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## Position paper

# EAACI/GA$^2$LEN Position paper: Present status of the atopy patch test*

A number of scientific reports have been published on patch tests with protein allergens performed on patients with atopic eczema (AE). Evaluation of eczematous skin lesions with an atopy patch test (APT) can be used as a diagnostic tool in characterizing patients with aeroallergen- and food-triggered AE. Indications for testing with APT, choice of allergens (aeroallergens and foods), test materials and technique, including present knowledge on sensitivity and specificity, are reviewed on the basis of available literature. This position paper also points out the need for future research on the clinical use of the APT.

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Atopic eczema (AE, atopic dermatitis) is a chronic inflammatory skin disease. The diagnosis is made by a combination of clinical features. AE is characterized by recurrent intense pruritus and a typically age-related distribution and skin morphology (1, 2). The role of allergy in eliciting and maintaining the eczematous skin lesions has been debated. Among the allergens found to be relevant in atopic eczema, food allergens (mostly in children) and aeroallergens are the most important. Avoidance strategies are therapeutic consequences based on the diagnosis of allergy. The relevance of (often multiple) IgE-mediated sensitizations for the skin disease has to be evaluated in patients with AE.

Environmental substances like aeroallergens produce flares in some patients with atopic eczema. Moreover, aeroallergen avoidance, especially with regard to house dust mites, can result in marked improvement of skin lesions (3). Patients with atopic eczema often have elevated serum levels of immunoglobulin E (IgE), which may correlate with the severity of the disease (4). This concept is derived from studies showing IgE and IgE-binding structures on the surface of epidermal Langerhans cells together with mite allergen (5, 6).

An epicutaneous patch test, atopy patch test (APT), with type 1 allergens known to elicit IgE-mediated reactions, and the evaluation of eczematous skin lesions after 24–72 h can be used as a diagnostic tool in characterizing patients with aeroallergen- and food-triggered AE. Allergen specific T cells have been cloned from APT biopsies (7, 8). These T cells showed a characteristic TH2 (T-helper cell subpopulation) secretion pattern initially, whereas after 48 h a TH1 pattern was predominant. This same pattern is also found in chronic lesions of AE (9). On a quantitative basis, it has been shown that

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APT reactions to inhalant allergens are also associated with specific T-cell responses to the corresponding allergen in the circulation (10).

Immunoglobulin E is commonly regarded as facilitating allergen presentation to skin-infiltrating T lymphocytes via its binding on Fc receptors on Langerhans cells (11). Several groups demonstrated that eczematous skin lesions can be induced in patients with AE by patch testing with aeroallergens and foods. Patch testing of aeroallergens especially in patients with AE was first documented in 1982 by Mitchell et al. (12). The first paper dealing with patch testing with foods dates from 1989 and describes a now discontinued commercial test kit DIMSOFT® used since 1980 (13). Subsequently, a number of authors studied the APT with foods in AE (14–17).

Due to variations in the applied methodology, varying percentages of positive APT results were obtained. For many of the models used, the sensitivity and specificity of experimental APT with regard to clinical history remained unclear. Moreover, in contrast to food allergy, no gold standard exists for the provocation of eczematous skin lesions in aeroallergen-triggered AE (18).

This paper aims to review the available data and to show the areas of future research on the clinical use of the APT. The target audience consists of all physicians caring for AE patients and patients with suspected food-related symptoms.

## Indication for testing

In children, AE is the most common disease associated with food allergy but the relationship between sensitization to foods and eczema is not exhaustively diagnosed by skin prick testing or by measurement of specific serum IgE to foods. Challenge-proven food allergy without systemic specific IgE has been diagnosed in children by several investigators, and the APT has been positive in some of those patients (19, 20). Moreover, Strömberg found the APT to be positive earlier than the skin prick test (SPT) in small children with food allergy proven by challenge positivity, especially with cereals (21).

Atopy patch test with foods (cow's milk, hen's egg, cereals and peanut) may increase the identification of food allergy in patients with AE in the following cases:

- suspicion of food allergy without predictive specific IgE levels or a positive SPT;
- severe and/or persistent AE with unknown trigger factors;
- multiple IgE sensitizations without proven clinical relevance in patients with AE.

