Prognosis and Therapy

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26.1 Prognosis

The course of contact dermatitis is variable. After the first contact, the condition may resolve, or recur in the same site, or else spread and become unpredictably chronic. Although rarely, it can be complicated by erythroderma, which is often irreversible, has a poor prognosis and can even be fatal [1, 2].

If we exclude the rare complication of erythroderma, the prognosis of contact dermatitis in its various clinical expressions is favorable. With the removal of the noxious agents and adequate therapy, the duration of the clinical manifestations can be significantly shortened. Various combinations of factors can influence the development of a chronic disease status and recurrences of contact dermatitis: the persistence of contact with the irritant or allergen, multisensitization and a possible cross-reactivity with chemically related substances. Bacterial infection or trauma, pressure, friction, irritants and improper medications can also contribute to turn contact dermatitis into a chronic disease. Finally, it may be impossible to eliminate contact with certain substances that are ubiquitous, such as metals and balsam of Peru. In fact, most recurrences are observed in patients who are allergic to these common substances.

26.1.1 Prognosis of Occupational Contact Dermatitis

In the occupational field it is important to understand the prognostic mechanisms underlying contact dermatitis in order to be able to predict the course of the dermatitis in the patient, to implement risk management of patients exposed to noxious substances, and plan preventive measures against forms of occupational dermatitis [3].

Various data in literature have demonstrated that the prognosis has improved in recent times thanks to improvements in health education and to effective preventive measures [4–6]. Complete clearance of occupational contact dermatitis is now reported to range from 8 to 77%, over follow-up periods ranging from 1 year to more than 10 years [4–8]. While in the 1960s and ‘70s total clearance was obtained only in 8–33% of the patients, after the 1990s the total clearance rate reached about 70%.

Most studies have not observed significant gender differences in the prognosis of

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occupational contact dermatitis [4, 6], nor does the age of onset of the dermatitis appear to influence its prognosis.

Most reports show that irritant contact dermatitis tends to have a poorer prognosis than allergic contact dermatitis [4–6]. Some occupational irritants, such as cutting fluids, are more likely to induce chronic disease than others [4]. Among occupational allergens, metals and rubber chemicals seem to be associated with poor prognosis, having a chronicity rate of 50% [4]. In Denmark, despite the introduction of ferrous sulphate in cement to reduce the hexavalent chromate concentration, chromate allergy continued to show poor prognosis and only 30% of workers who stayed on the job achieved clearance of their dermatitis [9].

Among the various occupations at particular risk, construction workers with contact allergy have the poorest prognosis, and a complete clearance rate of the dermatitis was only 20% over a 2 to 9-year follow-up period, compared with a clearance rate of 35% among hairdressers and food handlers and 40% among medical staff [5]. A poor prognosis was demonstrated also in metal workers suffering from cutting-fluid dermatitis [10, 11].

In previous work contexts no significant improvement in the prognosis of occupational contact dermatitis was found in most reports following a change of job [8, 12, 13], whereas today, workers who change their job tend to have a better outcome than those who do not. Nevertheless, many workers prefer to go on with their chosen job despite their dermatitis. In a 10 to 13-year follow-up study, only 20% of workers with occupational dermatitis stopped working because of their dermatitis; among those who continued to work, only about 18% of workers had clearance of the dermatitis [7]. Among hairdressers with dermatitis, a job change seems to confer a good prognosis [14].

A personal history of atopy, as compared to non atopic patients, significantly affects the prognosis of patients with occupational contact dermatitis according to some authors [5] but not others [6, 11, 15].

26.2 Management

The treatment of contact dermatitis relies first and above all on early recognition and proper management. These depend on: diagnosis, identification of the factors responsible, interpretation of the results of patch tests, and appropriate therapy [16].

In general the clinical diagnosis of contact dermatitis does not present particular problems. When considering the possibility of contact dermatitis, the patient's life can be subdivided into different areas (Table 26.1) [17]: personal, household and work. Identification of the factors involved in causing the contact dermatitis is absolutely essential to proper patient management. These factors can be constitutional (atopy), chemical, mechanical (trauma) and physical (climatic factors). The allergens responsible can be identified using patch tests, that should be performed if there is the least suspicion of allergy [18]. In fact, in most cases it is not possible to identify the allergens on the basis of clinical data alone, and these need to be checked in the light of the patient's personal, household and job contacts with substances. In cases of occupational contact dermatitis, examination of the work station is essential [19].

Table 26.1 Environmental areas posing a risk in patients with contact dermatitis

1. *Personal*
Cosmetics
Clothing
Medicaments
Personal hygiene
Partner (connubial dermatitis)
2. *Environmental*
A. Household
Various substances
Plants and flowers
B. Work
Office
Factory
C. Recreational
Hobbies
D. Occasional
Holidays

26.3 Therapy

The course of the disease can be stopped only if contact with the agent or agents responsible is avoided. Topical or systemic treatments are useful only to reduce the duration of the clinical episode.

26.3.1 Acute Contact Dermatitis

Irritant contact dermatitis presents variable clinical signs ranging from mild skin dryness to severe reactions that are indistinguishable from those of allergic contact dermatitis. Topical treatment and in part, systemic treatment are therefore largely similar in the two different forms, except in cases of chemical burns of a lesser or greater depth and severity. These need to be treated like all burns, from both the medical and surgical standpoints, and using specific medications to neutralize as much as possible the irritant substances involved.

