



S3 guidelines: Epicutaneous patch testing with contact allergens and drugs – Short version, Part 1

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Summary

Epicutaneous patch testing is the diagnostic standard for the detection of allergic contact dermatitis. The present guidelines are aimed at residents and board-certified physicians in the fields of dermatology and allergology as well as other medical specialties involved in establishing the indication for patch testing and its execution in patients with contact dermatitis and other forms of delayed-type hypersensitivity. The target audience also includes other health care providers and insurance funds.

Based on a systematic literature search and a formal consensus process (S3), the guidelines were developed by dermatologists in collaboration with pediatricians, occupational medicine physicians, nursing staff as well as patient representatives. The systematic methodological approach and appraisal of evidence upon which the recommendations are based are outlined in a separate method report that also contains evidence tables.

The guidelines address general aspects of patch testing as well as medicolegal issues. The recommendations given relate to topics such as the indication for patch testing, informed patient consent, as well as the choice of test substances, test chambers and test site, duration of exposure, reading times and interpretation of test reactions. Furthermore, recommendations are provided with respect to endogenous and exogenous factors, specific patient groups (children, pregnant women, immunosuppressed individuals) as well as possible risks and adverse events associated with patch testing using contact allergens.

Note: This publication is part 1 of the short version of the S3 guidelines for “Epicutaneous patch testing using contact allergens and drugs” (registry no. 013 – 018; date: March 20, 2019; valid until December 31, 2021). Part 2 of the short version will be published in the next issue. The long version of these guidelines can be accessed at www.awmf.org. The method report is available as online publication (<https://www.awmf.org/leitlinien/detail/II/013-018.html>) and contains the evidence tables in its appendix.

Introduction

The objective of the present guidelines is to offer office-based dermatologists and those working at hospitals evidence-based and consensus-based recommendations for conducting patch testing using contact allergens in patients (adults, adolescents and children) with delayed-type hypersensitivities. In these guidelines, the terms ‘hapten’ and ‘contact allergen’ are used synonymously, irrespective of the fact that – *in vivo* – a hapten requires binding to endogenous proteins for it to become an immunologically active contact allergen.

The present publication is a short version of the guidelines. The long version (see AWMF guideline registry) contains additional material, including information about the expert committee, guideline use, applicability and objectives as well as information about financing, implementation, circulation and conflicts of interest. The method report is also available there.

These guidelines are evidence based and consensus based (S3). Recommendations were developed in an evidence-based manner, based on a systematic literature search relating to predefined key

questions and a subsequent consensus-finding process by a representative, interdisciplinary committee of experts using a structured nominal group technique (see method report).

Uniform wording was used in an effort to standardize the recommendations provided in these guidelines.

Strength of recommendations – wording and symbols

Grading of recommendations	Syntax	Symbol
Strong recommendation	Is recommended	↑↑
Recommendation	Can be recommended	↑
Recommendation open	Can be considered	o
Negative recommendation	Cannot be recommended	↓

1 Patient history and information – expert consensus

Statement	Consensus
Prior to any patch testing, a thorough patient history taken by a physician trained in allergology is required and serves as the basis for individual testing.	Strong consensus (100 %)

As a bare minimum requirement, the patient history must include information on the following issues: current complaints (location of skin lesions, temporal course), occupational and recreational exposure (irritants and possible allergen contact), atopic diathesis, preexisting (skin) diseases and (concomitant) medications. Auxiliary tools relating to occupational exposure in particular may be useful in obtaining a full history [1]. Based on the information thus gathered, a customized individual testing program is put together (according to good medical practice) [1–4]. In this context, it is useful to observe the recommendations issued by the German Contact Dermatitis Research Group (DKG, Deutsche Kontaktallergie-Gruppe) (see DKG website: dkg.ivdk.org/).

Statement	Consensus
Prior to testing, every patient must be informed – preferably in writing – about the purpose, the actual procedure and possible risks and adverse events associated with patch testing (chapter 11, Table 8 in part 2 of the short version) as well as relevant legal privacy issues.	Strong consensus (100 %)

Reference: Mahler et al. 2017 [5]

Prior to testing, physicians are required to obtain the patient's informed consent for conducting the test and using the data obtained in the process. It is strongly advised to obtain written consent (especially given the shift of the burden of proof pursuant to Article 630h, Section 2, BGB of the German Social Code (Bürgerliches Gesetzbuch [BGB]); in addition, the patient should be handed a copy of both the written information provided and of the signed consent form (Article 630e, Section 2, BGB) [5]. A recommendation by the DKG on written informed consent is available on the DKG website (https://dkg.ivdk.org/dok/PatientenAufklaerung_ECT_Patchtest_2017_10_30.pdf [last accessed January 10, 2019]).

2 Indication for patch testing – first key question

Indication for patch testing

Patch testing involves the controlled application of contact allergens under standardized conditions in order to investigate whether it is possible to trigger a specific delayed-type immune reaction against a given allergen. Any contact sensitization is demonstrated by a localized, immunologically triggered eczematous reaction. If there is evidence of such a sensitization in combination with a corresponding history and clinical presentation, it may be inferred that a particular cutaneous or mucosal inflammatory reaction is/was caused by contact with that respective allergen. Without correlating the patch test results with the clinical findings and the patient history of allergen exposure, the allergen that tested positive may only be considered a possible cause of the clinical condition as well as a potential risk factor for contact allergy in the future.

Established as a diagnostic method more than 100 years ago, patch testing has since then evolved. In the medical literature, there is no doubt about its fundamental ability to detect allergic contact dermatitis as an underlying condition and to identify the causal agents (see chapter 6 on sensitivity and specificity of patch testing). There is a considerable number of epidemiological studies, case collections and individual case reports on patch testing that address aspects such as the choice of allergens, concentrations of test substances, and the relevance of test results. Based on long-term experience and clinical diagnosis according to good medical practice, there is very broad consensus as regards the ability of patch testing to uncover clinically relevant sensitizations to defined allergens under standardized conditions.

Another quality criterion of patch testing relates to the assessment of the potential medical and economic benefit of this diagnostic test; or to put it differently, what kind of harm may be caused by a patch test that is either not performed at all or conducted incorrectly? A retrospective monocenter analysis of test data highlighted the significance of carefully reviewing the indication for patch testing both in terms of patient selection and the spectrum of substances tested [6]. Analysis of multicenter data on the disease course in patients with contact dermatitis, who either received a patch test at various points in time or who underwent no diagnostic testing at all, revealed significant improvement in quality of life and a reduction of treatment costs for patients who were tested early on [7, 8].

