

Accuracy of a point-of-care testing device in children with suspected respiratory allergy

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ABSTRACT

Measuring IgE antibodies is useful in the diagnostic workup of allergy and asthma. This study was designed to assess the value of a new point-of-care test (ImmunoCAP Rapid Wheeze-Rhinitis Child [ICR]; Phadia AB, Uppsala, Sweden) in the diagnosis of atopy in children with allergy-like symptoms such as rhinitis, eczema, and recurrent episodes of wheezing. Patients ($n = 175$; average age, 7.2 years) referred from primary care were consecutively enrolled in two pediatric allergy referral centers in Italy and were assessed during a single visit. The ICR test included egg, milk, house-dust mite, timothy, mugwort, wall pellitory, birch, olive, cat, and dog allergens. ICR results were consistent with 78% of the positive clinical diagnoses. Agreement between negative ICR results and physician's clinical judgment ranged between 92 and 99% for the single allergens and averaged 96% for the complete profile. Overall agreement of ICR versus clinical diagnosis was 93%. A false positive ICR rate of 1% was recorded. ICR was positive for 94% of the patients with at least one positive clinical diagnosis. Based on the agreement between the physician's assessment of the clinical relevance of each allergen and the ICR results, we concluded that ICR could be a useful tool for primary care physicians to rule in or out the clinical relevance of single ICR allergens.

(Allergy Asthma Proc 31:e11–e17, 2010; doi: 10.2500/aap.2010.31.3323)

Key words: Allergic rhinitis, allergy, asthma, diagnosis, IgE, ImmunoCAP, pediatrics, point-of-care testing, primary care

The current diagnostic pathway in pediatric allergy is a layered process. Children with a complaint of a possible allergic nature often see various specialists before their allergy status is ascertained.¹ The management strategy chosen affects health care consumer and provider alike and varies between the decision to entrust the diagnosis to the general practitioners (GPs) or to refer all potentially allergic children to a tertiary structure. In a real-life situation, the vast majority of children with atopic dermatitis are cared for by GPs: according to epidemiologic studies,² a 17.4% prevalence of allergic diseases in Italian children translates into an expected number of 1,306,980 allergic children.³ Thus, in a large regional area, such as Lombardy in northern Italy (population of 0- to 14-year-old children, 1,313,000), 228,460 children are expected to suffer from allergic diseases. However, only 38,000 consultations are performed by pediatric allergists every year.⁴ Thus,

at least seven in eight allergic children are cared for by general pediatricians, a fixture of the National Health Service of Italy.

Diagnosing allergy itself is a difficult art in any setting and, in this era of managed care, allergists are increasingly seen as consultants of last resort.⁵ This dilemma has been accurately described as a decision in favor of "a pediatrician without any allergy training or an allergist who has little experience of treating children."⁶ Positioned at the border between family and clinical immunology medicine, allergists represent a labor- and resource-intensive tier of medical care with a battery of diagnostic tests at their disposal, which are sometimes difficult to interpret. Furthermore, members of the public are aware and informed⁷ of their stake in the management of their children's allergies and present to pediatricians with requests for precise answers ruling in or out their suspicions.¹

In respiratory allergy, the differential diagnosis rests on the assessment of the child's atopy status, the proximate measure of which is provided by skin-prick tests (SPTs) and/or the measurement of IgE antibody.⁸ Acquiring this knowledge is essential for implementing an evidence-based, stepwise strategy in the management of symptoms and evolving disease, which remains beyond the remit of most primary caregivers and places a burden on the health care system and the allergic patient community.¹ Point-of-care testing tech-

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C.J. Petersson and M.P. Borres are employees of Phadia AB

Funded by an unrestrained educational grant from Phadia AB of Uppsala, Sweden

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nology aimed at GPs, whose role is pivotal in allergy patient triage as they see most children with suspected allergy, would fill a niche the needs of which are currently clearly unmet. Pediatric allergists or allergist-immunologists (where available) are only able to confirm the atopic etiology of patient outcomes in the measure in which they transcend "turf wars"³ and the referral process is rationale based.⁹

In the present study, to address these clinical and health care issues, we set out to prospectively compare the performance characteristics of a point-of-care device featuring the qualitative determination of allergen-specific IgE antibodies from a whole blood sample against the clinical diagnosis of a hospital-based allergist in a population of referrals and against laboratory-specific IgE (sIgE) determinations.