In the management of contact dermatitis it is important to remember that even in mild cases of dermatitis the anatomo-physiological barrier functions are impaired and the skin will remain vulnerable for a number of weeks after apparent clinical resolution. Avoidance of the primary cause and continual skin protection with emollients will contribute to the complete recovery of these functions.

26.3.1.1 Topical Therapy

Local treatment of contact dermatitis relies on Galenic products, that serve to abbreviate the clinical course of the disease and prevent any septic complications. Such products include solutions or antiseptic tinctures, emulsions and soothing lotions, powders, pastes and creams [20, 21]. In cases of acute, congested, edematous and exudative dermatitis wet dressings are to be preferred, at room temperature, repeated 2–4 times a day. The most efficacious solutions are those that combine antiseptic, anti-exudation and detergent actions and entirely lack sensitizing powers, as follows:

1 Sodium hypochlorite (oxidizing agent), 1–3%.
2 Silver nitrate (effective astringent and antiseptic), 0.1–0.5%.
3 Aluminum acetate (Burow's solution, astringent and mildly antiseptic); the solution (aluminum sulphate, acetic acid, tartaric acid, and calcium carbonate) contains 5% aluminum acetate and is diluted 1:10–1:40 with water.
4 Potassium permanganate (oxidizing agent with an antiseptic and fungicidal activity). It is used at concentrations of 1:4000–1:25,000. It is important to remember that it is messy and stains the skin and other materials.

Phenolized fucsin or gentian violet tinctures, both brushed on at 1%, are advised in particular in cases of exudative manifestations of the skin folds (but they stain clothes).

In the congested and exudative phases of the dermatitis, aqueous oil and lime water emulsions can also be used, or water and glycerin or oil pastes (Darier paste: equal parts of zinc oxide, calcium carbonate, glycerin and distilled water; oil paste: olive oil, lime water, starch and zinc oxide in equal parts). In cases of intolerance to wet dressings, equal parts of zinc oxide, talcum and starch powder may be useful.

Apart from these Galenic products that have long been used, and whose utility and efficacy has recently been reconfirmed in view of their lack of sensitizing power, topical corticosteroids can be used, in different formulations: creams, lotions or gels. Among these medicaments, which should preferably be non fluorinated and used as a single daily dosage, compliance with some important criteria is necessary:

1. The steroid must not be used on wide surfaces to prevent the absorption of large quantities of drug from provoking systemic side effects.
2. In general, a period of 5–7 days is sufficient to resolve most active dermatitis forms; medication can then be continued with non steroid topical drugs (e.g. their bases) for another week. If necessary the steroid applications

can be repeated. In other words, the criterion is to alternate steroid and non steroid medications, also to avoid the tachyphylaxis phenomenon [9–11].

In cases of a superimposed bacterial infection, systemic antibiotic treatment is to be preferred, bearing in mind the potential harmful action of many topical antibiotics, that are highly sensitizing and photosensitizing.

26.3.1.2 Systemic Treatment

The goal of systemic treatment is to achieve specific desensitization but this problem is still unsolved. Oral or parenteral therapy with antihistamines and sedatives is important to calm the itching and other skin paresthesia and to eliminate reflex psychic phenomena, such as insomnia and erethism.

Systemic antiinflammatory treatment with corticosteroids is advisable only in special cases, when the normal treatments have failed, and in diffuse and severe cases.

26.3.2 Subacute Contact Dermatitis

The treatment is above all based on topical corticosteroids and Galenic products, or topical emollients in cream or gel formulations.

As regards topical corticosteroids, the above-mentioned criteria of using non fluorinated administered in a single daily dosage are again valid, as also the alternation of their bases. Among the 4 groups of corticosteroids subdivided by potency, light formulations can be used on the face, folds and genitals, and more powerful ones on the hands and feet, obviously for brief periods of treatment. Gels and lotions can be used on hairy zones and creams on all other skin areas. Emollient aqueous oily creams can be alternated with corticosteroids or can be used after their administration is concluded.

Systemic antihistamines and antiinflammatory products can be used as in the acute phase.

26.3.3 Chronic Contact Dermatitis

26.3.3.1 Topical Treatment

In this phase, topical treatment can be with Galenic products in the form of oily pastes like Lassar paste (modified: zinc oxide and starch, ana g 25, in white vaseline g 50), to which reducing substances like ichthyol and mineral tar can be added, and keratolytic substances like 2–5% salicylic acid.

In the chronic phase of the dermatitis, corticosteroids can also be used in the form of creams or ointments, alternated with oily bases.

26.3.3.2 Systemic Treatment

Antihistamines can be used for short or long periods to calm the pruritus. The sedative effect of first generation drugs must be stressed, and so great care must be taken when prescribing them for patients who carry out particular jobs, like drivers and builders, to ensure proper surveillance and adequate patient instruction.

Systemic corticosteroids are used only in forms that are highly refractory to other treatments, and in diffuse and erythrodermic forms. The dosage must be tapered and gradually suspended after obtaining remission of the clinical symptoms. Sudden suspension could induce a rebound effect and new exacerbation of the dermatitis.

