

Allergic Contact Dermatitis



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KEYWORDS

• Contact • Dermatitis • Allergen • T cell • Patch • Work related

KEY POINTS

- Allergic contact dermatitis (ACD) is one of the most common work-related conditions.
- Clinical features of chronic ACD and irritant contact dermatitis may overlap.
- Identification of the offending allergen in ACD is often circumstantial.
- New techniques are required to overcome these challenges.

INTRODUCTION

Allergic contact dermatitis (ACD) seems a straightforward and simple disease. The problem is easily defined: it is a cutaneous immune reaction against 1 or more nontoxic allergens that come in contact with the skin. All the patient should need to do is to get rid of the allergen. However, detection, allergen avoidance, and therapy are often very difficult. Therefore, ACD can affect patients for years and is a grave socioeconomic problem.

ACD and irritant contact dermatitis (ICD) can lead to mostly similar clinical phenotypes, even though the latter is much more common and not caused by an immune reaction to well-defined allergens. Together they make up more than 90% of occupational skin disorders. Affected patients have great impairment in their quality of life and experience long periods of sick leave, which has an important socioeconomic impact.

The 1-year prevalence for allergic contact eczema is about 15%.^{1,2} Therefore, it concerns groups of all ages with high prevalence and incidence, even though elderly people are often affected because of impaired epidermal barriers or alterations of immune reactivity.³ The 2 main groups of contact eczema coexist in many cases and differentiating between them often proves to be difficult. Both diseases can have similar clinical and histologic aspects.

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EPIDEMIOLOGY

Between 4% and 7% of all dermatology consultations are for contact dermatitis. In Sweden, about 10% to 12% of adults had hand eczema during a period of 1 year. However, the tendency for ACD is decreasing slightly, and is inversely mirrored by the increase of atopic dermatitis. The point prevalence of contact sensitivity is 15.2% in teenagers. In adults, this is much higher and can reach 18.6%. This higher rate may be mostly caused by the cumulative opportunities of sensitization rather than an effect of age, because the latter does not have a direct influence on capability for sensitization. The prevalence of pure ACD is difficult to measure because ACD and ICD usually coexist. The incidence of occupational dermatitis per 1000 workers per year is about 0.5 to 1.9 in most European countries.

PATHOMECHANISM

ACD develops only after an initial sensitization⁴ phase with usually innocuous substances; usually small molecules that cannot be recognized on their own by the adaptive immune system. However, when they are bound to cutaneous proteins they can associate with major histocompatibility complex (MHC) class II antigens (MHC II). Some chemicals can also directly bind to MHC II that are present on Langerhans cells and other epidermal antigen-presenting cells, mostly of dendritic origin. After application, it takes about 6 hours until the allergen is presented on these cells. Additional signals such as inflammatory cytokines (eg, tumor necrosis factor alpha, interleukin [IL] 1- β) can support sensitization and could arise from irritation of the skin, perhaps explaining the close connection of allergy and irritation in this disease. Also, MHC molecules are upregulated. The activation (priming) of specific T cells takes place in the lymph nodes. The antigen-presenting cells migrate there and depending on the nature of the antigen present it on MHC II (ie, a polar hapten) or MHC I (ie, the small lipid soluble molecule urushiol). T cells then proliferate in the lymph nodes, primed T-cell clones start to disseminate throughout the skin, and cutaneous lymphocyte antigen-positive T cells thereafter stay in the skin for long periods of time.⁵ Activated T cells produce cytokines such as interferon gamma, IL-2, and IL-17. They are attracted to the locus of inflammation by keratinocyte-derived CCL27, which binds to their CCR10. T cells have an apoptotic effect on keratinocytes because of their FasL and perforin expression. These combined effects ultimately lead to the clinical phenotype of ACD. Taken together, the delayed hypersensitivity reaction is caused by the previously activated T cells, which only at second contact cause rapid inflammation.^{6,7} As an exception, a single, prolonged contact with an allergen may lead to ACD, but this should require several days to develop. The sensitization phase is specific for ACD and is not a feature of ICD, even though similar clinical features develop in both conditions. In ICD, the inflammation is caused by the irritant, which (somewhat in contrast with ACD) is dose dependent.

