE-mediated immediate allergy and is suitable for standardized and non-standardized allergens. Note that toxic and irritating substances such as vasodilators should not be used for this test [43].

Skin prick test is also performed on the skin of the back or forearm. After disinfection of the test area, a drop of liquid allergen is added, and then a special blade or a needle point is stabbed into the skin's surface. Then, the needle is removed and the infusion is wiped off about 1 min later. The rest of the procedure is the same as the scratch test. A reaction with erythema with a diameter over 3 mm or at least 1/2 of that histamine-induced reaction is considered positive. This test is mainly used to detect IgE-mediated immediate allergy, especially for standardized antigens [169, 170].

Closed scratch test is applied when volatile allergens, such as plant juice, fruit juice, vegetable juice, and meat, are tested. After adding the allergen, the test spot was closed with a chamber, and the other procedures and result observation were the same as those of the scratch test [43, 171].

Application test is also performed on the back or forearm skin. The test substance (0.01 to 0.1 mL) was applied in the size of 1 cm × 1 cm–5 cm × 5 cm and rubbed off 15–16 min later. The results were observed for 30 min to 2 h. Solid material can be used as raw material, soaked with water and then placed on the skin. This experiment can be used to detect the immune and non-immune immediate contact response. Positive reaction is erythema, wheal, or a small blister. Generally, the original affected area of the skin can easily have a positive reaction, but for safety, the test should be conducted on skin without any lesions before. If this test is negative, then a test is performed on the affected area. The immune response usually occurs within 15–20 min, and the non-immune response usually occurs within 45–60 min [43].

Friction test is the application test with friction of the test skin to facilitate skin penetration. The detection range is the same as that of application test but more sensitive [172].

Antihistamines can inhibit these skin test reactions [173]. Most antihistamines should be discontinued for 3 days. Oral administration of prednisone over 10 mg per day also inhibits this reaction and should be discontinued for more than

2 weeks [174]. Theophylline, sodium chromoglycate, and other drugs should also be stopped for 48 h. Antihistamines have no effect on non-immunologic immediate contact reaction. For non-immunologic immediate reaction, the test should be done after 2–3 weeks of UV exposure as ultraviolet light can inhibit this reaction. NSAIDs, whether orally or topically, should be discontinued for 3 days before testing.

When a non-standardized allergen is positive on the IgE-mediated immediate reaction skin test, 50 patients with atopic constitutions should be selected as controls to rule out false-positive reactions [43].

Photopatch Test

Photopatch test is an important method for clinical diagnosis of PACD and detection of photoallergens by adding a certain dose and an appropriate wavelength of ultraviolet radiation on the basis of the skin patch test. The photopatch test experiment was first carried out by Epstein in 1939. Subsequently, this test was carried out all over the world, and its methodology was different between different countries or regions, so the lack of comparable data and information caused confusion for using this technology. It was not until the early 1980s that there was a unified standard for the methodology of the photopatch test. In 2004, the European expert group on photopatch testing reached consensus on the methodology of photopatch testing, catalogue of test objects, ultraviolet radiation dose, interpretation, and explanation of test results and formulated several agreements to standardize photopatch test technology, so as to make research information more effective and available [175].

In general, photopatch test is considered a supplement to regular patch test. Allergens are placed on the back skin in duplicate (day 1 of visit). One set of allergens is exposed to UV light 24 h later (day 2 of visit). Patches are read for the first time after another 24 h (day 3 of visit) and finally after another 48 h (day 5 of visit) [72].

Previous studies believed that the pathogenic spectrum of PACD is dominated by UVA, so UVA has been used as the testing light source in the photopatch test. However, some scholars found that UVB also plays an important role in the pathogenesis of PACD [176]. Schwarze et al. found that PACD occurred in a woman after she had taken the antihypertensive drug Aldactazine, and the photopatch test showed negative UVA PPT results and positive UVB PPT results. On withdrawal of Aldactazine, lesions disappeared. Therefore, the light source of the photopatch test should be UVA plus UVB [177]. Liu et al. found that ketoprofen followed by UVB irradiation can produce COX-2 and PGE₂, leading to inflammatory reactions and skin diseases [178]. A French study found that the photopatch test with full-spectrum light irradiation could reveal photosensitive reaction that could not be caused by UVA irradiation alone, so it is recommended

to use full-spectrum light during irradiation to avoid missed diagnosis [179].

