

Original article

The utility of specific immunoglobulin E measurements in primary care

Background: The identification of atopic patients may not be considered a necessary step in the diagnosis process in primary care. This study investigated the impact of the addition of a specific immunoglobulin E (IgE) antibody test on the current management by primary-care physicians of patients with respiratory and skin symptoms.

Methods: The study had a prospective before–after design. It was conducted in two geographic areas of Italy and Spain and consisted of two parts, Part I and Part II. In each part patients were recruited according to inclusion and exclusion criteria. After the clinical examination, the patients were classified into one of the following categories using a physician's classification: allergic, nonallergic or uncertain. A blood sample was taken from each included patient for specific IgE antibody determination using a Pharmacia CAP SystemTM, including either Phadiatop Infant (0–5 years of age) or Phadiatop and food mix (fx5e) (> 5 years of age). If a positive result was found, an additional 6–26 specific IgE tests were performed. In Part I the result of the specific IgE antibody determinations was not available before the physician's classification was made. In contrast, in Part II, the result of the IgE test was available at the time when the physician's classification was made. Between Part I and Part II an educational intervention for physicians to improve their knowledge of blood testing for IgE-mediated allergy was carried out.

Results: A total of 721 patients were included in the study. The agreement between classifications based on clinical data and IgE antibody results changed from a kappa coefficient of 0.13 in Part I to 0.86 in Part II. With regard to the allergic status the proportion of uncertain cases was reduced from 26.3% in Part I to 4.1% in Part II. The proportion of patients that were advised to avoid allergens increased from 18% in Part I to 62% in Part II in the group of patients classified both by the clinician and the IgE test.

Conclusions: The use of specific IgE antibody determinations improves the clinical management of patients with allergy related symptoms in primary care, allowing advice to be given on specific allergen avoidance. However, the applicability of this diagnostic tool in different areas and countries should be further assessed in cost-effectiveness studies.

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The prevalence of respiratory and skin symptoms associated with atopy has increased considerably over the last 20–30 years, particularly in Western industrialized countries (1–5). This is a cause for concern because of its impact on personal quality of life and the increasing costs to society (6–8). The present knowledge of risk factors for many of these symptoms indicates that opportunities for primary prevention are very limited. In contrast, secondary prevention is necessary and possible but its effectiveness may depend on the capacity to identify correctly atopic patients in primary care.

This may be a complex task for primary-care physicians if they do not use the appropriate tools available at present. Clinical judgement may not be enough to identify correctly atopic children since a number of symptoms or diseases may have various causes that are not easy to identify by clinical examination only. For instance, wheeze and cough are symptoms often seen by primary-care physicians and may be the result of a viral infection or an allergic condition or a combination of both (9,10). The probability of identifying an atopic individual is different for each specific symptom and varies according

to age, gender and geographic area (5,11,12). Indeed, approximately only 40% of adult patients with rhinitis or eczema have atopy (11). Furthermore, in the primary-care setting, the percentage of atopic patients correctly diagnosed according to medical history and physical examination is only 30–65%. With the addition of immunoglobulin E (IgE) antibody tests this figure increases to 85–97% (13,14).

Although all these difficulties may be recognized by clinicians and health-care planners, the identification of atopic patients is not considered a necessary step in the diagnosis process in asthma, eczema or rhinitis clinical guidelines and scientific society recommendations (15–17). Thus the pharmacological treatment and clinical management are often established without considering the presence of allergy. This observation can be applied when considering either asthma, eczema or rhinitis. This has important implications for the clinical management of patients where appropriate recommendations on avoidance of allergen exposure and on referral to a specialist physician have to be made. The scope for secondary prevention measures may be reduced.

Atopy can be confirmed by the presence of levels of allergen-specific IgE in the serum or by skin prick tests, but neither test is frequently used in the primary-care setting. However, this may not be considered necessary because the process is often regarded as lengthy, expensive and not likely to provide any clinically meaningful information. Instead of opting for an accurate diagnosis, symptoms are often treated with various medications (e.g. antihistamines, topical or inhaled steroids, antitussives, etc.) until an effect is observed. When this happens, the patient will most likely remain undiagnosed.

