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DOI: https://doi.org/10.1016/j.iac.2016.08.014

Originally published at:
Kostner, Lisa; Anzengruber, Florian; Guillod, Caroline; Recher, Mike; Schmid-Grendelmeier, Peter; Navarini, Alexander A (2017). Allergic contact dermatitis. Immunology and Allergy Clinics of North America, 37(1):141-152.
DOI: https://doi.org/10.1016/j.iac.2016.08.014

Allergic Contact Dermatitis

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KEY WORDS (5-8)

Contact, Dermatitis, Allergen, T cell, Patch, Work-related

KEY POINTS (3-5)

- Allergic contact dermatitis belongs to the most frequent work-related conditions
- Clinical features chronic allergic and irritant contact dermatitis may overlap
- Identification of the offending allergen in ACD is often circumstantial
- New techniques are required to overcome these old challenges

SYNOPSIS (1-paragraph)

Allergic contact dermatitis (ACD) is a frequent skin disease due to a T cell mediated immune reaction to usually innocuous allergens that get in contact with skin. In a chronic stage and especially when a work-related compound is the allergen, ACD can have grave medical and socio-economic consequences. ACD and irritant contact dermatitis (ICD) often occur together. A detailed history and clinical examination are crucial and guide patch testing that is the gold standard to diagnose ACD. T cell clones persisting in the skin may explain the tendency of ACD to relapse even after years of allergen avoidance. Traditional treatments for ACD are topical steroids, calcineurin inhibitors, phototherapy, retinoids including the recent alitretinoin, and immunosuppressants. Targeted therapies are as yet lacking.

Introduction

Allergic contact dermatitis (ACD) seems a straightforward and simple disease. The problem is easily defined – it's a cutaneous immune reaction against one or more non-toxic allergens that come in contact with the skin. So all the patient should need to do is getting rid of the allergen. But in reality, detection, allergen avoidance and therapy are often very difficult. Therefore, ACD can plague patients for years and is a grave socioeconomic problem today.

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

The one-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 due to marred epidermal barriers or due to alterations of immune reactivity [3]. The two main groups of contact eczema coexist in many cases and the differentiation between them often proves to be difficult. Both diseases can have similar clinical and histological aspects.

Epidemiology

4-7% of all dermatology consultations are due to contact dermatitis. In Sweden, about 10-12% of adults suffered of hand eczema during the span of one year. The tendency for ACD is dropping slightly, however, and inversely mirrored by the rise 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 may be mostly due to the cumulative opportunities of sensitization rather than an effect of the age, as the latter does not have a direct influence on capability for sensitization. The prevalence of pure ACD is difficult to measure as allergic and irritant contact dermatitis usually co-exist. The incidence of occupational dermatitis per 1000 workers and year is about 0.5 - 1.9 in most European countries.

Pathomechanism

The allergic contact dermatitis develops only after an initial sensitization [4] phase with usually innocuous substances. These are small molecules that cannot be recognized on their own by the adaptive immune system. When they are bound to cutaneous proteins, however, they can associate

with major histocompatibility antigens class II (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 (TNF-α, IL1-β, others) 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 class II (i.e. a polar hapten) or MHC class I (i.e. the small lipid soluble molecule urushiol). T cells will then proliferate in the lymph nodes, primed T cell clones will start to disseminate throughout the skin of the body, and cutaneous lymphocyte antigen (CLA) positive T cells stay thereafter in the skin for long periods of time [5]. Activated T-cells produce cytokines such as IFN-γ, IL-2 and IL-17. They are attracted by keratinocyte-derived CCL27 that binds to their CCR10 to the locus of inflammation. T cells have an apoptotic effect on keratinocytes due to their FasL and perforin expression. These effects combined ultimately lead to the clinical phenotype of ACD. Taken together, the delayed hypersensitivity reaction is due to the previously activated T-cells, which only at second contact causes 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 irritant contact dermatitis (ICD), even though in both conditions, largely similar clinical features develop. In ICD, the inflammation is rather due to the irritant itself, which – somewhat in contrast to 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 i.e. when liquid tracks are visible. Stronger reactions include spongiotic vesicles that itch and burst quickly, weeping intensively and crusting thereafter (Figure 1a,b). In ACD due to 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 fissuring become more prominent [9] (Figure 1c). The lesion is then less sharply circumscribed, infiltration and thickness of skin increases, lichenification marks develop and regional differences in the stage of the inflammation can be seen. The localization plays an important role for the morphology of ACD – even

though it can occur on every part of the body. Also, the body site gives important clues to the etiology of ACD and is the starting point for detailed history taking, which is crucial to guide patch testing for identification of the responsible allergen. When it comes to delicate areas with a thin stratum corneum such as the eyelids, penis and scrotum, erythema and edema usually outweight papules and vesicles. The same clinical features appear 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 routes [7]:

- *Autotransfer:* e.g. 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, vapours or gasses, e.g. from wall paint or pollen), typically clinical lesions on uncovered areas
- *Photo-allergic ACD:* from 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 can occur. 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 put forward 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 scleroderma-like 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, while 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 being various types of dermatitis of different etiology 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 where it occurs as a reaction to the mites' feces, in phthiriasis, mycoses including candidiasis, and impetiginous infections. On the other hand, rarely ACD can also hide behind non-eczematous lesions such as erythema-multiform-like [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 finally pemphigoid-like lesions [20].