In Vitro Allergen Test

The common in vitro allergen test is serum antigen-specific IgE (sIgE) measurement to confirm the food allergens (e.g., milk, egg, crab, beef, wheat, peanut, and mutton) and inhalant allergens (e.g., dust mite, cockroach, cat, dog, birch, and grass). The technical methods include radioallergosorbent (RAST), fluoroimmunoassay (FIA), and enzyme-linked immunosorbent assay (ELISA). The sIgE measurement is a good method for diagnosis of immediate contact reaction, especially for patients with extensive skin lesions on which in vivo skin test cannot be conducted. It is also applicable to patients with a history of severe allergic reaction and patients who are taking antihistamines, which may lead to inaccurate skin test results, and some antigens which cannot be skin tested [180]. Quantitative sIgE test has a high reliability, with specificity and sensitivity ranging from 85 to 95%. A higher level of sIgE has a stronger correlation with clinical disease [181].

The total serum IgE measurements are also often used in clinical practice. It includes sIgE and non-specific IgE in the serum. Many factors can affect the level of total IgE, such as genetics, age, race, sex, smoking, infant feeding patterns, and parasites. Although the total IgE is not specific to what substance the patient is allergic to, it may be useful in differentiating between allergic and non-allergic conditions. The data showed that 78% of the patients with allergic diseases had a total serum IgE higher than 110 kU/L, while 84% of the patients without the allergic diseases had a total serum IgE lower than 25 kU/L, and about 20–30% of the patients with allergic diseases had high sIgE but normal total IgE. However, elevated total serum IgE can be also seen in patients with parasitic infections, as well as other diseases such as selective IgA deficiency, myeloma, Hodgkin's disease, nephrotic syndrome, and liver disease. Therefore, a high total IgE may indicate a high probability of sensitization, and a normal total IgE does not rule out specific allergy [180, 181].

On the other hand, sIgE measurements require suspected allergen as an available allergosorbent and only provide information on allergen sensitization but not on biological reactivity. Some in vitro tests could overcome the limitations of sIgE measurements, such as lymphocyte transformation test (LTT), basophil histamine release assay, passively sensitized basophil histamine release assay, basophil activation test (BAT), and leukocyte migration inhibition test. Some studies have displayed the clinical utility of these tests. However, due to their complexity and being time-consuming and the lack of standardization, they cannot replace skin tests and sIgE measurements [182].

Qualitative and Quantitative Tests of Allergen

The demonstration of the allergen source in the patients' real life is an important part of the diagnosis and prevention of contact dermatitis. For example, if a patient is found allergic to nickel by patch test, it is necessary to find which substances the patient is exposed to in daily work and life contain it. However, it is difficult to know all the compositions of a product because most products are not adequately labeled. A lot of chemical methods can be used to demonstrate the presence or absence of known allergens, such as thin-layer chromatography (TLC), high-performance liquid chromatography (HPLC), and gas chromatography (GC). Moreover, some methods can isolate and identify new allergens, including mass spectrometry (MS), nuclear magnetic resonance spectroscopy (NMR), and infrared spectrophotometry (IR). However, these chemical methods still have some limitations, and false-positive as well as false-negative results can be obtained.

Challenge Tests

Challenge tests can be used to confirm contact allergy especially when patch test is negative or doubtful. Use test or application test is to let the patient re-use the suspected allergen to see if any reactions occur. When it is not applicable, repeat open application test (ROAT) can be performed. Oral challenge tests are mainly used in the diagnosis of systemic contact dermatitis. For example, the oral challenges of nickel, chromium, and cobalt can be used in patients with dyshidrotic eczema who test negative in the conventional patch test.