A common issue in everyday practice is the question whether certain oral symptoms might be caused by dental prosthetic materials. While the relevant literature on this

topic is highly inconsistent, patch testing is the only procedure used and recommended for in vivo diagnosis [9]. It is important to emphasize that testing is only useful if the patient shows visible signs of mucosal or labial inflammation. Any positive test results require particularly critical evaluation as to their relevance (Table 1).

In general, contact allergens contained in implants can also be identified by patch testing. However, if a sensitization has been detected, the difficult question remains in each individual case whether that sensitization is actually the pathogenetic cause of the intolerance to a particular implant. For this reason, there are great inconsistencies in the literature regarding the clinical significance of such test results. There is, however, no doubt as regards the fundamental ability of patch testing to detect a particular sensitization in this context. The highest level of evidence for this indication does not rise above the level of “recommendations based on expert consensus” [10, 11].

On the other hand, patch testing is unsuitable for the diagnostic workup of immediate-type hypersensitivity reactions as well as internal and neurological diseases and disorders of the autonomic nervous system. The pathophysiological processes of contact allergic reactions do not plausibly result in any such clinical presentations. It is therefore completely irrelevant if there is a positive reaction to any suspected allergens, as it is impossible to deduce any causal link between such test results and the aforementioned clinical conditions. There is no evidence in the literature that disorders of other organ systems are more frequently associated with certain contact sensitizations.

Any patch test strictly shows an existing sensitization. It is pathophysiologically impossible to predict any potential future sensitization; such testing is therefore contraindicated.

In individual cases, testing may be considered to rule out a sensitization that might have occurred based on the patient's history but that has not yet resulted in an objectifiable

Table 1 Indications for patch testing.

Indication	Evidence level/references	Consensus	Derived recommendation	Strength
Suspected allergic contact dermatitis of the skin; allergic contact reaction of adjacent mucous membranes or of the oral mucosa, for instance, reaction to dental prostheses associated with mucosal lesions	Standard procedure in the literature [4 according to OCEBM/ Rajagopalan & Anderson 1997; 4 according to OCEBM/ Rajagopalan et al. 1998; 4 according to OCEBM/van der Valk et al. 2003; 4 according to OCEBM/ Raap et al. 2009]	Strong consensus (100 %)	Is recommended	↑↑
Suspected delayed-type immune reaction to components of implants associated with local inflammatory reaction to the implant	[4 according to OCEBM/Schallock et al. 2011; 4 according to OCEBM/ Thomas et al. 2015] Expert consensus	Strong consensus (100 %)	Can be recommended	↑
Workup of immediate-type hypersensitivity reactions as well as neurological or internal diseases and disorders of the autonomic nervous system	Expert consensus	Strong consensus (100 %)	Cannot be recommended	↓
“Prophetic” (predictive) testing in the absence of a history of allergic symptoms to predict possible future sensitization	Expert consensus	Consensus (92 %)	Cannot be recommended	↓
Testing in the absence of a history of allergic symptoms prior to exposure in order to assess the presence of “silent” sensitization	Expert consensus	Consensus (75 %)	Can be considered in individual cases	o

disease (silent sensitization). Such a situation may arise if relevant exposure is expected in the future and failure to conduct the test could lead to significant disadvantages for the patient (e.g., if the patient is denied a job or a medical procedure).

Protein contact dermatitis differs from contact allergy in terms of its etiopathogenesis. The diagnostic approach therefore differs from standardized patch testing (in some cases even significantly) and is continuously evaluated by groups of experts in order to arrive at defined recommendations. Both indication and diagnostic approach require a separate review that is not part of the present guidelines.

Suspicion of a photoallergic or phototoxic reaction warrants a modified test procedure (photopatch testing). This too requires a discussion outside of the present guidelines.

Patch testing in drug hypersensitivity (to systemically administered agents)

Patch testing is employed in the diagnosis of T cell-mediated drug reactions (type IV reactions according to Coombs and Gell), delayed-type drug hypersensitivity; latency period of sensitization 5–10 days; following re-exposure, the earliest

onset of the reaction occurs 1–6 hours after the drug has been administered [12, 13]. In this context, the methodology is primarily based on extensive expert experience. Not only is there a lack of systematic methodological studies (suitable test concentrations, test vehicle, reading of the test), the specificity and sensitivity of patch testing are unknown for most pharmaceutical drugs. The diagnostic workup is also complicated by the complex process of metabolization, which may show significant interindividual differences. In addition, drug reactions to many pharmaceutical agents involve different co-factors and – compared to the skin – distinct immunological processes (Table 2).

Indication

Delayed-type hypersensitivity reactions caused by systemic administration of pharmaceutical agents include maculopapular drug rash (the most common such manifestation) as well as generalized/systemic contact dermatitis, localized delayed-type hypersensitivity reactions to subcutaneously injected heparins, *symmetrical drug-related intertriginous and flexural exanthema* (SDRIFE) – formerly also referred

Table 2 Indications for patch testing in the diagnostic workup of drug reactions.

Indication	Evidence level/references	Consensus	Derived recommendation	Strength
Maculopapular rash	5 according to OCEBM; [Barbaud A et al. Curr Allergy Asthma Rep 2014; 14: 442] 3b according to OCEBM; [Lammintausta K & Kortekangas-Savolainen O. Br J Dermatol 2005; 152: 968–74] 3b according to OCEBM; [Osawa J et al. J Dermatol 1990; 17: 235–9] 5 according to OCEBM; [Barbaud A. Toxicology 2005; 209: 209–16]. 5 according to OCEBM; [Barbaud A. Immunol Allergy Clin North Am 2009; 29: 517–35] 2b according to OCEBM; [Barbaud A et al. Br J Dermatol 1998; 139: 49–58]	Strong consensus (100 %)	Can be recommended	↑
SDRIFE	5 according to OCEBM; [Barbaud A. Immunol Allergy Clin North Am 2009; 29: 517–35]	Consensus (92 %)	Can be recommended	↑
AGEP	5 according to OCEBM; [Barbaud A. Curr Allergy Asthma Rep 2014; 14: 442] 2b according to OCEBM; [Barbaud A et al. Br J Dermatol 2013; 168: 555–62] 4 according to OCEBM; [Duong T et al. Eur Ann Allergy Clin Immunol 2010; 42: 62–3] 2b according to OCEBM; [Wolkenstein P et al. Contact Dermatitis 1996; 35: 234–6]	Strong consensus (100 %)	Can be recommended	↑

Continued

Table 2 Continued.

