

A pilot study of the usefulness and safety of a ready-to-use atopy patch test (Diallertest) versus a comparator (Finn Chamber) during cow's milk allergy in children

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Background: Patch testing is used in the diagnosis of food allergy, especially during delayed manifestations.

Objective: A ready-to-use atopy patch test (APT), the Diallertest, was compared with another APT device, the Finn Chamber, in pediatric cow's milk allergy.

Methods: This prospective study involved 49 children (34.3 ± 17 [mean ± SD] months of age), with cow's milk allergy manifested by atopic dermatitis (10.2%), digestive manifestations (40.8%), or both (49%). All children underwent both APT techniques, with a reading 72 hours after application, followed by a milk elimination diet for 4 to 6 weeks and open cow's milk challenge.

Results: A positive result was seen in 22 (44.8%) versus 13 (26.5%) patients with the ready-to-use and the comparator APTs, respectively. No side effects were recorded. Both techniques were concordant in 67.3% of patients. Of the total 41 open cow's milk challenges, 60.9% had positive results, with 8 patients lost to follow-up. The performances of the ready-to-use and comparator APTs were as follows: sensitivity, 76% (95% CI, 59.2% to 92.7%) versus 44% (95% CI, 24.5% to 63.4%; $P = .02$); specificity, 93.8% (95% CI, 81.9% to 100%) versus 93.8% (95% CI, 81.9% to 100%); positive predictive value, 95% (95% CI, 85.4% to 100%); 1 false-positive result) versus 91.7% (95% CI, 76% to 100%); 1 false-positive result); negative predictive value, 71.4% (95% CI, 52% to 90.7%; 6 false-negative results) versus 51.7% (95% CI, 33.5% to 69.8%; 14 false-negative results); and test accuracy, 82.9% (95% CI, 71.3% to 94.5%) versus 63.4% (95% CI, 48.6% to 78.1%; $P = .05$).

Conclusion: The ready-to-use APT exhibited a good sensitivity and specificity, with no side effects. (J Allergy Clin Immunol 2005;116:1321-6.)

Key words: Cow's milk allergy, children, ready-to-use atopy patch test

Food allergy is a common problem in toddlers and small children, involving 8% of French children in a recent population study of food allergy.¹ The current clinically validated method to demonstrate food allergy is elimination and challenge with the suspected food, either using the double-blind, placebo-controlled food challenge (DBPCFC)² or according to simplified procedures exhibiting a good correlation with the DBPCFC.³⁻⁶

For IgE-mediated disorders, skin prick tests (SPTs) guided by clinical history provide a rapid method to screen patients for sensitivity to specific foods. Negative SPT responses essentially confirm the absence of IgE-mediated allergic reactivity with a negative predictive accuracy of greater than 95%,⁷ but do not detect delayed-onset, non-IgE-mediated allergies.⁶ In the absence of immediate clinical reactions,⁸ delayed-onset allergies, most of the time related to a non-IgE-dependent mechanism, still present diagnostic difficulties, a situation specifically of concern during digestive manifestations sometimes associated with eczema in the young child.⁹

Several authors have therefore investigated the use of the atopy patch test (APT) for the diagnosis of non-IgE-mediated food allergy, primarily in patients with atopic dermatitis and digestive disorders.⁹⁻¹⁵ The APT results were positive in 89% of children with delayed-onset reactions, despite frequently negative SPT responses.^{6,16} Both in clinical practice and in clinical trials, several drawbacks of patch testing originate from its tedious preparation and a lack of standardized antigen preparation, leading to considerable intra-assay and interassay variations.¹⁷ An acceptable standardization of APTs would greatly improve the accuracy of this noninvasive tool for the detection of food allergy. Previous attempts include the development of an optimal vehicle for the allergen inside the patch device.¹⁸

The aim of our study was to assess the correlation and safety of a ready-to-use APT (Diallertest; DBV-Technologies, Boulogne-Billancourt, France) and compare it with that of another APT (Finn Chamber; Epitest Ltd, Hyrylä, Finland) in the evaluation of pediatric cow's milk allergy (CMA), together with its usefulness in the diagnosis of CMA, as determined by using an open cow's milk challenge.