Caution should be exercised in oral challenges to drugs. Due to the wide variety and diversity, few drugs have established standardized patch test so far. Therefore, allergy cannot be ruled out for patients with negative patch test results. If multiple tests are negative and the patient must know if there is a response, then oral challenges can be performed under close supervision. The test should not be implemented for suspected type I allergy patients or patients with a history of type I allergy.

Oral challenges do not fully detect systemic contact dermatitis. Five cases of systemic contact dermatitis caused by positive pressure apparatus were reported, of which one case was positive for both patch test and oral challenge, three cases were negative for patch test but positive for oral challenge, and one case was negative for oral challenge but positive for patch test [183].

Management

Before treatment, the suspected irritants or allergens should be avoided completely. This includes both the

removal of the patient from the environment that contains those and the promotion of the metabolism and expulsion of the allergens that has been absorbed by the body [184]. Early and appropriate treatment of skin irritants/allergens is an important measure to prevent further deterioration of the condition. For example, calcium gluconate and Hexafluorine are selected to neutralize hydrofluoric acid [184].

The maintenance of the skin barrier is very important; it is not only related to the effectiveness of the treatment of the disease, but also affects its prognosis. The recovery of skin barrier does not mean a normal appearance, but also physiological function recovery and tolerance to irritation. It usually takes a few weeks to several months. Chronic contact dermatitis takes longer to recover than acute contact dermatitis [185].

For ICD, firstly, immediately leave the source of irritation. Immediately rinsing with plenty of water for 10–30 min is the cheapest and most effective method to remove corrosive chemicals from skin [186]. Soap, alcohol, and gasoline dissolve organic irritants. Activated carbon adsorbs irritant gas. Then, choose different reagents to neutralize the irritant. A strong alkali can be neutralized with acetic acid, boric acid, and other weak acid solutions, and a strong acid can be neutralized with sodium bicarbonate and other weak base solutions. Calcium gluconate is combined with hydrofluoric acid for external use, local injection, intravenous injection, and other ways to become non-toxic calcium fluoride to prevent hydrofluoric acid from further penetrating into deep tissue. In addition, the use of a physiological lipid moisturizer can help to recover the skin barrier function [187].

The use of topical glucocorticoids in ICD therapy has been controversial, with some authors reporting no benefit and others reporting the opposite, with some believing they can only relieve the symptoms of ICD [184]. It is well known that prolonged topical use of glucocorticoids can cause epidermal atrophy, damage the skin barrier, and increase sensitivity to irritants. Even short-term use of topical corticosteroids may damage the skin barrier [187]. Therefore, long-term topical corticosteroid therapy for ICD cannot be recommended. Patients with combined systemic damage should be referred accordingly. Immunosuppressants, such as azathioprine, cyclosporine, and *Tripterygium wilfordii*, can be used in the treatment of chronic severe ICD, which is commonly manifested as hand eczema, but has little benefit and is not recommended [184].

According to the evidences from some clinical trials and case reports, the first-line treatments of ICD consist of physical protection of skin, protective cream/emollient, topical corticosteroids, and topical tacrolimus/pimecrolimus. When the effects of the above treatments are suboptimal, cyclosporin, ultraviolet therapy (PUVA (psoralen + UVA), UVB), and bexarotene gel could be used as the second-line treatments.

Superficial radiation therapy and oral alitretinoin are the third-line treatments for chronic severe ICD if the above treatments fail [188].

