

Paediatric allergy diagnosis in primary care is improved by *in vitro* allergen-specific IgE testing

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Allergy testing is an important pre-requisite for both early identification of infants at increased risk for later development of allergic diseases and for specific allergy treatment including specific allergen avoidance measures, pharmacotherapy and specific immunotherapy. The aim of this study was to investigate the influence of *in vitro* allergen-specific immunoglobulin E (IgE) testing on the primary care physician's diagnosis and clinical management of children with symptoms of eczema, wheezing/asthma and rhinitis. The trial was a prospective study performed at 14 paediatric primary care practices in Germany, covering 380 children below 6 yr of age. For one group of children the physician received the IgE test results as soon as possible and used them as an additional tool when diagnosing and giving clinical management advice. For the other group of children the IgE test results were not made available to the physician until the children were brought to a second visit, about 7 wk later. When diagnosis was made without access to allergen-specific IgE results, 8% of the children were diagnosed as allergic, 6% as non-allergic and in 86% of the cases the physician was uncertain. With access to allergen-specific IgE results the figures were 13%, 65% and 22%, respectively. Concerning clinical management advice no statistically significant differences between the two study groups were observed. When comparing the first and second visits of the patients coming for a second visit advice to reduce aeroallergen exposure was given to 27% of the patients at visit 1 and to 36% of the patients at visit 2 ($p = 0.002$). The difference between the first and second visits of the other clinical management advice studied did not reach statistical significance. In this study the availability of IgE test results to the primary care physician had an impact on the decision-making process of the diagnosis but not on the pharmaceutical or avoidance advice given. The reason why IgE test results were not fully exploited needs to be further scrutinized.

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Allergic diseases, such as atopic eczema, food allergy, rhinitis and wheezing disorders, are among the most common complaints making demands on paediatric primary care. However, accurately diagnosing these diseases early in life, e.g. in infancy, is often difficult solely using clinical aspects. The need for primary care to provide frontline care for allergy has been recognized. Primary care physicians are not

trained sufficiently in the management of allergic diseases and general practitioners have in a survey expressed concern about their ability to diagnose and manage children with allergic problems (1, 2).

There is agreement that allergy testing is an important pre-requisite for both early identification of infants at increased risk for later development of allergic diseases and for specific

allergy treatment including specific allergen avoidance measures, relevant pharmacotherapy and specific immunotherapy (3, 4). On the other hand, pharmacological treatment and clinical management are frequently recommended without considering the presence of allergy. This is particularly important in the case of suspected food-related symptoms possibly leading to advice, which may be unnecessary or even harmful to the child (5). Official guidelines may be helpful by indicating how primary care physicians should proceed. However, the extent to which health care personnel follow these guidelines is not known.

The aim of this study was to investigate the influence of *in vitro* allergen-specific immunoglobulin E (IgE) test results on the primary care physician's diagnosis and clinical management of children with symptoms of eczema, wheezing/asthma and rhinitis.

Subjects and methods

Study design

The trial was a prospective study performed at 14 paediatric primary care clinics in Germany. The centres were located in four different regions in Germany. The only inclusion criterion of the paediatricians was the willingness to participate.

The study comprised two inclusion periods, the first from November 2004 to March 2005 (infection season) and the second from May to September 2005 (pollen season). Children were enrolled consecutively as described next. Case history, allergy-like symptoms, exposure to cat, dog or tobacco smoke at home and any on-going symptomatic treatment were documented and a venous blood sample was drawn.

The blood sample was sent to a central laboratory where allergen-specific IgE antibodies were analysed and the children randomly allocated to study arm A or B. For study arm A subjects, the physician received the IgE test results within three working days and used them as an additional tool when diagnosing and giving clinical management advice. The advice to the parents was given by telephone. For children randomized to study arm B the IgE test results were not made available to the physician until the children came to a second visit, about 7 wk later. At the first visit the physician made a diagnosis and gave clinical management advice without access to the IgE test results. At the second visit the IgE test results were available and the physician could either confirm or change the diagnosis and/or the clinical management advice

given at the first visit. The study was approved by the Ethics Committee, Freiburg, Germany. Informed consent was given by the parents of all children prior to enrolment in the study.

