

The Use of Patch Testing in the Diagnosis of Food Allergy

Jonathan M. Spergel, MD, PhD, and Terri Brown-Whitehorn, MD

Address

Allergy Section, Division of Allergy and Immunology, The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Wood 5, Philadelphia, PA 19104, USA.
E-mail: spergel@email.chop.edu

Current Allergy and Asthma Reports 2005, 5:86–90
Current Science Inc. ISSN 1529-7322
Copyright © 2005 by Current Science Inc.

Diagnosing food allergies can be challenging to the practitioner. Our armamentarium includes standardized skin prick testing, radioallergoimmunosorbent (RAST) testing, and food challenges. These methods have certainly been helpful in the IgE-mediated disorders, including urticaria and anaphylaxis. However, diagnosing patients who have the non-IgE (cell-mediated) or mixed (IgE and cell-mediated) disorders remains challenging with our current diagnostic methods. Recent studies have examined the use of patch testing for these food-allergic patients, specifically those with atopic dermatitis and eosinophilic esophagitis. In this article, we review literature regarding patch testing: its methods, its statistical usefulness, and its potential future role.

Introduction

Food allergy is a common disorder in the westernized world, affecting between 2% and 8% of infants and young children. Thirty-five percent of children with moderate to severe atopic dermatitis have IgE-mediated food allergy [1••]. But, atopic dermatitis (AD) is thought to have mixed IgE and non-IgE mechanisms [2•]. AD is not the only food-allergic disease that is mixed IgE- and non-IgE-mediated. Eosinophilic esophagitis (EE) also has been recently reported to have a similar etiology [3••].

Atopy patch testing (APT) has been used for the diagnosis of non-IgE, cell-mediated immune responses in which T cells play a prominent role. The earliest publication on patch testing in eczema was described in 1937 [4], but the earliest control trial was in 1982 [5]. Since then, many European centers have used patch testing to aide in the diagnosis of food allergy in children with atopic dermatitis, the results of which are thought to be indicative of late-phase reactions. We have recently reported the use of patch testing along with skin testing in patients with EE [3••].

Atopy patch testing involves prolonged contact of the allergenic extract to the skin, with the goal of mimicking a similar immune response. In fact, biopsy specimens of the patch test sites in patients with atopic dermatitis were found to have initial T_H2 cell infiltration, followed by a predominance of T_H1 cytokines and eosinophils [6]. Similar biopsy findings have been observed in the skin of atopic dermatitis patients during acute and chronic lesions. T_H2 cytokines predominate earlier in the disease, with a transformation to T_H1 predominance in the chronic lesions [2•].

Methods of Patch Testing

In comparison with skin prick testing, one of the difficulties in patch testing is the lack of standardization. In reviewing the literature, it can be determined that many researchers utilize similar methods. The goal is to have the same concentration of the food product in the patch test that is typically ingested/challenged. We dilute 2 g of dry food with 2 mL isotonic saline solution. The mixtures are then placed in aluminum cups (Finn Chambers on Scanpore, Allerderm Laboratories, Inc., Petaluma, CA) on uninvolved areas of the patient's back [3••]. We and other groups also use fresh foods directly in the Finn Chambers. Niggemann *et al.* [7,8] found that the sensitivity, specificity, positive predictive value (PPV), and negative predictive value improved when using the 12-mm chamber compared with the 6-mm size. Rance [9] found the optimal occlusion time to be 48 hours compared with 24 hours. The back is evaluated 20 minutes after removal and again at 72 hours. Interestingly, Perackis *et al.* [10] found that there was no difference between the age of children undergoing patch test and their predictive capacity. We and others have incorporated these findings into a standard protocol. In fact, the European Task Force of Atopic Dermatitis (EFTAD) has recently published standardized APT techniques [11••]. Most centers now use 12-mm chambers with 48-hour occlusion time reading done at 72 hours. Reactions are traditionally classified as +—erythema and slight infiltration; ++—erythema and papules; and +++—erythema and vesicles. The EFTAD has expanded the range to —negative; ?—erythema only; +—erythema and infiltration; ++—erythema and a few papules; +++—erythema and many papules; and ++++—erythema and vesicles.