Indication	Evidence level/references	Consensus	Derived recommendation	Strength
DRESS	5 according to OCEBM; [Barbaud A. Curr Allergy Asthma Rep 2014; 14: 442] 2b according to OCEBM; [Barbaud A et al. Br J Dermatol 2013; 168: 555–62]	Strong consensus (100 %)	Can be considered	o
SJS/TEN	5 according to OCEBM; [Barbaud A. Immun Allergy Clin North Am 2009; 29: 517–35] 2b according to OCEBM; [Barbaud A et al. Br J Dermatol 2013; 168: 555–62] 2b according to OCEBM; [Wolkenstein P et al. Contact Dermatitis 1996; 35: 234–6] 2b according to OCEBM; [Barbaud A et al. Br J Dermatol 1998; 139: 49–58]	Strong consensus (100 %)	Can be considered	o
Immune complex vasculitis	5 according to OCEBM; [Barbaud A. Toxicology 2005; 209: 209–16]	Strong consensus (100 %)	Cannot be recommended	↓
Progressive pigmented purpura, delayed urticarial reactions	5 according to OCEBM; [Brockow K et al.; Allergy 2002; 57: 45–51]	Strong consensus (100 %)	Can be considered	o
Fixed drug eruption	3b according to OCEBM; [Brahimi N et al. Eur J Dermatol 2010; 20: 461–4] 4 according to OCEBM; [Duong T et al. Eur Ann Allergy Clin Immunol 2010; 42: 62–3] 5 according to OCEBM; [Barbaud A. Curr Allergy Asthma Rep 2014; 14: 442] 3b according to OCEBM; [Lammintausta K, Kortekangas-Savolainen O. Br J Dermatol 2005; 152: 968–74] 2b according to OCEBM; [Barbaud A et al. Br J Dermatol 1998; 139: 49–58] 5 according to OCEBM; [Barbaud A. Immun Allergy Clin North Am 2009; 29: 517–35]	Strong consensus (100 %)	Can be recommended (testing at the site of the reaction)	↑
Multiform rashes	2b according to OCEBM; [Barbaud A et al. Br J Dermatol 1998; 139: 49–58]	Strong consensus (100 %)	Can be considered	o

Abbr.: OCEBM, Oxford Centre for Evidence-based Medicine; SDRIFE, symmetrical drug-related intertriginous and flexural exanthema; AGEP, acute generalized exanthematous pustulosis; DRESS, drug rash with eosinophilia and systemic symptoms; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis.

to as baboon syndrome, acute generalized exanthematous pustulosis (AGEP), fixed drug eruption (patch testing at the site of the reaction), and photosensitivity. In said conditions, patch testing (photopatch testing in case of photosensitivity) is considered helpful [13, 14]. Even in the workup of severe and potentially life-threatening T cell-mediated drug reactions such as *drug rash with eosinophilia and systemic symptoms* (DRESS) *syndrome* and Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) [14–17], patch

testing is generally deemed useful and safe. In this context, it is essential to bear in mind that there is always a chance that patch testing with pharmaceutical drugs may trigger a flare-up of the drug rash, even though such cases are rare [14, 15, 18–21]. The patient must be informed accordingly. The validity of the patch test depends on the drug itself as well as the type of adverse drug reaction [15]. While patch testing may generally be considered in cases of immune complex-mediated vasculitis, progressive pigmented purpura

(PPP) and delayed urticarial reactions [13], it is not thought to be conclusive [18].

For the diagnosis of fixed drug eruptions (FDEs), it may be recommended to do patch testing at the site of the reaction, especially if acetaminophen (paracetamol) or other NSAIDs (nonsteroidal antiinflammatory drugs) are involved as possible culprit agents [22]. Given that patch testing has been shown to successfully detect delayed-type sensitization to multiple related drugs [23], this test procedure appears to be useful (recommendation open) to confirm immunological cross-reactivities to drugs with similar chemical structures.

Recommendation	Strength	Consensus
In cases where an immediate-type reaction, especially to β -lactam antibiotics, cannot be definitively ruled out based on history, it is recommended to rule out an immediate-type sensitization prior to patch testing (e.g., by immediate reading after patch test application, detection of specific IgE antibodies, prick testing, intradermal testing) in order to be on the safe side.	↑↑	Strong consensus (100 %)

Evidence base: Barbaud et al. 2005 (5 according to Oxford Centre for Evidence-based Medicine [OCEBM]); Brockow et al. 2015 (5 according to OCEBM); Brockow et al. 2002 (5 according to OCEBM) [13, 18, 24]

Procedure

In general, skin testing should be conducted no sooner than one month after resolution of a non-IgE-mediated adverse drug reaction and no later than one year after the occurrence of such a reaction [19]. Test reading is usually performed according to the ESCD guidelines for conducting patch tests [2].

Please refer to the long version of these guidelines (see AWMF guideline registry) regarding *reading intervals, test vehicles and concentrations as well as risks of patch testing used in the diagnosis of drug hypersensitivity reactions*.

Sensitivity, specificity, clinical relevance

Sensitivity and specificity of patch testing vary, depending on the reaction itself as well as on the drug tested. The percentage of positive patch test reactions in the workup of T cell-mediated drug reactions is generally around 30–40 % [25]; please refer to the AWMF guidelines for the “Diagnosis of drug hypersensitivity reactions” [24]. With regard to maculopapular drug rashes, the percentage of positive

patch test reactions is reported to be even higher [20]. A retrospective analysis of cutaneous drug reactions in 200 patients (excluding TEN, SJS, DRESS, vasculitis and urticarial reactions following NSAID intake) found 42 positive reactions (10.4 %) following oral challenge testing (n = 403) in patients who had previously had negative skin tests (including 403 patch tests). This corresponds to a negative predictive value of skin testing of 89.6 % [26]. In a study of 900 patients who underwent skin testing (including patch testing) predominantly with antibiotics, 9.6 % of 229 skin test-negative patients as well as 13 (81.2 %) of 16 patch test-positive patients showed a positive reaction to oral challenge [27].