METHODS

Study Population and Design

The study was prospectively planned and performed at the allergy clinics of the Ospedale Pediatrico Bambino Gesù in Rome and at Melloni Paediatrica in Milan, Italy. Starting in May 2005, patients aged 0–18 years referred from primary care were consecutively enrolled and were assessed at a single visit according to a standard diagnostic flowchart based on Global Initiative for Asthma and Allergic Rhinitis and Its Impact on Asthma statements,^{10,11} including when necessary, SPT (SPT cut point, wheal diameter of ≥ 3 mm) and/or specific IgE determinations (cut point, ≥ 0.35 kU_A/L).

At the referral visit, a study nurse performed ImmunoCAP Rapid Wheeze-Rhinitis Child (ICR; Phadia AB, Uppsala, Sweden). It was analyzed in a blinded manner and the physicians' diagnosis of respiratory allergy was used as a reference standard in calculating the performance characteristics of the ICR. The main outcome measure was classification with IgE-mediated respiratory symptoms, without such symptoms, or with an inconclusive diagnosis.¹² "Inconclusive diagnosis" classified children with asthma and/or rhinitis when no clear relationship with allergic reactions that could be established by history. The study aims and design were approved independently by the internal review boards of both our institutions. Informed consent forms were signed by the parents of all participants before enrollment.

The Point-of-Care Test Method

ICR is a point-of-care device for the qualitative determination of allergen-specific IgE antibodies in whole blood. The assay comprises eight inhalant and two food allergens, all commonly causing symptoms related to wheeze/asthma and rhinitis in European children. The specific allergens on the ICR are tim-

othy (g6), birch (t3), olive (t9), wall pellitory (w21), mugwort (w6), cat (e1), dog (e5), house-dust mite (d1), hen's egg (f1), and cows' milk (f2) (the specific allergens on the ICR for US are e1, d1, g6, and e5 [common with the ICR in this study] and Bermuda grass [g2], common ragweed [w1], oak [t7], *Alternaria alternata* [m6], elm [t8] and house dust mite [*Dermat. farinae*] [d2]).¹³ One hundred ten microliters of whole capillary blood from a fingertip puncture was applied into the device well. After elimination of blood cells by a filter present in the well, blood plasma migrated along nitrocellulose strips containing 10 allergen zones. IgE antibodies present in the sample, specific to any of the allergens in the test, bound to the relevant areas on the strips. After 5 minutes a developer solution was added in the developer solution well, releasing a dried gold-anti-IgE conjugate. The conjugate formed a complex with the IgE antibodies, visible as pink-red lines in the two test windows. The remaining conjugate continued to migrate, forming pink-red lines in two control windows. The control line appeared regardless of whether the sample was positive or not, indicating that the test has been performed correctly. After 15 minutes, the allergen results were visually read. Any pink-red line of an allergen area indicated a positive result and the absence of color indicated a negative result. The test results were read by the same person at each center.

Data Analysis and Statistical Methods

Demographic and clinical information was analyzed descriptively. The ICR performance characteristics were calculated for each allergen and for the panel against the reference standard. To compare testing methods, the test performance characteristics of ICR were also calculated against laboratory allergen-specific IgE (using cut points of 0.35 and 1.0 kU_A/L). For the ICR and SPT, the posttest probabilities were calculated of being specifically IgE sensitized for positive and negative results.¹⁴

RESULTS

Patients

A total of 175 patients were enrolled at both institutions, the characteristics are displayed in Table 1. Grass and house-dust mites were the most commonly reported triggering allergens (in 20 and 15% of the patients, respectively). Cow's milk was reported as a symptom trigger by 6% of patients ($n = 10$) and hen's egg was reported by 4 or 7% of patients. Infection was the most common nonallergen triggering factor and was reported by 10% of participants.

