Basics in Diagnostic Work Up and Assessment of Clinical Relevance

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5.1 Basics in Diagnostic Work Up

The point of departure for the investigation of allergic contact dermatitis in adults is the available baseline series for the geographical region in question. Advice on testing children can be found in Chap. 10.

As examples Table 5.1 gives the allergens in the European baseline series, Table 5.2 the North American core series and Table 5.3 the Chinese baseline series. Several other baseline series exist and the composition reflects the allergens that are considered to be relevant for exposures in the geographical region. This information can usually be found in the catalogues of the patch test suppliers or in publications from the scientific societies [1, 2].

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J.D. Johansen et al. (eds.), *Quick Guide to Contact Dermatitis*,
DOI 10.1007/978-3-662-47714-4_5

Table 5.1 European baseline series (by January 2015)

Compound	Concentration in investigator filled chambers	Mg per patch in pre-filled patch tests[a]	Type
Potassium dichromate	0.5 % pet	0.019	Metal
p-Phenylenediamine (PPD)	1.0 % pet	0.073	Dye
Thiuram mix	1.0 % pet	0.020	Rubber
Neomycin sulfate	20.0 % pet	0.19	Antibiotic
Cobalt(II)chloride hexahydrate	1.0 % pet	0.016	Metal
Benzocaine	5.0 % pet	NI	Local anesthetic
Nickel(II)sulfate hexahydrate	5.0 % pet	0.16	Metal
Clioquinol	5.0 % pet	Quinolin-mix 0.041	Antibiotic
Colophonium	20.0 % pet	0.69	Resin (glue)
Paraben mix	16.0 % pet	0.80	Biocide
N-Isopropyl-N-phenyl-4-phenylenediamine (IPPD)	0.1 % pet	Black rubber mix: 0.060	Black rubber
Lanolin alcohol	30.0 % pet	0.81	Wool oil
Mercapto mix	2.0 % pet	0.060	Rubber chemical
Epoxy resin, bisphenol A	1.0 % pet	0.041	Two component glue
Myroxylon pereirae resin	25.0 % pet	0.65	Fragrance/aroma
4-tert-Butylphenolformaldehyde resin (PTBP)	1.0 % pet	0.041	Glue
2-Mercaptobenzothiazole (MBT)	2.0 % pet	0.061	Rubber chemical
Formaldehyde	2.0 % aq	0.15	Biocide
Fragrance mix I	8.0 % pet	0.35	Fragrance
Sesquiterpene lactone mix	0.1 % pet	NI	Plant
Quaternium-15	1.0 % pet	0.081	Biocide
2-Methoxy-6-n-pentyl-4-benzoquinone (primin)	0.01 % pet	NI	Plant
Methylchloroisothiazolinone + methylisothiazolinone 3:1	0.02 % aq	0.0032	Biocide
Budesonide	0.01 % pet	0.0008	Corticosteroid
Tixocortol-21-pivalate	0.1 % pet	0.0024	Corticosteroid
Methyldibromo glutaronitrile	0.5 % pet	NI	Biocide
Fragrance mix II	14.0 % pet	NI	Fragrance
Hydroxyisohexylcyclohexene carboxaldehyde	5.0 % pet	NI	Fragrance
Methylisothiazolinone	0.2 % aq	NI	Biocide
Textile dye mix	6.6 % pet	NI	Dyes

[a]True Test® is the only available system of prefilled chambers
NI not included, *aq* aqua, *pet* petrolatum

Table 5.2 North American core series [1]

Compound	Concentration in %
Benzocaine	5.0 pet
2-Mercaptobenzothiazole (MBT)	1.0 pet
Colophonium	20.0 pet
p-Phenylenediamine (PPD)	1.0 pet

Table 5.2 (continued)