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Abbreviations used

APT:	Atopy patch test
CMA:	Cow's milk allergy
CMP:	Cow's milk protein
DBPCFC:	Double-blind, placebo-controlled food challenge
SPT:	Skin prick test

METHODS**Patients**

A prospective study was carried out between November 2003 and September 2004 in a population of 49 children (mean $\pm$ SD age, 34.3 ± 7 months; range, 5-78 months), 18 girls and 31 boys, enrolled after referral to an outpatient clinic for food allergy. Children exhibited at least one symptom of allergy, the main symptoms being atopic dermatitis ($n = 5$, 10.2%), digestive manifestations (eg, loose stools, colic, vomiting, gastroesophageal reflux, and failure to thrive; $n = 20$, 40.8%), and combined manifestations ($n = 24$, 49%). All abnormal digestive reactions were analyzed by the parent's child and then validated by the physician. Children were not enrolled if maintaining an exclusion diet for cow's milk protein (CMP), presenting with important skin lesions impeding APT application, or having been treated with antihistamines and oral or cutaneous steroid medications for the last week.

Study design

On an outpatient basis, children were routinely tested by means of a blood sample for measurement of specific CMP IgE levels and underwent skin testing on the basis of CMP SPT and CMP APT by using both the ready-to-use technique (Diallertest) and the comparator (Finn Chamber). All enrolled children were randomized for the application of both APT techniques on the right or left side of the back. After the initial standardized evaluation, children were requested to follow a CMP elimination diet based on an extensively hydrolyzed whey protein formula or an amino acid-derived formula for 4 to 6 weeks combined with an open cow's milk challenge. Atopic dermatitis was assessed by using a routine local score on the basis of the severity and extension of eczematous skin lesions as follows: no, mild, moderate, and severe atopic dermatitis. This assessment was performed at enrollment, during the 4 to 6 weeks of the CMP elimination diet, and after the cow's milk challenge. The physician responsible for the open cow's milk challenge was blinded to the results of CMP IgE measurement, SPTs, and both APTs and vice versa. All side effects related to both APT techniques were recorded throughout the study duration according to a questionnaire explained by the research nurse. The protocol was approved by the local ethical committee, and written parental consent was obtained in all cases from both parents.

Specific cow's milk protein IgE (CMP IgE)

Sera CMP IgE was analyzed with the RAST Cap System (Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden) calibrated with reference to the World Health Organization standards for IgE. Its specificity was already assessed,¹⁹ and its use in children has already been reported.^{20,21} Reference data for specific CMP IgE levels were those of the manufacturer, considering values of less than 0.35 KU/L to be nondetectable.^{22,23}

CMP SPT

SPTs were performed with a drop of pasteurized half-skimmed cow's milk on the backs of children if aged less than 12 months and

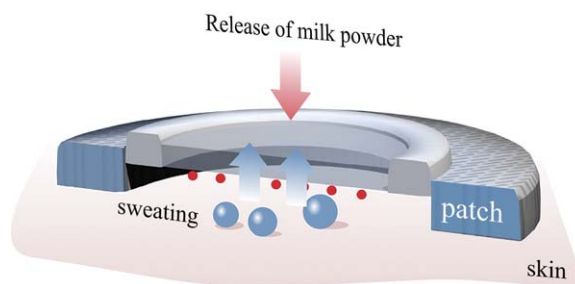


FIG 1. The ready-to-use CMP APT (Diallertest), 26 mm in diameter, consists of 3 parts: (1) a central transparent plastic membrane (11 mm in diameter) of polyethylene charged with electrostatic forces able to retain powdered cow's milk for a long period and to allow a visual monitoring of cutaneous reactions; (2) a biadhesive mousse layer (25 mm in diameter) enclosed by 2 liner sheaths; and (3) an adhesive sheath of nonwoven film.

on the volar part of the forearm in those older than 12 months. Histamine dihydrochloride (ALK, Copenhagen, Denmark), 10 mg/mL, and glycerosaline were used as positive and negative controls, respectively. A positive reaction was defined as a wheal diameter 3 mm larger than that elicited by the negative control after 15 minutes.