CLINICAL FEATURES

ACD presents with erythema, edema, vesicles, oozing, and notably intense pruritus. In the mildest form, only erythema is visible at the site of contact; sometimes, the type of substance can be already suspected (ie, when liquid tracks are visible). Stronger reactions include spongiotic vesicles that itch and burst quickly, weeping intensively and crusting thereafter (Fig. 1A, B). In ACD caused by a single exposure, all lesions are at the same stage in this process.⁸ When it becomes chronic, the term eczema is used and features such as hyperkeratosis, desquamation, lichenification, and

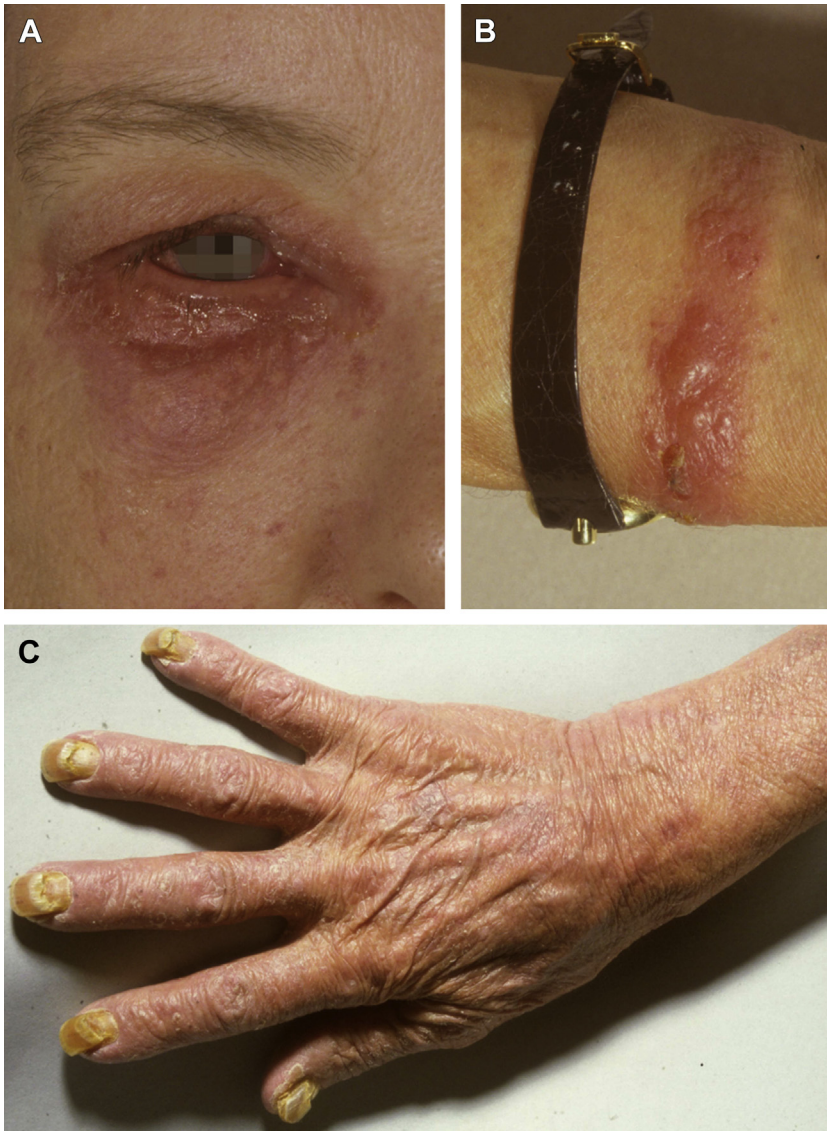


Fig. 1. (A) Acute ACD to neomycin eye drops; (B) acute ACD to chromium; (C) chronic ACD.