26.3.4 Immunomodulation

Immunological tolerance is a highly experimental phenomenon characterized by failure of the immune system to respond to a given hapten that would normally induce a response in a non sensitized subject [22]. In general, oral, intravenous or intraperitoneal administration of a hapten induces immunotolerance when the same substance is later applied to the skin or introduced subcutaneously. Tolerance has also been induced by applying the hapten on skin irradiated with UVB rays [23, 24], or using chemical

substances that have been modified as compared to the sensitizing substance. Tolerance to poison ivy can be obtained in this way using pentadecylcatechol and its derivatives [25] and to dinitrofluorobenzene using dinitrocyanobenzene [26, 27].

In the infiltrate of allergic contact dermatitis lesions, T cells with a CD4+ phenotype are predominant over those with a CD8+ phenotype. As the dermatitis evolves there will be a gradual increase of cells expressing receptors for IL-2 and Ki-67+ [28]. The tolerance is linked to a lymphocytes suppressor clone specific to the hapten that inhibits the immune response effector lymphocytes. The suppressor cells tend to develop when the antigen is not presented by the epidermic Langerhans cells presenting the antigen (LC/PC). The inappropriate presentation of the antigen stimulates the proliferation of the specific suppressor lymphocytes clones, that block the cascade of events leading to sensitization. This mechanism, that is useful to evade immune surveillance, can also be induced by UVB rays [29–32]. In fact, at low doses the latter, used in experimental animals, make them unable to become sensitized by inducing a lymphocytes suppressors clone [24]. In vitro, the same UVB doses inhibit antigen presentation by LC/APC [29], although this phenomenon is not constant in all subjects [30] and seems to be genetically determined [31].

However, in clinical practice patients are already sensitized when they come under observation. Is it therefore possible to modulate the skin reactivity using chemicals with a suppressive action? Sometimes desensitization occurs spontaneously, even if it is not yet known if this is linked to some specific allergens, to the individual due to genetic reasons, or to an inability to respond, as occurs in immunodepressed subjects [33]. In fact, it is known that subjects with AIDS are unable to develop sensitization to dinitrochlorobenzene [34].

Spontaneous desensitization, meaning negative results to previously positive patch tests, can anyway be clinically observed after some years, as shown in subjects who underwent re-patch tests [35–37]. In some of these subjects there was a correlation between the cessation of exposure (prevention) to the sensitizing hapten and the negative results to later patch tests.

The various attempts at immunomodulation made in contact allergy subjects using physical and chemical substances are reported below [2, 16, 22, 38–42].

Ultraviolet Light. The inhibition of contact allergy exerted by ultraviolet rays (UVR) is linked to the reduction of Langerhans cells and hence antigen presentation, the inhibition of T lymphocytes and the induction of suppressor lymphocytes, as well as a possible blockade of mast cells mediators release and endothelial damage.

Short-wave ultraviolet light (UVB) and PUVA (psoralen plus UVA) are effective in chronic dermatitis, most notably in hand dermatitis [43–49]. In some forms of hand dermatitis,

Table 26.2 General guidelines for the treatment of hand eczema

· Wash hands with warm water and the mildest, unscented soaps or hand cleansers free from dyes or antiseptics. Rinse and dry carefully with a cotton towel. Do not wash hands more than three times a day. Each time, rings must be taken off (soap under rings can induce a flare-up of the dermatitis)
· Avoid hobbies and household jobs that involve direct contact with solvents, turpentine, waxes, and adhesives: if necessary, protective gloves must be used
· Avoid touching fruit juices, fruits, vegetables, raw meats, fish, and especially raw onions and garlic, with bare hands
· Avoid touching hair tonics and lotions (use a cotton-tipped swab), and shampoos (use vinyl gloves)
· Babies can be washed with bare hands because the soaps used for this purpose are mild and do not generally cause irritation
· When using rubber gloves, white cotton gloves must be worn underneath them. In cases of contact allergy to rubber, use heavy-duty vinyl gloves. Wear cotton gloves during dry, dusty and dirty housework. Vinyl gloves offer better protection against some chemicals than latex rubber gloves. However, neither vinyl nor rubber gloves can prevent the penetration of some chemicals, such as many solvents. Plastic polymer gloves are usually more protective. Limit the time wearing gloves to approximately 30 min or less at a time, and wear thin cotton gloves even underneath vinyl gloves to absorb perspiration

topical application of psoralens is useful during PUVA therapy in order to intensify the therapeutic effect. It seems to be possible to obtain a certain degree of "protective hardening" using UVB [50]. Good results can also be obtained using UVA1 and narrow-band UVB, particularly in dermatitis of the hands [51–53].

Grenz Rays. These inhibit contact allergy by blocking the Langerhans cells. The dermatitis and relative positive patch tests are inhibited for up to 3 weeks after the treatment with 3Gy once weekly for 3 weeks. The same treatment induces the inhibition of the Langerhans cells even after 6 weeks [54]. In various studies, Grenz ray therapy has proven helpful in the treatment of contact dermatitis [55–58]. However, due to harmful cumulative effects of these rays to the skin, these treatments are contraindicated today and justified only in exceptional cases [58].