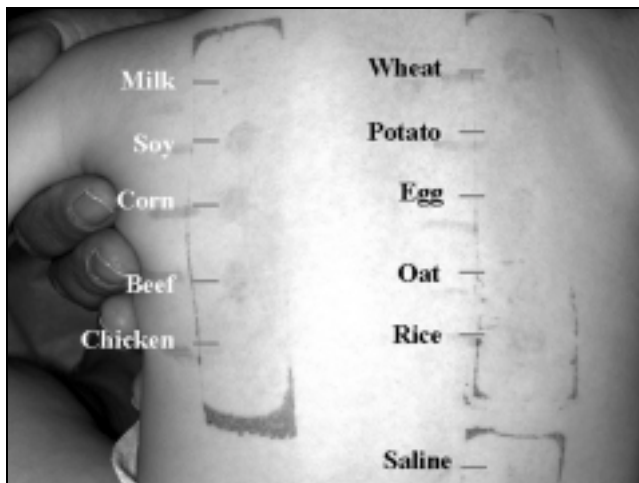


Figure 1. Food patch testing. Positive reactions are observed to soy, corn, beef, and wheat. By the EFTAD scale, soy and corn are +++, and beef and wheat are ++. EFTAD—European Task Force of Atopic Dermatitis.

A representative patch test is shown in Figure 1. Based on the EFTAD scale, the reading of these patch tests are: beef ++; soy, corn, and wheat +++; and rice “?”.

Any food can be assessed with patch testing, although cow's milk, hen's egg, wheat, and soy have been studied most extensively [3••,12–15,16•,17,18,19•,20]. In our study, we found reproducible results with a variety of other foods in concentrations similar to what is ingested [3••]. For grains, egg, and soy, we and others have found that ideal concentration is 1 g/mL [3••,18,19•]. Milk requires a higher concentration at 3 g/mL for ideal testing [3••,17].

Side effects of patch testing are uncommon, although reports of contact urticaria in small numbers of patients have been reported [16•]. Irritation reactions have been described in other patients as well [17,18,21]. Patch testing should not be performed if the underlying skin is inflamed.

Patch testing does not make standardized skin prick testing, radioallergosorbent assays (RAST), or double-blind, placebo-controlled food challenge (DBPCFC) studies obsolete. DBPCFC studies remain the gold standard for the diagnosis of food allergy [1••,20]. We and others are evaluating whether patch testing can make a significant improvement in our diagnostic abilities, with the standardized assays, in children with mixed IgE and non-IgE reactions to foods.

Recent Clinical Studies in Atopic Dermatitis

Role of milk

The most commonly studied foods used in patch testing include cow's milk, chicken's egg, soy, and wheat. Isolauri and Turjanmaa [19•] first reported the combination of skin prick testing and patch testing in infants with atopic dermatitis. They looked at milk allergy in 183 children who were between 2 and 36 months of age with DBPCFC. In patients with acute reactions, 67% of them had positive skin testing and none of them had positive patch testing. In patients with delayed reactions, 89% of patients had positive patch tests

and none of them had positive skin testing. The most severe patients (40 of the 143) could not have diagnostic testing due to the condition of their skin, which might skew some of their results. Nevertheless, they concluded that parallel skin prick and patch testing will enhance the early identification of food allergy in infants with atopic dermatitis that may have been missed by skin prick testing alone. Their study led to a variety of other studies and publications that focused on the role of patch testing in patients with food allergy and atopic dermatitis [22••].

Most others found similar results; however, Vanto *et al.* [21] did not find that patch testing distinguished between immediate, delayed, or negative reactions. They studied 301 milk-allergic infants by RAST, prick, and patch testing who had positive DBPCFC. They concluded that patch testing was not helpful in this cohort of patients and that there was no association between the patch test and the reaction of the challenge. They did not have an explanation of the conflicting results, but referred to the young age of their cohort and perhaps the differences in interpretation of delayed reactions.