fissuring become more prominent⁹ (Fig. 1C). The lesion is then less sharply circumscribed, infiltration and thickness of skin increase, lichenification marks develop, and regional differences in the stage of the inflammation can be seen. The localization plays an important role in the morphology of ACD, even though it can occur on every part of the body. Also, the body site gives important clues to the cause of ACD and is the starting point for detailed history taking, which is crucial to guide patch testing for identification of the responsible allergen. In delicate areas with a thin stratum corneum, such as the eyelids, penis, and scrotum, erythema and edema usually outweigh papules and vesicles. The same clinical features develop in allergic contact stomatitis and

vulvitis.⁹ An allergic contact reaction is typically not sharply limited. It is predominant in the area of contact, but can widely spread to other areas. In ectopic ACD, the allergen reaches the patients' skin by exceptional routes⁷:

- Autotransfer: for example, with nail lacquer located on the eyelids or on the neck (transfer by fingers)
- Heterotransfer: transfer of the allergen to another person, mainly the partner, also known as connubial ACD
- Airborne ACD: transport of the contact allergen by air (dust particles, vapors, or gasses; eg, from wall paint or pollen), typically clinical lesions on uncovered areas
- Photoallergic ACD: from ultraviolet (UV) light, clinical lesions on light-exposed zones; typically spares areas covered with clothes or shaded by hair, such as ears or scalp

Sometimes, generalized contact dermatitis occurs. The pathomechanism remains unclear. Exposure to high doses of allergens, dissemination via blood vessels, or a generalized activation of immunologic effector cells have all been suggested as potential explanations.¹⁰ Atypical forms of ACD are dyshidrotic and pompholyx-type contact dermatitis, erythema multiforme-like reactions, pigmented purpura, pustular reactions, granulomas, and sclerodermallike lesions.⁸

In contrast, acute irritative-toxic dermatitis can present, apart from edema, erythema, vesicles, bullae, and oozing, with pustules, ulceration, and necrosis. It can also be characterized by dryness and roughness, whereas the chronic stadium is similar to chronic ACD. Pruritus may be present, but the main symptoms may be burning and pain. It is usually sharply defined and does not disseminate.⁹

DIFFERENTIAL DIAGNOSES

Numerous differentials must be considered, the primary one being various types of dermatitis of different causes, including irritative-toxic dermatitis, atopic dermatitis, dyshidrotic dermatitis, nummular dermatitis, stasis dermatitis, and lichen simplex chronicus.¹¹ Imitators of ACD that differ in pathophysiology and response to treatment include psoriasis, seborrheic dermatitis, pityriasis rosea, palmoplantar pustulosis, lichenoid dermatitis, lymphoma, and tinea manuum.¹² Eczema can also occur as a secondary phenomenon, such as in scabies, in which it occurs as a reaction to the mites' feces; in phthiriasis; mycoses, including candidiasis; and in impetiginous infections. In contrast, ACD can, rarely, also be concealed by noneczematous lesions such as erythema multiform-like lesions,^{13,14} urticarial papular plaques, lichen planus-like and lichenoid eruptions,¹⁵ purpuric petechial reactions,¹⁶ dermal reactions,¹⁷ lymphomatoid contact dermatitis,¹⁸ granulomatous and pustular reactions,¹⁹ and pemphigoidlike lesions.²⁰

DIAGNOSIS

Because it is difficult to differentiate clinically between the various eczema entities, the collection of a precise medical history and a correct assignment of the morphologic patterns are the fundamental steps leading to a proper diagnosis and guiding subsequent patch tests.