The aim of this study was to investigate the impact of adding a specific IgE test to the primary-care physician's

current management of patients with respiratory and skin symptoms.

Materials and methods

Study design and methods

The study was a before and after multicenter study that involved 22 centres in Magenta, Italy ($n = 10$) and Sabadell, Spain ($n = 12$). In Italy all the participating clinicians were pediatricians. In Spain, in six centres the participating clinicians were also pediatricians and in the other six they were general practitioners. None of the participating clinicians used, on a regular base, specific IgE antibody tests in their normal routines to distinguish atopic individuals from nonatopic.

The study consisted of two parts, Part I and Part II (Fig. 1). In Part I for about 10 weeks, all patients attending clinical practice in the participating centres and fulfilling the inclusion/exclusion criteria were invited to participate in the study. Inclusion criteria were: age between 0 and 14 years for patients recruited in Italy and between 0 and 55 years for those recruited in Spain, and presence of at least one of the following symptoms at any time during the last year: wheezing in the chest, shortness of breath not correlated to physical exercise, long-standing cough, itchy throat, recurrent symptoms of a cold, recurrent sneezing, runny or blocked nose when not having a cold, eczema, urticaria and angio-edema. Patients with an allergy test (skin prick or specific IgE) performed during the last 12 months the result of which was known by the clinician were excluded, as were human immunodeficiency virus-infected patients and those with a history of hepatitis.

Based only on clinical judgement, all patients included in the study had to be classified by the clinician into three categories: allergic, nonallergic, or uncertain. In addition to this classification, information was collected regarding the following clinical management actions: (i) advice to avoid allergens; (ii) patient's referral to another clinician; (iii) schedule of a new appointment; (iv) telephone calls for the follow-up were planned; (v) *in vitro* tests other than the study test were performed. In all patients, specific IgE antibodies were measured with the Pharmacia CAP System™ (Pharmacia Diagnostics AB, Uppsala, Sweden), including Phadiatop Infant®

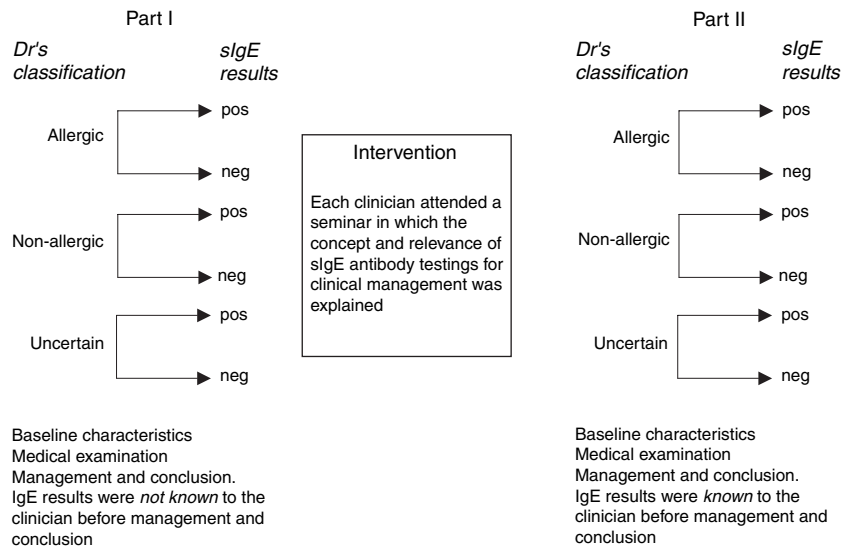


Figure 1. Flowchart of the study design.

