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Allergy screening in asthma and allergic rhinitis

Which allergens should be used?

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To detect atopy by a screening method employing skin prick testing with a limited number of allergens, the test results of 939 patients with allergic airways diseases were analysed. It was found that an allergen panel consisting of cat, timothy and house dust mite could detect 85 % of atopic patients with asthma and/or rhinitis. For subgroups of patients the results were even more favourable. Thus 98 % of atopic patients with seasonal allergic rhinitis were detected by an allergen panel consisting of timothy, birch and mugwort. It is concluded that screening methods using only three of four allergens could be used for detecting atopy in patients with airways diseases. The method should be most valuable for *in vitro* tests used in combination with standardized questionnaires.

Key words: allergen; allergic rhinitis; allergy diagnosis; bronchial asthma; skin test.

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CLINICAL ASPECTS

The study shows that a limited number of allergens suffice for eliciting atopic patients among adult individuals with asthma or rhinitis. This finding should be utilized to elaborate efficient screening methods, in order to make allergy diagnosis less expensive.

Asthma and rhinitis can, according to etiologic, pathogenetic and other factors, be divided into several types. From a practical therapeutic point of view, a division into allergic and non-allergic diseases is essential, since the latter can be treated with specific therapy: elimination and/or immunotherapy. For this reason, screening methods for allergy are valuable.

The patients' histories often give guidance in the question: allergy or not? (2). Recommendations for the general practitioner's handling of allergy diagnosis on the basis of simple clinical data have been suggested (6). Determination of total IgE has been proposed by others as a way of screening for allergy (11). However, a broad overlap in IgE values between allergic and non-allergic patients makes this method less valuable (3). Screening with a few allergens used in the RAST or skin prick test has also been suggested. Pantin & Merret (9) have shown that 95 % of British patients having positive RAST are RAST-positive to a mini-panel consisting of three allergens only (grass, mite and cat), which thus could be used as a screening panel. Herbert et al. (7) found that 90 % of atopic asthmatics could be detected by skin prick test with four allergens, or by total IgE in combination with five RAST analyses.

An allergen panel used for screening purposes must obviously depend on the patients' environments and thus must vary from one country to another. The purpose of the present study was to determine which allergens to select if a mini-panel of allergens was to be used for allergy screening in Sweden.

PATIENTS AND METHODS

The patients consist of 1186 consecutive adult patients referred for allergy diagnosis at our

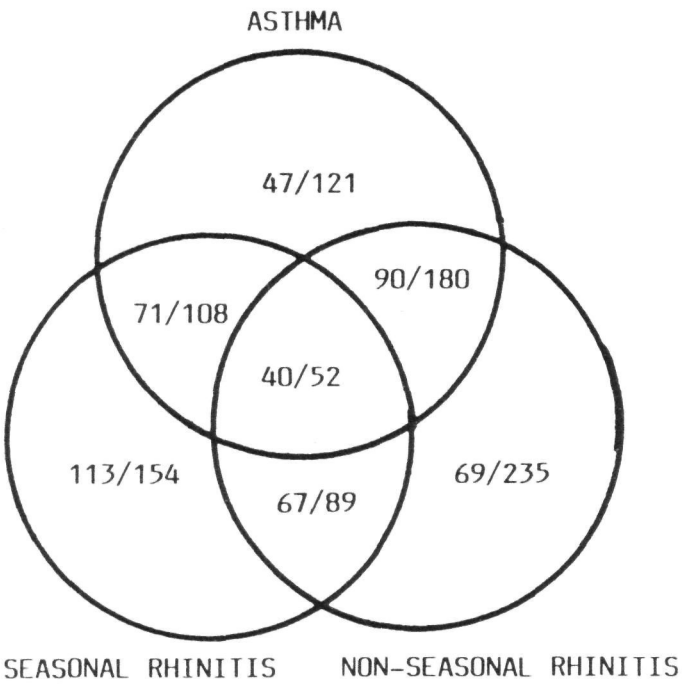

Fig. 1. Distribution of patients with asthma and/or rhinitis in diagnostic groups. The figures indicate number of atopics/total number of patients in the group.

allergy unit. Their mean age was 33 years (range 9–82). Most of the patients, 939, had asthma and/or rhinitis. The number of patients with the various combinations of airways diseases is seen in Fig. 1.