CMP APT

The comparator CMP APT Finn Chamber. A mixture consisting of two thirds of a powdered cow's milk product (Régilait, Saint-Martin-Belle-Roche, France) and one third of a hypoallergenic infantile cow's milk formula with a protein molecular weight of less than 5000 d (Nidal HA; Nestlé, Marne-la-Vallée, France) was diluted in water (13.5 g/100 mL), and 1 drop was applied on uninvolved skin on the patient's back with aluminum cups (Finn Chamber, Epitest Ltd) and Scanpore tape (Alpharma Norgesplaster AS, Vennesia, Norway), the paper inside the chamber being thus soaked with 880 μ g of CMP. Isotonic saline solution was used as a negative control.

The ready-to-use CMP APT Diallertest. The ready-to-use CMP APT (Diallertest, DBV-Technologies), 26 mm in diameter, consisted of 3 parts: (1) a central transparent plastic membrane (11 mm in diameter) of polyethylene charged with electrostatic forces able to retain a powdered material for a long period and to allow a visual monitoring of cutaneous reactions; (2) a biadhesive mousse layer (25 mm in diameter) enclosed by 2 liner sheaths (liner 1 and 2); and (3) an adhesive sheath of nonwoven film. The same mixture as the cow's milk-based product used for the comparator CMP APT Finn Chamber was deposited on the central plastic support in the form of microgranules (5-40 μ m), forming a homogeneous monolayer retained by electrostatic forces. Each APT thus contained 250 μ g of CMP with 60% casein and 40% lactosoluble protein (intact and derivatives). The ready-to-use APT serving as a control had the same structure but was deprived of any cow's milk powder in the central part (Fig 1).

Trial design for APT techniques. A telephone call was made 24 hours after application of the APTs to assess the safety of the ready-to-use APT, a specific surveillance of the reaction through the transparent patch membrane being requested from parents. The occlusion time was 48 hours, and the results were read by the same investigator 20 minutes and 24 hours after removal of the devices (ie, at 72 hours). Numeric photographs were taken at 48 and 72 hours and archived into a computer. Reactions were considered as negative, irritation, significant erythema, and erythema with eczema or edema.⁶ The reaction was considered positive if at 72 hours the CMP APT exhibited a stronger skin reaction than the negative control (ie,

presence of clear redness and palpable infiltration or eczema), as described by Majamaa et al.²⁴

Open oral cow’s milk challenge

The methodology based on open challenge in this pilot trial was chosen because it has been shown to be a reliable method in young children when performed under experienced professional observation.^{6,25} The open challenge was started either in the hospital for children presenting with a risk of anaphylaxis manifested by previous severe immediate clinical manifestations and/or positive CMP IgE result and/or CMP-SPT result or directly at home in case of delayed manifestations and negative CMP IgE and CMP SPT results. The challenge used a standard cow’s milk–based infant formula. In the hospital increasing doses (1, 5, 10, 50, and 100 mL) were given at approximately 30-minute intervals for 6 hours under close medical supervision before discharge. At home, after the first day in the hospital, when applicable, the tolerance of increasing doses was monitored by a parental record of the child’s symptoms. CMA was defined as the disappearance of symptoms under cow’s milk elimination and an unequivocal adverse reaction to challenge. Children presenting at enrollment with a history of severe unequivocal adverse reaction to cow’s milk ingestion with positive CMP IgE results, CMP SPT results, or both and having completely recovered with a cow’s milk elimination diet were not submitted to an open challenge and were considered to have CMA. A reaction within 2 hours of challenge was regarded as immediate-onset type, and others were regarded as delayed-onset type. The challenge was discontinued when a clinical reaction was noticed. A DBPCFC was supposed to be prompted by the presence of dubious symptoms, as already described.²⁶ All patients with a negative challenge result at the end of the first week of surveillance continued to consume cow’s milk and were seen 4 to 6 weeks later to judge long-term tolerance and detect any false-negative results.