Diagnosis

Since it is very 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 find a proper diagnosis and guide subsequent patch tests.

A useful history should include

- Time of onset and possible contact with allergens or irritants (temporal relationship)
- Contact area corresponding to reaction area
- Initial clinical patterns and evolution of morphology
- Working environment: exposure to potential allergens (even as unexpected as in phonecards [21]), dose, frequency, duration, protective measures such as gloves, masks and barrier creams and concomitant factors such as humidity, temperature, occlusion, friction
- Similar situation in co-workers
- Leisure activities
- Domestic products, protective measures regarding cleaning works
- Skin care products, fragrances, nail and hair products
- Jewellery and clothing, communication devices
- Suspicion regarding autotransfer, heterotransfer (e.g. connubial dermatitis), aerogen dermatitis, photo allergic 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, 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 co-existent. Also it is known that an allergic contact dermatitis often develops on the basis of an irritant CD. 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 there rarely occur type I hypersensitivity reactions such as the protein contact allergy [22], the overwhelming part of ACD is due to T-cell-mediated delayed type IV reactions.

Patch Test

Patch testing is by 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 in 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 T.R.U.E. 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 patch test system and tape and on the exposure time. The standardized T.R.U.E.-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 that 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 sulphate 0,25 % or nonanionic acid, can be applied as a positive control to check the skin's irritability at the time of exposure. A positive reaction of the sodium lauryl sulphate does not indicate an allergic reaction, 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 is even more important as 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 are removed at 24 hours already. 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 above), then after 72 hours and another time after 96 hours, especially if there are questionably positive results at 72 hours. A repeated reading after 1 week is highly suggested to not miss a delayed reaction (e.g. neomycin, corticosteroids) [9]. As for the analysis there are several scoring systems, a commonly used evaluation method is the system according to *Wilkinson et al.* [26] (see Table 2). Reading and scoring have to be repeated at each individual visit to check the progression or regression of the reaction (day 2, day 3, day 4, or day 7). A modification has been proposed by *Menné et al.* (Table 3) [27], but to date, a world-wide consensus is lacking. Follicular reactions are not uncommon, i.e. to metals, and can be noted with an "f" beside the reaction intensity.

An increasing reaction (*crescendo*) in patch testing is compatible with an allergic contact dermatitis, an initially positive and subsequently waning reaction (*decrescendo*) rather suggests an irritative cause.

Positive reactions to chemically similar allergens may indicate cross reactions. Positive reactions to more than 5 non-related substances can on one hand indicate polysensibilisation [28], on the other hand an „angry back/excited skin syndrome" must be considerered as well. [29, 30]. The latter can be ruled out by repeated 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 finally the score grading of patch test reactions.

The amount of allergen is important, as the reactions can provoke either false-positive (e.g. by using an exaggerated quantity of the allergen, causing an irritation instead of an allergic reaction) or false-negative reactions (e.g. by using too little amount of the allergen). Ready-made tests or testing preparations seek to overcome this problem. Petrolatum is the most commonly used carrier for allergens, with exception of the T.R.U.E. 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 non-

satisfactory chemical stability caused by oxidation-progresses [9]. The highest objectivity in reading and scoring can be achieved by detailed description of the reaction seen, beside using a standardized score.

Other disadvantages in patch testing are the possibilities to induce or reactivate hypersensitivity in sensibilized patients. Also, it can only be performed if there is no more active inflammation. The result could otherwise be false positive. No florid eczema or intense exposition to UV-light should precede the test. There is no data available regarding patch testing in pregnancy. For this reason the *ICDRG* advises against testing pregnant women [7]. Relating to medicaments and patch testing there is only unclear or controverse data available. As for corticosteroids there has not been found a consensus yet, but according to *Lachapelle et al.* patch testing in patients undergoing corticosteroid-therapy requires great caution in the evaluation phase [7] and we advise against it (see above). Likely, for antihistamines there is no general agreement, wherefore in most centers the treatment with antihistamines is paused while testing [31]. Finally, immunomodulators as a whole could alter the results [32] and whenever possible, they should be avoided during testing.

Survey of Patch Test Reactions via Digital Imaging

A recent pilot study, published by *Boone et al.* aims to distinguish doubtful (+?) allergic contact reactions from (IR) irritant reactions. As a High-Definition Optical Coherence Tomography (HD-OCT) it offers a non-invasive in vivo real-time three-dimensional measurement of the epidermal thickness. It showed that an increased thickness of the epidermis correlates with irritant reactions, which may be counter-inuitive for some experts. Furthermore, specific HD-OCT features corresponded with the severity of visual scoring. This peculiarity might lead to more objectivity in scoring of inflammatory reactions [33]. Standard three-dimensional photography may soon be available at sufficient resolution to reliably allow grading of reactions.