Compound	Concentration in %
Imidazolidinyl urea	2.0 pet
Cinnamal	1.0 pet
Amerchol L-101	50.0 pet
Carba mix	3.0 pet
Neomycin sulfate	20.0 pet
Thiuram mix	1.0 pet
Formaldehyde	2.0 aq
Ethylenediamine dihydrochloride	1.0 pet
Epoxy resin, bisphenol A	1.0 pet
Quaternium-15	2.0 pet
4-tert-Butylphenolformaldehyde resin (PTBP)	1.0 pet
Mercapto mix	1.0 pet
N-Isopropyl-N-phenyl-4-phenylenediamine (IPPD)	0.1 pet
Potassium dichromate	0.25 pet
Myroxylon pereirae resin	25.0 pet
Nickel(II)sulfate hexahydrate	2.5 pet
Diazolidinyl urea	1.0 pet
DMDM hydantoin	1.0 pet
Bacitracin	20.0 pet
Mixed dialkyl thiourea	1.0 pet
Methylisothiazolinone + methylchloroisothiazolinone	0.02 aq
Paraben mix	12.0 pet
Methyldibromo glutaronitrile	0.5 pet
Fragrance mix I	8.0 pet
Glutaral	0.5 pet
2-Bromo-2-nitropropane-1,3-diol	0.5 pet
Sesquiterpene lactone mix	0.1 pet
Fragrance mix II	14.0 pet
Propylene glycol	30.0 aq
Benzophenone-3	10.0 pet
Chloroxylenol (pcmx)	1.0 pet
Ethyleneurea, melamine formaldehyde mix	5.0 pet
Iodopropynyl butylcarbamate	0.2 pet
Disperse Blue mix 106/124	1.0 pet
Ethyl acrylate	0.1 pet
Glyceryl thioglycolate	1.0 pet
Toluenesulfonamide formaldehyde resin	10.0 pet
Methyl methacrylate	2.0 pet
Cobalt(II)chloride hexahydrate	1.0 pet
Tixocortol-21-pivalate	0.1 pet
Budesonide	0.01 pet
Compositae mix II	5.0 pet
Hydrocortisone-17-butyrate	1.0 pet
Dimethylol dihydroxy ethylene urea	4.5 aq
Cocamidopropyl betaine	1.0 aq
Methylisothiazolinone	0.2 % aq

pet petrolatum, *aq* aqua

Table 5.3 Chinese baseline series (January 2015) [1]

Compound in Chinese	Compound in English
巯基苯丙噻唑	2-Mercaptobenzothiazole (MBT) 1 % pet
松香	Colophonium 20 % pet
对苯二胺	P-Phenylenediamine (PPD) 1 % pet
咪唑烷基脲	Imidazolidinyl urea 2 % pet
肉桂醛	Cinnamal 1 % pet
阿莫醇	Amerchol L 101 50 % pet
卡巴混合物	Carba mix pet 3 % pet
秋兰姆混合物	Thiuram mix 1 % pet
乙二胺二盐酸盐	Ethylenediamine dihydrochloride 1 % pet
双酚A型环氧树脂	Epoxy resin, bisphenol A 1 % pet
夸特15	Quaternium-15 2 % pet
4-叔丁基酚甲醛树脂	4-tert-Butylphenolformaldehyde resin (PTBP) 1 % pet
巯基混合物(硫氢基混合物)	Mercapto mix 1 % pet
氮-异丙基-氮-苯-4-苯二胺	N-Isopropyl-N-phenyl-4-phenylenediamine (IPPD) 0.25 % pet
重铬酸钾	Potassium dichromate 0.25 % pet
秘鲁香脂	Myroxylon pereirae resin 25 % pet
硫酸镍	Nickel(II)sulfate hexahydrate 5 % pet
双咪唑烷基脲	Diazolidinyl urea 1 % pet
二烷基脲混合物	Mixed dialkyl thiourea 1 % pet
分散橙3	Disperse orange 3 1 % pet
尼泊金混合物(对苯类)	Paraben mix 12 % pet
甲基二溴戊二腈	Methyldibromo glutaronitrile 0.5 % pet
芳香混合物	Fragrance mix I 8 % pet
戊二醛	Glutaral 0.5 % pet
溴硝丙醇	2-Bromo-2-nitropropane-1,3-diol 0.5 % pet
倍半萜烯内酯混合物	Sesquiterpene lactone mix 0.1 % pet
蜂胶	Propolis 10 % pet
二苯酮-3	Benzophenone-3 10 % pet
4-氯3,5-二甲苯酚	Chloroxylenol (pcmx) 1 % pet
乙烯脲、密胺甲醛混合物	Ethyleneurea, melamine formaldehyde mix 5 % pet
2-叔丁基-4-甲氧基酚	2-tert-Butyl-4-methoxyphenol (BHA) 2 % pet
金硫代硫酸钠	Gold(I)sodium thiosulfate dihydrate 0.5 % pet
丙烯酸乙酯	Ethyl acrylate 0.1 % pet
甘油基单硫甘醇酸酯	Glyceryl thioglycolate 1 % pet
甲苯磺酰胺甲醛树脂	Toluenesulfonamide formaldehyde resin 10 % pet
甲基丙烯酸甲酯	Methyl methacrylate 2 % pet
氯化钴	Cobalt(II)chloride hexahydrate 1 % pet
椰子二乙醇胺	Cocamide DEA 0.5 % pet
茶树油	Tea tree oil oxidized 5 % pet
芳香混合物	Fragrance mix II 14 % pet
分散黄3	Disperse yellow 3 1 % pet
水杨酸苄酯	Benzyl salicylate 10 % pet
十二烷基葡糖苷	Decyl glucoside 5 % pet
2-羟乙基甲基丙烯酸酯	2-Hydroxyethyl methacrylate 2 % pet
乙内酰脲	DMDM hydantoin 1 % pet