Previous studies suggest a high sensitivity and specificity. Depending on the causative drug, the sensitivity of patch testing in the workup of AGEP is higher than for SJS/TEN [15, 17, 21]. In case of DRESS, false negative test results were observed repeatedly, e.g. in patch testing with allopurinol [19].

3 Choice and application of test substances (including testing with non-approved substances/own substances) – expert consensus

Recommendation	Strength	Consensus
Notwithstanding the fact that the choice of test substances is generally based on patient history, it is recommended to test the “standard series”.	↑↑	Strong consensus (100 %)

As a general rule, the choice of allergens to be tested shall be based on history and therefore include all exposures elicited from the patient [1, 3]. However, exclusive testing of the suspected trigger is usually not sufficient, given that unexpected contact allergens are also frequently identified as relevant causative agents in patients with contact allergy. As a consequence, routine testing of the “standard series” is also recommended in addition to substances to which the patient is exposed based on history. The “standard series” contains contact allergens that are either very common or that are frequent causes of sensitization (> 0.5–1.0 % in patch testing cohorts suspected of having contact dermatitis) [2, 28, 29].

The “standard series” requires regular modifications in order to reflect local circumstances [30–33]. The current standard series and additional test series defined by the DKG can be found on the DKG website (dkg.ivdk.org/).

Screening tests using mixes (e.g., fragrance mix I, II, thiuram mix) is a space-saving option. Both false-positive and false-negative reactions have been reported.

Recommendation	Strength	Consensus
In case of positive patch test reactions to mixes, an itemized breakdown of the contact allergens contained therein <i>is recommended</i> . If there is clear suspicion based on history, individual testing of the allergens contained in a given mix (as well as other potential allergens if necessary) <i>is recommended</i> .	↑↑	Strong consensus (100 %)

Pursuant to Article 4, Section 5, of the German Medicinal Products Act (Arzneimittelgesetz, AMG), test allergens are medicinal products as specified in Article 2, Section 1, of the AMG [34]. In Germany, some test preparations that are diagnostically useful and necessary based on patient history are not commercially available as approved/marketable substances.

Recommendation	Strength	Consensus
<i>It is recommended</i> – if available – to use allergen preparations that have been pharmaceutically tested and that are approved or marketable as medicinal products.	↑↑	Strong consensus (100 %)

In addition to the standard series and special test series based on patient history, it may be necessary to test certain products or substances that the patient has used and brought in for testing but that are not commercially available as test preparations [4]. Especially novel contact allergens are frequently not detected by commercial test series.

Statement	Consensus
Pursuant to Article 67 of the AMG, physicians are required to notify once the competent state health authority (GCP inspectorate) of the use of test preparations made of the patient's own materials.	Strong consensus (100 %)

Pursuant to the exception rule in Article 13, Section 2b, of the AMG [34], physicians are allowed to manufacture a medicinal product “for the purpose of personal use in an individual patient” without the manufacturing permit usually

required by law. Formal approval as medicinal product is not required either in cases where a public or hospital pharmacy manufactures a test allergen preparation ordered by a physician (as “office material”) that he/she intends to use on his/her patients at his/her medical office. Use of test substances manufactured from the patient's own materials requires a patient's informed consent – just like testing with commercially available substances. Moreover, pursuant to Article 67 of the AMG (general notification requirement), physicians are required to notify once the competent GCP inspectorate [5].

Testing of the patient's own materials – determination of proper test concentrations in particular – follows certain rules that are not addressed in the present guidelines [2, 35–37].

Recommendation	Strength	Consensus
Testing with substances (or mixtures thereof) of unknown chemical identity or unknown biological effects <i>cannot be recommended</i> and is to be declined.	↓	Strong consensus (100 %)

Appropriate measures – such as refrigeration, protection from light, storage in closed containers, or observance of the expiration date – are required to ensure the proper quality of any given test preparation at the time of use.

Commercially available products are recommended as carrier systems and should – likewise – be subject to standardization and adequate clinical testing (see chapter 7). Prior to patch testing and application of the carrier systems, the skin must be inspected for its testability. It must be ensured that a sufficient quantity of the test preparation will stay in close contact with the skin for the entire duration of the intended exposure time.

Recommendation	Strength	Consensus
In order to assess skin irritability at the time of testing, concomitant application of the irritant sodium lauryl sulfate (SLS 0.25% in aqueous solution) <i>can be recommended</i> .	↑	Consensus (83 %)

Reference: Löffler et al. 2005 [38]

If there is erythema after occlusive application of SLS 0.25 % for 24–48 hours, this indicates nonspecific increased skin sensitivity at the test site (back) at the time of testing. As a consequence, erythema or weak (+) reactions to contact allergens with inherent irritant potential should only very cautiously be interpreted as having an allergic origin [38].

4 Test site, time of application, duration of exposure and time of reading – second key question

Site of application

There have only been few studies that compared the reactivity to patch testing at different sites of the body.

It has been shown that application of nickel sulfate onto the skin of nickel-sensitive test subjects leads to markedly different reactions in terms of severity depending on the test site: reactivity decreases in the following order: chin, back, neck, upper arms, thighs and palms [39]. Another study of nickel-sensitized individuals revealed greater patch test reactivity on the back than on the forearm [40].

In test subjects with a history of sensitization, application of patch test allergens on the upper and lower back showed no obvious differences between the two sites in terms of reactivity [41]. Similarly, simultaneous application of nickel sulfate on the upper and lower back of test subjects did not result in any visible differences in the assessment of skin test reactions [42].

Laser Doppler flow measurements, on the other hand, showed greater mean blood flow at test sites on the upper back than at those on the lower back [41].

Any differences in patch test reactivity between various sites of the body might – among other things – be caused by varying densities of antigen-presenting cells in the skin [43] as well as by differences in the thickness of the epidermis, respectively the stratum corneum.