Modifications of Patch Testing

1. *Strip Patch Test* can increase sensitivity of patch testing by decreasing the thickness of the stratum corneum which results in a higher penetration of the allergens
2. *ROAT* (= repeated open application test): repeated open application of an allergen over a few days, e.g. when patch testing in negative but ACD from a specific allergen is highly probable

3. *Atopy Patch Test*: regarding diagnosis of areogenic or alimentary allergens in patients with atopic history, not yet sufficiently validated
4. *Scratch Testing*
5. *Prick Testing* in suspicion of type I allergy, such as protein contact allergy [3]

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 validated very well. *In vitro* assays allow more control but have several disadvantages. For one, allergens must be free of non-specific stimulatory compounds such as lipopolysaccharide. Secondly, a proliferation to an allergen does not allow the conclusion that a manifest allergy is present. Thirdly, due to newer data [34] we are aware that the great majority of allergen-specific T cells are in the skin. Thus, the sensitivity of tests with peripheral blood mononuclear cells may not be very high. Fourth, the *in vitro* tests are very labour-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, 35].

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 due to work or environmental circumstances. In these cases, patients need to be carefully instructed about protecting arrangements such as the wearing of appropriate clothes (e.g. 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 of steroid-induced atrophy, quite often some atrophy is observed after long-term treatment and may contribute to the areas' risk of being a *minoris locus resistentiae* to eczema. In these situations, and especially in areas with thinner epidermis such as the face of intertriginous areas, topical calcineurin-inhibitors (e.g. 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 [36]. In some cases, antihistamines can also reduce pruritus.

Individuals with chronic allergic contact dermatitis may benefit from narrow-band UVB phototherapy or psoralen plus ultraviolet-A (PUVA) treatments. Systemic retinoids, foremost the new alitretinoin, but also acitretin, are very successful in treating eczema. Due to their teratogenicity, contraception is key. In special cases, a short systemic corticosteroid therapy can be useful, particularly in cases of systemic contact allergies as a result of hematogenic dissemination. Rarely also immunosuppressive agents such as cyclosporine, azathioprine or mycophenolate are used in chronic ACD [3]. It remains unknown so far whether biologics such as the IL-4/-13 antagonist dupilumab or the IL-6 antagonist tocilizumab [37] are beneficial in ACD.

Current controversies

There may be 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 rule of thumb is that patch testing should produce positive test results between 30 and 65% of the time [38]. This may help clinicians to adjust their threshold of ordering patch tests accordingly, but helps little to decide whether a single patient should be patch tested or not. The most promising candidates for patch testing are eczematous disorders where 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, as it is different in every country? This is indeed 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 play a role on the outcome of patch testing.

The interpretation of relevance of positive patch test reactions is a challenge for all dermatologists [39]. 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 context with the patient's history and clinical features.

Our understanding of the pathophysiology of ACD may soon change somewhat. Traditionally, ACD is thought to be dependent on systemic presence of primed T cells that are expected to be everywhere

in the skin. Therefore, a negative reaction in patch test is 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 well be that some contact allergies are local phenomena.

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

As to therapy of (atopic) eczema, some controversy was stirred by a recent paper showing application of topical steroids on presoaked skin (wet-wrap technique) not achieving improved outcome than application of topical steroids on dry skin [40].

Taken together, the fascinating field 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, we may see new forms of contact allergy diagnostics and hopefully standardized procedures for testing and interpretation of relevance of positive findings.

Figure legend

Figure 1

A: Acute ACD to neomycin eye drops; B: Acute ACD to chromium; C: Chronic ACD

Table legend

Table 1:

Standard patch test series recommended by the German Contact Dermatitis Research Group (DKG) [3].

Table 2:

Scoring of patch test reactions according to Wilkinson et al., on behalf of the ICDRG [26]

Table 3:

Scoring of patch test reactions, on behalf of ECDS and EECDRG [27]

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Table 1:

Name of substance	Vehicle	Concentration
Potassium dichromate	PET	0.5 %
Thiuram mix	PET	1 %
Cobalt (II) chloride, 6*H2O	PET	1 %
Balsam of Peru	PET	25 %
Colophony	PET	20 %
N-isopropyl-N'-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) sulphate, 6*H2O	PET	5 %
Paratertiarybutyl 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(diethyldithiocarbamate)	PET	1 %
Dibromodicyanobutane (methyldibromo glutaronitrile)	PET	0.2 %
Propolis	PET	10 %
Bufexamac	PET	5 %
Compositae mix II	PET	5 %
Mercaptobenzothiazole	PET	2 %
Hydroxymethylpentylcyclohexenecarboxaldehyde (Lyral)	PET	5 %
Bronopol (2-bromo-2-nitropropane-1,3-diol)	PET	0.5 %
Fragrance mix II	PET	14 %
Sodium lauryl sulphate	AQU	0.25 %
Ylang-ylang (I + II) oil	PET	10 %
Sandlewood oil	PET	10 %
Jasmine absolute	PET	5 %

Table 2:

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

Table 3:

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