Table 5.3 (continued)

Compound in Chinese	Compound in English
依兰油	Cananga odorata oil 2 % pet
异丙基豆蔻酸酯	Isopropyl myristate 20 % pet
吐温80	Polysorbate 80 5 % pet
2-正辛基-4-异噻唑啉-3-酮	2-n-Octyl-4-isothiazolin-3-one 0.1 % pet
分散蓝106/124	Disperse Blue mix 106/124 1 % pet
苯基过氧化物	Benzoylperoxide 1 % pet
对甲氧基肉桂酸异戊酯	Isoamyl p-methoxycinnamate 10 % pet
新铃兰醛	Hydroxyisohexyl 3-cyclohexene (Lyral) 5 % pet
辛基水杨酸盐	Ethylhexyl salicylate 5 % pet
甲醛	Formaldehyde 1 % aq
甲基氯异噻唑(原名:CL+ME异噻唑)	Methylisothiazolinone + methylchloroisothiazolinone 0.01 % pet
芳樟醇氢过氧化物	Hydroperoxides of linalool 1 % pet
柠檬烯氢过氧化物	Hydroperoxides of limonene 0.3 % pet
纺织燃料混合物	Textile dye mix 6.6 % pet
甲基异噻唑啉酮	Methylisothiazolinone 0.2 % aq,

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pet petrolatum, *aq* aqua

The baseline patch test series contains allergens, which are frequent (give positive reactions in more than 1 % of those tested), or which are difficult to suspect from the clinical presentation e.g. corticosteroids.

It is called 'baseline series' or 'core series' to indicate that other allergens should be included in the patch test depending on the patient's exposures [3].

The patient should be asked to bring the products used for personal hygiene, skin care and other kinds of cosmetics. This should also include soaps, skin cleansers and skin care products from the work place. These products should also be considered for inclusion in the patch test (see Chap. 4). In case a specific product is suspected to have caused or contributed to the dermatitis, its composition should be reviewed to make sure that the relevant potential causative allergens are included in the patch test. In case the product under suspicion is intended for skin contact, a use test can be made with the product simultaneously with the patch test (see Chap. 3).

The use test (repeated open application test) is more sensitive than the patch test and thus more likely to reveal an allergic reaction [4].

The occupation of the patient, if suspected to cause the dermatitis, will also influence the diagnostic work up. For some occupations or exposures special series are available e.g. metal working fluid series or dental personnel series. Most such series varies between different patch test suppliers, and there is no consensus regarding the exact composition of these. Nevertheless such series are usually helpful, as relevant allergens may otherwise be overlooked. The use of patch test series does not replace an exposure assessment, which should always be performed.

5.2 Tools in Exposure Assessment

5.2.1 Patient's Characteristics and History

The medical history is crucial as it provides an overview of all the possible contact allergens the patient may have been exposed to, and therefore makes the basis for correct allergen selection.

It can sometimes be very difficult to get a good understanding of complex occupational cases, but with patience, imagination and perhaps the use of drawings [5], it is often possible to reliably determine significant exposures. However, sometimes work place visits are necessary to better understand work procedures and allergen exposures. Important clues can be retrieved from the clinical presentation (see Chap. 2). The history should cover exposure both at leisure and work. It is important to ask about use of protective equipment at work, as e.g. gloves are frequent causes of allergy. The history should also cover topical treatments as secondary allergies to e.g. corticosteroids and antiseptics can develop. Remission during times off work supports an occupational aetiology of dermatitis, but is not obligatory as the dermatitis may have become chronic.

It can be helpful to ask about rashes to specific product types e.g. perfumes, creams, gloves, shoes, tools, jewellery etc. depending on the localisation of eczema and the allergy under investigation.

5.2.2 Ingredient Labelling

The ingredient labels are valuable sources of information concerning exposures to allergens.

In many countries, cosmetics carry full information about ingredients on the label except for the composition of the fragrance formula. In the European Union, 26 individual fragrance ingredients have to be mentioned on the label if present in certain concentrations (see Chap. 12).