(0–5 years of age) or Phadiatop® and food mix (fx5e) (> 5 years of age). According to the test results, patients were classified as specific IgE positive, (sIgE⁺), or specific IgE negative (sIgE⁻). Clinicians were unaware of the IgE results when they had to classify the patients.

After Part I and before the start of Part II, clinicians attended a seminar in which the principles of blood testing for IgE-mediated allergy and its clinical usefulness for the patient's management in the daily practice were explained in detail (Fig. 1). This intervention was executed by personnel who were well trained in the area of in vitro allergy testing.

In Part II, patients were included according to the same criteria as Part I and as in Part I the patients had to be classified by the clinician into three categories. However, in this part, in contrast to Part I, patient classification was made according to the clinical judgement with the addition of the specific IgE antibody results. As in Part I information was collected on the actions taken for the clinical management of patients.

Based on the combined result of the clinician's classification and the specific IgE results, patients in Part I and Part II were divided into six groups (Table 1).

Outcome measures

To assess the impact of specific IgE antibody testing on the clinical management of patients with allergy-related symptoms outcome measures were (1) the ability of clinicians to classify patients according to their allergic status in Part I and Part II and (2) in each group (Table 1), changes between Part I and Part II in the clinical management actions as described above.

Statistical analyses

A descriptive analysis of demographic characteristics and clinical symptoms was carried out. Categorical variables were presented by counts and percentages. The chi-square test or, when appropriate, Fischer's exact test were used to compare proportions. All tests were performed on unweighted data, two-tailed and considered significantly different at the 0.05 level. For each study part, the agreement between the physician's classification and classification based only on IgE results, was measured by the kappa coefficient. Clinical management actions in Part I were compared to clinical management actions in Part II for all six groups. A logistic regression analysis was performed to determine factors associated with the advice to avoid allergens. The SAS and STATA statistical software packages were used for the analysis of data.

Table 1. Group definition based on specific IgE results and clinician's classification

	Specific IgE results		Clinician's classification			Group combination*
	Negative	Positive	Nonallergic	Allergic	Uncertain	
Group 1	X		X			sIgE ⁻ Dr ⁻
Group 2	X			X		sIgE ⁻ Dr ⁺
Group 3		X	X			sIgE ⁺ Dr ⁻
Group 4		X		X		sIgE ⁺ Dr ⁺
Group 5	X				X	sIgE ⁻ Dr ^u
Group 6		X			X	sIgE ⁺ Dr ^u

* sIgE⁻, specific IgE-negative; sIgE⁺, specific IgE-positive; Dr⁻, clinician's classification negative; Dr⁺, clinician's classification positive; Dr^u, clinician's classification uncertain.

Results

Patient characteristics

In total, 721 patients (380 in Part I and 341 in Part II) were included in the study. Table 2 shows the distribution of patients by demographic characteristics and participating country in the two parts of the study. There was a significant difference in the gender distribution between the two countries in each of the two study parts. However, no difference was found when gender was compared between Part I and Part II. The difference in the age-class distribution between the two countries as shown is due to the difference between the age inclusion criteria between both countries. Table 3 shows the distribution of patients according to the respiratory and skin symptoms by country and study part. In Part I, 326 (86%) patients had respiratory symptoms, and 176 (46%) had skin symptoms. A total of 122 (17%) had both respiratory and skin symptoms. No significant differences were found in the distribution of symptoms and groups of symptoms between the two study parts.

Study outcomes

The ability of clinicians to classify patients according to their allergic status was poor in Part I. The agreement, measured by the kappa coefficient, between the clinician's classification based only on clinical judgement and that based on the IgE results was 0.13 (Table 4). In contrast, when IgE results were used in addition to the physician's clinical judgement (Part II of the study) in the physician's classification, the kappa coefficient was 0.86. The kappa value was also low in Part I when the agreement was measured for each symptom separately whereas it was high in Part II for all symptoms. The number of uncertain cases was 100 (26.3%) in Part I in contrast to 14 (4.1%) in Part II.