A useful history should include:

- Time of onset and possible contact with allergens or irritants (temporal relationship)

- Contact area corresponding with reaction area
- Initial clinical patterns and evolution of morphology
- Working environment: exposure to potential allergens (even unexpected allergens, such as phone cards²¹); dose; frequency; duration; protective measures, such as gloves, masks, and barrier creams; and concomitant factors, such as humidity, temperature, occlusion, friction
- Similar situation in coworkers
- Leisure activities
- Domestic products, protective measures used while cleaning
- Skin care products, fragrances, nail and hair products
- Jewelry and clothing, communication devices
- Suspicion regarding autotransfer, heterotransfer (eg, connubial dermatitis), aero-gen dermatitis, photoallergic dermatitis
- History of previous dermatitis (past contact dermatitis, patch testing, atopic diathesis, family history)

The clinical investigation should always register the body site and try to differentiate between probably primary site and spreading. It should be noted whether symmetry is present, erythema, fragile vesicles or dyshidrosiform sago-type vesicles, papules, scales, hyperkeratosis, lichenification, or infiltration. Lesions compatible with a differential of ACD should be sought, including for lichen planus and scabies. The nails must be examined for signs of dystrophy, onychomycosis, or psoriasis (oil spots).

ACD and ICD are often coexistent. It is also known that an ACD often develops from an ICD. Constant irritation may lead to increased penetration of potential allergens. The detailed evaluation of a patient's medical history and clinical features guides the selection of allergens for the patch test, which is the gold standard for diagnosis. Even though type I hypersensitivity reactions such as the protein contact allergy rarely occur,²² the overwhelming part of ACD is caused by T cell-mediated delayed type IV reactions.

PATCH TEST

Patch testing is now the gold standard in diagnosing allergic contact eczema. It is the *in vivo* proof of the disease-causing effect of renewed contact with the allergen and evokes on a small scale the elicitation phase of a delayed hypersensitivity (type IV) reaction. It involves the application of a series of allergens in specific chambers directly on the skin (mostly the upper back).

Usually the specific allergens are carried on petrolatum-based vehicles in hypoallergenic chambers, which are attached on the patient's upper back. The standard series includes the most common allergens according to the German Contact Dermatitis Research Group (**Table 1**). A commercially available ready-made chamber system is called the TRUE Test, which guarantees an exact standardized dosage and a high bioavailability for the allergens. Bioavailability depends on many factors, such as intrinsic penetration capacity, concentration, vehicle, occlusivity of the patch test system and tape, and on the exposure time. The standardized TRUE system therefore is a good option to avoid biased results,^{23,24} even though it is limited to a standard series of 35 common allergens and shows only partial overlap with the recommended standard series.³

In addition, the patients' history and clinical features should prompt selection of additional panels for testing, as well as the patient's own products in case of suspicion. Furthermore, an obligate irritant, such as sodium lauryl sulfate 0.25% or nonionic acid, can be applied as a positive control to check the skin's irritability at the time of

Table 1**Standard patch test series recommended by the German Contact Dermatitis Research Group**

Substance	Vehicle	Concentration
Potassium dichromate	PET	0.5%
Thiuram mix	PET	1%
Cobalt (II) chloride, 6(H ₂ O)	PET	1%
Balsam of Peru	PET	25%
Colophony	PET	20%
<i>N</i> -Isopropyl- <i>N'</i> -phenyl paraphenylenediamine	PET	0.1%
Wool alcohols	PET	30%
Mercapto mix without MBT (only CBS, MBTS, MOR)	PET	1%
Epoxy resin	PET	1%
Nickel (II) sulfate, 6(H ₂ O)	PET	5%
Para tertiary butyl phenol formaldehyde resin	PET	1%
Formaldehyde	AQU	1%
Fragrance mix	PET	8%
Turpentine	PET	10%
(Chloro)-methylisothiazolinone (MCI/MI)	AQU	100 ppm
Paraben mix	PET	16%
Cetyl stearyl alcohol	PET	20%
Zinc bis(diethylthiocarbamate)	PET	1%
Dibromodicyanobutane (methylidibromo glutaronitrile)	PET	0.2%
Propolis	PET	10%
Bufexamac	PET	5%
Compositae mix II	PET	5%
Mercaptobenzothiazole	PET	2%
Hydroxymethylpentylcyclohexenecarboxaldehyde (Lyrall)	PET	5%
Bronopol (2-bromo-2-nitropropane-1,3-diol)	PET	0.5%
Fragrance mix II	PET	14%
Sodium lauryl sulfate	AQU	0.25%
Ylang-ylang (I + II) oil	PET	10%
Sandalwood oil	PET	10%
Jasmine absolute	PET	5%