Subjects

Children below 6 yr of age with symptoms of eczema and/or wheezing/asthma and/or rhinitis presented at any time during the previous year were included. The share of children below 1 yr of age was maximized to approximately 10% of the included children as food allergy is quite common among children below 1 yr and also difficult to diagnose without performing a food challenge. Children were not included if they had already been diagnosed with an allergy or if the physician knew the result of a previous allergy test. Children with serious co-morbid conditions or acute respiratory tract symptoms judged by the physician to be caused by an infection were not included.

The severity of eczema was defined as mild if the extent of the affected skin was less than 10% of the body, sleep was undisturbed and there was no itching, as moderate if at least one of the following criteria was fulfilled: extent 10–40%, occasional sleep disturbances or some itch during the day and as severe if at least one of the following criteria was fulfilled: extent of the affected skin more than 40%, several sleep disturbances or itching most days. The severity of wheezing/asthma and rhinitis was defined as mild if there had been one to two episodes during the previous 12 months, as moderate with three to five episodes and as severe with more than five episodes. The participating doctors based further clinical manifestations on their clinical judgement.

Laboratory assessments

The physician could choose testing of allergen-specific IgE antibodies with one, two or all of the German symptom profiles 'ImmunoCAP®Eczema' [egg white, cow's milk (CM), wheat, soy, house dust mite], 'ImmunoCAP®Asthma/Rhinitis Seasonal' (birch, timothy, mugwort, *Alternaria alternata*) or 'ImmunoCAP®Asthma/Rhinitis Perennial' (house dust mite, cat epithelium and dander, dog dander, *Penicillium notatum*, *Cladosporium herbarum*, *Aspergillus fumigatus*, *A. alternata*) (Phadia AB, Uppsala, Sweden). Concentrations above 0.35 kU_A/l were considered positive. All IgE laboratory analyses took place at the allergy laboratory of the Department of Paediatric

Pneumology and Immunology, Children's Hospital Charité, Humboldt University, Berlin, Germany.

Outcome measure: diagnosis

The physician allocated a child to 'allergy', 'non-allergy' or 'uncertain' in accordance with established routines at the respective clinic on basis of case history and a physical examination. The agreement between the diagnosis and the allergen-specific IgE result was calculated for the two study arms and compared.

Outcome measure: clinical management advice

Information was collected on the advice given by the physicians to reduce allergen exposure or to avoid foods [in particular hen's egg (HE), CM, wheat, soy] and/or aeroallergens (in particular cat, dog, mite). Also, the particular avoidance advice given for aeroallergens [adopted from Prevention of Allergy and Allergic Asthma (6)] was recorded. Information on the following advice was collected: extensive cleaning, keep the cat/dog out of the child's bedroom, remove the cat/dog and other furred pets from the home, cover mattress and pillow with dust mite-resistant covers, wash bedding in hot water or put in freezer weekly, avoid pollen by staying indoors, use air filters, close windows etc., increase the ventilation in the home, remove wall-to-wall carpets, use air cleaner/humidifier, reduce indoor relative humidity in the home, any other recommendation(s). Furthermore, the referrals to other physicians were recorded. Finally, information was recorded on the medication used, e.g. antihistamines, corticosteroids, decongestants, bronchodilators, cromones, antibiotics and ointments other than corticosteroids and antibiotic ointments.

Statistical analysis

The comparisons between arms A and B were made with the Cochran-Mantel-Haenszel test of general association, stratified for clinics. Comparisons between visits within arm B were made with the two-sided McNemar test for paired two-by-two tables, and with the Stuart-Maxwell test (7) for the paired three-by-three table. The tests were based on permutation distributions.

Missing data was not replaced. Two patients in study arm B did not return for the second visit, and could not be included in the comparisons between visits within arm B. A significance level of 5% was used. All tests were performed using

the coin package (8) within the R software system v 2.3.0 (9).