Of the five items regarding clinical management, 'advice to avoid allergens' showed the greatest change between the two study parts. Although the highest proportion of 'advice to avoid allergens' was found in

Table 2. Demographic characteristics of patients by study part and country

	Part I			Part II		
	Italy (n = 194) n (%)	Spain (n = 186) n (%)	Total (n = 380) n (%)	Italy (n = 150) n (%)	Spain (n = 191) n (%)	Total (n = 341) n (%)
Gender						
male	83 (43)	109 (59)	192 (51)	68 (45)	109 (57)	177 (52)
female	111 (57)	77 (41)	188 (49)	82 (55)	82 (43)	164 (48)
Age (years)						
<5	104 (54)	41 (22)	145 (38)	68 (45)	35 (18)	103 (30)
5 to <15	90 (46)	52 (28)	142 (37)	82 (55)	60 (32)	142 (42)
≥15		93 (50)	96 (25)		96 (50)	93 (28)

Table 3. Respiratory and skin symptoms of patients by study part and country

Symptoms	Part I			Part II		
	Italy (n = 194) n (%)	Spain (n = 186) n (%)	Total (n = 380) n (%)	Italy (n = 150) n (%)	Spain (n = 191) n (%)	Total (n = 341) n (%)
Respiratory	161 (83)	165 (89)	326 (86)	140 (93)	155 (81)	295 (87)
wheezing in the chest	93 (48)	75 (40)	168 (44)	61 (41)	77 (40)	138 (41)
shortness of breath	62 (32)	14 (8)	76 (20)	32 (21)	17 (9)	49 (14)
long-standing cough	96 (50)	43 (23)	139 (37)	71 (47)	36 (19)	107 (31)
itchy throat	37 (19)	33 (18)	70 (18)	38 (25)	34 (18)	72 (21)
recurrent cold	102 (53)	73 (39)	175 (46)	81 (54)	65 (34)	146 (43)
recurrent sneezing	71 (37)	80 (43)	151 (40)	70 (47)	78 (41)	148 (43)
runny or blocked nose	82 (42)	88 (47)	170 (45)	77 (51)	83 (44)	160 (47)
Skin	103 (53)	73 (39)	176 (46)	59 (39)	82 (43)	141 (41)
eczema	92 (47)	46 (25)	138 (36)	40 (27)	57 (30)	97 (28)
urticaria	20 (10)	36 (19)	56 (15)	22 (15)	44 (23)	66 (19)
angioedema	1 (0.5)	11 (6)	12 (3)	3 (2)	6 (3)	9 (3)

Table 4. Agreement between specific IgE antibody results and results from clinical judgement for single and combined groups of symptoms

Symptoms	Part I		Part II	
	Agreement %	Kappa	Agreement %	Kappa
Respiratory	60.1	0.12*	92.6	0.84*
wheezing in the chest	58.5	0.13**	94.6	0.89*
shortness of breath	69.8	0.18**	89.1	0.74*
long-standing cough	58.6	0.10**	91.2	0.82*
itchy throat	64.4	0.07	94.4	0.88*
recurrent cold	60.7	0.08	92.2	0.83*
recurrent sneezing	61.3	0.05	89.7	0.75*
runny or blocked nose	66.7	0.14*	92.2	0.82*
Skin	54.6	0.10**	95.6	0.91*
eczema	53.1	0.10**	94.7	0.89*
urticaria	61.9	0.06	96.8	0.93*
All	59.1	0.13*	93.2	0.86*

*P < 0.001; **P < 0.05.

group 4 (Fig. 2), this item was distributed over all six groups in Part I. In Part II the advice was found in only two of the six groups but mainly in group 4.

Overall, compared to Part I the likelihood of being referred to other physicians was higher in Part II, OR = 1.6 (95% CI 1.0–2.5). However, although overall differences in referrals were found, there were no significant differences between the study parts in any of the six groups. The highest proportion of referrals was found in group 4 where 17.3% and 21.7% of patients were referred to other physicians in parts I and II of the study, respectively. The likelihood of being referred to other physicians in group 4 in Part II of the study compared to Part I was 1.3 (95% CI 0.7–2.3).