Corticosteroids. Systemic corticosteroids are well known immunosuppressors in inflammatory skin diseases in general. They induce a non specific inhibition of the expression and action of most cytokine cascades involved in the Th0, Th1, and Th2 pathways [41].

To control acute flares in severe chronic contact dermatitis, systemic corticosteroids can provide temporary relief. However, steroid-sparing is important, both in terms of duration and of concentrations, to prevent major adverse effects [39, 59], such as the inhibition of the hypothalamic-pituitary-adrenal axis, diabetes, Cushing's disease, hypertension, osteonecrosis, peptic ulcer, hirsutism, skin atrophy, osteoporosis, and the risk of opportunistic infections. Triamcinolone 40 mg can be administered intramuscularly in acute forms of contact dermatitis. Nevertheless, the use of tapered oral prednisone (1 mg/kg/day) is preferable since it allows monitoring of improvements of the dermatitis or flare during tapering [60].

Before performing patch tests, it is necessary to wait about 6 weeks after the completion of a cortisone therapy cycle. Dosages of 10 mg of oral prednisone significantly reduced positive patch tests to various substances [60]. Dosages of 20 mg suppressed nickel sensitivity [61], while dosages of 40 mg induced the complete suppression of responses to most allergens [62].

When prescribing topical corticosteroids various factors need to be considered, such as the site and frequency of application, the vehicle (ointment, cream, gel, lotion, solution, foam), and the quantity to be used. Although topical corticosteroids have shown some efficacy in the treatment of allergic contact dermatitis [63, 64], their role in irritant contact dermatitis remains controversial [40]. Triamcinolone acetonide 0.05% cream has been assessed in the treatment of irritant contact dermatitis induced by repetitive short exposure to a low molarity sodium dodecyl sulfate (SDS) solution [65]. Twenty-four volunteers, patch tested with SDS (0.2%) for four hours for five consecutive days, were monitored clinically (erythema), functionally (TEWL), and on cell biology (by skin biopsies, assessing any upregulation of proliferative cells measured by the expression of Ki-67-antigen and of differentiation markers, such as involucrin). While little effect was elicited on erythema and TEWL, triamcinolone cream induced a significant reduction in the number of cycling keratinocytes and a decrease in involucrin-positive cell layers in the epidermis [65]. Betamethasone-17-valerate was efficacious in SDS-induced irritant contact dermatitis in vivo [40], showing a significant reduction in the number of cycling cells and a decrease of erythema and TEWL. The effects on erythema and TEWL can be attributed to the higher potency of betamethasone-17-valerate compared to triamcinolone acetonide.

Other authors found corticosteroids ineffective in the treatment of surfactant-induced irritant contact dermatitis, induced in six healthy volunteers with an open application of 10% sodium lauryl sulfate (SLS) fives times in one day on the hands [66]. Open application to induce irritant contact dermatitis may more closely mimic real-life scenarios compared to closed patch tests. Low (hydrocortisone 1%) and medium (0.1% betamethasone-17-valerate) potency steroids have been employed in petrolatum. The parameters used to assess the response were visual grading of erythema and dryness,

bioengineering techniques (TEWL and chromometry), and squamometry. After 5 days, no significant difference was observed between corticosteroid-treated and untreated skin.

In short, the efficacy of topical corticosteroids in irritant contact dermatitis remains unclear and warrants further studies.

Antimetabolites. At the origin of contact allergy there are some particular cell lines, such as Th1 lymphocytes and APCs: the allergens at skin level are detected by APCs (Langerhans or dendritic cells) that then trigger adaptive Th1 responses. Immunosuppression using therapeutic measures involves destroying the action of these cells, inhibiting their production or proliferation, or else inducing apoptosis. Among immunomodulators, the antimetabolites class (methotrexate, azathioprine, and mycophenolate mofetil) exert their action by suppressing the proliferation of rapidly producing cells in general [41]. Methotrexate, a folic acid analog, acts by inhibiting purine and pyrimidine synthesis of DNA in rapidly dividing cells [67]; it also inhibits the migration of T cells to some tissue locations and shows anti-inflammatory effects due to increasing adenosine production [68].

In literature, some studies have demonstrated its efficacy in the treatment of allergic contact dermatitis. In 32 patients treated with methotrexate 15–30 g/wk, 78% of them showed a clinical improvement [69]. Improvement of the contact dermatitis due to *Parthenium* was also obtained in 7 patients after 6 months of therapy, although in 3 of them the response could have been confounded by the concomitant use of prednisolone during the first 2–4 weeks of treatment [70].

Azathioprine, a purinic analog which inhibits mitotic cellular division, has been used to treat refractory chronic hand eczema (off-label), particularly the vesicular type, along with airborne *Parthenium* dermatitis (off-label) [70–75]. A delayed onset (8–12 weeks) should be expected, along with a relatively safe side effect profile.

Mycophenolate mofetil, an antimetabolite agent, has been used in many cases of atopic dermatitis, but its action in allergic contact dermatitis is not well documented. In a guinea pig model of allergic contact dermatitis due to dinitrofluorobenzene, a topical preparation of mycophenolate mofetil improved the dermatitis for up to 3 days [76]. The drug proved efficacious in a patient with combined atopic dermatitis and contact allergic dermatitis, but then the patient developed hepatitis [77].