Results

Demographic and baseline characteristics

In total, the diagnosing behaviour and the clinical management of 14 physicians were studied in 380 children fulfilling the inclusion and exclusion criteria. The number of children enrolled by the primary care clinics varied from 13 to 48 children. One hundred and eighty-eight children were randomized to study arm A and 192 children to study arm B, 53% were included during infection season and 47% during pollen season. The baseline demographic and clinical characteristics are shown in Table 1 and baseline data on exposure at home, food-related symptoms and medication at enrolment is shown in Table 2. In arm A, 21% of the children had a

Table 1. Baseline demographic and clinical characteristics

	IgE results available (study arm A) n = 188	IgE results not available (study arm B) n = 192
	n (%)	n (%)
Gender:		
Male	109 (58)	121 (63)
Female	79 (42)	71 (37)
Age (years):		
<1	27 (14)	18 (9)
1 to <2	36 (19)	35 (18)
2 to <6	125 (66)	139 (72)
Symptoms (presence):		
At least eczema	91 (48)	82 (43)
At least wheezing/asthma	112 (60)	114 (59)
At least rhinitis	78 (42)	84 (44)
Symptoms (severity)*:		
Eczema:		
Mild	19 (21)	11 (13)
Moderate	57 (63)	54 (66)
Severe	15 (16)	17 (21)
Wheezing/asthma:		
Mild	39 (35)	44 (39)
Moderate	52 (46)	56 (49)
Severe	21 (19)	14 (12)
Rhinitis:		
Mild	27 (35)	37 (44)
Moderate	29 (37)	30 (36)
Severe	22 (28)	17 (20)
Number of different symptoms:		
1	108 (57)	116 (60)
2	67 (36)	64 (33)
3	13 (7)	12 (6)

*In the symptom severity section of the table the stated percentages in each study arm are based on the patients having the symptom, not on the total number of patients.

IgE, immunoglobulin E.

Table 2. Baseline data on exposure at home, food-related symptoms and medication at enrolment

	IgE results available (study arm A) n = 188	IgE results not available (study arm B) n = 192
	n (%)	n (%)
Exposure at home:		
At least cat	29 (15)	26 (14)
At least dog	20 (11)	24 (12)
At least tobacco smoke	47 (25)	56 (29)
No. of children being exposed	77 (41)	85 (44)
Food-related symptoms:		
At least egg	1 (1)	3 (2)
At least milk	9 (5)	4 (2)
At least wheat	3 (2)	0 (0)
At least soy	0 (0)	0 (0)
At least one other	22 (12)	17 (9)
No. of children having symptoms	29 (15)	22 (11)
Medication at enrolment:		
At least antihistamines	27 (14)	30 (16)
At least corticosteroids	47 (25)	55 (29)
At least antibiotics	24 (13)	19 (10)
At least bronchodilators	68 (36)	69 (36)
At least cromones	12 (6)	13 (7)
At least decongestants	48 (26)	51 (27)
At least ointments	51 (27)	56 (29)
At least one other	49 (26)	58 (30)
No. of children with medication	158 (84)	169 (88)

IgE, immunoglobulin E.

positive allergen-specific IgE result to at least one of the tested allergens, and in arm B 28%. The most common sensitizations in children below 2 yr were egg white (8%) and CM (3%). The children aged 2–6 yr were most commonly sensitized to timothy (15%), birch (12%), house dust mite (9%) and egg white (7%).

Diagnosis

When diagnosis was made without access to allergen-specific IgE results (arm B) 8% of the children were diagnosed as allergic, 6% as non-allergic and in 86% of the cases the physician was uncertain. With access to allergen-specific IgE results (arm A) the figures were 13%, 65% and 22%, respectively (Fig. 1). Of the 42 children with an uncertain diagnosis eight had a positive IgE test. Only three of them had a specific IgE antibody level above 1.0 kU_A/l (13.5, 2.78 and 2.07 kU_A/l, respectively). The child with the highest IgE value was sensitized to birch and had symptoms of asthma and rhinitis. Making the diagnosis without access to allergen-specific IgE results gave an agreement between diagnosis and allergen-specific IgE results in 11% of the cases. The corresponding figure with access to IgE results was 71% ($p < 0.001$).