Allergens

All patients were skin-tested with an allergen panel consisting of one mite *(Dermatophagoides pteronyssinus),* one mould *(Cladosporium),* three animal dander allergens (horse, dog and cat) and one pollen allergen from each of the three botanical groups of allergological importance in Sweden: tree pollen (birch), grass pollen (timothy) and *Asteraceae* pollen (mugwort). This allergen panel is, according to clinical experience, adequate for detecting clinically relevant allergies in the region.

The allergens used were with the exception of *Cladosporium* biologically standardized glycerinated Soluprick extracts with a labelled activity of 5 HEP (600 patients) or 1 HEP (586 patients) from Allergologisk Laboratorium, Copenhagen, Denmark. (HEP = Histamine equivalent Prick). The *Cladosporium* allergen used was a 1:20 (w/v) extract from the same laboratory.

Skin test

Skin prick tests were performed on the volar side of the forearm. A drop of allergen was placed on the skin, and a prick test lancet with a 1 mm point (13) was jabbed through the drop, held at an angle of 90° to the skin. The weal reactions were read after 15 min and recorded in accordance with the recommendations of the Standardization Committee of the Northern Society of Allergology (1). Thus a weal reaction of the same size as that of a histamine reference (histamine 1 g/l) was recorded as three plus (3 +). A reaction of half the size of the histamine reference was recorded as 2 + whereas a reaction intermediate between the size of a 2 + reaction and that of the negative reference (isotonic phosphate saline) was recorded as 1 + . The mean (± 1 SD) diameter of the weals elicited by the histamine reference was 3.9 ± 0.9 mm.

Although there exists a quantitative correlation between the degree of skin test reactivity and clinically relevant allergy, it is not possible to divide patients with 100 % precision into allergic and non-allergic. One has to choose a cut-off point between positive and negative test results which minimize the number of falsely positive as well as falsely negative test results (4). On the basis of clinical experience with the allergens used, as well as of the results of earlier studies (5), skin prick test reactions recorded as 1 + were in this study regarded as negative and reaction of ⩾ 2 + as positive.

Calculations

To find out the allergen panels most suitable for screening purposes, if 1, 2, 3, etc. allergens were to be used, the allergen giving the highest number of positive reactions was first calculated. All individuals having a positive reaction with this allergen were then excluded from the following calculations. The allergen to which most of the remaining patients reacted was then sought and all individuals showing positive reaction to this allergen were excluded from the

next calculations. The process was repeated until all individuals having a positive skin test reaction had been excluded. A similar method has been described earlier (14).

RESULTS

Of the 1186 patients 613 were found to have one or more positive skin prick test result ($\geq 2+$). The prevalence of positive test results in various age groups is seen in Table 1, showing the highest figures in the youngest groups.

The results found when the test results of each allergen were correlated to those of each of the other allergens are seen in Table 2. The highest value of the Spearman's correlation coefficient was found for the correlation between dog and cat (R = 0.64).

Table 1

Positive skin test reactions in various age groups (n = 1186)

	Age group					
	10–19	20–29	30–39	40–49	50–59	≥ 60 years
No. of patients	226	380	249	166	106	59
Positive (%)	64	62	43	37	24	28

Screening of allergy in allergic airways disease

For analysis of test results in patients with allergic airways diseases, 247 patients who had only other diseases (urticaria, Quincke oedema, etc.) were excluded from the calculations. Of the remaining 939 patients 497 had positive skin tests. As seen from Table 3, cat tops the list of positive tests. Thus if one allergen only was to be used for screening, cat should be used and would detect 52% of the allergic patients. The two-allergen combination that detected the highest number of test-positive patients was cat + timothy, detecting 74% of the patients (Table 3). If three allergens should be used for screening, mite allergen should be added. If these three allergens were used 85% of the allergic patients would be detected. The results found when using a higher number of allergens are seen in Table 3.