Of those who studied cow's milk alone, Majamaa *et al.* [17] investigated 143 infants younger than 2 years who had undergone diagnostic cow's milk challenges. Sixty-eight patients had skin issues, 21 had gastrointestinal symptoms, and 54 had both skin and gastrointestinal issues. Cow's milk RAST, prick, and patch test were performed. If infants had a clear history and positivity on testing, they were not challenged. Of those tested, 72 (50%) of the children had positive challenges: 22 immediate and 50 delayed. The skin patch test was positive in 44% of patients positive to cow's milk challenge, of whom all had negative skin prick, and was highly associated with delayed-type reaction. As did Isolauri and Turjanmaa [19•], Majamaa *et al.* found that being patch-test positive was highly associated with delayed-type reaction to oral challenge. This study also revealed false negatives to all diagnostic tests, stressing the importance of clinical assessment and food challenges when in doubt.

Role of wheat

The Finnish group also investigated the role of patch testing to wheat in 39 infants suspected of wheat allergy as noted by skin reaction, gastrointestinal reaction, or a combination of the two [18]. They found that 56% had positive food challenges (5 immediate, 17 delayed reactions)—20% positive RAST, 23% positive skin prick test, and 86% positive patch. In this study, patch testing was found to be a more sensitive method to diagnose wheat allergy in children with atopic dermatitis. They found the sensitivity of patch testing to be 86% compared with 20% for RAST testing and 23% for prick testing (Table 1).

Role of peanut

Seidenari *et al.* [23] evaluated the combination of skin prick testing and patch testing in relationship to peanut-

Table 1. Sensitivity, specificity, PPV, and NPV from patch testing

Food	Patients, <i>n</i>	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Study
Milk	205	37	95	88	62	Perackis <i>et al.</i> [10]
	71	47	96	95	51	Roehr <i>et al.</i> [13]
	143	44	71	63	52	Majamaa <i>et al.</i> [17]
	183	61	81			Isolauri <i>et al.</i> [19,30]
	301	18	87	40	69	Vanto <i>et al.</i> [21]
	141	60	97	95	75	Seidenari <i>et al.</i> [23]
Egg	111	42	89	85	50	Perackis <i>et al.</i> [10]
	42	57	93	94	52	Roehr <i>et al.</i> [13]
	141	71	97	96	73	Stromberg [24]
Soy	90	47	91	50	90	Perackis <i>et al.</i> [10]
	25	75	86	50	95	Roehr <i>et al.</i> [13]
Wheat	92	35	32	67	75	Perackis <i>et al.</i> [10]
	35	89	94	94	89	Roehr <i>et al.</i> [13]
	39	86	35	63	67	Majamaa <i>et al.</i> [18]
	141	90	94	92	93	Stromberg [24]
Rye	141	93	90	88	95	Stromberg [24]
Peanut	132	75	87	36	97	Seidenari <i>et al.</i> [23]
Milk, egg, soy, wheat	133					Seidenari <i>et al.</i> [23]
Early phase		33	95	81	67	
Late phase		76	95	81	93	

NPV—negative predictive value; PPV—positive predictive value.

allergic patients with atopic dermatitis. They studied 132 patients with eczema and found that 9% had positive reactions to challenges. The PPV was found to be 36% in patch-positive children and 25% in skin test-positive patients. The sensitivity of patch testing was found to be 75% in patch test-positive patients compared with 33% of skin test-positive patients. They summarized that patch testing may represent a useful integration to standard testing in atopic children with peanut allergy.

Studies of Multiple Foods

Other groups looked at several foods on food-allergic patients. Stromberg [24] studied the diagnostic accuracy of patch test and prick testing in 141 children 2 months to 4 years with eczema (30% had gastrointestinal symptoms) and food allergy. They found the sensitivity/specificity of patch testing to be 60%/97% for milk, 71%/97% for egg, 90%/97% for wheat, and 93%/90% for rye. The sensitivity/specificity of skin testing was 41%/99% for milk, 60%/97% for egg, 13%/98% for wheat, and 15%/99% for rye. As noted by their results, patch testing seemed to be superior to skin testing, with increased sensitivity and equivalent specificity.