Statistical analysis

All statistical tests were performed with the Statview program (Abacus Concepts, Berkeley, Calif). Calculation of means, SDs, 95% CIs, medians, and extremes was done for all quantitative parameters. Differences between qualitative parameters were analyzed by using the χ^2 test. A *P* value of less than .05 was accepted as statistically significant. The results of both APTs (Diallertest and Finn Chamber) were compared with those of oral cow’s milk challenge, with calculation of sensitivity (the proportion of true-positive results detected), specificity (the proportion of the true-negative results detected), positive predictive value (the proportion of symptomatic individuals among those with positive test results), negative predictive value (the proportion of symptomatic individuals among those with negative test results), and test accuracy (the overall proportion of true-positive and true-negative results detected) with their 95% CIs.

RESULTS

Among the 49 enrolled children, 5 (10.2%) exhibited positive specific CMP IgE results, and 1 (2%) had a positive SPT result. Results of the ready-to-use APT and the comparator were positive, respectively, in 22 (44.8%) and 17 (34.6%) patients (not significant) at 48 hours and 22 (44.8%) and 13 (26.5%) patients (not significant) at 72 hours. Both techniques appeared concordant in 32 (65.3%) patients at 48 hours and 33 (67.3%) patients at 72 hours.

TABLE I. The evolution of eczematous lesions in the 13 children with positive cow’s milk challenge results at enrollment, during the 4 to 6 weeks of the CMP elimination diet, and after the cow’s milk challenge

	At enrollment (n)	During the 4- to 6-wk CMP elimination diet (n)	After cow’s milk challenge (n)
Isolated eczema n = 1	Moderate	Moderate	Severe
Combined eczema and digestive manifestations n = 4*	Mild	Mild	Mild
n = 1	Mild	Absent	Mild
n = 1	Moderate	Absent	Severe
n = 1	Moderate	Moderate	Severe
n = 3	Moderate	Mild	Severe
n = 1	Severe	Absent	Moderate
n = 1	Severe	Mild	Moderate

*These 4 patients exhibited a complete recovery of their digestive manifestations during the 4 to 6 weeks of CMP elimination diet, contrasting with their reappearance after the cow’s milk challenge.

Open challenges were carried out in 41 children, with 8 being lost of follow-up. No DBPCFC was considered requested. Results were positive in 25 (60.9%), the patients with so-called CMA, mostly in the form of combined eczematous and digestive reactions. Among the 25 positive challenge results, 15 were carried out at home, resulting in 4 immediate and 11 delayed reactions, and 3 were carried out in the hospital, resulting in delayed reactions. A history of severe unequivocal adverse reaction to cow’s milk ingestion at enrollment was seen in 7 children. Of the 16 negative challenge results, 14 were carried out at home. Results of the ready-to-use APT and the comparator were positive in 19 (76%) of 25 and 11 (44%) of 25 of the patients with CMA versus 1 (6.25%) of 16 of the nonallergic patients with both techniques (*P* < .001).

Twenty-nine children presented with eczema, either isolated or combined with digestive manifestations (4 patients were lost to follow-up), and 13 had positive CMP challenge results. The evolution of eczematous lesions in those 13 children at enrollment, during the 4 to 6 weeks of the CMP elimination diet, and after the cow’s milk challenge is summarized in Table I. The remaining 12 children with negative CMP challenge results exhibited moderate eczematous lesions, remaining unchanged from enrollment, during the 4 to 6 weeks of the CMP elimination diet, and after the cow’s milk challenge.

When compared with food challenges, the ready-to-use APT exhibited versus the comparator, respectively, 6 versus 14 false-negative results and 1 versus 1 false-positive results (Table II). The performances of the ready-to-use APT versus the comparator were thus characterized by a higher sensitivity (76% [95% CI, 59.2% to 92.7%] vs 44% [95% CI, 24.5% to 63.4%], *P* = .02) and test accuracy (82.9% [95% CI, 71.3% to 94.5%] vs 63.4% [95% CI, 48.6% to 78.1%], *P* = .05), with both techniques

TABLE II. Patients with false-positive and false-negative results with the ready-to-use (Diallertest) and comparator (Finn Chamber) APTs at 72 hours compared with oral cow's milk challenge