The proportion of new appointments was relatively high in all groups in both study parts, ranging from 42% to 68% in Part I and from 33% to 100% in Part II. In group 4, this proportion was around 68% and 74% in

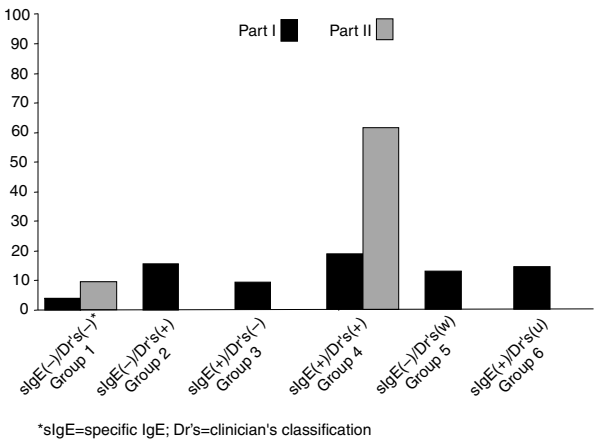


Figure 2. Proportion of patients that received advice to avoid allergens from the clinicians by classification group and study part.

Part I and Part II, respectively. This means that 25–30% of atopic patients did not have a follow-up appointment. The likelihood of a new appointment with other physicians in this group in Part II compared to Part I was OR = 1.3 (95% CI 0.8–2.1).

The proportion of patients who were contacted by telephone during the follow-up was low. In this respect, there was a large difference between the two countries in the study. In Spain 1.6% and in Italy 27% of the patients received a telephone call as a method of follow-up. The likelihood of receiving a telephone call as a method of follow-up was lower in Part II compared to Part I, OR = 0.41 (95% CI 0.2–0.9).

Data regarding other tests performed were similar to the results of the telephone calls. Here also there was a large difference between the two countries in the study. A total of 1.9% of patients in Spain and 15% of patients in

Table 5. Factors associated with the advice to avoid allergens given by the clinicians in the group of patients who were classified as allergic both by specific IgE test and clinical judgement

	Unadjusted model		Adjusted model	
	OR	(95% CI)	OR	(95% CI)
Study part				
Part I	1		1	
Part II	6.9	(4.08–11.7)	8.2	(4.7–14.5)
Country				
Italy	1		1	
Spain	0.45	(0.28–0.72)	0.33	(0.20–0.61)

Italy were sent for a further test, other than the specific IgE test. No clear pattern between groups and study parts could be seen.

The determining factors for the clinical management action, advice to avoid allergens in group 4, were study part and country. As compared to Part I, in Part II the likelihood of being advised to avoid allergens, was higher, OR = 8.2 (95% CI 4.7–14.5) (Table 5). Furthermore, in Spain compared to Italy the likelihood of being advised to avoid allergens was lower, OR = 0.33 (95% CI 0.2–0.6) (Table 5). Neither respiratory nor skin symptoms were found to be associated with the advice to avoid allergens.

Discussion

The main result of this investigation is that the ability of clinicians to identify atopic patients improves when they are able to use IgE results in addition to their clinical judgement. The use of a specific IgE antibody test had three major effects: (1) reduction of patients' misclassification, (2) reduction of the number of uncertain cases, and (3) the change in advice to avoid allergens.

The first important effect was that the agreement between clinical classification of patients and the classification based on the IgE results improved towards high levels of agreement in Part II compared to Part I. This improvement was found in both countries, Italy and Spain.

In Part II, however, no full agreement was reached since some patients who were IgE positive were classified as nonallergic by the clinician. This may be explained by two facts. First, a disagreement between the clinical judgement and the IgE results. One explanation could be that the sensitivity and specificity of the Phadiatop test are both about 98% and therefore in some cases clinicians may have used their own judgement only. Second, the clinician reported an incorrect classification by mistake, although this possibility seems unlikely.