Table 2

Relationship between skin test results with different allergens in 1186 patients. The table is symmetrical. The upper right consists of 2 × 2 tables. The figures indicate percentages. The lower left gives Spearman's coefficients for the correlation between the test results with the corresponding allergens

Allergen	Mite		Cladosporium		Horse		Dog		Cat		Timothy		Mugwort		Birch	
			–	+	–	+	–	+	–	+	–	+	–	+	–	+
			83	3	79	7	71	15	68	18	68	18	72	14	72	14
		+	12	2	11	3	8	6	7	7	9	5	10	4	10	4
Cladosporium	0.22				–		87	8	78	17	73	22	74	21	79	16	78	17
					+		3	2	2	3	2	3	3	2	3	2	3	2
Horse	0.13		0.27				–		77	13	73	17	71	19	75	15	75	15
							+		2	8	2	8	6	4	7	3	6	4
Dog	0.19		0.25		0.49				–		71	9	66	13	69	10	70	10
									+		4	16	11	10	13	8	12	8
Cat	0.21		0.15		0.40		0.64				–		65	11	66	9	67	8
											+		12	12	15	10	14	11
Timothy	0.12		0.07		0.16		0.30		0.36				–		69	8	69	8
													+		13	10	12	11
Mugwort	0.14		0.16		0.11		0.24		0.29		0.37				–		73	9
															+		9	9
Birch	0.12		0.10		0.16		0.28		0.35		0.40		0.39					

Screening of allergy in subgroups of patients

If only patients with *bronchial asthma,* without rhinitis, were included in the calculations, the best 3-allergen combination was dog + mite + cat, detecting 85% of the allergic asthmatic patients (Table 4).

For patients with *rhinitis* only the best allergen combination was timothy + cat + birch which detected 86% of rhinitis patients having positive skin tests (Table 5). For *seasonal rhinitis,* the optimal allergen choice was timothy + birch +

Table 3

Rank order of allergens for screening of allergy in 497 patients with asthma and/or rhinitis and positive skin tests

Allergen	No. patients with positive SPT		
	Total in patient group	Not reacting to previous allergens in screening panel	Proportion (%) of patients detected by screening panel
1. Cat	261	-	52
2. Timothy	243	109	74
3. Mites	136	53	85
4. Mugwort	188	35	92
5. Birch	193	24	97
6. Dog	215	11	99
7. Horse	106	4	99
8. Cladosporium	50	2	100

For explanations, see Methods (Calculations). From the table one can see e.g. that 134 (243-109) of the 243 patients with positive skin test against timothy were detected already by testing with allergen No. 1, cat. Of the 136 patients reacting against mites, 83 (136-53) were detected by testing with allergens No. 1 and 2. 85% of all the allergic patients had one or more positive test results when an allergen panel consisting of allergens No. 1, 2 and 3 was used.

Table 4

Rank order of allergens for screening of allergy in 47 patients with asthma and positive skin tests

Allergen	No. patients with positive SPT		
	Total in patient group	Not reacting to previous allergens in screening panel	Proportion (%) of patients detected by screening panel
1. Dog	27	-	57
2. Mite	19	10	79
3. Cat	23	3	85
4. Timothy	14	2	89
5. Mugwort	13	2	94
6. Horse	14	1	96
7. Birch	10	1	98
8. Cladosporium	5	1	100

For explanations see Table 3.

Table 5

Rank order of allergens for screening of allergy in 249 patients with rhinitis only (seasonal and/or non-seasonal) and positive skin tests

Allergen	No. patients with positive SPT		
	Total in patient group	Not reacting to previous allergens in screening panel	Proportion (%) of patients detected by screening panel
1. Timothy	142	-	57
2. Cat	107	45	75
3. Birch	118	28	86
4. Mugwort	97	15	92
5. Mite	47	8	96
6. Dog	78	7	98
7. Horse	43	3	99
8. Cladosporium	18	1	100

For explanations see Table 3.