	False-positive results, Finn Chamber, n = 1	False-negative results, Finn Chamber, n = 14	False-positive results, Diallertest, n = 1	False-negative results, Diallertest, n = 6
Clinical manifestations				
Eczema, n = 1	1	0	0	0
Digestive, n = 7	0	7	0	4
Both, n = 10	0	7	1	3
Positive cow's milk prick test result	0	1	0	0
Negative cow's milk prick test result	1	13	1	6
Not done cow's milk prick test result	0	0	0	0
Positive cow's milk specific IgE result	0	1	0	1
Negative cow's milk specific IgE result	1	12	1	5
Not done cow's milk specific IgE result	0	1	0	0

TABLE III. Performances of the ready-to-use (Diallertest) and comparator (Finn Chamber) APTs at 72 hours compared with open oral cow's milk challenge (n = 41)

	Diallertest	Finn Chamber	P value*
Sensitivity (95% CI)	76 (59.2-92.7)	44 (24.5-63.4)	.02
Specificity (95% CI)	93.8 (81.9-100)	93.8 (81.9-100)	NS
Positive predictive value (95% CI)	95 (85.4-100)	91.7 (76-100)	NS
Negative predictive value (95% CI)	71.4 (52-90.7)	51.7 (33.5-69.8)	NS
Test accuracy (95% CI)	82.9 (71.3-94.5)	63.4 (48.6-78.1)	.05
False-negative result (n)	6	14	
False-positive result (n)	1	1	

NS, Not significant.

*According to χ^2 test, $P < .05$.

exhibiting high specificity and positive predictive value (Table III).

In the 8 children lost to follow-up because of parents' refusal of the food challenge, the clinical manifestations were of digestive type in 4 and combined in 4. Among them, 2 children had positive specific CMP IgE results, and none had a positive SPT result. The ready-to-use APT and the comparator showed positive results, respectively, at 48 hours in 2 and 3 patients and at 72 hours in 2 and 1 patient.

No immediate reaction was reported by parents during the first hours of testing with the ready-to-use device, and no side effect was recorded with either APT technique in any children.

DISCUSSION

Our study shows that in the population of patients with CMA tested, with mostly delayed-onset reactions, the

ready-to-use APT exhibited a significantly higher sensitivity (76% vs 44%) and test accuracy (82.9% vs 63.4%) than the comparator, whereas both techniques exhibited high specificity and positive predictive value and were devoid of any side effects.

Several authors underlined the usefulness of the APT in the diagnosis of food allergy in children with atopic dermatitis. In 183 patients with atopic dermatitis suspected of having CMA and evaluated by Isolauri and Turjanmaa,⁶ SPT results were positive in 67% of patients with acute-onset reactions to challenge, whereas APT results were positive in 89% of those with delayed-onset reactions. Combining SPTs and APTs significantly enhanced the diagnostic accuracy of specific food allergies (86% sensitivity and 72% specificity) in patients with atopic dermatitis.⁶ SPT and APT reactivity actually seems related to the heterogeneity of atopic eczema in infants, with immediate-type reactions being associated with SPT positivity and delayed reactions with APT positivity.²⁷ Niggemann et al⁸ found similar results in 75 children with atopic dermatitis, with immediate-type reactions being associated with positive SPT and CMP IgE results, and late-onset reactions being associated with positive APT results (76% sensitivity and 95% specificity).

Saarinen et al²⁸ studied the usefulness of the SPT with cow's milk and the APT with CMP fractions, together with other diagnostic tools for CMA in a cohort of unselected infants. In the children with CMA, at a mean age of 6.9 months, the APT sensitivity ranged from 26% to 43%, and the specificity ranged from 72% to 92%, and in contrast with previous studies, APT positivity tended to correlate also with immediate-type reactions. For Roehr et al,¹² the APT was the best single predictive test when evaluating CMA in children with atopic dermatitis. Finally, a recent study²⁹ found the APT to be a more sensitive method than the SPT in diagnosing CMA in children under 2 years of age with atopic dermatitis, with 60% sensitivity and 97% specificity for the APT versus 41% and 99% for the SPT, thus confirming the role of the APT in increasing the chances of early detection of food allergy in infants.^{6,24}