The second important effect was that the number of uncertain cases in Part II was clearly reduced. In Spain, the number of uncertain cases was higher compared to Italy. This may be explained by differences in the age of

patients or differences in the clinical criteria used by pediatricians and general practitioners.

The third important effect was the change in the frequency of counselling 'to avoid allergens' between the two parts of the study. In Part I, an important proportion of IgE-negative patients received this advice. However, the advice could not be appropriate because of the lack of knowledge of the specific allergen. This situation may have created unnecessary anxiety to the patients and also resulted in unnecessary and costly interventions to avoid allergens by the patients. On the other hand, patients who were found to be sensitized to one or more specific allergens could have been inappropriately advised in the sense that no advice at all was given. In Part II, since a much higher proportion of atopic patients was correctly identified, the advice to avoid allergens was consequently more appropriately given.

The correct identification of atopic patients may have two important effects. First, several studies (of both food and indoor allergens) have shown decreased symptoms (both eczema and asthma) and reduced medication (18–20) resulting in a better outcome for the patient and less cost when avoidance recommendation was effectively carried out. Secondly, an early diagnosis and targeted medication may also lead to a better prognosis and may delay or prevent the onset of asthma in allergic dermatitis patients as well as further deterioration of lung function in asthma patients (21,22).

However, it has to be recognized that the beneficial or risk effects of some specific allergens are still not well understood. For instance, it has been shown in a recent meta-analysis that cat exposure effect may depend on the age at exposure (23). These controversial issues may lead to different attitudes and actions taken by the clinicians with regard to the avoidance of allergens. In addition, this may explain why the effect of the intervention in this study was lower in Spain in comparison with Italy. However, it is clear that avoidance of allergen exposure can reduce the number of exacerbation episodes, for example, in asthma patients (15,16).

The effect of the patient's referral to another clinician and planning telephone calls for the follow-up was less clear. There was no significant change in the number of referrals between Part I and Part II in any of the six groups. This may be explained by factors that do not depend on clinicians' decisions. The criteria for referrals may be set up or determined by planners, managers, local guidelines or the availability of units for specialized care and the gatekeeper role of primary-care physicians as has been established in Italy and Spain (24). This may vary between centres within one country or between countries. In the present study, however, these aspects were not evaluated. Besides the fact that no change was observed, the limited number of referrals may indicate that a substantial proportion of children may not have access to appropriate specialist care for correct diagnosis and treatment, as has been shown in the USA (25). The

number of new appointments was in general high and no intervention effect was found except for group 1. This may indicate a positive attitude to follow-up patients according to clinical guidelines and recommendations but it was difficult to interpret this finding. It was also difficult to interpret the reduction in the number of telephone calls to follow-up patients. This may be explained by the high number of new appointments.

The results of this study indicate that knowledge of specific IgE helps primary-care physicians to improve the diagnostic process in patients with respiratory and skin symptoms, as previously observed for the diagnosis of allergic rhinitis (13). In the case of allergy diagnosis, this may result in more appropriate treatment (e.g. allergen avoidance advice, referral to a specialist). However, the correct identification of nonallergic patients is just as important to prevent unnecessary treatments and allergen avoidance recommendations, which may be expensive, harmful (particularly in the case of food allergies) or upsetting (e.g., removal of a family pet). Negative IgE results also indicate that allergy is not the cause of a patient's symptoms and therefore may highlight the need for further investigations to establish the appropriate

treatment. Our study suggests that in the primary care setting many nonallergic patients without allergy testing will be wrongly identified as allergic.

In conclusion, the results showed that the use of specific IgE antibody determinations improves the clinical management of patients with allergy-related symptoms in primary care, allowing advice on specific allergen avoidance. To be able to evaluate the cost-effectiveness of this diagnostic tool fully in different areas and countries further research is needed.

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