*IFN-ɣ Antagonists. C*ontact allergy is known to be supported by a complex interplay between both the Th1 and Th2 axes of immunity; nonetheless, IFN-ɣ and its associated chemokines (IFN-ɣ-induced protein 10, IFN-inducible T-cell α chemoattractant, and monokine induced by IFN-ɣ) play an essential role in the generation of contact sensitization [78], particularly toward some allergens such as nickel [79] and dinitrochlorobenzene [80]. In theory, there is a scientific rationale underlying the efficacy of IFN-ɣ inhibition for the treatment of allergic contact dermatitis, although further studies are needed to confirm this.

Cyclosporin, a calcineurin inhibitor, primarily inhibited the TH1-mediated production of IL-2 and IFN-ɣ necessary for CD8+ activity and decreased histamine release from mast cells [81, 82]. A reduction of the Langerhans cells in the epidermis has also been reported, and a reduction of IL-1 [83]. Overall, therefore, a reduction of antigen presentation by the Langerhans cells, and so also the keratinocytes, occurs. The reduced cellular immune response is also linked to the failed clonal expansion of CD4+ lymphocytes owing to the blockade of the production of IL-2. Cyclosporin therefore intervenes above all in blocking the induction phase of contact allergy and therefore seems useful in particular in the acute phase of the dermatitis. There is limited clinical experience of cyclosporin used in the treatment of allergic contact dermatitis, but the results are encouraging [84]. In our experience, cyclosporin induced a rapid regression of the skin symptoms and pruritus, already after 5 days of administration of a dosage of 5 mg/kg/die [85]. Off-label use of cyclosporin has been reported for severe cases of contact dermatitis refractory to topical steroids and of chronic hand eczema [86]. However, some negative results have also been reported in the literature,

featuring a lack of efficacy, as well as exacerbation of the allergic contact dermatitis [87, 88].

Apremilast, an oral phosphodiesterase 4 inhibitor, has a limited off-label use in allergic contact dermatitis [89, 90]. Although the systemic reduction of IFN-ɣ+CD3+Th1 cells and IL-17+CD3+Th17 cells and the increase in regulatory B and T cells should benefit particular subsets of patients with allergic contact dermatitis, a study of 10 subjects with recalcitrant allergic contact or atopic dermatitis demonstrated minimal effectiveness after 20 mg apremilast treatment twice daily for 12 weeks [91].

TNF-α Antagonists. Cytokine tumor necrosis factor α, a mediator of systemic inflammation, has an important role in the development of allergic contact dermatitis in both the sensitization and the elicitation phase [92]. After the innate immune system has been activated by the hapten, TNF-α released during the sensitization phase promotes the migration of the Langerhans cells into draining lymph nodes to interact with naïve T cells for the differentiation of Th0 to CD8+and Th17 T cells [93, 94]. TNF-α also upregulates the expression of leukocytic adhesion molecules that are essential for the recruitment of CD8+and memory T cells in response to hapten reexposure [95].

Infliximab, a well known anti-TNF-α-based chimeric monoclonal antibody, indirectly reduces the differentiation and proliferation of Th1-mediated CD8+T cells [92]. Few reports in lierature have considered the role of infliximab in the treatment of contact allergy [96–99]. Apart from the drug effectiveness, some studies have demonstrated the absence of a suppressive effect on patch test results in psoriasis patients [96, 97, 99].

Etanercept, a TNF receptor 2-Fc fusion protein inhibitor, was used in a study of allergic contact dermatitis induced by injections of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*. A modest reduction in the magnitude of the acute-phase reaction was observed, but no response as regards the late-phase reaction [100]. In the authors' view, these results indicate that TNF receptors may have a role in allergic contact dermatitis but may be less effective in atopic dermatitis [100].

IL-4 Receptor-α Antagonists. Interleukin 4 is a Th2-mediated signal with a well known role in mediating type I hypersensitivity reactions and Th2 lymphocyte-mediated adaptive humoral immunity [41]. IL-4, however, can also have a differentiation, proliferation and immunosuppression effect on allergic contact dermatitis [101], that has traditionally been considered a Th-1-mediated process. More recent studies, in fact, have shown that certain contact allergens can preferentially elicit a Th2 response [102–107].

Dupilumab, a human monoclonal IgG 4 antibody to the IL-4 receptor α chain, seems to be an effective treatment option in patients with recalcitrant allergic contact dermatitis, as demonstrated in various studies [104, 108–112]. It is important to stress that various authors have suggested that nickel, balsam of Peru, colophony, formaldehyde, cocamidopropyl betaine, textile dyes, and rubber may elicit Th2 signature responses in some patients, given their response to dupilumab. In patients treated with dupilumab, patch tests are reported to be efficacious [108, 111].

Calcineurin Inhibitors. The immunosuppressive action of this drugs group relies on the inhibition of protein calcineurin, that subsequently prevents the dephosphorylation of the nuclear factor of activated T cells, a transcription factor [113]. As a result, the signal trasduction pathways in T cells are blocked, and inflammatory cytokine production is inhibited [110].