Majamäa et al²⁴ were the first to report children suspected to have CMA with gastrointestinal symptoms among children with atopic dermatitis. In the children with challenge-proved CMA, 26% had increased CMP IgE levels, 14% had a positive SPT result, and 44% had a positive APT result. Interestingly, in most patients with positive APT results, the SPT result for cow's milk was negative. In a previous personal study in children with CMA and gastrointestinal symptoms and using the comparator APT with pasteurized half-skimmed milk, we reported 79% sensitivity and 91% specificity, contrasting with 9% positivity in the control group.⁹ The prospective prolongation of this study led to the evaluation of 73 infants with chronic digestive symptoms, mostly gastroesophageal reflux, diarrhea, and colic.³⁰ Among patients with CMA, the APT result was positive in 52% of patients younger than 1 year and in 85% of patients older than 1 year. Positive cow's milk-specific IgE levels (>0.6 KUI/L) were seen in 3 children of the CMA group together with the APT, whereas the SPT result with native cow's milk was always negative.³⁰ The sensitivity of APTs during this study was slightly lower than that reported before,⁹ a change likely to be due to a greater number of patients younger than 1 year of age.³⁰

The present study is based on a ready-to-use novel type of patch testing. The basis of the test relies on the ability to provide to the skin intact protein molecules devoid of any solvent and able to be solubilized through the sole sweat secretion. This technique exhibits several advantages compared with the comparator APT, both in terms of practical easiness and of standardization. The amount of milk deposited on the patch is constant and easily measurable. It represents a quantity calculated at 1 mg, with variations from test to test calculated at $\pm 10\%$, a value indicating an appropriate control of the manufacturing process. When applied, the device delivers to the skin the total amount of milk deposited on the patch, whereas in any other kind of testing, the exact amount of food delivered to the skin is difficult to assess: when present in the form of pureed food, only a part of the food comes in close contact with the skin, and when the food is deposited on a blotting paper, a large amount remains inside the paper. It is likely that standardization of APTs requires not only standardizing the amount of antigen deposited in the device but also the amount of antigen able to reach the reactive cells.

The ready-to-use APT proved more sensitive, albeit not more specific, than the comparator Finn Chamber APT. It is likely that the full availability of the protein deposited on the plastic membrane in the ready-to-use APT compensated for the lack of availability of the higher amounts of proteins retained in the paper mesh in the Finn Chamber. This indicates that future standardization probably needs to evaluate both the quality and amount of antigen used in each test but also the availability for the skin of the allergen tested. In that respect the traceability of the antigens in this ready-to-use APT is easy to conduct because both the quality of the allergens and the amount deposited on the device are controlled by the manufacturer. Standardization

was also used in the design of the study: all cutaneous reactions were photographed and filed in a central computer to be able to make any a posteriori control of the reading by the investigator. The generalization of this reading technique might be considered when attempting a standardized reading of the APT.

We show that this ready-to-use cow's milk APT tends to be accurate in the diagnosis of CMA in a population of patients whose standard allergic evaluation on the basis of SPT and CMP IgE results is mostly negative. In clinical practice several advantages might be drawn from this ready-to-use device. The test can be applied by the parents to the child 3 days before the reading by the physician, thus avoiding a second consultation. Also, the plastic backing of the APT is transparent and allows direct visual monitoring of immediate or delayed cutaneous reactions. Because of this reliability, handling easiness, and non-invasiveness, one might propose it as a first-line diagnosis, at least when delayed reactions are suspected, with SPTs and IgE measurements being then carried out on a second-line basis.

In conclusion, in a population of children with non-IgE-mediated late-onset reactions (digestive and eczematous) and with reference to an open oral cow's milk challenge, the ready-to-use APT exhibited versus the comparator a significantly higher sensitivity (76% vs 44%) and test accuracy (82.9% vs 63.4%), with both techniques exhibiting high specificity and positive predictive value and being devoid of any side effects. Also, this APT is easy to use and provides the basis for standardization of the technique. Future work is needed for establishing its performance in various clinical environments.

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Correction

With regard to the December 2005 article entitled “A pilot study of the usefulness and safety of a ready-to-use atopy patch test (Diallertest) versus a comparator (Finn Chamber) during cow’s milk allergy in children” (J Allergy Clin Immunol 2005;116:1321-6): in the “Statistical analysis” section, “negative predictive value” was defined as “the proportion of symptomatic individuals among those with negative test results.” It should have been defined as “the proportion of asymptomatic individuals among those with negative test results.”