Recommendation	Strength	Consensus
Application of patch test allergens on the back <i>is recommended</i> for practical reasons.	↑↑	Strong consensus (100 %)
Application on the upper arms or thighs <i>can be considered</i> .	o	

Evidence base: Lindelöf 1992 (3b according to OCEBM); Memon & Friedmann 1996 (3b according to OCEBM); van Strien & Korstanje 1994 (3b according to OCEBM); Simonetti et al. 1998 (3b according to OCEBM) [39–42]

Duration of exposure

Should exposure (occlusion) last for 24 hours (= 1 day) or 48 hours (2 days)?

It has been shown that a shorter exposure (occlusion) time (1 day) results in a smaller number of questionable and ir-

ritant test reactions than longer exposure (2 days) [44, 45]. Compared to one-day exposure, on the other hand, two-day exposure is known to be associated with greater sensitivity for the detection of allergic test reactions [46]. Uter et al. found significantly more ‘crescendo reactions’ (negative reaction on day 2, positive on day 3) in patch tests using two-day exposure than for one-day exposure. This highlights the fact that short occlusion might result in false-negative test results, possibly due to insufficient allergen penetration [47]. Studies conducted by Goh und Skog [48, 49] found no improved sensitivity regarding the detection of allergic test reactions; however, both publications do have some methodological limitations. In summary, longer allergen exposure is associated with greater sensitivity for the detection of allergic test reactions, while the risk of irritant and questionable test reactions also increases.

Recommendation	Strength	Consensus
With regard to high sensitivity, two-day exposure <i>is recommended</i> .	↑↑	Strong consensus (100 %)
With regard to high specificity, limiting the exposure to one day <i>can be considered</i> .	o	

Evidence base: Brasch et al. 1994 (3b according to OCEBM); Brasch et al. 1995 (4 according to OCEBM); Kalimo & Lamintausta 1984 (3b according to OCEBM); Uter et al. 1996 (4 according to OCEBM); Goh et al. 1994 (3b according to OCEBM); Skog & Forsbeck 1978 (3b according to OCEBM) [44–49]

Reading times

The first reading is usually performed at least 15 minutes after the patch has been removed (which is generally done after 48 h).

Necessity for a second reading after the first: after 72 h (= day 3) / 96 h (= day 4)?

- Up to one-third of all positive test reactions in the standard series manifest themselves only after the day 2 reading on day 3 or day 4 [47, 50–52]. Thus, if there is only one reading after 48 hours, the test may be falsely negative.
- Moreover, if there is only one reading after 48 hours with no subsequent readings, this is associated with the risk of falsely interpreting irritant reactions (positive after 48 hours but negative after 72 hours) as allergic reactions [47, 51, 53].
- It has been shown that readings after 72 hours resulted in higher reaction indices than readings after 48 hours, thus

suggesting that fewer irritant reactions are seen after 72 hours than after 48 hours [44].

2. Should the second reading be performed after 96 hours (day 4) or after 72 hours (day 3)?

In a study by Geier et al., a second reading on day 3 was superior to a second reading on day 4 in terms of detecting positive test reactions [54]. In an IVDK study, readings on day 3 and day 4 were equally suited to detect positive test reactions [47]. On the other hand, a single day 4 reading was shown to detect a greater number of positive test reactions than a single day 3 reading (95 % vs. 85 %) [55].

Recommendation	Strength	Consensus
A second reading after the first is mandatory and is recommended on day 3 or day 4.	↑↑	Strong consensus (100 %)

Evidence base: Uter et al. 1996 (4 according to OCEBM); Shehade et al. 1991 (4 according to OCEBM); Soni 1997 (4 according to OCEBM); Thyssen et al. 2008 (3b according to OCEBM); Rietschel et al. 1988 (4 according to OCEBM); Brasch et al. 1995 (4 according to OCEBM); Geier et al. 1999 (4 according to OCEBM); Todd et al. 1996 (3b according to OCEBM) [44, 47, 50–55]

3. Is it useful to do a third reading (late reading) after 7–10 days?

In patch tests with a broad panel of allergens, up to 15 % of positive reactions are not detected if there is no subsequent reading after day 3 (15 % [56]; 13.5 % [57]; 12.8 % [58]; 3 % [59].

Recommendation	Strength	Consensus
Another reading after 7–10 days can be recommended.	↑	Strong consensus (100 %)

Evidence base: Dickel et al. 2000 (4 according to OCEBM); Madsen & Andersen 2012 (4 according to OCEBM); Saino et al. 1995 (4 according to OCEBM) [56, 57, 59]

Figure 1 depicts the chronological sequence of patch testing.

4. For which allergens does it make sense to perform late readings after 7–10 days?

- Allergens with a high percentage of late reactions:
- Corticosteroids [Davis et al. 2005 (4 according to OCEBM); Isaksson 2000 (3b according to OCEBM); Jonker & Bruynzeel 2000 (4 according to OCEBM); Madsen & Andersen 2012 (4 according to OCEBM)] [57, 60–62].
 - Antibiotics: neomycin [Dickel et al. 2000 (4 according to OCEBM); Jonker & Bruynzeel 2000 (4 according to OCEBM); MacFarlane et al. 1989 (3b according to OCEBM); Massone et al. 1989 (4 according to OCEBM); Madsen & Andersen 2012 (4 according to OCEBM); Matiz et al. 2011 (3b according to OCEBM)] [56, 57, 62–65]
 - Formaldehyde, formaldehyde releaser, formaldehyde resins [Dickel et al. 2000 (4 according to OCEBM); Jonker & Bruynzeel 2000 (4 according to OCEBM); MacFarlane et al. 1989 (3b according to OCEBM); Massone et al. 1989 (4 according to OCEBM); Madsen & Andersen 2012 (4 according to OCEBM); Matiz et al. 2011 (3b according to OCEBM)] [56, 57, 62–65]

