Increased serum IgE and increased prevalence of eosinophilia in 9-year-old children of smoking parents

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We studied the relationship of serum IgE levels and eosinophil counts with passive smoking in 9-year-old, nonselected children from three Italian towns near Rome. Male children of smoking parents had a significantly higher total count and percentage of eosinophils (p = 0.008) and higher IgE levels (p = 0.01) than male children of nonsmoking parents. Prevalence of eosinophilia (defined as ≥4% of total white blood cell count) was significantly correlated with the number of cigarettes smoked by parents among boys (p = 0.003) but not among girls (p = 0.20). There was a significant trend (p = 0.008) for prevalence of eosinophilia to increase with increasing levels of serum IgE. For any given level of serum IgE, the frequency of eosinophilia was higher among children of smoking parents than among children of nonsmoking parents. When parental smoking was studied in a multivariable analysis and after controlling for the other variable, it was still significantly associated with eosinophilia in the children of these smoking parents but not with serum IgE levels. We conclude that parental smoking is associated with a significant enhancement of the expression of the most important markers of allergic sensitization in the children of smoking parents. This is particularly evident for boys and may explain, at least in part, the increased frequency of respiratory symptoms in children of smoking parents. (J ALLERGY CLIN IMMUNOL 1990;86:400-7.)

Voluntary tobacco smoking has been found to be associated with an increase in serum IgE levels[1, 2] and in eosinophil counts[3] and percentages.[4] Very little is known, however, about the relationship between these parameters and involuntary tobacco smoke inhalation, particularly in children. The study of this relationship may be of particular relevance in our understanding of the role of environmental factors in the development of the atopic state.

Weiss et al.[5] first described a 2.2-fold increased risk of being atopic (as defined by the presence of at least one positive allergy skin test) in children of smoking mothers. Subsequently, our group of investigators[6] confirmed that parental smoking increased the prevalence of atopy in 9-year-old male children. We also described a "dose-response" relationship in these boys between the total numbers of cigarettes smoked by parents and a skin test index obtained by adding the diameters of the wheals elicited by the allergens.[6] Since we also found that bronchial responsiveness was significantly more frequent among male children of smoking parents, we hypothesized that parental smoking may increase the incidence of respiratory illnesses in childhood, at least in part, by increasing the risk and severity of atopic manifestations.

In this article, we extend those observations by studying the relationship between involuntary tobacco-smoke inhalation, eosinophilia, and total serum IgE levels, using data derived from the same sample of 9-year-old children.

SUBJECTS AND METHODS

The target population consisted of 179 9-year-old children, that is, all fourth-grade students in three Italian towns in the Viterbo province (Ronciglione, Caprarola, and Carbognano) near Rome. All subjects were of Italian ancestry.

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TABLE I. Distribution of blood leukocytes (white blood cells) and eosinophil counts, percentage of eosinophils, and total serum IgE levels, by sex

Sex (N)	Male (81)	Female (78)	*p*
WBC (10^3 × cells/cu mm)	7.18* (6.83-7.54)	7.83 (7.38-8.28)	0.03
Blood eosinophils (cells/cu mm)	160.1 (138.5-185.1)	118.0 (97.7-142.3)	0.001
Eosinophils (as % WBC)	2.3 (2.0-2.6)	1.6 (1.3-1.9)	0.001
Total serum IgE (IU/ml)	77.4 (56.2-106.5)	57.1 (41.7-78.1)	0.2

WBC, White blood cell.
*For WBCs, values are mean (95% confidence interval of the mean). For all other variables, values are geometric mean (95% confidence interval of geometric mean).

TABLE II. Blood leukocytes (white blood cells) and eosinophil counts, percentage of eosinophils, and serum total IgE levels by sex and by parental smoking habits

	Nonsmoking parents			One or more parent(s) smoke(s)		
Sex (N)	Male (21)	Female (23)	*p**	Male (60)	Female (55)	*p**
WBC (10^3 × cells/cu mm)	6.95† (6.17-7.73)	8.18 (7.16-9.19)	0.07	7.27 (6.86-7.67)	7.68 (7.19-8.17)	0.2
Blood eosinophils (cells/cu mm)	115.2 (87.1-152.3)	132.7 (104.7-168.2)	0.5	179.5‡ (152.8-210.8)	112.2 (87.6-143.6)	0.002
Eosinophils (as % WBC)	1.7 (1.3-2.2)	1.7 (1.3-2.1)	0.9	2.5‡ (2.2-3.0)	1.5 (1.2-1.9)	<0.001
Total serum IgE (IU/ml)	39.0 (20.9-72.9)	59.1 (33.7-103.7)	0.3	98.5‡ (69.0-140.1)	56.3 (38.4-82.5)	0.04

WBC, White blood cell.
*P for the differences between sexes within each parental smoking group.
†See legend for Table I.
‡$p \leq 0.01$ when compared to male infants of non-smoking parents.