Further studies of the performance of APT are needed with other food allergens and other disease categories, such as patients presenting with gastrointestinal symptoms without AE (22, 23). APTs are indicated for aeroallergens in the following situations:

- suspicion of aeroallergen symptoms without proof of positive specific IgE and/or a positive SPT;
- severe and/or persistent AE with unknown trigger factors;
- multiple IgE sensitizations without proven clinical relevance in patients with eczema.

Besides clinical indications, the APT has been used to study the pathomechanism of AE where it continues to yield useful new information (24–26).

## APT technique

As a result of methodological studies with aeroallergens, APT with significant correlations to clinical parameters like allergen-specific IgE or patients' history is today performed with a similar technique to conventional patch tests for the diagnosis of classical contact allergy (27–30). In Europe, the efforts for the standardization of aeroallergen APT are coordinated in the European Task Force on Atopic Dermatitis (ETFAD) which has also performed and published an extensive multicentre trial on this issue (31). A novel technique for APT with milk in a commercially available test kit was recently introduced in France (Diallertest®) and compared with APT with Finn Chamber (Epitest Ltd Oy, Tuusula, Finland) in 49 children with milk allergy (32). The results showed good sensitivity and specificity without side-effects.

## Allergens for testing – test materials

For certain aeroallergens, the diagnostic sensitivity and specificity of some commercial preparations have been tested by Darsow et al. in a European Multicenter Study (31). House dust mite extract is also commercially available as a mixture (Der p and Der f) in a 20% solution in petrolatum, but the concentration is probably much too high (33).

To date, the APT with foods is not well standardized, and different methods in preparing the test materials are likely to cause controversial results. Most studies with foods have been performed with cow's milk, hen's egg and wheat only. Until validation data are available, fresh foods should be preferred for testing over commercial extracts. For future studies, the use of recombinant proteins, some of which are available, might be interesting, as has been shown for Malassezia furfur allergens (34).

## Vehicles

Aeroallergen extracts have been tested in different vehicles by various authors; petrolatum proved to be advantageous in those studies (28). Allergen extracts and

recombinant allergens have also been used in aqueous solution in PBS (34). Foods have been used with and without vehicles leading to similar results. Therefore, no recommendations can be given. Recently, APTs with allergens dissolved in aqueous solution on tape-stripped skin were compared with petrolatum without tape stripping. Both methods gave positive reactions in equal numbers, but the reactions were significantly stronger with petrolatum. No differences were found in histological examination of the reactions (35).

## Concentrations

### Aeroallergens

Atopy patch tests with several aeroallergens were performed with 3000, 5000, 7000 and 10 000 protein nitrogen units per gram in a dose–response study performed by Darsow et al. (30, 36): 5.000 PNU/g showed the highest diagnostic efficacy for grass pollen and 7.000 PNU/g for cat dander and Der p. For children, lower concentrations were possible (27). The stuff provided by Stallergènes S.A. (Antony Cedex, France) was used in a concentration of 200 index of reactivity IR/g of allergens in a petrolatum vehicle. The potency of 100 IR/g was designated as the strength of allergenic extract that elicited a geometric mean wheal diameter of 7 mm on SPT in 30 subjects sensitive to the corresponding allergen. Bygum et al. found a significant positive correlation between a positive APT, allergen dose and increase in transepidermal water loss and erythema. They used *Dermatophagoides pteronyssinus*, grass pollen, cat dander and *Pityrosporum ovale* in the highest concentration available from ALK-Abellò (Hørsholm, Denmark) and in a fourfold dilution thereof (37).

### Foods

In a study performed by Niggemann et al. food allergens were tested in parallel in a 1 : 10 solution to exclude false-positive results by irritant reactions (20). The authors found positive reactions in 18 of 77 (23%) patients with the 10% diluted APT, and these were seen in the patients with the strongest reactions to the undiluted APT. Furthermore, all these patients showed late eczematous reactions in the DBPCFC, mostly to wheat ($n = 10$). The authors concluded that the APT results are not biased by unspecific, irritant reactions and that undiluted native foods should be used.