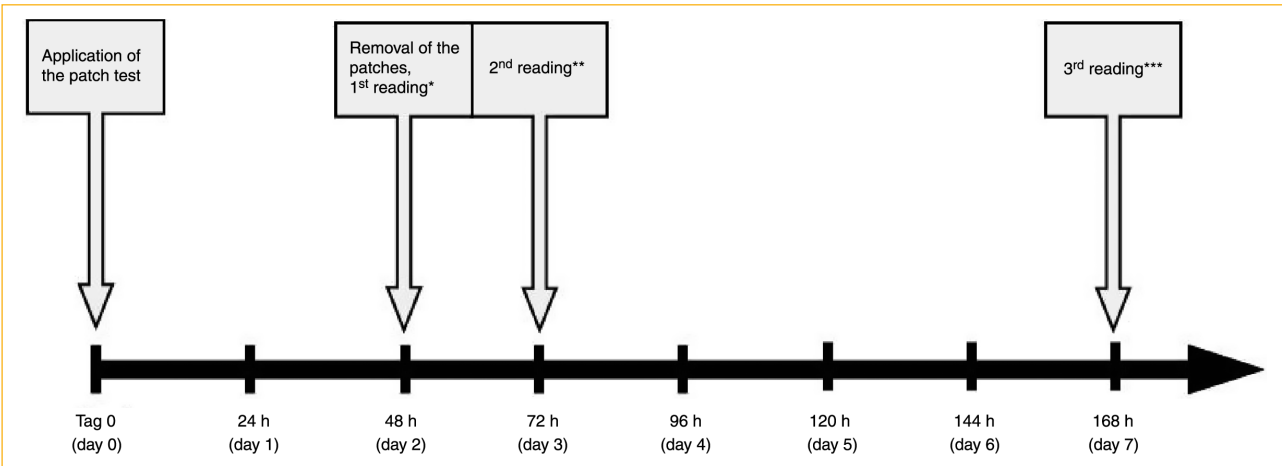


Figure 1 Chronological sequence of patch testing. *1st reading alternative - at reduced sensitivity-: on d1; **2nd reading on d3 (alternatively on d4); ***3rd reading alternative on d8–d10.

- *p*-phenylenediamine [Dickel et al. 2000 (4 according to OCEBM); Madsen & Andersen 2012 (4 according to OCEBM); MacFarlane et al. 1989 (3b according to OCEBM)] [56, 57, 63]
- (Dental) metals [Koch & Bahmer 1999 (3b according to OCEBM)] [66]

Recommendation	Strength	Consensus
A late reading after 7–10 days is recommended particularly in suspected sensitization to corticosteroids, aminoglycosides, formaldehyde, formaldehyde releasers, formaldehyde resins, <i>p</i> -phenylenediamine and metals.	↑↑	Strong consensus (100 %)

Time of application

Recommendation	Strength	Consensus
Based on clinical experience, it is recommended that patch testing ideally be performed only after resolution of acute dermatitis lesions; otherwise, ‘angry back’ reactions and flare-up reactions must be expected.	↑↑	Strong consensus (100 %)

5 Test reading and interpretation of test reactions (especially negative and questionable test reactions as well as “problem allergens”) – expert consensus

Recommendation	Strength	Consensus
It is recommended that patch test readings be performed strictly based on morphological criteria (Table 3).	↑↑	Strong consensus (100 %)

Patch test reactions are assessed by *visual inspection*. If papules or infiltration are not readily visible, palpation may be useful. At every reading, the skin reaction is classified based on defined morphological criteria (Table 3) [67]; knowledge of the substance in question is not required. Training in patch test reading may involve virtual online tools [68] or training courses with real patch test patients [69].

Interpretation of all test reactions with respect to their etiopathogenesis is done after the last reading. Aspects to be considered include morphology, the applied substance (including concentration and vehicle), and the temporal course of the reaction. For well-validated test preparations, the interpretations listed in the right column of Table 3 usually apply. Reactions classified as positive based on morphology may, however, also represent irritant in nature. The temporal course of a reaction is only to a certain extent useful for classifying it as either allergic or irritant: a rapid decrescendo, especially from a positive reaction to a “?” reaction on day 3 or 4 is suggestive of an irritant origin. On the other hand, a reaction that becomes stronger until day 3 (crescendo) does by itself not prove an allergic etiology, as such reactions may also be elicited by irritants such as (low-dose) sodium lauryl sulfate (0.25 % in aqueous solution) [70]. In very rare cases, non-eczematous test reactions may be observed, including lymphomatoid, lichenoid, erythema multiforme-like, and granulomatous reactions [71].

Provided the test was performed correctly, a *negative patch test result* largely rules out contact sensitization to any of the test substances. This too may constitute an important outcome for the patient. In this context, however, it is essential to bear in mind that a false-negative test result may also be due to the fact that the test substance used is not identical to the form of the allergen that caused the sensitization. For instance, this may be the case if a prehapten is tested whose oxidation product(s) constitute(s) the actual sensitizer [72].

A definitively *irritant test reaction* is present when the substance tested is a pure irritant, e.g., sodium lauryl sulfate (see chapters 3 and 9). A test reaction is likely irritant in nature if (1) the agent has significant irritant potential (e.g. surfactants, shampoo or liquid soap used by the patient), and if (2) there are morphological signs of skin irritation (‘cigarette paper-like’ wrinkling or craquelé-like fine cracks in the skin surface, shiny appearance, punctate erosions or crusts, sharp delineation or scaling). Cobalt chloride hexahydrate in petrolatum may crystallize during storage and subsequently lead to irritant reactions [73]. If performed properly, patch testing should never result in severe irritant (toxic) reactions characterized by sharply demarcated inflammatory lesions, blistering and eventual ulceration.

On principle, *erythematous test reactions* are etiologically indeterminate unless there are signs of irritation (see above). In certain cases, a ‘?’ reaction may be classified as allergic: (1) with certainty, if higher test concentrations of the substance have led to an unequivocal allergic reaction in concomitant or previous tests; (2) likely, if other allergens from the same ‘allergen group’ [74] have led to unequivocal allergic reactions, e.g., formaldehyde and formaldehyde releasers,

Table 3 Classification of patch test reactions, according to DKG [1] and ICDRG, modified after Lindberg & Matura [67].

DKG (Deutsche Kontaktallergie-Gruppe, German Contact Allergy Group)		ICDRG (International Contact Dermatitis Research Group)		
Symbol	Description of clinical morphology*	Symbol	Description of clinical morphology	Interpretation
–	No reaction	neg.	No reaction	Negative
?	Erythema only	?+	Mild erythema (questionable reaction)	Unclear (allergic or irritant)
f	Few follicular papules			Unclear (allergic or irritant)
+	Erythema, infiltration, possibly mild papules	+	Erythema, infiltration, possibly papules	Weak positive reaction (usually allergic)
++	Erythema, infiltration, papules, vesicles	++	Erythema, infiltration, papules, vesicles	Strong positive reaction (allergic)
+++	Erythema, infiltration, confluent vesicles	+++	Severe erythema and infiltration with confluent vesicles	Extreme positive reaction (allergic)
Ir	**	IR	Irritant reactions of various types	Irritant
n.t.		NT		Not tested

*The morphological aspects associated with a given reaction intensity must all be present (and are not optional) for a reaction to be assigned to that particular intensity.