Table 1 Basic characteristics of the study population

	Rome	Milan	Total
No. of included patients, <i>n</i> (%)	100 (57)	75 (43)	175 (100)
Gender			
Male, <i>n</i> (%)	61 (61)	44 (59)	105 (60)
Female, <i>n</i> (%)	39 (39)	31 (41)	70 (40)
Age, yr median (minimum–maximum)	7.5 (2.2–18.3)	6.0 (1.0–16.8)	7.2 (1.0–18.3)
Reported with asthma, <i>n</i> (%)	47 (47)	36 (48)	83 (47.4)
Reported with wheezing, <i>n</i> (%)	37 (37)	40 (53.3)	77 (44)
Reported with rhinitis, <i>n</i> (%)	33 (33)	43 (57.3)	76 (43.4)
Reported with eczema, <i>n</i> (%)	24 (24)	13 (17.3)	37 (21.1)
Reported with urticaria, <i>n</i> (%)	19 (19)	3 (4)	22 (12.6)

Table 2 Agreement of ImmunoCap Rapid Wheeze-Rhinitis Child with clinical judgment (no. and %) for patient level and all allergens together

Clinical Judgment	Patients			Allergens		
	Positive	Negative	Total	Positive	Negative	Total
Positive	120 (94)	7 (6)	127	189 (78)	54 (22)	243
Negative	0 (0)	23 (100)	23	47 (4)	1135 (96)	1182
Uncertain	15 (60)	10 (40)	25	51 (40)	78 (60)	129
Total	135	40	175	287	1267	1554
	Sensitivity*: 94.5% Specificity: 100%			Sensitivity: 77.8% Specificity: 96.0%		

*Sensitivity and specificity calculated without uncertain cases.

Clinical Judgments of Allergic Status

Overall, 1750 allergen-specific diagnoses were performed in the study. Among these, 250 single allergens were considered clinically significant, 1363 were negative, and 137 were uncertain. House-dust mites, timothy, cats, olive pollen, and *Parietaria* were the allergens most frequently relevant (for 46, 42, 12, 9, and 8% of the patients, respectively). Uncertain judgments were most frequent in the case of dog, cat, birch, and house-dust mite allergen assessments (19, 10, 9, and 9%, respectively). One hundred and twenty-seven patients (or 73%) were positively assessed as allergic to at least one allergen and accordingly assigned a positive clinical judgment on a patient level. Twenty-three patients (13%) with negative clinical judgment for all 10 of the investigated allergens were assigned a negative clinical judgment, and the remaining 25 patients were considered uncertain.

In Vitro Sensitization Pattern

Laboratory allergen-specific IgE analyses were performed in 110 of 175 (63%) patients for a total of 914 allergens. Sensitization to house-dust mites was most common (65% of the tested patients), followed by sensitization to timothy (44%), olives (38%), and dogs

(35%). Twenty to 25% of the tested patients had specific IgE antibodies to the other six allergens. Five patients had IgE antibodies to 9 of the 10 tested allergens and as many as 27 patients were monosensitized, most commonly to house-dust mites (20 patients). Ninety-six of the 110 patients (87%) were positive in the laboratory allergen-specific IgE tests for at least one of the allergens included in ICR and thus were considered positive on a patient level. The remaining 14 patients (13%) were negative for the 10 allergens.