## Control material in APT

In several studies, no control material has been used or it has not been mentioned. In some other studies, various control materials have been used but they have not been compared with each other. The vehicle has been used as a negative control in some recent studies. Darsow et al. found positive reactions to the vehicle in three of 302 patients (0.99%) (31). Holm et al. left the control material (petrolatum) for 72 h under occlusion before biopsy. The tests were clinically negative, but in three control patches there was a slight cellular infiltration in patients with elevated amounts of specific IgE to *D. pteronyssinus* in serum (26). A vehicle control with PBS was performed (34). One of 10 patients showed a positive APT reaction to the negative control with physiological saline (38). Microcrystalline cellulose moistened with physiological saline was used as a negative control in several studies from Finland and Sweden, but no results are given concerning possible reactions (17, 21, 39, 40). Seidenari et al. used empty chambers with filter paper (41). In control areas, vehicles without allergens were tested. The vehicle additive isopropyl myristate (10%) and a 0.5% solution of sodium lauryl sulphate as an irritant were also included in the test panel (36).

## Place of application and reproducibility

In 16 adult patients with AE and a positive APT reaction to one of the four allergens, house dust mite (Der p), cat dander, grass pollen or birch pollen, the corresponding aeroallergen was simultaneously retested on both forearms and the back (42). The test was read after 48 and 72 h (ETFAD key). Results showed a high reproducibility over time (93.8%) for the APT within an average of 16 months. A reaction was more frequently positive on the back (94%) in comparison with the arms (69%). Heinemann et al. found the same unsatisfactory reproducibility when comparing test results first on the back and later on the arms (43). Bygum et al. tested 23 adults with AD and 25 healthy controls with standard inhalant allergens on the back (*D. pteronyssinus*, grass, cat). The reproducibility rates in 6 weeks were 0.69–0.81 in patients and 0.60–0.96 in controls (37). Intraindividual duplicate testing of *Dermatophagoides* mix and *Alternaria alternata* in petrolatum on the upper back (left *vs* right, ETFAD reading) showed a 100% agreement. For *Dermatophagoides*, the intensity agreement was also satisfactory (kappa = 0.80) (44). Relatively good reproducibility over time was found when 10 of 13 patients showed positive results with reapplication of the same allergen (26). For foods, no comparative studies on the value of the location are available. Usually, for children the back is chosen.

## Chamber material and size

So far, all studies published, except Diallertest®, have used the aluminium chamber (Finn Chamber, Epitest Ltd Oy). For aeroallergens both 8 mm (standard) and 12 mm (large) cup sizes have been used. An intraindividual comparison using Der p, cat dander as well as birch and

grass pollen allergens (Stallergènes, 200 IR/g) showed better results with large Finn Chambers (U. Darsow Personal communication).

Concerning foods, Niggemann et al. compared standard and large cup sizes (45). They found that the large (12 mm) cup size should be used for APTs with food, even in infants and small children. On the other hand, other investigators have found good correlation between APT results using the 8 mm size cups and challenge test (17, 19, 21, 39, 40).

### Concomitant treatment

A few studies have investigated the possible modulation of the APT by an anti-inflammatory skin treatment: glucocorticosteroids and tar were both able to reduce the macroscopic outcome of the APT reaction and the influx of inflammatory cells, however, all cell types remained present (46). For the topical immunomodulators, tacrolimus and pimecrolimus, a similar effect can be assumed (47). One group studied the effect of a fatty acid-rich emollient on APT reactions and found that pretreatment had a prophylactic effect in patients with AE (48). Both authors conclude that the APT can be used to evaluate the effect of topical anti-inflammatory treatments. The practical consequence is that the APT should be performed on skin with no previous local treatment.

No information is available concerning treatment with oral antihistamines. Considering the pathomechanisms of the T-cell-mediated late phase reaction of the APT, no influence would be expected, however, erythema may be decreased. Therefore, antihistamines should be withdrawn at least 72 h prior to the APT (depending on the substance).

### Age dependency

A general problem is that the APT with foods (e.g. with cow's milk or hen's egg) has mostly been studied in infants and children, since food allergy plays a role especially in this age group, whereas aeroallergens (e.g. house dust mite) have been studied more intensively in adults. This presents a bias in the methodological evaluation of age as an influencing factor.