**Various manifestations are possible depending on the irritant agent, its concentration, duration of exposure, and other factors; e.g., soap effect, edge effect, erythema, erosions, blisters, necrosis.

wool wax alcohols and Amerchol L101; or (3) if concomitant testing of the substance in a mix has led to an allergic reaction; or (4) if delayed reading shows a ‘?’ reaction for the first time. If the substance is highly relevant (e.g., occupational exposure), repeat testing after an appropriate interval (usually at least one month) or even challenge testing should be considered to make a definitive diagnosis.

It has been shown that certain “*problem allergens*” (see also chapter 9) are more frequently associated with questionable or irritant reactions than with + to +++ reactions [75]; or the number of + reactions is vastly preponderant among all “positive” reactions [76]. This may suggest inadequate quality of a given test substance and will result in uncertainties in the interpretation of + reactions as either allergic or irritant. In order to detect any increased skin irritability at the time of testing, the DKG standard series includes sodium lauryl sulfate (0.25 % in aqueous solution) as irritant control [38]. An irritant reaction to SLS will more likely lead the investigator to consider a morphologically ‘weak positive’ reaction to be false positive than this would be the case in a patient without increased irritability. A definitive diagnosis will require a confirmation test (repeated open application test [ROAT] in particular, see chapter 6).

Recommendation	Strength	Consensus
<i>It is recommended to assess all non-negative reactions as to their etiopathogenesis (allergic/irritant/unclear). It is recommended to assess allergic reactions as to their clinical relevance.</i>	↑↑	Strong consensus (100 %)

“*Clinical relevance*” refers to the significance of a positive (allergic) patch test reaction for the patient. In this context, current (previous) relevance exists if the sensitization ‘explains’ current (previous) episodes of allergic contact dermatitis (due to exposure to that particular allergen). Such exposures must be identified by taking a targeted (repeat) history at the conclusion of the patch test; this requires great care on the part of both physician and patient. Frequently, a distinction is also made between occupational and recreational relevance (current or previous), and the certainty of attribution is divided into categories such as ‘certain’ or ‘probable’ [77]. In some cases, a single substance may be relevant in more than one respect. If no previous or current exposure to the substance can be ascertained, the clinical relevance will remain unclear; however, it will usually not be possible to rule it out *with certainty*. At any rate, assessment

of clinical relevance cannot refer to future events. Therefore, even sensitizations of doubtful relevance should be disclosed to the patient in order to enable him/her to actively avoid these substances [78].

6 Diagnostic validity: sensitivity, specificity, predictive values; reproducibility – third key question

Patch testing is the standard procedure in the diagnosis of specific contact sensitizations [2]. When it comes to quantifying its diagnostic quality (sensitivity, specificity, positive predictive value [PPV] and negative predictive value [NPV]), it is thus difficult to name another “gold standard” that is at least as valid in providing evidence of the actual disease state. The only procedures that may be considered in this context (with certain limitations) are the repeated open application test with contact allergens and taking an allergen-specific history.

In general, sensitivity, specificity and predictive values depend significantly on the choice of the test concentration.

In various ROAT studies, particularly with fragrances, the sensitivity was usually (almost) 100 %, with a lower CI of about 71 to 84 %. Specificity ranged from 50–80 %; the PPV in this setting was between one-third and 100 %; the NPV was almost always 100 %. Given the typically small sample sizes, the precision of these estimates is low.

In the context of a clearly defined ‘positive history’, the following sensitivity (specificity) estimates were found in 787 consecutively tested patients: nickel: 50.8 % (95.5 %); dichromate: 35.7 % (96.4 %); wool wax alcohols: 0 % (99.1 %). The PPV (NPV) for nickel was 55.4 % (91.1 %); for dichromate, 27.0 % (97.6 %); for wool wax alcohols, 0 % (99.0 %) [79].

Other studies investigated the extent to which test reactions to allergen mixes used for screening matched test reactions to the individual components. In the validation study for fragrance mix II (14 % in petrolatum), the sensitivity according to this definition was 92.3 %, with a specificity of 98.4 %; PPV, 48.0 %; and NPV, 99.9 % [80]. In another study, 1,951 consecutive patients underwent patch testing using fragrance mixes I and II as well as all individual components of these mixes, usually at a concentration that was higher than in the mixes [81]. Comparing the test reactions, fragrance mix I (and II) showed a calculated sensitivity of 58.3 % (52.4 %); a specificity of 96.9 % (97.8 %); a PPV of 54.0 % (34.4 %); and an NPV of 97.4 % (98.9 %).

The synchronous reproducibility of identical test systems has been studied repeatedly. In a DKG study of 1,285 patients who were tested with 10 selected allergens from the then-current standard test series, two-day exposure resulted

in Cohen’s kappa coefficients between 0.5 (formaldehyde) and 0.89 (thiomersal) [74]; limitations in terms of allergens in aqueous solution might suggest dosing problems. The T.R.U.E. test® in 589 patients showed a kappa of 0.99 for nickel sulfate and of 0.94 for potassium dichromate [82]. The overall agreement in 220 consecutive patients tested with ten allergens from the standard series yielded a kappa of 0.95 [83].

7 Quantity of test substances, concentration, chamber size and chamber filling – expert consensus

Both prefilled (by the manufacturer) and user-filled test systems have proven useful in routine clinical practice. The advantage of user-filled test systems is that they enable testing of just about any allergen, including individual allergen preparations. One disadvantage is that they are not fully standardized; in addition, filling of the test chambers requires time and personnel. In prefilled test systems, the manufacturer determines the allergen dose. The only such test currently available in Germany is the T.R.U.E. test® (Thin-Layer Rapid Use Epicutaneous Test) in which the test allergens are incorporated into an inert matrix (which may contain the following components: hydroxypropyl cellulose, methyl cellulose, povidone, butylhydroxyanisole, butylhydroxytoluene, sodium bicarbonate, sodium carbonate, β -cyclodextrin). This system is well standardized as regards allergen concentrations and area of application [84–87]. However, in a study that simultaneously examined two test preparations of fragrance mix I (petrolatum-based test preparation versus T.R.U.E. test®), the latter showed a markedly lower sensitivity [88]. Currently, only 36 substances of the expanded standard series are available (<http://www.truetest.com/global/patientinfo.htm> [last accessed January 11, 2019]).