Table 6

Rank order of allergens for screening of allergy in 113 patients with seasonal rhinitis and positive skin tests

Allergen	No. patients with positive SPT		
	Total in patient group	Not reacting to previous allergens in screening panel	Proportion (%) of patients detected by screening panel
1. Timothy	85	-	75
2. Birch	65	20	93
3. Mugwort	50	6	98
4. Dog	23	2	100
5. Cat	38	0	-
6. Horse	12	0	-
7. Mite	9	0	-
8. Cladosporium	4	0	-

For explanations see Table 3.

mugwort detecting 98 % of the patients (Table 6) whereas the combination cat + mugwort + mite was the best choice for *non-seasonal rhinitis,* detecting 83 % of the allergic patients in the group (Table 7). In patients with the combination of *seasonal and non-seasonal rhinitis*, the three allergens timothy + birch + dog gave positive reactions in 88 % of the patients (Table 8).

For patients with *non-seasonal rhinitis and asthma* the best allergen combination for screening was cat + mite + mugwort which could detect 98 % of the allergic individuals (Table 9). Cat + timothy + mugwort detecting 92 %, was the optimal combination for patients with *seasonal rhinitis and asthma* (Table 10). In the remaining small group of patients with a combination of

Table 7

Rank order of allergens for screening of allergy in 69 patients with non-seasonal rhinitis and positive SPT

Allergen	No. patients with positive SPT		Proportion (%) of patients detected by screening panel
	Total in patient group	Not reacting to previous allergens in screening panel	
1. Cat	35	-	51
2. Mugwort	24	14	71
3. Mite	26	8	83
4. Horse	17	4	88
5. Timothy	16	2	93
6. Dog	30	2	96
7. Birch	18	2	96
8. Cladosporium	11	1	100

For explanations see Table 3.

Table 8

Rank order of allergens for screening of allergy in 67 patients with combined seasonal and non-seasonal rhinitis and positive skin tests

Allergen	No. patients with positive SPT		Proportion (%) of patients detected by screening panel
	Total in patient group	Not reacting to previous allergens in screening panel	
1. Timothy	41	-	61
2. Birch	35	11	78
3. Dog	25	7	88
4. Cat	34	3	92
5. Mugwort	23	3	97
6. Mite	12	1	98
7. Horse	14	1	100
8. Cladosporium	3	0	-

For explanations, see Table 3.

Table 9

Rank order of allergens for screening of allergy in 90 patients with non-seasonal rhinitis and asthma and positive skin tests

Allergen	No. patients with positive SPT		Proportion (%) of patients detected by screening panel
	Total in patient group	Not reacting to previous allergens in screening panel	
1. Cat	63	-	70
2. Mite	35	18	90
3. Mugwort	23	7	98
4. Horse	24	1	99
5. Birch	22	1	100
6. Dog	50	0	-
7. Timothy	23	0	-
8. Cladosporium	9	0	-

For explanations, see Table 3.

Table 10

Rank order of allergens for screening of allergy in 71 patients with asthma and seasonal rhinits and positive skin tests

Allergen	No. patients with positive SPT		Proportion (%) of patients detected by screening panel
	Total in patient group	Not reacting to previous allergens in screening panel	
1. Cat	42	-	59
2. Timothy	41	15	80
3. Mugwort	32	8	92
4. Birch	29	3	96
5. Mite	19	2	99
6. Dog	36	1	100
7. Horse	14	0	-
8. Cladosporium	11	0	-

For explanations, see Table 3.

seasonal and non-seasonal rhinitis and asthma, the allergen combination cat + mugwort + mite was sufficient to detect 95% of the allergic patients (Table 11).

Most of the patients who were not detected by the 3-allergen combinations only had weakly positive skin reactions of questionable clinical relevance.

DISCUSSION

Most adult patients with asthma or rhinitis can be adequately treated by non-specific pharmacotherapy. An allergological investigation should be performed only when it is likely that the establishment of a specific allergy will lead to a meaningful allergen specific therapy. Recommendations for the management of patients with asthma according to this principle have been presented earlier (6).