Diagnostic Performance of ICR and Clinical Allergy Diagnosis

Of the 127 patients with at least one positive clinical judgment of allergic status, 120 had at least one positive ICR result, corresponding to a sensitivity of 94.5%. For the 23 patients with negative clinical judgment for all 10 of the investigated allergens, all ICR results were also negative, corresponding to a specificity of 100%. The estimated positive and negative predicted values were 100 and 77%, respectively.

The sensitivity and specificity for all 10 allergens together was calculated for the 243 observations of positive judgments and the 1182 observations of negative judgments with a corresponding ICR result. A sensitivity of

Table 3 Agreement of ImmunoCap Rapid Wheeze-Rhinitis Child with clinical judgment, per allergen*

Allergen	No. of Positive (p) and Negative (n) Clinical Judgments	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
House dust mite	p = 80; n = 79	89	92	92	89
Timothy	p = 72; n = 89	71	97	94	80
Wall pellitory	p = 14; n = 147	71	95	59	97
Olive pollen	p = 16; n = 143	69	94	58	96
Birch	p = 11; n = 146	91	99	91	99
Mugwort	p = 8; n = 158	#	96	#	96
Cat	p = 21; n = 136	90	94	70	98
Dog	p = 8; n = 131	#	98	#	96
Cow's milk	p = 7; n = 77	#	99	#	100
Egg white	p = 6; n = 76	#	93	55	100

*Results for uncertain clinical judgments not included.

#Sensitivity not calculated for allergens with <10 positive clinical judgments, positive predicted values were not calculated for allergens with <10 positive.

Table 4 Agreement of ImmunoCAP Rapid Wheeze-Rhinitis Child (ICR) and skin-prick test (SPT) with laboratory allergen-specific IgE, on patient level (no. of patients, sensitivity, specificity, positive predicted values (PPV) and negative predicted values (NPV))

Laboratory Allergen-Specific IgE	ICR			SPT		
	Positive	Negative	Total	Positive	Negative	Total
Positive	92	4	96	94	2	96
Negative	1	13	14	4	10	14
Total	93	17	110	98	12	110
	Sensitivity: 95.6%			Sensitivity: 97.9%		
	Specificity: 92.8%			Specificity: 71.4%		
	PPV: 98.9%; NPV: 76.5%			PPV: 95.9%; NPV: 83.3%		

78% and a specificity of 96% was obtained, giving an overall diagnostic efficiency of 93% (Table 2). The results for the individual allergens are shown in Table 3. The sensitivity varied from 69% for olive pollen to 91% for birch and the specificity from 92% for house-dust mites to 99% for birch and cow's milk.

Diagnostic Performance of ICR and SPT in Relation to Laboratory Allergen-Specific IgE

Results for the diagnostic accuracy of the ICR and SPT using the specific IgE results as reference are represented in Table 4. These results are based on 110 patients who had been measured with ICR, SPT, and laboratory serum allergen-specific IgE.

Sensitivity, specificity, positive, and negative predictive values are quite similar for both tests compared with the serum-specific IgE outcome except for the figure for specificity. For SPT this value was considerably lower than for ICR, around 20 percent-

age points (71.4% versus 92.8%). ICR correctly classified subjects as allergic and nonallergic in 105 of 110 cases (*i.e.*, overall accuracy, 95.5%). Similar figures were found for SPT, 104 of 110 cases (overall accuracy, 94.6%).

The posttest probabilities of IgE sensitization with a positive test was 99 and 96%, respectively for ICR and SPT, whereas the posttest probabilities of sIgE sensitization with a negative test result were 24 and 16% for ICR and SPT, respectively. Because the predictive values of either test depended on the prevalence rate of sIgE sensitization observed in this study (which is different from those found in other referral populations), posttest probabilities for ICR and SPT, respectively, at different prevalences were calculated using the observed sensitivity and specificity (Fig. 1). In the range of prevalence between 10 and ~70%, a positive SPT result had less contribution to predict specific IgE sensitization (or allergy) compared with a positive ICR