Tacrolimus and pimecrolimus are calcineurin inhibitors with a macrolactam structure. Unlike cyclosporin, that as a topical preparation has a limited penetration through the epidermis, both tacrolimus and pimecrolimus have been shown to be efficacious anti-inflammatory drugs for topical use. Topical tacrolimus, initially licensed in 1984 for the treatment of atopic dermatitis, was later used also in allergic contact dermatitis. Tacrolimus 0.1% ointment proved efficacious in the treatment of nickel-induced allergic contact dermatitis, showing positive results against erythema, vesiculation, induration, and pruritus

[114]. The most common side effects were burning and stinging at the side of application; however, long term effects such as any potential carcinogeneticity have still to be determined and monitored. Tacrolimus does not cause skin atrophy, which is associated with long-term steroid use.

Pimecrolimus, with its higher lipophilicity (it is 20-fold more lipophilic than tacrolimus), is a more skin-selective compound [115]; in addition, it is 3-fold less potent an inhibitor of calcineurin than tacrolimus and cyclosporin [115]. In 66 adult subjects with nickel-induced allergic contact dermatitis, pimecrolimus 0.2 and 0.6% cream were compared to the vehicle and betamethasone-17-valerate 0.1% cream. Pimecrolimus 0.6% cream was comparable to betamethasone-17-valerate 0.1% cream and was more effective than the vehicle [115]. The most common side effect was a transient burning sensation at the site of application, lasting up to 3 days in most individuals.

In various nations, calcineurin antagonists are only approved for the treatment of atopic dermatitis. In general, they are less effective than strong corticosteroids in allergic contact dermatitis [116–119]. However, in cases of long-term therapy, calcineurin antagonists, as compared to corticosteroids, may be more indicated particularly in sensitive areas of the skin, such as the face and intertriginous areas, since they do not cause skin atrophy [120].

26.3.5 Repair of Damaged Skin

Approaches to contact dermatitis treatment have increasingly incorporated repair of the damaged skin as one of the major elements [38, 39, 42, 121–126]. Restoration of the skin barrier function can be achieved using creams and ointments as they act as moisturizers (they contain humectants that bind water molecules to hydrate the stratum corneum) [127] and emollients (they form a semi-occlusive layer on the surface of stratum corneum that prevents water from evaporating from the skin surface, allowing it to penetrate the stratum corneum and increase skin hydratation) [128]. Moreover, emollients produce a protective layer that reduces the penetration of harmful chemicals into the skin [129]: emollients with a rich lipids content (nonpolar) reduce the penetration of water-soluble chemicals, whereas water-rich emollients (polar) reduce the penetration of lipophilic chemicals. Furthermore, emollients are able to restore the barrier function, which relieves the itch and inflammation associated with contact dermatitis [129]. Use of an emollient alone, without a corticosteroid cream, is usually sufficient to treat mild cases of contact dermatitis.

Emollients also offer a valid support in contact dermatitis prevention. Daily use of emollients can improve the integrity of the skin barrier in subjects with contact dermatitis [124]. The use of emollients should therefore be a part of the normal skin care routine of all people with skin barrier problems. It has been demonstrated that daily emollient usage leads to a statistically significant reduction in the cumulative incidence of atopic dermatitis in children with a family history of atopic disease [130].

Regular prophylactic application of skin creams is widely recognized to be an effective prevention strategy also against occupational contact dermatitis. In this sector, however, compliance rates remain low [131, 132]. In this regard, an expert panel of dermatologists identified three times when best to apply skin cream in the work place, namely before starting a work period, after hand washing, and after work [132].

Nevertheless, it is important to remember that in some cases excessive use of emollients is inadvisable. In cases of airborne contact dermatitis due to fibers or sharp dust particles, for example, moisturizing creams are contraindicated as they may exacerbate the irritation and increase allergen penetration [133].

26.3.6 Management of Hand Dermatitis

Hand eczema is one of the most frequent dermatological disorders encountered in clinical practice. It is usually long-lasting [134–136], is

caused by a combination of endogenous (individual susceptibility, atopy) and exogenous (exposure to irritants and allergens) factors [137], and is more common in women and in younger subjects [138]. The estimated prevalence in the general population is about 4%; the 1-year prevalence is nearly 10% [138]. However, various authors have stressed that only about 44% of subjects with hand eczema actually seek medical advice and treatment [139, 140].

In cases of chronic hand eczema, a subset of hand eczema with a multifactorial aetiology, it is rarely possible to identify all causative factors and remove them [141, 142]. Severe chronic hand dermatitis can cause a grave impairment of the quality of life, prolonged sick leave, loss of the job, sometimes early retirement, and high direct and indirect costs [143–145].

In a cross-sectional multicentre study including 14 Italian centres, 981 patients with hand eczema, consecutively accessing the centres over a 6-month period, were enrolled. Hand eczema was chronic in 83.5% of the cases; 21.3% had severe eczema, and 62.0% of these patients were refractory to standard therapy. Food processing and related work, the health professions, crafts and related trade work (building, plumbing, electrical), hairdressing, beauty and handicraft work were most frequently associated with chronic hand dermatitis. Severe forms of hand eczema most often affect men, older patients and those with less education. Unemployed and atopic subjects were most often affected by severe, refractory hand eczema [146].