The first measure is to record a thorough history, which with some allergens will give a reliable diagnosis (2, 4, 5). However, the history has a low diagnostic precision for non-seasonal allergens (10). Thus, some kind of allergy testing often has to be performed. For physicians in regions where complete allergy skin testing is not available, a screening method for atopy would be valuable. When choosing a mini-allergen panel for screening one should not just choose the three or four allergens showing the highest number of positive reactions. Depending on cross-reactivity, such a panel would not be the most efficient (14). In the present study the patients' concomitant reaction to two or more allergens was taken into account in order to find the optimal allergen panel.

The study corroborates other studies, showing that 80–90% of allergic patients can be detected with a screening allergen panel of 3–5 allergens in the skin test (7) or the RAST (7, 9). The study also shows that different allergen panels should be chosen depending on the patient's allergy diagnosis: asthma, seasonal or non-seasonal rhinitis (Table 12). The best diagnostic precision is found, as could be expected, when such a screening allergen panel is used in patients with seasonal rhinitis.

It should be stressed that the allergen panel will of course vary from region to region. Nevertheless, the optimal screening panel found for the whole group of patients was the same as that found by Pantin & Merret (9) for screening with the RAST in British patients: Grass, mite and cat.

Table 11

Rank order of allergens for screening of allergy in 40 patients with asthma and seasonal and non-seasonal rhinitis and positive skin tests

Allergen	No. patients with positive SPT		
	Total in patient group	Not reacting to previous allergens in screening panel	Proportion (%) of patients detected by screening panel
1. Cat	26	-	65
2. Mugwort	23	9	88
3. Mite	14	3	95
4. Timothy	23	2	100
5. Dog	24	0	-
6. Birch	14	0	-
7. Horse	11	0	-
8. Cladosporium	7	0	-

For explanations, see Table 3.

Table 12

The best screening panel for various allergic airways diseases using three allergens

Diganosis	Allergen panel	Proportion (%) of allergic patients detected
All patients	Cat, timothy, mite	85
Asthma	Dog, mite, cat	85
Rhinitis	Timothy, cat, birch	86
Seasonal rhinitis	Timothy, birch, mugwort	98
Non-seasonal rhinitis	Cat, mugwort, mite	83
Seasonal and non-seasonal rhinitis	Timothy, birch, dog	88
Non-seasonal rhinitis and asthma	Cat, mite, mugwort	98
Seasonal rhinitis and asthma	Cat, timothy, mugwort	92
Seasonal and non-seasonal rhinitis and asthma	Cat, mugwort, mite	95

The present study and other studies showing the value of a mini-panel for screening of allergy (7, 9) were based on the results of indirect tests (skin tests or RAST). It should be noted that neither the skin prick test, nor the RAST, give a definite answer to the question: has the patient clinically relevant allergy or not? Only strong skin prick test reactions or high levels of specific IgE in the serum show a high correlation to the results of positive provocation tests (4, 5, 6).

Although the conclusions of this study originate from the results of skin prick tests, they can with certain reservations also be applied to the RAST or other *in vitro* methods. Although the diagnostic precision, i.e. the agreement with the results of provocation tests, is roughly the same for skin tests and the RAST (about 80 %) the distribution of falsely negative tests and falsely positive tests is not the same (4). Nevertheless, even if the figures for the proportion of patients to be detected with the screening panel, will differ somewhat, the optimal screening allergen panel should roughly be the same with the RAST as with skin tests. Due to the costs, mini-screening panels should be more valuable for *in vitro* tests than for skin tests.

A multi-RAST, performed by adding aliquots of three different microcrystalline cellulose allergen-immunosorbents to the same tube to test for the presence of IgE antibodies of different specificities simultaneously, has been described by Ownby et al. (8). They found their multi-RAST to be a useful and cost-effective screening test for inhalant allergy in children. Another multi-RAST method, using nine different allergens coupled to a RAST-disc, has recently been commercially available (Phadiatop®, Pharmacia Diagnostics, Uppsala, Sweden). Clinical studies indicate that it has a very high diagnostic efficiency (12). The diagnostic usefulness of a combination of a standardized questionnaire and a multi-RAST for screening of atopy should be evaluated.

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