Concerning the APT using foods, one study investigated various paediatric age groups, 0–11, 12–35, 36–59 months and children $>60$ months, and found no significant difference in the APT in terms of sensitivity, specificity or positive or negative predictive values when double-blind, placebo-controlled food challenges were taken as the gold standard (49). Another study looked at children below and $>2$ years and reported that the frequency of positive APT results was lower in children $>2$ years compared with younger children (21).

Only one study has investigated the APT with food in children and adults using the same design (41). This study used peanut, which cannot be compared with other studies. The authors found that an APT positivity was more frequent in children $<6$ years compared with older children and adults. In general, results seem to be less impressive in adults compared with infants and children; one hypothesis may be that the skin of children is thinner and allergens can penetrate easier to the antigen-presenting Langerhans cells.

For aeroallergens, many studies have investigated the APT in adults, while very few studies on childhood populations have been published (27).

### Control individuals

In most studies, nonatopic control individuals were found to be nonreactive. The proportion of positive patch test reactions varied from 15% to 70% in patients with AE in different studies. Some studies investigating the clinical relevance of patch test reactions with inhalant allergens point to a high frequency of positive results in patients with eczematous skin lesions that are predominantly on air-exposed skin sites (29, 30).

Ingordo et al. performed APTs with house dust mite (HDM) extracts in 77 adults with AE, 47 atopic subjects without eczema and 33 nonatopics. Reactions with two different extracts of HDM were positive in 37.7%/41.6% of the patients with AE, 10.6%/19.1% of the atopics without eczema and 12.1%/12.1% of the nonatopics. Even if patients with AE have significantly more positive reactions than nonatopics, there is much nonspecific reactivity with APT (50). There is a little information on atopy patch testing with foods in healthy individuals. In Denmark, 486 unselected children 3 years of age were investigated for the relevance of APT in predicting hypersensitivity to cow's milk and hen's egg. A total of 330 children without AE were patch tested with hen's egg and with cow's milk: 294 were totally negative to egg, 24 showed irritant reactions and only two children showed a positive patch test reaction. In milk patches, 312 were negative, 24 irritant and two positive. Altogether 0.6% of the tested children without AE showed positive APT responses (51). However, this study used small Finn Chambers which are usually not recommended for APT.

### APT readout

Atopy patch test was shown to give clinically relevant results with the 'International Contact Dermatitis Research Group' (ICDRG) reading key for conventional patch testing (30, 52). Consensus meetings of most groups performing APT with aeroallergens for clinical use in Europe were held in 1997 and 1998 (53). One

Table 1. Revised European Task Force on Atopic Dermatitis (ETFAD) key for atopy patch test (APT) reading

| | |
|---|---|
| – | Negative |
| ? | Only erythema, questionable |
| + | Erythema, infiltration |
| ++ | Erythema, few papules |
| +++ | Erythema, many or spreading papules |
| ++++ | Erythema, vesicles |

result of these meetings was a consensus APT reading key for describing the intensity of APT reactions. This key has more options to describe the different morphology of positive APT reactions. It was used in a multicentre trial in six European countries (31). More recently, the key was revised according to the 2003 ETFAD Meeting Protocol (Table 1). It would seem more important to distinguish clear-cut positive reactions from negative or questionable ones, since only reactions showing papules or at least some degree of infiltration could be correlated to clinical relevance (30, 52). Thus, only erythematous reactions with aeroallergens are being considered as questionable and repetition of the test is recommended in these cases. For a low reaction intensity (persisting oedema without papules) there is still a need for further studies to clarify clinical relevance. A very recent study proposed a standardized interpretation of the APT in children with AE and suspected food allergy, indicating that the presence of both infiltration and at least seven papules had the greatest diagnostic accuracy for predicting the outcome of DBPCFC (54).