Niggemann *et al.* [16,25] studied patch testing using milk, egg, soy, or wheat in 209 challenges—133 with allergen and 76 with placebo. Of the patients with allergen-positive food testing, 77 had positive challenges, whereas two receiving placebo had positive challenges. They looked at the role of patch testing, RAST testing, and skin testing in this cohort of patients. The sensitivity of the late-phase reaction was 76% for patch testing compared with 58% for

skin testing and 71% for RAST testing. The specificity of late-phase reaction was 95% for patch testing compared with 70% for skin testing and 29% for RAST testing. They concluded that the patch test was a valuable addition in the diagnostic workup of children with atopic dermatitis.

Within that same group of patients, Niggemann *et al.* [8] sought to characterize and evaluate the percentage of children with atopic dermatitis and positive DBPCFC results without known IgE sensitization. They looked at the same 139 children with 208 challenges. Twelve of the 111 children with positive challenges had negative skin and RAST testing. Fifty-eight percent of those children had positive patch testing. They had expected that the patch testing would reach statistical significance for late-phase reactions, but this was not the case. Positive challenge in non-IgE, patch-positive patients occurred more in wheat-sensitive patients compared with those sensitive to egg and milk. They also found that 10% of the positive challenges were not IgE-mediated in their group of children with eczema.

Ability to Avoid Food Challenges

Roehr *et al.* [13] published a report to see whether tests could improve the diagnostic value so that food challenges could be avoided. They performed food challenges on 173 children and found 98 (55%) to be positive. They found 95% PPV to patch testing to milk, and if either RAST or skin test was added, the PPV is 100%. Similarly, patch tests produced 94% PPV to egg and were the single best test.

Table 1 reveals sensitivity, specificity, PPV, and negative predictive values of the published studies cited earlier. Patch testing in general has high specificity, but a significantly lower

sensitivity for individual foods. The negative predictive value is not as high as skin testing, which approaches 95%; the PPV is similar to skin testing ranging 50% to 90%.

Recent Clinical Studies in Eosinophilic Esophagitis

In the review of the data from Isolauri and Turjanmaa's study of children with atopic dermatitis [19•], 61 of 183 patients had a concomitant gastrointestinal reaction. They found that more than 80% of patients with delayed reactions of vomiting and diarrhea after a food challenge had positive patch test to a food antigen, whereas 25% had positive skin test. This study suggests that patch testing might detect gastrointestinal food allergies.

We recently published an article examining the role of patch testing in patients with EE. A link between food allergies and EE had been suggested initially by case reports in which food removal improved symptoms [26–28]. We examined 26 patients with EE confirmed on biopsy. These patients underwent skin testing and patch testing. The combination of skin testing along with patch testing improved diagnosis in 75% of patients. In fact, removal of the causative food led to complete resolution of symptoms, and eosinophils in biopsy samples performed after a restricted diet returned to normal levels. For the 25% of patients who continue to have symptoms or eosinophils on biopsy, 99% of patients improve on an elemental diet.

Our expanded look at EE in 170 patients found similar results (Brown and Spergel, Unpublished data, 2004). Seventy-one percent of patients had resolution of their EE, with normalization of their biopsies when they eliminated foods identified by skin test and patch testing. Fifteen percent had partial improvement of their biopsies, and 14% had no response. The inability to find the causative food in the remaining 29% of the EE patients could be due to three possible reasons: 1) the causative food was not tested; 2) patients were not compliant with their diet; or 3) testing did not detect the food. Egg, milk, soy, and peanut were identified most frequently with prick testing, whereas corn, wheat, soy, and chicken were identified most frequently with patch testing. However, for the non-responders, all but three have responded to an elemental diet. These results indicate that foods are a causative item in EE.