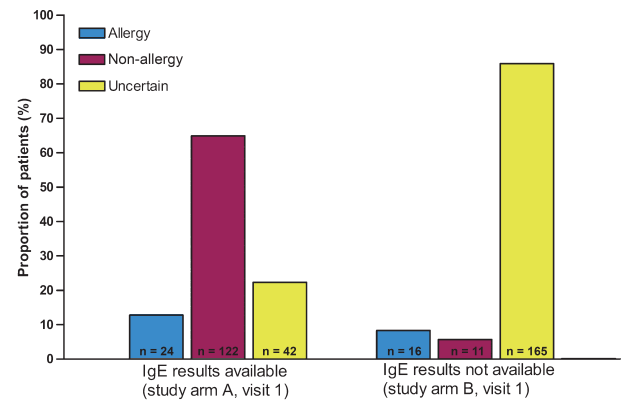


Fig. 1. Diagnoses of patients in study arms A and B at visit 1.

Clinical management advice

Advice to avoid certain foods was given to 17% of the children in arm A and to 15% of the children in arm B. Advice to reduce aeroallergen exposure was given to 31% of the children in arm A and to 28% of the children in arm B. Referrals to another physician, mostly ear, nose and throat specialists, was made for 6% of the children in arm A and 4% of the children in arm B. A recommendation to use antihistamines was given to 13% of the children in arm A and 16% of the children in arm B (Table 3). The differences were not statistically different.

Food avoidance advice

The most common food advice was to avoid CM. This was given to 7% of the children in arm A and to 6% of the children in arm B. Of the 25 children advised to avoid CM, eight had symptoms in connection with CM ingestion, four were sensitized to CM and no child had symptoms and was also sensitized. Three were diagnosed as allergic, six as non-allergic and sixteen as uncertain (Tables 4 and 5a). The corresponding figures for HE, wheat and soy are shown in Table 5a.

Aeroallergen avoidance advice

No significant difference was observed for the general and more specific aeroallergen avoidance advice given in the two study arms. Eighty-one children were advised to avoid cat. Of these, 27 were exposed at home, 6 were sensitized to cat and 2 were both exposed at home and sensitized to cat. As many as 44 cases with an uncertain diagnosis were given the advice to avoid cat. Of the 67 children advised to avoid dog 11 were exposed at home, only 3 were sensitized to dog

Table 3. Clinical management advice given after diagnosis

	IgE results available (study arm A, visit 1) n = 188	IgE results not available (study arm B, visit 1) n = 192		IgE results not available (study arm B, visit 1) n = 190	IgE results available (study arm B, visit 2) n = 190	
	n (%)	n (%)	p-value	n (%)	n (%)	p-value
Advice to avoid certain foods	32 (17)	28 (15)	0.57	28 (15)	32 (17)	0.30
Advice to reduce aeroallergen exposure	64 (31)	55 (28)	0.41	50 (27)	70 (36)	0.002
Referral to other physicians	12 (6)	8 (4)	0.36	8 (4)	8 (4)	1.0
Recommendation to use antihistamines	24 (13)	30 (16)	0.45	30 (16)	24 (13)	0.15

IgE, immunoglobulin E.

Table 4. Specific clinical management advice

	IgE results available (study arm A) n = 188	IgE results not available (study arm B) n = 192
	n (%)	n (%)
Foods to be avoided:		
At least milk	13 (7)	12 (6)
At least egg	8 (4)	7 (4)
At least wheat	2 (1)	0 (0)
At least soy	3 (2)	3 (2)
At least one other	18 (10)	19 (10)
No. of children advised to avoid any food	32 (17)	28 (15)
Aeroallergen exposure to be avoided:		
At least cat	44 (23)	37 (19)
At least dog	34 (18)	33 (17)
At least mite	39 (21)	33 (17)
At least one other	11 (6)	11 (6)
No. of children advised to avoid any aeroallergen	59 (31)	53 (28)
Medication after diagnosis:		
At least antihistamines	24 (13)	30 (16)
At least corticosteroids	39 (21)	32 (17)
At least antibiotics	8 (4)	6 (3)
At least bronchodilators	44 (23)	43 (22)
At least cromones	9 (5)	11 (6)
At least decongestants	12 (6)	19 (10)
At least ointments	46 (24)	49 (26)
At least one other	46 (24)	37 (19)
No. of children advised to use medication	130 (69)	136 (71)

IgE, immunoglobulin E.

and none was both exposed at home and sensitised (Table 5b).