It should be remembered that the names on the patch test preparations often are chemical names (e.g. INN) and it can be necessary to look up synonyms to do an effective exposure assessment. Labelling on medicinal products follows INN. Household detergents label preservatives and fragrances according to the requirements of cosmetic products in the European Union.

5.2.3 Safety Data Sheets

In case of a complex work environment, safety data sheets may be available for certain products.

The Safety Data Sheets (also called Material Safety Data Sheets) only provide limited information concerning allergens. As a general rule, an allergen should be present in a product in a concentration of least 1 % to prompt labelling and warnings with H317: 'May cause an allergic skin reaction', while it is required that the name of the allergen is mentioned down to the concentration of 0.1 %. For certain allergens lower limits apply. The naming of the allergens is not standardized, so e.g. colophony could be called rosin. Current investigations have shown that around one out of five safety data sheets do not contain information about specific allergens in spite of their presence in the product [6]. It is important to be critical about the information given in safety data sheets and ask the producer for the full recipe, if in doubt about the completeness of the information.

5.2.4 Spot Tests and Chemical Analysis

Commercially available spot tests exist for nickel and cobalt, which are quick and easy ways to assess exposures. The nickel spot test is the best validated and has a high specificity and moderate sensitivity in detecting a level of nickel ion release, which may cause dermatitis [7]. In case of suspected occupational exposures, the nickel spot test can be used directly on the hands [8] (see Chap. 11). The cobalt test is based on similar principles, but is more difficult to read and there is less experience with the test (see Chap. 11). The formaldehyde spot test requires laboratory facilities, but can detect small levels of formaldehyde of clinical relevance in those sensitized. More advanced chemical analysis can also be performed, but this is usually only done in highly specialized departments.

5.3 Assessment of Clinical Relevance

The assessment of clinical relevance is, together with many other steps in patch testing, an essential part of the patient work-up [2]. Here, the physician synthesizes the medical history and the outcome of patch testing. This means that all the information that has been gathered so far needs to be carefully reviewed for missing parts and then integrated in the clinical decision process (Box 5.1). Thus, if some information has not come to the attention of the physician, this is the last opportunity to do something about it. Obviously, the clinical relevance of positive patch test reactions can only be sufficiently determined if the physician is aware of all exposures, their magnitude and frequency. Collectively, before the assessment of clinical relevance of positive patch test reactions, the physician is granted a final chance to collect information on missed allergen exposure.

Box 5.1 Assessment of Relevance of Positive Patch Test Reactions

Perform a standardized and thorough medical history
Atopic dermatitis (past or present)
Where did dermatitis begin (was it at a site with contact to an item or product)
How did dermatitis present in the beginning and how did it develop (vesicles increase suspicion of allergic etiology)
Does dermatitis improve or clear during e.g. holidays
Domestic exposures (consider cosmetics, jewellery, wet tissues, plants etc.)
Occupational exposures (detailed, consider work place visits)
Perform a detailed physical examination
Determine distribution of dermatitis and consider specific locations (e.g. textile dermatitis is located to sites of contact with tight clothing; nail lacquer dermatitis may be seen on the neck and around the eyes)
Identify sources of allergenic exposure
Product information (e.g. ingredient labeling, contact manufacturer or supplier, review material safety data sheets and product databases)
Chemical analysis of suspected products, e.g. by use of spot tests
Skin deposition tests (e.g. acid wipe sampling following normal work procedures with metal contact)
If possible, identify allergen concentrations in suspected products
Repeat the patch test and/or perform use test (ROAT)
Consider retesting a suspected allergen in a different vehicle, or use higher test concentration
Perform repeated open application test

Assessment of the clinical relevance of positive patch test reactions should not be mixed with patch test reading. These are two separate entities. Thus, begin by reading the patch test reactions (see Chap. 3), and once positive and doubtful positive reactions have been identified, the evaluation of clinical relevance can then begin. Importantly, positive patch test reactions only indicate that the patient has been previously exposed and sensitized to a chemical, but does not prove that the allergen is responsible for the patient's current problem of contact dermatitis.

Overall, positive test reactions should be categorized into three entities based on the medical history [2]:

- Current clinical relevance
- Past clinical relevance
- Unknown clinical relevance

'Current' or 'present' relevance is applied if an existing exposure to the sensitizer in question can be demonstrated, and this exposure fully or partly can explain the localization and course of the dermatitis. This means that the diagnosis allergic contact dermatitis can be made.

'Past relevance' signifies a past clinical disease explained by the sensitizer, but not directly related to the current symptoms. Positive patch test reactions that are considered to be of 'current clinical relevance' should furthermore be linked to the dermatitis as a primary cause or an aggravating cause.