There were no significant differences between towns in parental smoking habits or in markers of atopy in children, and male and female children were equally distributed in all three towns. Details of the methods of enrollment, questionnaire administration, and skin prick tests have already been published.[6]

Briefly, a standardized questionnaire on personal and family history of respiratory and allergic diseases was administered to one parent. Parents were also asked to classify themselves into groups according to the numbers of cigarettes each smoked at the time of questionnaire administration (0, 1 to 10, 11 to 20, 21 to 30, or 31 to 40 cigarettes per day). Data for each parent were used to classify households into similar groups. Four mothers and nine fathers reported they had smoked in the past but had stopped smoking during the child's life; since results for their children were not different from results for children whose parents had never smoked, these two groups were combined.

Questions on the total number of years of formal education for each parent (as an index of socioeconomic status) were also included.

Blood samples were obtained from 159 (95.8%) of the 166 children for whom informed consent was obtained from parents. Seven children refused to cooperate and are not included in the analyses. Leukocyte total and standard differential eosinophil counting of 10,000 leukocytes were performed with an H6000 Tecnicon (Technicon Instruments Corp., Tarrytown, N.Y.) at the Department of Hematology, University of Rome. This is the device used for clinical hematologic evaluation at that department, and accuracy controls are made on a daily basis. Eosinophilia was defined as a percentage of eosinophils ≥4, based on an upper limit of normal range for pediatric age of 3%, as defined by the most widely used textbook of pediatrics.[7] Levels of total serum IgE were determined by the PRIST assay with commercially available kits. Since blood eosinophil counts per

TABLE III. Prevalence of eosinophilia by parental smoking habits and by sex

	Male			Female			
	No.	% With eosinophilia*	OR†	N	% With eosinophilia	OR	OR adjusted by sex† (95% CI)
Nonsmoking parents	21	4.8	1	23	4.3	1	1
One parent smoking	42	19.0	4.7	37	13.5	3.4	4.9 (1.1-21.6)
Both parents smoke	18	44.4	16.0	18	16.7	4.4	8.8 (1.7-45.9)
p for χ^2 for trend		0.003			0.20		

OR, Odds ratio; *CI*, confidence interval.
*Eosinophilia was defined as a percentage of eosonophils ≥ 4%.
†Sex-stratified odds ratios and 95% confidence intervals were calculated from a linear regression applied to the three levels of parental smoking.[8]

cubic millimeter, percentage of eosinophils, and total serum IgE levels demonstrated a log-normal distribution, the natural logarithm of these variables was used in statistical calculations; IgE groups were also determined with a geometric scale.

Standard Student's unpaired t tests were used to compare means. Kendall's tau was used as a test of nonparametric correlation. Linear trends in proportions were tested according to the methods proposed by Rothman.[8] To obtain sex-adjusted odds ratios and their 95% confidence intervals, the odds of having eosinophilia for each level of parental smoking were treated with a least-square regression analysis for multiple levels of exposure.[8] Log-linear analysis[9] was used to study the relationship between eosinophilia in children and smoking by their parents while total serum IgE levels, sex, and a diagnosis of asthma were being controlled.

Statistical significance was defined as a two-tailed $p < 0.05$.

RESULTS

There was no relationship between number of years of formal education (elementary, high school, or college levels) in either parent and parental smoking, serum IgE, or eosinophilia in their children. Boys and girls were also equally distributed in the different parental education groups.

The sex distribution of leukocytes per cubic millimeter, eosinophils per cubic millimeter of blood and as a percentage of total white blood cells, and of serum IgE levels is presented in Table I. Male children had significantly higher levels of eosinophils but not of IgE compared to female children. Conversely, boys had significantly lower numbers of white blood cells than girls.

These same data are presented after stratifying by the presence of smokers among parents in Table II. Male children of smoking parents had a significant increase in eosinophils ($p = 0.008$) and higher IgE levels ($p = 0.01$) when they were compared to male children of nonsmoking parents. There was no significant difference in the numbers or percentages of eosinophils between female children of smoking parents and female children of nonsmoking parents. Likewise, no significant differences in total serum IgE or in eosinophil counts were found between sexes among children of nonsmoking parents.