Recommendation to use antihistamines

A recommendation to use antihistamine was given to 24 children (13%) in arm A and 30 children (16%) in arm B (Table 4). Of these 54 children, 23 had eczema, 20 had wheezing/asthma and 36 had rhinitis. Twenty-eight of the 54 children were sensitized to at least one allergen and 16 were diagnosed as allergic (Table 5c).

Comparison of the two visits of the patients in arm B

For 98 of the 164 patients in arm B (60%) given an 'uncertain' diagnosis at visit 1 and returning for visit 2 the diagnosis was changed to non-allergy at visit 2, when the specific IgE result was available. For 29 patients (18%) the diagnosis was changed to allergy, while 37 patients (23%) were still diagnosed as 'uncertain' at visit 2 (Fig. 2). For two patients the diagnosis was changed from non-allergy at visit 1 to 'uncertain' at visit 2. The agreement between the diagnosis and the allergen-specific IgE result was 11% at visit 1 and 76% at visit 2 ($p < 0.001$). Advice to reduce aeroallergen exposure was given to 27% of the patients at visit 1 and 36% of the patients at visit 2 ($p = 0.002$). Of the 20 children that received advice to reduce aeroallergen exposure at visit 2 but not at visit 1, 8 were advised to avoid cat, 10 to avoid dog and 11 to avoid mites. Of these 5 had a positive specific IgE test results to cat, 7 to dog and 10 to mite. The difference between visits 1 and visit 2 for the other clinical management advice studied did not reach statistical significance (Table 3).

Discussion

The results of this study show that knowledge of IgE test results to the primary care physicians had an impact on the decision-making process of the diagnosis. However, this information had little or no influence on the therapeutic advice given to the families. The advice given was mainly directed towards elimination of food allergens, avoidance measures of aeroallergens or general health matters.

The clinicians remarkably changed their way of making diagnosis when they were able to use the IgE test results. They were able to reduce the group of uncertain diagnoses from 80% to 20%. The reason why this group was not reduced to zero was that these children had symptoms but no detectable IgE antibodies and therefore were diagnosed as uncertain. The eight children that

Table 5. Food (a) and aeroallergen (b) avoidance advice and recommendation to use antihistamines (c) in relation to symptoms, exposure and sensitization

Therapeutic advice	Given to n children	n	n	n	Diagnosis		
					Allergic (n)	Non-allergic (n)	Uncertain (n)
(a) Advice to avoid at least		Symptoms in connection with ingestion	Sensitized to egg, milk, wheat and soy, respectively	Symptoms and sensitized			
Milk	25	8	4	0	3	6	16
Egg	15	3	6	2	2	3	10
Wheat	2	1	1	0	1	1	0
Soy	6	0	2	0	1	1	4
(b) Advice to avoid at least		Exposed at home	Sensitized to cat, dog and mite, respectively	Exposed and sensitized			
Cat	81	27	6	2	12	25	44
Dog	67	11	3	0	9	22	36
Mite	72	an	7	na	10	25	37
(c) Recommendation to use antihistamines		Eczema (and sensitized to at least one allergen)	Wheezing/asthma (and sensitised to at least one allergen)	Rhinitis (and sensitised to at least one allergen)			
	54	23 (11)	20 (9)	36 (22)	16	6	32

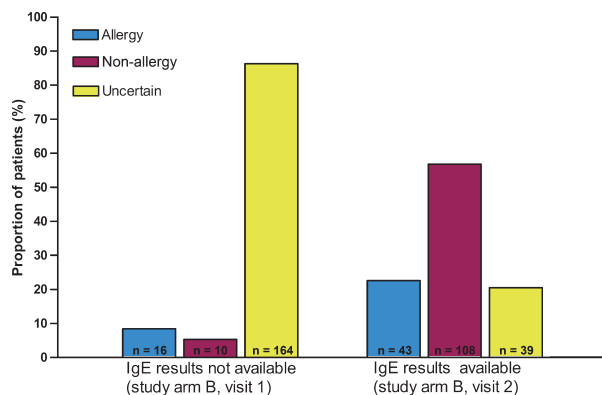


Fig. 2. Diagnoses of patients in study arm B at visits 1 and 2.

had antibodies were low-grade sensitized which is always difficult to interpret, especially for the primary care physicians.