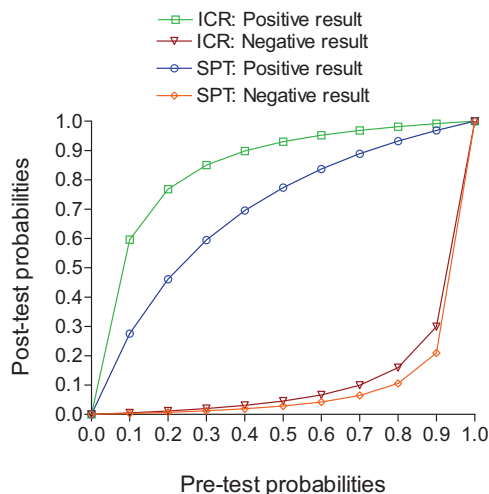


Figure 1. Curve for posttest probability of being specific IgE sensitized after positive and negative ImmunoCAP Rapid Wheeze-Rhinitis Child (ICR) and skin-prick test (SPT) results, respectively.

result. This difference could not be established for negative test results.

Using laboratory benchmarks of 0.35 and 1 kU_A/L as the cutoff, sensitivities, specificities, and overall accuracies were calculated for ICR and SPT versus the 914 specific IgE determinations obtained in 110 patients. Table 5 shows that using a cutoff of 1 kU_A/L yields an overall accuracy of 90.9% for ICR and 86.2% for SPT.

DISCUSSION

In most European countries, GPs and pediatricians untrained in allergy medicine bear the worst of the onslaught of the allergy public health problem and in many places they do not perform allergy testing. Thus, a discriminating point-of-care method able to perform a sort of triage is in order. In our caseload, an important discrepancy between reported triggers and specific clinical judgment indicates that many patients are completely unaware of their triggers before the diagnostic process. To the best of our knowledge, this is the first study to evaluate the performance characteristics of ICR, a device reflecting the European epidemiology of allergic sensitization,^{15,16} in a well-defined population of children referred for allergy evaluation.

Four main comparisons were made in the study: (i) allergen-by-allergen comparisons between physicians' judgments and ICR result; (ii) patient-by-patient comparisons between physicians' judgments (on a patient level) and the overall ICR result; (iii) allergen-by-allergen comparisons between laboratory allergen-specific IgE and ICR and SPT results; (iv) patient-by-patient comparisons between laboratory serum-specific IgE results and ICR and SPT results, respectively.

Our data support the use of this test across the three levels of care. The obtained overall sensitivity of the

test in the studied population is 78%, higher for house-dust mites, cats, and birch. For these allergens, sensitivities of $\sim 90\%$ at ICR will—together with case history and physical examination—allow the physician to predict a correct diagnosis. This was not so evident, however, with other allergens; *e.g.*, timothy shows sensitivity in this study of no more than 71%. Conversely, an overall specificity value of $\sim 93\%$ allows a confident exclusion of allergic conditions.

When evaluating the ICR test with a clinical judgment as reference, it can be argued that an objective test is compared with a subjective reference. Therefore, ICR was also evaluated with another objective test, the laboratory-specific IgE, following a strategy used to establish the best cutoff levels for SPTs.¹⁷ The idea with this was to present agreement figures for ICR (and SPT) with an already established method for allergy workup. The accuracy values of ICR against sIgE are far better, although both sensitivity and specificity of ICR and SPT versus sIgE changes when the reference cutoff was increased from 0.35 to 1 kU_A/L . Using 0.35 kU_A/L as the cutoff for the reference gave a sensitivity of 62% for the ICR and 66% for SPT. At 1 kU_A/L , the corresponding figure was 76.1% for both ICR and SPT. On a patient level, corresponding figures increased with additional 15% units to above 90% for each of the two test procedures. Thus, both ICR and SPT showed better discriminating power at the higher reference cutoff.