Abbreviations: CBS, N-Cyclohexyl-2-benzothiazole-sulenamide; MBT, Mercaptobenzothiazole; MBTS, Mercapto Benzo Thiazole Sulphate; MOR, Morpholinylmercaptobenzothiazole; PET, Petrolatum.

Data from German Dermatological Society, Erlangen, Germany. Available at: <http://dkg.ivdk.org/dkgblo.html>. Accessed October 2016.

exposure. A positive reaction to the sodium lauryl sulfate does not indicate an allergic reaction because it is purely irritant.²⁵ Patients under immunosuppression (including systemic steroids or active phototherapy at the side of testing) should not be tested because of false-negative results. This requirement is even more important because the patch test does not include a positive control.

The first reading of the test is performed at 48 hours, when the patches are removed again. In some clinics, patches have already been removed at 24 hours. There is no strict agreement whether to keep it on for 24 hours or 48 hours. The reading should be done about half an hour after removing the test (after 48 hours, see earlier discussion), then after 72 hours, and at another time after 96 hours, especially if there are

questionably positive results at 72 hours. A repeated reading after 1 week is highly suggested in order to avoid missing a delayed reaction (eg, neomycin, corticosteroids).⁹ For the analysis, there are several scoring systems, but a commonly used evaluation method is the system described by Wilkinson and colleagues²⁶ (Table 2). Reading and scoring have to be repeated at each visit to check the progression or regression of the reaction (day 2, day 3, day 4, or day 7). A modification version has been proposed by Menné and White²⁷ (Table 3), but, to date, a worldwide consensus is lacking. Follicular reactions are common, such as to metals, and can be noted with an “f” beside the reaction intensity.

An increasing reaction (*crescendo*) in patch testing is compatible with an ACD; an initially positive and subsequently waning reaction (*decrecendo*) suggests an irritative cause.

Positive reactions to chemically similar allergens may indicate cross reactions. Positive reactions to more than 5 nonrelated substances can indicate polysensibilization,²⁸ but a so-called angry back/excited skin syndrome must be considered as well.^{29,30} Angry back/excited skin syndrome can be ruled out by repeat testing of selected allergens about 2 months later.

LIMITATIONS OF PATCH TESTING

Pooling of data and objective comparisons are limited by the current lack of standardization, which includes the source and amount of allergens, variation in materials (chambers, vehicles), variation in the type of occlusion, the duration of application, reading times, and the score grading of patch test reactions.

The amount of allergen is important, because the reactions can provoke either false-positive (eg, by using an increased quantity of the allergen, causing an irritation instead of an allergic reaction) or false-negative reactions (eg, by using too little of the allergen). Ready-made tests or testing preparations seek to overcome this problem. Petrolatum is the most commonly used carrier for allergens, with the exception of the TRUE system, which takes advantage of a dried-in-gel vehicle such as polyvidone or a cellulose derivate. Not all allergens are stable over time; several have a unsatisfactory chemical stability because of oxidation.⁹ The highest objectivity in reading and scoring can be achieved by detailed description of the reaction seen, as well as using a standardized score.