## Occlusion time/reading time

One study compared occlusion times of 24 and 48 h for the APT with hen's egg, cow's milk, wheat and peanut (55). The study was performed in 48 children with AE aged 3–29 months (median 14 months). A 48-h occlusion time gave better results (Table 2). With the 24-h occlusion time, the sensitivity was 0.15, specificity 0.91, PPV 0.86 and NPV 0.63. With the 48-h occlusion time, the sensitivity was 0.98, specificity 0.90, PPV 0.87 and NPV 0.92. The occlusion time should be 48 h for the APTs with foods in children with AE, as for contact allergens. No information was given on a 20-min occlusion time. In another study with 314 patients with AE, the APTs with both aeroallergens and foods were applied for 48 h, but after 24 h the reactions were read and test cups reapplied with further readings at removal of the tests at 48 h and later at 72 h. Readings of APT at 24 h gave a very few reactions in comparison to the 48–72-h readings, which are recommended (31).

Table 2. Performance characteristics of the APT for the two occlusion times with different food allergens, in 48 children with atopic dermatitis (55)

| Allergen: | Hen's egg | | Cow's milk | | Wheat | | Peanut | |
|---|---|---|---|---|---|---|---|---|
| Occlusion time (h): | 24 | 48 | 24 | 48 | 24 | 48 | 24 | 48 |
| Se (%) | 15 | 97 | 18 | 89 | 25 | 83 | 13 | 71 |
| Sp (%) | 83 | 71 | 100 | 96 | 100 | 94 | 97 | 82 |
| PPV (%) | 86 | 95 | 100 | 94 | 100 | 71 | 67 | 66 |
| NPV (%) | 12 | 83 | 63 | 92 | 94 | 97 | 72 | 85 |

APT, atopy patch test; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value.

## Sensitivity and specificity

There are obvious variations in the figures for sensitivity and specificity both with SPT and APT in patients with AE (Table 3) (56–59). For instance, in the diagnosis of cow's milk allergy, SPT and APT yield nearly similar mean sensitivity (0.53 and 0.51, respectively) and specificity figures (0.81 and 0.86, respectively), but the sensitivity varies in the SPT from 0.14 to 0.78 and in the APT from 0.18 to 0.89 in different studies. This may reflect differences in the study populations and/or test materials and methods.

## Side-effects

In the literature, there are only few comments on side-effects using APTs. Egg caused local urticaria and itching 5–15 min after administration of APT in six children (20). One egg-allergic child showed severe urticaria and rhinoconjunctivitis shortly after application of APT with egg (38). One adult patient with facial dermatitis developed extended dermatitis of face, trunk and flexural areas within 1–2 days after APT (60). In two studies, infiltration and redness of the patch test area persisted for several weeks (21, 59). Among 253 patients tested, 11 showed local eczema flare, two contact urticaria, two irritation from adhesives, two bronchial asthma and two systemic reactions. No reactions to the vehicle were observed. None of the reactions was regarded as a severe side-effect. The allergens used were *D. pteronyssinus*, cat dander, grass pollen, birch pollen and mugwort pollen (30). In 314 patients reported by Darsow et al., adverse effects were recorded in 7.7%. They were mostly mild, including local flares, contact urticaria, irritation from adhesive tapes and local itching (31). There are so far no reports in the literature indicating sensitization by using APTs with aeroallergens and foods.

## Future activities

### General comments

When a diagnostic test is evaluated, there should be an independent, blind comparison with a reference (gold)

Table 3. Sensitivity (Se) and specificity (Sp) of the skin prick test (SPT) and the atopy patch test (APT) with different allergens and in different patient populations