The paediatricians did not fully utilize the IgE test results in terms of treatment and avoidance advice. One explanation for this unexpected finding may be that the paediatricians participating in this study lacked specialization in allergology. Emphasis has been made during recent years to increase the educational standard for this group in Germany. For example, nearly 2000 German paediatricians are organized in the 'German Society for Pediatric Allergology and Environmental Medicine' and around 450 primary care paediatricians so far hold the specialization of allergology.

The primary care paediatricians in this study were quite generous with their therapeutic advice concerning allergen avoidance, and such advice was given even for children with no symptoms corresponding to the allergen they were advised

to avoid. One probable explanation for this is that allergen avoidance advice was given also for primary preventive reasons – especially if the correct allergy diagnosis was not yet known. Knowing the correct allergen diagnosis can therefore lead to focus avoidance measures and by this to save money and avoid giving unnecessary allergen avoidance advice that might deprive quality of life for the children and their families. In a study by Weinmann et al. (10), it was shown that the cost of allergy diagnostics accounts for only 1% of the total costs for health care of children with asthma, eczema and rhinitis. The cost of an IgE test early in life would thus be much cheaper for society than for instance years of unnecessary use of antihistamines.

In our study, the advice to avoid CM and HE was given quite frequently with no difference in the two study arms. Elimination of CM, as the most important baseline food for infants and young children, represents a major intervention, which makes the life of the families complicated and expensive. Furthermore, elimination can lead to states of deficiency, if no adequate substitute formula is offered (11). In several cases in our study the recommendation to eliminate CM did not correlate to symptoms or specific IgE results. The knowledge of sensitization to important foods can therefore avoid unnecessary specific eliminations diets, e.g. by subjecting these children to oral food challenges. In contrast, recommendations to avoid aeroallergens can be given for therapeutic and preventive purposes without causing harm. Therefore, it is strange that the aeroallergen advice was given more frequently when IgE test results were available but not so

for food. The participating clinicians did not perform food challenges. They had not been trained in using specific IgE as a tool to decide whether or not to perform a food challenge (12). This could be an explanation why they did not change their management of food allergies when IgE test results were available.

The included children were below 6 yr of age. Especially among the youngest the presence of food-specific IgE antibodies without any clinical symptoms on ingestion of a particular food is not uncommon. An oral food challenge is most often required to verify the diagnosis of suspected food allergy. However, the study aimed at investigating the behaviour of the physicians in their daily practise, which does not include performing an oral food challenge on a routine basis. Instead, the number of children below 1 yr of age was limited.

The study has some limitations. On a day-to-day basis, physicians have very limited possibility to make an 'uncertain' diagnosis. One may speculate that the knowledge of being in a controlled two-arm study facilitated the choice of this otherwise unrealistic allocation, especially because de-blinding was offered after 7 wk. Unfortunately, we cannot say how the paediatricians would have decided without this third alternative. Another limitation is that we did not collect information about the family history of the children nor the duration of breast-feeding, which might have been helpful. The behaviour of the paediatricians may have been influenced by this information.

A similar study was performed in primary care in Spain and Italy (13). None of the participating physicians were using *in vitro* testing for IgE in their daily practice before the study, and a different study design was used: in a first inclusion period, all diagnoses were given with no access to IgE results. In the second inclusion period, all diagnoses were made with access to IgE results. Between the two inclusion periods the primary care physicians were educated about blood testing for allergy. The study revealed that the use of specific IgE antibody determinations improved the clinical management of patients with allergy-related symptoms in primary care, allowing advice to be given on specific allergen avoidance. Thus, in that study knowledge of IgE antibody results had an impact on treatment advice.

In conclusion, although the knowledge of IgE test results had an impact on the decision-making process of the diagnosis of the primary care paediatrician, this information in the present study had no influence on the avoidance and pharmaceutical advice given to the families. This

resulted in cases with unnecessary dietary avoidance or medication leading to increased costs both for families and health care as well as decreased quality of life for the children and families.

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