Infants without known EE often present with nonspecific, persistent digestive symptoms. De Boissieu *et al.* [29] investigated 35 infants with possible cow's milk allergy to determine the role of patch testing in addition to skin prick testing in this cohort of patients. They found that the sensitivity of patch testing was 79% and the specificity was 91%, leading to the conclusion that patch testing could improve the detection of cow's milk allergy.

How Do We Use Patch Testing?

Currently, patch testing is performed in our institution on all children with EE. Our recommendation for the identification of causative foods in patients with EE involves both skin prick testing and patch testing to identify the relevant food. We test for the most common 20 foods (meats, grains, milk, soy, egg, peanut, and selected fruits and vegetables) in the diet. We have been highly successful in the treatment of EE, with a 75% success rate based on positive foods found on APT and skin testing without resorting to elemental diet. We are also using patch testing on selective patients with a history of non-IgE-mediated food allergy. The results of this testing is inconclusive at this time.

Conclusions

Despite advances in the understanding of mechanisms, the diagnostic accuracy of the methods for early detection of clinically significant food allergy is poor. The PPV in skin testing is only approximately 50%, the PPV in RAST testing varies by each individual food, and the PPV of patch testing varies by food and disease studied. Patch testing may add another dimension to our ability to diagnose food allergy, especially in those children with atopic dermatitis or EE. In fact, the combination of RAST, skin testing, and patch testing may help to reduce the need for time-consuming food challenges. Patch testing appears to be helpful in non-IgE-mediated diseases, in particular gastrointestinal disorders.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

- 1.•• Sampson HA: **Update on food allergy.** *J Allergy Clin Immunol* 2004, **113**:805–819.
Excellent general review on food allergy.
2. Leung DY, Bieber T: **Atopic dermatitis.** *Lancet* 2003, **361**:151–160.
Outstanding review on the pathogenesis of atopic dermatitis.
- 3.•• Spergel JM, Beausoleil JL, Mascarenhas M, Liacouras CA: **The use of skin prick tests and patch tests to identify causative foods in eosinophilic esophagitis.** *J Allergy Clin Immunol* 2002, **109**:363–368.
First article discussing patch testing in food allergies other than atopic dermatitis.
4. Rostenberg A, Sulzberger M: **Some results of patch tests.** *Arch Dermatol* 1937, **35**:433–454.
5. Mitchell EB, Crow J, Chapman MD, *et al.*: **Basophils in allergen-induced patch test sites in atopic dermatitis.** *Lancet* 1982, **1**:127–130.
6. Darsow U, Ring J: **Airborne and dietary allergens in atopic eczema: a comprehensive review of diagnostic tests.** *Clin Exp Dermatol* 2000, **25**:544–551.
7. Niggemann B, Ziegert M, Reibel S: **Importance of chamber size for the outcome of atopy patch testing in children with atopic dermatitis and food allergy.** *J Allergy Clin Immunol* 2002, **110**:515–516.
8. Niggemann B, Reibel S, Roehr CC, *et al.*: **Predictors of positive food challenge outcome in non-IgE-mediated reactions to food in children with atopic dermatitis.** *J Allergy Clin Immunol* 2001, **108**:1053–1058.