In Table 26.2 some general guidelines of management of hand eczema are reported [121].

26.3.6.1 Principles of Treatment

In the acute phase of dermatitis, cold water compresses are effective. In the presence of infection, the addition of Burow's solution (1 tablespoon to a pint of cold water) is indicated. It is better to avoid wet dressings with a potassium permanganate base because they can cause skin dryness and discoloration of the nails.

After using wet dressings, topical corticosteroids must be employed, preferably creams by day and ointments overnight (in particular on the palms), wearing polyethylene gloves at night to enhance the effect of the ointment.

If a secondary infection develops, with fissuring and scabs, antibiotic creams are necessary. Oral antibiotics may also be useful.

In cases of severe eczema that do not respond quickly to topical remedies, systemic corticosteroids are indicated: 1 mg/kg of prednisone or its equivalent for several days; the dosage should be decreased by 10–15 mg every few days over about 2 weeks. At the discretion of the dermatologist, other systemic immunomodulant treatments or physical alternatives (PUVA therapy, Grenz ray treatment) can be employed.

In cases of pruritic and sleepless patients, antihistamines (such as cyproheptadine hydrochloride 4 mg twice a day or other similar products) can be introduced.

26.3.7 Oral Hyposensitization in Nickel Contact Allergy

Nickel is the most common contact allergen in industrial countries. The prevalence of nickel allergy in the general population ranges between 8 and 17% in females and between 1 and 5% in males [147–150]. With a few exceptions, nickel allergy is a lifelong condition [35], and this is why interventions aimed at reducing nickel hypersensitivity offer an attractive alternative to current immunosuppressive strategies.

Oral tolerance is a mechanism that impedes the development of undesired immune responses towards dietary antigens [151, 152]. Animal models have clearly shown that oral administration of haptens, including nickel, leads to a state of immunological unresponsiveness that prevents subsequent sensitization through the skin. Tolerance induced by oral feeding is long-lasting, hapten-specific, and can be transferred into naïve animals with CD4+T lymphocytes [153, 154].

Multiple mechanisms can explain the induction of tolerance [155], including the expansion of CD4+CD25+T regulatory cells (Tregs) [156], augmented secretion of interleukin (IL)-10 in response to hapten challenge [157],

induction of suppressive CD8+T cells [152, 158], apoptosis of effectors T lymphocytes [159], intervention of natural killer T cells [160], and the suppressive function of plasmacytoid dendritic cells [161]. Whether single or multiple mechanisms are simultaneously armed following antigen feeding is still debated. Possibly, the dose of antigen administered is critical for tolerance induction. In mice, oral tolerance can be induced either with a single administration of a high dose of antigen or with repeated low-dose exposures. The current view is that low-dose tolerance depends on the expansion of Tregs, whereas high-dose tolerance relies on the induction of anergy/apoptosis of effectors lymphocytes. However, the definition of "low" or "high" is somewhat arbitrary, being highly dependent on the antigen considered, and on the characteristics of the recipient of the hyposensitization protocol.

Although in vitro evidence has been provided that human allergic contact dermatitis due to nickel is a highly regulated process [162, 163], the possibility of inducing specific tolerance in vivo has not been adequately investigated. Indirect evidence that nickel allergy can be modulated and/or prevented in vivo has been provided by epidemiological studies reporting a lower frequency of nickel allergy in children wearing orthodontic braces prior to ear piercing [164, 165].

More direct evidence has been provided by attempts to induce specific oral tolerance to the metal in nickel-allergic individuals. In a double-blind study, oral administration of 5 mg of nickel sulfate once weekly reduced the in vitro response of T cells to the metal in allergic patients, but failed to improve the clinical expression of the dermatitis [166]. In contrast, other reports showed that oral administration of 3.5 or 5 mg, but not 0.5 mg, of nickel sulfate once weekly for 6 weeks, as well as sublingual adminstration, significantly improved cutaneous manifestations and nickel reactivity [167, 168].

To investigate the efficacy of oral hyposensitization in nickel-allergic subjects and how this affects in vitro T cell responsiveness to the metal, Bonamonte and Coll. conducted an open multicenter study in 28 nickel-allergic patients, involving the oral administration of a daily dose of 50 μg of elemental nickel (given as $NiSO_4 \cdot 6H_2O$) in cellulose capsules for 3 months. The severity of clinical manifestations, in vivo nickel responsiveness and in vitro T cells responses to the metal were assessed after 1 and 3 months [169]. All patients enrolled had a history of contact dermatitis caused by nickel lasting at least 4 months (mean, 14 years), confirmed by patch testing with nickel sulfate 5% pet. At T0 (first visit), T1 (at 1 month of treatment), and T3 (at 90 days), apart from evaluating the affected body surface area (BSA), patch tests were performed with scalar concentrations (2.5%, 1%, 0.5%, 0.1%, and 0.05% wt/vol) of $NiSO_4 \cdot 6H_2O$ in water, as well as taking blood samples for immunological investigation (performed in 12 patients). Two patients discontinued the protocol because of adverse effects: one patient, a 55-year-old female, complained of itching, abdominal distension, dyspnoea and flushing after 3 days of treatment; and a 54-year-old female complained of worsening of skin changes at day 20 of treatment. Twenty-six patients finished the study. In these patients, oral hyposensitization improved the clinical manifestations despite continued nickel exposure: BSA decreased from 6.34% (range 2–18%) to 3.65% (range 0–12%) at T1, and to 2.11% (range 0–9%) at T3. As regards the patch tests, the minimal eliciting concentration progressively increased from 0.49% (range 0.05–1%) to 0.69% (range 0.1–1%) at T1, and to 1.54% (range 0.1–5%) at T3.