Patch test results are – in part – always determined by the parameters of the test system used [89]. In particular, this includes the concentration of the hapten, the matrix, the size of the chamber volume and contact area, as well as – very crucially – the resultant dose per unit area. The latter is a key factor in terms of the sensitivity of a patch test [90, 91]. It is therefore useful to specify the exposure concentration using “mg/cm²” as unit [91, 92] and to standardize this approach for the various test chambers available [69, 93, 94]. Within a certain range of concentrations, there is a clear dose-response curve [89]. The size of the skin area exposed to a hapten under the test chamber has an impact on the test reaction as well [95, 96]. Larger test sites tend to more frequently result in positive reactions than smaller areas exposed to the same allergen concentration. Indeed, it has been shown

Table 4 Optimum chamber filling according to the manufacturers (quantity of test preparations: columns 3 and 4) of commercially available test chamber systems.

Test chamber system (shape, inner surface area)	Manufacturer/distributor	Medium: petrolatum	Medium: liquid	Calculated filling quantity for equivalent dose per unit area*
IQ-Ultra (square; 64 mm ²)	Chemotechnique, Vellinge, Sweden	20 mg	23–25 µL	25 mg
allergeEAZE patch test chamber woven (square; 64 mm ²)	Smart Practice, Arizona, Phoenix, USA	20 mg	20 µL	25 mg
allergeEAZE patch test chamber clear (square; 64 mm ²)	Smart Practice, Arizona, Phoenix, USA	20 mg	20 µL	25 mg
Curatest (8 mm diameter) (round; 50.26 mm ²)	Lohmann & Rauscher GmbH & Co. KG, Rengsdorf, Germany	10 mg	50 µL	20 mg
Finn Chamber (8 mm diameter)* (round; 50.26 mm ²)	Smart Practice, Phoenix, Arizona, USA	20 mg	15 µL	Reference: optimal quantity determined experimentally: 20 mg
Torii (9 mm diameter) (round, 63.61 mm ²)	Torii Pharmaceutical Co. Ltd, Tokyo, Japan	50 mg	50 µL	25 mg
Van der Bend (8 mm diameter) (square; 64 mm ²)	Van der Bend, Brielle, Netherlands	20 mg	30–35 µL	25 mg
*Systematic studies on the optimal dose per unit area were predominantly conducted using the Finn Chamber system (8 mm) [91, 92, 106]. Calculated equivalent filling quantities (rounded) for other chamber systems are listed in column 5 (experimentally determined filling quantities for other chamber systems may vary) [106].				

that different test systems may lead to somewhat different test results, even when using identical allergen concentrations [97–103].

The occlusive or semi-occlusive test chambers offered by various manufacturers differ in terms of material, shape, volume, contact area and fill volumes considered optimal (as per the manufacturer's instructions) (Table 4). This impacts their suitability for allergen preparations using different bases [104]. The chambers are usually filled by hand without a dosing device. It has been shown that even well-trained and experienced personnel exhibit marked intraindividual and interindividual variations in the quantity of petrolatum-based allergens applied during patch testing [105–107]. For liquid allergens, small patches of filter paper are soaked in allergen solutions and then inserted into the test chambers. Dosing is usually done using a dropper bottle. The drop volume also depends on the allergen preparation [108]. If the liquid allergen is applied with a prefilled syringe, the drop size will vary considerably. Application of the required 15 µL (for small Finn chambers) is therefore best done with a micropipette [109] in order to avoid high concentrations per unit

area, which may result in doubtful, irritant or erythematous/infiltrated (nonspecific) reactions.

Commercially available allergen preparations may show differences in terms of the actual hapten concentration and distribution in the carrier substance [110–112]. It is the investigator's responsibility to ensure the highest possible consistency of important parameters in order to avoid variations in allergen exposure [110, 113]. The vast majority of allergens are incorporated into white petrolatum, which has proven to be a stable, nonallergenic, inert and cheap carrier substance [104, 114–116]. Allergens that do not mix with petrolatum must be incorporated into other carriers (emulsifying bases, water, and others). In addition, the carrier itself has a significant impact on the elicitation of a reaction [117, 118]. The distribution of allergenic material within the carrier may differ among the various commercial test preparations [93, 110, 112, 119]; indeed, the nominal test concentration may not even be achieved [111]. For cobalt chloride hexahydrate, it has been reported that clumping phenomena may result in patch test reactions that are reminiscent of petechial bleeding [73]. In such cases,

lack of experience may lead to erroneous assessment as an allergic reaction.

Test preparations should be stored in closed containers and kept refrigerated in order to ensure stable allergen concentrations. This is especially important for certain fragrances, acrylates, isocyanates, formaldehyde and glutaraldehyde [117, 120–122]. For practical reasons, testing chambers are sometimes filled at other times than directly before use on the patient. If this is unavoidable, appropriate measures should be taken to avoid evaporation or degradation of allergens in the interval prior to application [116, 119, 123].

In Germany, the German Contact Dermatitis Research Group (DKG, Deutsche Kontaktallergie-Gruppe) in particular, a working group within the German Society of Dermatology, is involved in the standardization of patch testing. The recommendations for test allergens published by DKG, which are usually also adopted by allergen manufacturers, are predominantly based on studies with user-filled, round aluminum test chambers with a circular contact area of about 50 mm², a diameter of 8 mm and a chamber volume of about 20 µL (small Finn Chambers® or TROLAB® Patch Test). For petrolatum-based allergens, the recommended fill volumes for these chambers are 12–15 µL [110, 113], respectively 20 mg [106]. In case of liquid allergen preparations, about 15 µL should be applied to a filter paper patch [108], which is then inserted into the test chamber. Dosing is best performed using a micropipette [109]. If the allergen preparations recommended by the DKG are used in other test systems, it is important to observe the different parameters associated with those systems [124]. In order to facilitate the comparison of patch test results, it is recommended to always specify the exact method used (chambers, allergen preparations).

Conflict of interest

See AWMF guideline registry.

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