9. Rance F: **What is the optimal occlusion time for the atopy patch test in the diagnosis of food allergies in children with atopic dermatitis?** *Pediatr Allergy Immunol* 2004, **15**:93–96.
 10. Perackis K, Celik-Bilgili S, Staden U, *et al.*: **Influence of age on the outcome of the atopy patch test with food in children with atopic dermatitis.** *J Allergy Clin Immunol* 2003, **112**:625–627.
 11. •• Kerschenlohr K, Darsow U, Burgdorf WH, *et al.*: **Lessons from atopy patch testing in atopic dermatitis.** *Curr Allergy Asthma Rep* 2004, **4**:285–289.
- Excellent review on atopy patch testing.
12. Turjanmaa K: **“Atopy patch tests” in the diagnosis of delayed food hypersensitivity.** *Allergie et Immunologie* 2002, **34**:95–97.
 13. Roehr CC, Reibel S, Ziegert M, *et al.*: **Atopy patch tests, together with determination of specific IgE levels, reduce the need for oral food challenges in children with atopic dermatitis.** *J Allergy Clin Immunol* 2001, **107**:548–553.
 14. Ring J, Darsow U, Gfesser M, Vieluf D: **The ‘atopy patch test’ in evaluating the role of aeroallergens in atopic eczema.** *Inter Arch Allergy Immunol* 1997, **113**:379–383.
 15. Niggemann B: **Evolving role of the atopy patch test in the diagnosis of food allergy.** *Curr Opin Allergy Clin Immunol* 2002, **2**:253–256.
 16. • Niggemann B, Reibel S, Wahn U: **The atopy patch test (APT): a useful tool for the diagnosis of food allergy in children with atopic dermatitis.** *Allergy* 2000, **55**:281–285.
- Article describing the use of atopy patch testing in the diagnosis of food allergy in atopic dermatitis.
17. Majamaa H, Moisisio P, Holm K, *et al.*: **Cow's milk allergy: diagnostic accuracy of skin prick and patch tests and specific IgE.** *Allergy* 1999, **54**:346–351.
 18. Majamaa H, Moisisio P, Holm K, Turjanmaa K: **Wheat allergy: diagnostic accuracy of skin prick and patch tests and specific IgE.** *Allergy* 1999, **54**:851–856.
 19. • Isolauri E, Turjanmaa K: **Combined skin prick and patch testing enhances identification of food allergy in infants with atopic dermatitis.** *J Allergy Clin Immunol* 1996, **97**:9–15.
- Early study examining patch testing in atopic dermatitis.
20. Breuer K, Heratizadeh A, Wulf A, *et al.*: **Late eczematous reactions to food in children with atopic dermatitis.** *Clin Exp Allergy* 2004, **34**:817–824.
 21. Vanto T, Juntunen-Backman K, Kalimo K, *et al.*: **The patch test, skin prick test, and serum milk-specific IgE as diagnostic tools in cow's milk allergy in infants.** *Allergy* 1999, **54**:837–842.
 22. •• Niggemann B: **The role of the atopy patch test (APT) in diagnosis of food allergy in infants and children with atopic dermatitis.** *Pediatr Allergy Immunol* 2001, **12**(Suppl14):37–40.
- Excellent review on atopy patch testing.
23. Seidenari S, Giusti F, Bertoni L, Mantovani L: **Combined skin prick and patch testing enhances identification of peanut-allergic patients with atopic dermatitis.** *Allergy* 2003, **58**:45–49.
 24. Stromberg L: **Diagnostic accuracy of the atopy patch test and the skin-prick test for the diagnosis of food allergy in young children with atopic eczema/dermatitis syndrome.** *Acta Paediatr* 2002, **91**:1044–1049.
 25. Niggemann B, Sielaff B, Beyer K, *et al.*: **Outcome of double-blind, placebo-controlled food challenge tests in 107 children with atopic dermatitis.** *Clin Exp Allergy* 1999, **29**:91–96.
 26. Gawrieh S, Shaker R: **Treatment options for eosinophilic esophagitis: elemental diet.** *Curr Gastroenterol Rep* 2004, **6**:189.
 27. Liacouras CA, Markowitz JE: **Eosinophilic esophagitis: a subset of eosinophilic gastroenteritis.** *Curr Gastroenterol Rep* 1999, **1**:253–258.
 28. Kelly KJ, Lazenby AJ, Rowe PC, *et al.*: **Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula.** *Gastroenterology* 1995, **109**:1503–1512.
 29. De Boissieu D, Wagué JC, Dupont C: **The atopy patch tests for detection of cow's milk allergy with digestive symptoms.** *J Pediatr* 2003, **142**:203–205.
 30. Isolauri E, Sutas Y, Mäkinen-Kiljunen S, *et al.*: **Efficacy and safety of hydrolyzed cow milk and amino acid-derived formulas in infants with cow milk allergy.** *J Pediatr* 1995, **127**:550–557.