Importantly, the clinical improvement was accompanied by a significant reduction of in vitro nickel responsiveness of both CD4+ and CD8+T lymphocytes in all but one patient. All except the 1 patient showed a significant reduction of T cell proliferation in vitro (ranging from 28 to 95%). Decreased T cell proliferation was parallelled by impaired secretion of IFN-ɣ and TNF-α, whereas the secretion of IL-10 remained unchanged. In the 1-year follow-up, 50% of patients experienced relapses of the clinical manifestations at sites of topical exposure to nickel.

Despite the various protocol limits (dose and duration of treatment, further functional studies required to investigate the mechanisms underlying the induction of nickel oral tolerance), the results show that oral hyposensitization is a promising approach in the management of nickel allergy [169, 170].

26.3.8 Nickel Elimination Diets

Hyposensitization therapy with oral nickel seems currently to be the only treatment acting on the pathogenic mechanisms underlying nickel allergy, so it could be considered the only effective treatment [170]. There are, however, other therapeutic measures aimed at alleviating contact allergy symptoms, such as a special diet. There is some evidence to support the benefits of low nickel diets in some nickel-allergic subjects [171, 172]. As is well known, nickel is present in various foods in a normal diet, some of which have a very high nickel content. However, the nickel content in specific foods can vary greatly depending on a number of factors, so the daily intake of nickel is highly variable both in different populations and even in the same individual, in different seasons and even different days. It is therefore difficult to suggest a useful quantitative and qualitative low-nickel diet composition [40, 173].

26.3.9 Nickel Dermatitis and Chelating Agents

Another nickel-specific therapeutic option is the use of chelating agents, such as diethyldithiocarbamate (DDC), tetraethylthiuramdisulfide (TETD) (disulfiram or Antabuse®, also used in the treatment of chronic alcoholism; in the circulation it splits into two DDC molecules), and trientine [174–179]. The underlying rationale is to increase the excretion of nickel penetrating the organism through the skin or food, prevent its binding with the specific vector and remove from the epidermis the nickel bound to the membrane antigens of the Langerhans cells. In this way, the antigenic stimuli can be reduced.

The chelating agents shown to be most efficacious are DDC and TETD, whereas trientine did not yield satisfactory results. Such treatment is not free from side effects [180] and should be given under close biohumoral monitoring (liver function should be monitored before and during treatment). Absolute avoidance of alcohol is essential during the treatment because alcohol intake will cause nausea and vomiting. This treatment (the chelating agent binds nickel and allows it to be excreted in the urine and stool) should only be used in cases refractory to other tretaments, and lacking any possible prevention methods, for brief periods and at low dosage. It is necessary to associate the treatment with an iron-rich diet, the administration of polyvitamins, and as already stated, to avoid alcohol.

26.3.10 Oral Hyposensitization in Plant Dermatitis

Parthenium hysterophorus has caused contact dermatitis of epidemic proportions in Northern India [181–183]. The onset of the dermatitis can occur after direct contact with the plant, or as a result of airborne contact dermatitis. The principal allergens are sesquiterpene lactones, parthenin and ambrosin, present in the trichomes of the plant. During the dry season, these are scattered by the wind and can cause airborne contact dermatitis [181–183]. The clinical picture may be further complicated by the development of photosensitivity [184].

Twenty four subjects with positive patch test reactions to *P. hysterophorus* were enrolled in a study to investigate the effect of oral administration of parthenium extract [184]. At the start of treatment and at the end of the study (12 weeks) a clinical severity score and any change in the contact hypersensitivity titres calculated using serial dilutions of the patch tests concentrations were recorded. Ether extract of dried parthenium leaves was diluted in corn oil to produce a stock solution of 1000 μg/ml. The first dilution used was 10,000 μ/ml. Oral hyposensitization was started at 1 dilution lower than the patient's own titre, determined after patch testing with

serial dilutions. Initially started at 5 drops/day, the dose was increased over a week, up to a maximum of 30 drops/day. This therapy was associated with antihistamines and topical corticosteroids only after the first 2-weeks follow-up.

Of the 24 patients enrolled, 4 dropped out and 20 completed the study; among the latter, 6 patients (30%) experienced exacerbation and hence interruption of the therapy. In the remaining 14 patients, there was a gradual fall in the mean clinical severity score. However, there was no significant change in the individual contact hypersensitivity titres after treatment [184].

Studies of oral hyposensitization were also made in patients with contact allergy to rhus/urushiol [185, 186]. Epstein and Coll. [185] observed a decrease in patch test positivity after the oral administration of urushiol when the therapy was extended to 6 months.

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