Table 2
Scoring of patch test reactions according to Wilkinson and colleagues²⁶ on behalf of the International Contact Dermatitis Research Group

Score	Interpretation
–	Negative reaction
?+	Doubtful reaction; faint erythema only, not considered proven allergic reaction
+	Weak (nonvesicular) reaction; erythema, slight infiltration
++	Strong (edematous or vesicular) reaction; erythema, infiltration, vesicles
+++	Extreme (bullous or ulcerative)
IR	Irritant reactions of different types
NT	Not tested

From Wilkinson DS, Fregert S, Magnusson B, et al. Terminology of contact dermatitis. *Acta Derm Venereol* 1970;50(4):287–92; with permission.

Table 3**Scoring of patch test reactions, on behalf of European Contact Dermatitis Society and European Environmental and Contact Dermatitis Research Group**

Score	Interpretation
+	Homogeneous redness in the test area with scattered papules
++	Homogeneous redness and homogeneous infiltration in the test area
+++	Homogeneous redness and infiltration with vesicles
++++	Homogeneous redness and infiltration with coalescing vesicles

From Menné T, White I. Standardization in contact dermatitis. *Contact Dermatitis* 2008;58(6):321; with permission.

Other disadvantages in patch testing are the possibilities to induce or reactivate hypersensitivity in sensitized patients. Also, it can only be performed if there is no more active inflammation, otherwise the result could be a false-positive. No florid eczema or intense exposition to UV light should precede the test. There are no data available regarding patch testing in pregnancy. For this reason, the International Contact Dermatitis Research Group advises against testing pregnant women.⁷ For medications and patch testing there are only unclear or controversial data available. For corticosteroids there is no consensus yet, but, according to Lachapelle and Maibach,⁷ patch testing in patients undergoing corticosteroid therapy requires caution in the evaluation phase and we advise against it (see earlier). For antihistamines there is no general agreement, so in most centers treatment with antihistamines is paused during testing.³¹ In addition, immunomodulators may alter the results³² so, whenever possible, they should be avoided during testing.

SURVEY OF PATCH TEST REACTIONS VIA DIGITAL IMAGING

A recent pilot study by Boone and colleagues³³ was designed to distinguish doubtful (+?) allergic contact reactions from irritant reactions. High-definition optical coherence tomography (HD-OCT) offers noninvasive, in vivo, real-time, three-dimensional measurement of the epidermal thickness, and it showed that an increased thickness of the epidermis correlates with irritant reactions, which may be counterintuitive for some experts. Furthermore, specific HD-OCT features corresponded with the severity of visual scoring. This peculiarity might lead to more objectivity in the scoring of inflammatory reactions. Standard three-dimensional photography may soon be available at sufficient resolution to reliably allow grading of reactions.

MODIFICATIONS OF PATCH TESTING

1. Strip patch testing: can increase the sensitivity of patch testing by decreasing the thickness of the stratum corneum, which results in a higher penetration of the allergens
2. Repeated open application test: repeated open application of an allergen over a few days; for example, when patch testing is negative but ACD from a specific allergen is highly probable
3. Atopy patch testing: for the diagnosis of aerogenic or alimentary allergens in patients with atopic history; not yet sufficiently validated
4. Scratch testing³⁴
5. Prick testing: in suspicion of type I allergy, such as protein contact allergy³

IN VITRO TESTS

In vitro lymphocyte stimulation tests expose blood-derived lymphocytes to controlled, purified amounts of allergens. A proliferation (traditionally measured with H_3 thymidine incorporation) correlating with increasing titers of allergen is interpreted as allergen-specific reaction. Especially for metal salts, these assays are very well validated. In vitro assays allow more control but have several disadvantages. First, allergens must be free of nonspecific stimulatory compounds, such as lipopolysaccharide. Second, a proliferation to an allergen does not allow the conclusion that a manifest allergy is present. Third, newer data³⁵ have shown that most allergen-specific T cells are in the skin. Thus, the sensitivity of tests with peripheral blood mononuclear cells may not be high. Fourth, the in vitro tests are very labor intensive and have limited sensitivity and specificity. They are not standardized enough to be available as kits; instead, the tests must be performed by experienced, specialized laboratories and results must be carefully evaluated. Thus, they are not used for routine diagnostics for ACD.^{3,36}

TREATMENT

One of the most important measures in the prevention of ACD is avoidance of contact with the respective allergens. Often this is not feasible because of work or environmental circumstances. In these cases, patients need to be carefully instructed about protective arrangements, such as the wearing of appropriate clothes (eg, gloves, masks) and barrier creams.