| | | | | | SPT* | | APT | |
|---|---|---|---|---|---|---|---|---|
| Reference | Allergen | *n* | Age (months/years) | AE prev. (%) | Se | Sp | Se | Sp |
| 17 | Milk | 183 | 2–36 months | 100 | 0.48 | 0.86 | 0.61 | 0.81 |
| 39 | Milk | 143 | <24 months | <85 | 0.14 | 0.98 | 0.44 | 0.71 |
| 60 | Milk | 179 | <12 months | 74 | 0.69 | 0.91 | 0.18 | 0.87 |
| 57 | Milk | 71 | 2–134 months | 100 | 0.78 | 0.69 | 0.47 | 0.96 |
| 58 | Milk | 239 | <12 months | 84 | 0.61 | 0.76 | 0.37 | 0.77 |
| 21 | Milk | 141 | 2–48 months | 100 | 0.41 | 0.99 | 0.6 | 0.97 |
| 56 | Milk | 48 | 3–29 months | 100 | 0.59 | 0.5 | 0.89 | 0.96 |
| 57 | Egg | 42 | 2–134 months | 100 | 0.89 | 0.57 | 0.57 | 0.93 |
| 21 | Egg | 141 | 2–48 months | 100 | 0.6 | 0.97 | 0.71 | 0.97 |
| 56 | Egg | 48 | 3–29 months | 100 | 0.93 | 0.5 | 0.97 | 0.71 |
| 38 | Egg | 30 | 10–101 months | 100 | 1 | 0.85 | 0.6 | 0.9 |
| 57 | Wheat | 35 | 2–134 months | 100 | 0.67 | 0.53 | 0.89 | 0.94 |
| 21 | Wheat | 141 | 2–48 months | 100 | 0.6 | 0.97 | 0.71 | 0.97 |
| 59 | Wheat | 90 | 2–36 months | 100 | 0.23 | 1 | 0.67 | 0.79 |
| 56 | Wheat | 48 | 3–29 months | 100 | 0.75 | 0.5 | 0.83 | 0.94 |
| 40 | Wheat | 22 | <24 months | 92 | 0.23 | 1 | 0.86 | 0.35 |
| 21 | Rye | 141 | 2–48 months | 100 | 0.15 | 0.99 | 0.93 | 0.9 |
| 41 | Peanut | 132 | 36–336 months | 100 | 0.33 | 0.9 | 0.75 | 0.87 |
| 56 | Peanut | 48 | 3–29 months | 100 | 0.7 | 0.5 | 0.71 | 0.7 |
| 57 | Soy | 25 | 2–134 months | 100 | 0.5 | 0.9 | 0.75 | 0.86 |
| 30 | HDM | 253 | 15–63 years | 100 | 0.69 | 0.52 | 0.56 | 0.69 |
| 53 | Grass pollen | 79 | 5–69 years | 100 | 1.00 | 0.33 | 0.75 | 0.84 |
| 30 | Grass pollen | 253 | 15–63 years | 100 | 0.82 | 0.44 | 0.46 | 0.87 |
| 30 | Cat dander | 253 | 15–63 years | 100 | 0.80 | 0.53 | 0.42 | 0.52 |

AE prev., the prevalence of atopic eczema in the study population; HDM, house dust mite (*D. pteronyssinus).*
*SPT cut-off 3 mm (mean diameter).

standard of diagnosis (61). The problem with aeroallergens is that a 'gold' standard of provocation test in atopic eczema does not exist (31). Therefore, at present, less reliable standards, e.g. a patient's clinical history, must be used for comparison. In the future, studies should be undertaken to evaluate and standardize topical *in vivo* challenge procedures in AE (62).

When evaluating APT with food allergens, the diagnostic performance of the test can be evaluated by comparing the results with double-blind, placebo-controlled food challenges (DBPCFC). A recent European position paper gives guidelines for the standardization of food challenges in patients with immediate reactions to foods (63), but subjects with AE sometimes show only delayed reactions in food challenges (64, 65). There should be an attempt to standardize the challenge procedures also for delayed reactions (dosing and length of exposure and observation, wash-out periods, etc.), but that is beyond the scope of this task force.

To ensure an independent, blind comparison of the APT result with the reference standard the test application and the reading should be performed by different investigators. The reading of the reactions should be performed by an investigator without knowledge of the (control) test sites or patient's history. Until now, a few studies have purported to fulfil these criteria (31). An ultimate goal of the studies of APT performance is to show that the test results can predict the long-term outcome of aeroallergen and food avoidance in subjects with AE.

### Specific comments

There are several aspects of APT that deserve further investigation to achieve better standardization. These include:

- optimum allergen concentrations (28, 31, 55, 58);
- vehicles for different allergens (17, 28);
- optimum sizes of Finn chambers for different allergens (45);
- other materials for occlusion than Finn chambers (32).

It has to be demonstrated that the actual test preparation is nonirritant and nontoxic in healthy control subjects (38) as well as in subjects with AE (64). Wheat gluten in particular has been suspected of causing false positive (irritant) reactions (64). The preferred way of evaluating these and other aspects of standardization is to perform prospective, multicentre studies in clinics with adequate experience of patch testing and challenge/allergen avoidance procedures.

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