A limitation of our study is the low number of children allergic to mugwort, dogs, cow's milk, and egg whites. An estimated sensitivity based on such low numbers of observations would have been very uncertain and was therefore not calculated. A more thorough sensitivity evaluation of these allergens remains to be done and prevalence figures in patients with rhinitis symptoms of 3–11% and 31% for sensitization against dogs and mugwort, respectively, as reported^{18,19} emphasize the importance of these allergens on the ICR. Another shortcoming was the group of uncertain diagnoses, 137 of 1750. These results were not included in the evaluation (in the uncertain group, 60% were negative in ICR).

In the present study, the test performance statistics not linked to the prevalence of the condition (sensitivity and specificity and positive and negative predictive values) are impressive but not expendable and their proper use in clinical settings requires recognition of the prior probability of having the disease. We calculated the posttest probability of being allergic in two populations of patients, those with negative or positive results for ICR (and for SPT). Given our prevalence (87%) with the obtained sensitivity and specificity for ICR (and SPT in comparison), the positive posttest probability (equal to the positive predictive value) was quite similar for ICR and SPT while the negative post-

Table 5 Number of observations, sensitivity, specificity, and overall accuracy of ImmunoCAP Rapid Wheeze-Rhinitis Child (ICR) skin-prick test (SPT) vs laboratory-specific IgE at cutoff 0.35 and 1 kU_A/L, respectively

	Laboratory sIgE					
	Cutoff = 0.35 kU _A /L			Cutoff = 1 kU _A /L		
	Positive	Negative	Total	Positive	Negative	Total
ICR vs						
Positive	182	15	197	166	31	197
Negative	111	606	717	52	665	717
Total	293	621	914	218	696	914
	Sensitivity: 62.1% Specificity: 97.6% Overall accuracy: 86.2%			Sensitivity: 76.1% Specificity: 95.5% Overall accuracy: 90.9%		
SPT vs						
Positive	193	47	240	166	74	240
Negative	100	574	674	52	622	674
Total	293	621	914	218	696	914
	Sensitivity: 65.9% Specificity: 92.4% Overall accuracy: 83.9%			Sensitivity: 76.1% Specificity: 89.4% Overall accuracy: 86.2%		

test probability differed evidently. Simulating posttest probabilities at different pretest probabilities (prevalence) showed that the ICR behaved more like the laboratory-specific IgE test than did SPT for the positive posttest probability.

There are several reasons for the need of a simple, fast, easy-to-perform, and accurate test for capturing allergic-sensitized patients:

- The percentage of allergic patients correctly diagnosed according to medical history and physical examination is probably low (30–65%) while the burden of management is increasing and referrals to specialists is likely avoided by those children most in need.^{4,5} When specific IgE antibody testing is added, this low to middling figure increases (85–97%).^{20,21} Data from GPs' setting in Italy as reported elsewhere²² showed that the frequency of uncertain cases was reduced from 26 to 4% when also specific IgE testing was added to the diagnosing procedure.
- Patients need to be given appropriate therapy and management according to their status,²³ *e.g.*, in the decision to start with immunotherapy.
- With the increased prevalence of sensitization and allergy, the majority of symptomatic patients will have their first contact in a primary care setting creating a need for an accurate, easy to perform, rapid test in the diagnostic workup.

Today, in most European countries, GPs and pediatricians untrained in allergy medicine do not perform allergy testing at all. Our data support the use of a new rapid allergy diagnostic device in these settings. We have

showed that it can definitely be used to capture the sensitized patient on an overall level but also with a high probability to capture specific sensitizations to house-dust mites, cats, and birch. Thus, point-of-care whole blood monitoring and/or screening tests are convenient and represent a sustainable first-line-of-care solution to the growing demand for hospital-based specialist allergy services.

ACKNOWLEDGMENTS

The technical skills of S. Patané, The Melloni University Hospital, Milan, Italy, for statistical assistance are gratefully acknowledged.

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