Most frequently, acute and chronic ACD are treated with topical corticosteroids (class II–III, most usually mometasone furoate or betamethasone). Even though palms and soles are not considered high-risk regions for steroid-induced atrophy, some atrophy is often observed after long-term treatment and may contribute to the areas' risk of being a *minoris locus resistens* to eczema. In these situations, and especially in areas with thin epidermis, such as intertriginous areas, topical calcineurin inhibitors (eg, tacrolimus, pimecrolimus) are good choices for maintenance therapy after a short spell of steroids to reduce inflammation. They do not cause skin atrophy and have been shown to be useful to dampen chronic inflammation in atopic dermatitis.³⁷ In some cases, antihistamines can also reduce pruritus.

Individuals with chronic ACD may benefit from narrow-band UV-B phototherapy or psoralen plus UV-A (PUVA) treatments. Systemic retinoids, especially the new retinoid alitretinoin but also acitretin, are very successful in treating eczema.³⁸

Because of their teratogenicity, contraception is key. In special cases, a short course of systemic corticosteroid therapy can be useful, particularly in cases of systemic contact allergies as a result of hematogenic dissemination. Rarely, immunosuppressive agents such as cyclosporine, azathioprine, or mycophenolate are also used in chronic ACD.³ It remains unknown whether biologics such as the IL-4/IL-13 antagonist dupilumab or the IL-6 antagonist tocilizumab³⁹ are beneficial in ACD.

CURRENT CONTROVERSIES

There are few fields more controversial than ACD and its diagnostic techniques. Since the conception of the patch test by Josef Jadassohn (1863–1936) and further development by Bruno Bloch (1878–1933), every aspect of diagnosis and test has been challenged.

Who should be patch tested? Every eczematous dermatosis? A general rule is that patch testing should produce positive test results between 30% and 65% of the

time.⁴⁰ This guide may help clinicians to adjust their thresholds of ordering patch tests, but is little help in deciding whether a given patient should be patch tested or not. The most promising candidates for patch testing are eczematous disorders in which ACD is suspected or failing to respond to treatment, chronic hand and foot dermatitis, or stasis eczema, and also scattered generalized distribution of dermatitis.

What standard series should be used? It is different in every country. This question is controversial and not all selections seem to be strictly evidence based and in accord with locally prevalent allergies. Also, minor factors, such as the size of testing chambers, can affect the outcome of patch testing.

Interpretation of the relevance of positive patch test reactions is a challenge for dermatologists.⁴¹ The circumstantial nature of the patch test does not allow a direct conclusion on the allergen causing the ACD, therefore each reaction must be considered in the context of the patient's history and clinical features.

Understanding of the pathophysiology of ACD may soon change. In the past, ACD was thought to depend on the systemic presence of primed T cells that were expected to be everywhere in the skin. Therefore, a negative reaction in a patch test was usually interpreted as an absence of sensitized T cells against the respective allergen in the tested patient. However, because newer data showed predominant numbers of T cells residing in the skin and staying locally for prolonged periods of time, it could be that some contact allergies are local phenomena.

The reasons for irritant and allergic reactions showing similar histologic (including T-cell infiltrates) and clinical patterns remain unclear. It could be that latent, perhaps nonspecific, T cells are expanded on irritation of the skin, but this remains largely unproved.

Taken together, the study of ACD continues to thrive and evolve. These conditions affect a high percentage of the population and are ideal targets for further investigation for prevention and treatment. In the future, new forms of contact allergy diagnostics and, it is hoped, standardized procedures for testing and interpretation of the relevance of positive findings may be developed.

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