In case no clinical relevance can be demonstrated, the term 'unknown clinical relevance' is used, as the overall assessment of clinical relevance is complex.

The physician should attempt to carefully integrate all the pieces of information and synthesize a conclusion. Expertise comes with experience, especially for uncommon allergens, as the physician needs to suspect that allergens categorized as being of 'no clinical relevance' might indeed be relevant to the patient's current dermatitis. Thus, a clear limitation in clinical decision making is gaps in the knowledge of allergen exposure. Here, good text books as well as case reports on uncommon allergen exposures may be useful. Also, communication with more experienced colleagues can be valuable. Thus, in some cases, a positive reaction is incorrectly judged as 'nonrelevant' owing to insufficient environmental information.

Doubtful patch test reactions means that the morphology is not clear-cut 'irritant' or 'allergic'. Patch test reactivity can vary for many reasons, including internal and external factors; so a doubtful reaction might become positive if retesting is done, or the concentration slightly increased or the vehicle changed. This means that further investigations may have to be done (see Chap. 2). The weak patch test reaction may also be due to cross-reactivity to another substance, which is the true cause of sensitization and thus be clinically relevant.

A shortcut to assessment of clinical relevance is to test the patients with their own products [9].

In case of a positive patch test reaction to a product used by the patient and an ingredient in the product, it is likely that the patch test reaction is clinically relevant.

5.4 Overview of Diagnostic Work-Up

The flow of an investigation can be as in Fig. 5.1. First based on the patient's characteristics, history and the exposure analysis, a patch and possibly skin prick test is planned. If the outcome of the skin tests are negative, the exposures are reviewed to make sure that an allergen has not been overlooked. In case of a significant exposure to irritants, the diagnosis of irritant contact dermatitis can be considered (see Chap. 6).

In case of unexpected positive reactions at patch or skin prick testing, the environment is examined for the presence of the allergen; this includes reviewing the history of the patient again, ingredient labels and safety data sheets, if available. In case of a positive patch test reaction to nickel or cobalt, spot tests can be used to detect exposure in the home or work environment from metal objects. The assessment should lead to a decision on clinical relevance and thus the diagnosis (Fig. 5.1).

Such systematic step-wise exposure assessment has proven valuable in detecting additional relevant allergies [10].

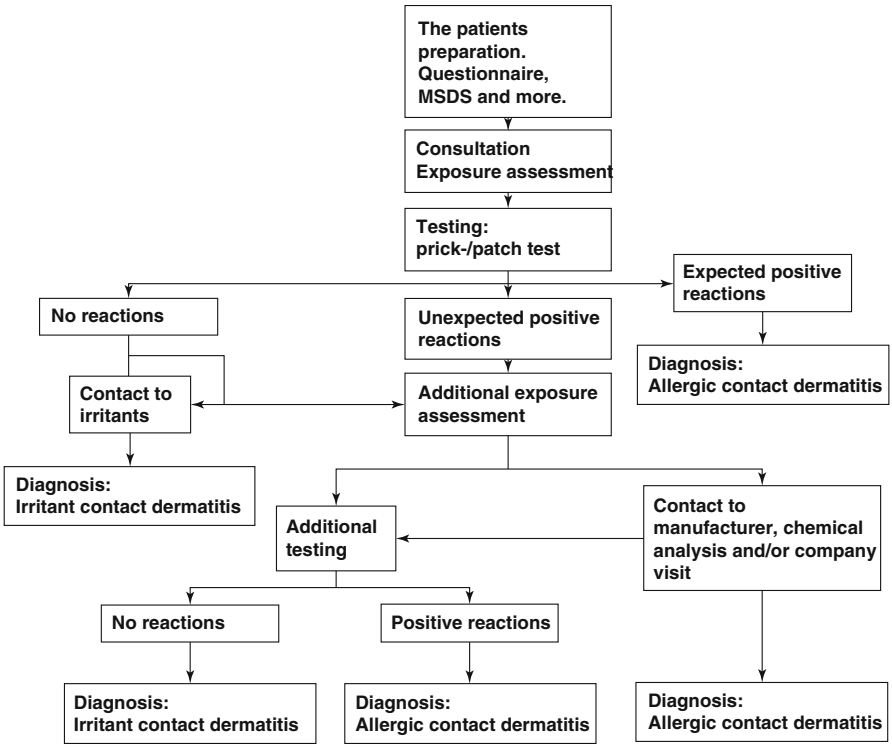

Fig. 5.1 Flow diagram of the investigation of patients with suspected allergic contact dermatitis

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