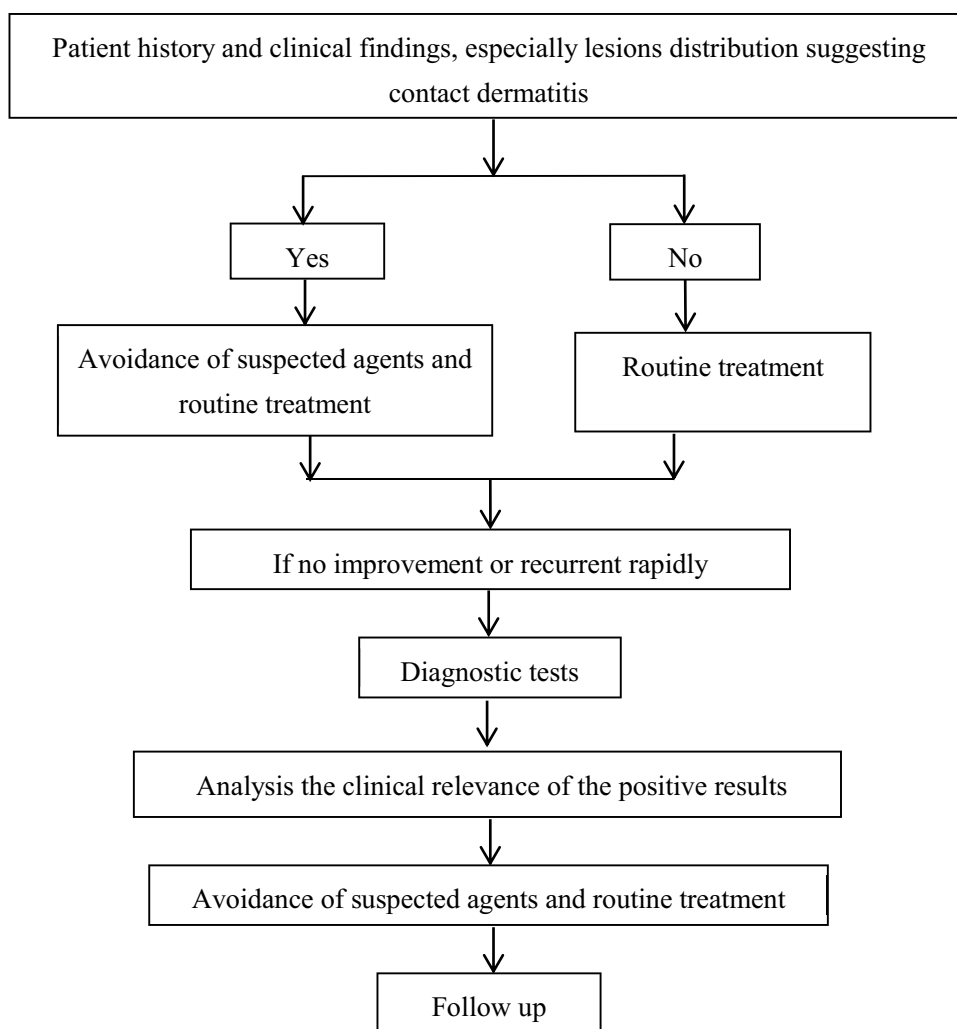
For ACD, strict avoidance of contact allergens (including cross-allergens) is necessary. There is also a need to avoid water, soap, oil, overheating, sweat, dust, and friction irritation from doing further damage to the skin barrier. The skin should be kept in a weak acid environment with a pH value of around 5.5, which can effectively inhibit the reproduction of microorganisms on the skin surface and provide a suitable physiological environment for enzymes on the skin surface [189, 190]. Topical glucocorticoids are the mainstay for the treatment of ACD. For chronic hyperkeratotic lesions, potent steroids should be selected. Topical calcineurin inhibitors may also be used, especially for users who are expected to apply them for longer periods of time. Notably, its anti-inflammatory titer was comparable only to topical glucocorticoids of moderate strength and/or below (e.g., 0.1% hydrocortisone butyrate cream) [191]. If the treatment of chronic dermatitis is initially effective and long-term topical corticosteroids do not improve or even aggravate the

dermatitis, the possibility of corticosteroid allergy should be considered, and a patch test should be considered to confirm the diagnosis. General application of tixocortol-21-pivalate and budesonide in the screening of topical glucocorticoids is able to detect 91.3% of allergic patients [192].

In hand dermatitis, retinoids can be used if the rash does not heal over a long period of time, affecting the quality of life. A European multi-center, randomized, double-blind, controlled study of 319 patients showed that oral alitretinoin can substantially clear hand rashes in patients with no improvement to routine treatment [193]. Broadband and narrowband UVB or PUVA and UVA1 also have good effects in the treatment of chronic hand eczema, which can be used for reference in the treatment of chronic ACD. However, both UVB and PUVA regimens may cause cancer, and long-term use should be avoided.

Glucocorticoids (such as prednisone 0.5–1 mg/kg day) can be taken orally for a short period of time to control the disease. Although systematic use of cyclosporine in the treatment of chronic hand eczema has been reported, a double-blind study of 41 patients with refractory hand eczema showed that

Fig. 14 Schematic diagram of approach to patient with possible contact dermatitis



oral administration of cyclosporine at 3 mg/kg day for 6 weeks resulted in a 43% improvement in symptoms, comparable only to topical external-use propionate betamethasone, with modest overall benefit [194]. It is well known that high doses of cyclosporine over long periods of time increase the risk of cancer [195]. Cyclosporine should not be used in combination with PUVA, which increases the risk of skin cancer. Azathioprine can be used alone or as an alternative glucocorticoid to treat contact dermatitis, but there is also less supporting evidence [196]. The late onset of clinical efficacy, about 4–8 weeks, and the side effects of azathioprine, such as bone marrow suppression and hepatotoxicity, limit its use in ACD. Methotrexate (5–20 mg/week) should not be recommended for non-severe cases of ACD, although it is occasionally used with good results in refractory eczema [197]. Patients with combined systemic damage should be referred accordingly.

According to the evidences from some clinical trials and case reports, the first-line treatments of ACD include avoidance of allergens, skin care education, personal protective equipment, emollients and soap substitutes, protective cream, topical corticosteroids, topical tacrolimus/pimecrolimus, local and systematic application of antibiotics, oral prednisone, and alitretinoin. As the second-line treatments, ultraviolet therapy (PUVA, UVB), azathioprine, methotrexate, acitretin, and low-nickel diet could be considered if the first-line treatments fail [198].

For photoinduced contact dermatitis, avoiding sun exposure by personal protection, such as wearing sunscreen with a high SPF and PA, wearing a hat or, holding an umbrella, is necessary. Local and systemic photosensitive substances should be also avoided. Systemic glucocorticoid is effective for photoallergic dermatitis, but not as effective as might be expected for acute phototoxic reactions. In contrast, oral administration of NSAIDs may be preferred for the improvement of local pain, such as aspirin or indomethacin. Topical corticosteroids combined with cold compress can quickly relieve symptoms. Patients with severe disease can choose oral azathioprine, cyclosporin, hydroxychloroquine, or PUVA and UVB phototherapy, as well as topical glucocorticoid preparations and topical calcineurin inhibitors.

For SCD and non-eczematous contact dermatitis, identification and avoidance of the causative agents are important, such as drugs, metals, plants, propylene glycol, and sorbic acid, and then they are treated as ACD [199–201]. SCD is usually severe and should not be limited to local treatment. Figure 14 shows the schematic diagram of approaches to patient with possible contact dermatitis.

Prevention of Contact Dermatitis

Patients should be taught how to care for and protect themselves from exposure to irritants, including how to wash

their hands, use emollients, and how to wear gloves and protective clothing. Primary prevention should be recommended for those with high risk such as people with atopic constitution and those with an occupation in the medical, hairdressing, or chemical industry, to name a few [184].

Accurate identification of contact allergens and avoiding further exposure is essential for the prevention of ACD.

Gloves are important part of personal protective equipment and protect workers from exposure to multiple irritants/allergens. But many chemicals, especially organic molecules, can penetrate vinyl synthetic rubber gloves or natural latex gloves. Cotton gloves should be worn under rubber or leather gloves for long periods of hot work to prevent allergies to rubber promoters and chromate [202]. Wearing protective gloves is the most effective way to prevent this, and greasy moisturizers are no substitute for gloves [203].

Declarations

Ethical Approval and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest The authors declare no competing interests.

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