Significances were unchanged when children who had ever had a diagnosis of asthma were excluded from the analyses.

The proportion of subjects with eosinophilia by number of smoking parents in the household and by sex and the corresponding odds ratios is presented in Table III. There was no difference in the prevalence of eosinophilia in households in which only the mother smoked compared to households in which only the father smoked; therefore, these two groups were combined. A trend for eosinophilia to increase with increasing number of smoking parents was present. Sex-adjusted odds of having eosinophilia were five times higher when one parent smoked, and almost nine times higher when both parents smoked, lower limits of the 95% confidence interval being above unity in both cases. When both sexes were studied separately, however, trends were statistically significant for boys ($p = 0.003$) but not for girls ($p = 0.20$).

Sex-stratified odds of having eosinophilia were also found to increase in an approximately linear way with the total numbers of cigarettes smoked by parents (Table IV, last column). Lower limits of the 95% confidence intervals were more than unity for all levels

TABLE IV. Prevalence of eosinophilia by number of cigarettes smoked by parents and by sex

	Male			Female			
	No.	% With eosinophilia*	OR	N	% With eosinophilia	OR	OR adjusted by sex† (95% CI)
Nonsmoking parents	21	4.8	1	23	4.3	1	1
1-10 cigarettes/day	13	15.4	3.6	9	22.2	6.3	2.5 (0.9-5.2)
11-20 cigarettes/day	21	23.8	6.3	17	5.9	1.4	4.5 (1.2-16.0)
21-30 cigarettes/day	12	33.3	10.0	16	18.8	5.1	6.7 (1.6-27.6)
>30 cigarettes/day	14	35.7	11.1	13	15.4	4.0	9.0 (2.0-39.5)
p of χ^2 for trend		0.01			0.27		

OR, Odds ratios; *CI*, confidence interval.
*Eosinophilia was defined as a percentage of eosionphils ≥ 4%.
†Sex-stratified odds ratios and 95% confidence intervals were calculated from a linear regression applied to the five levels of parental smoking.[8]

for more than 10 cigarettes per day. Again, when both sexes were studied separately, trends were statistically significant only for male children.

In boys, but not in girls, eosinophil counts were linearly correlated with the total number of cigarettes smoked by parents (Table V).

The relationship is illustrated in Fig. 1 between total serum IgE and frequency of eosinophilia by parental smoking habits. As expected, prevalence of eosinophilia increased linearly with increasing levels of IgE (chi-square for trend, 6.98; $p = 0.008$), but it was also higher in children whose parents smoked independent of IgE level ($p = 0.01$).

A log-linear analysis was performed to determine the independent effects of parental smoking on eosinophilia and serum IgE levels, while eosinophilia and serum IgE levels, sex, and diagnosis of asthma were being controlled. Serum IgE levels were introduced into the model in three groups (both parents nonsmokers, only one parent smoked, or both parents smoked). Parental smoking was still significantly associated with eosinophilia in children of smoking parents ($p = 0.003$) but not with serum IgE levels ($p = 0.20$). The interaction between sex, eosinophilia, and parental smoking did not reach statistical significance.

DISCUSSION

The most important findings reported in this study are (1) children whose parents smoke have increased levels of total serum IgE and increased absolute counts and percentages of eosinophils, compared with children of nonsmoking parents, and this effect is statistically significant only in male children, (2) a higher frequency of eosinophilia for any given level of serum IgE was observed in children of smoking parents, and (3) there was an approximately linear relationship between frequency of eosinophilia (or eosinophil counts) and total numbers of cigarettes smoked by parents (or number of smoking parents); this trend was, again, significant only in boys.

We found both paternal and maternal smoking to have similar effects on serum IgE levels, eosinophil counts, and percentages in the children of smoking parents. Most studies of effects of parental smoking on children's respiratory health have found maternal smoking to be a much more important factor.[10] As we have previously reported,[6] only a small minority of mothers and most fathers smoked in this population sample. Smoking mothers seldom (2.4%) consumed more than 20 cigarettes per day, compared to >21% of fathers. This, and differences in social habits and in structure and size of homes, may explain the significant role of paternal smoking described in this study.

There are no published studies of a relationship between eosinophil counts or percentages and involuntary tobacco smoke inhalation. Wagner et al.[11] described a significant increase in serum IgE levels in children of smoking parents. Osaka et al.[12] observed an increase of mite-specific IgE levels in Japanese children of smoking mothers, but no sex differences

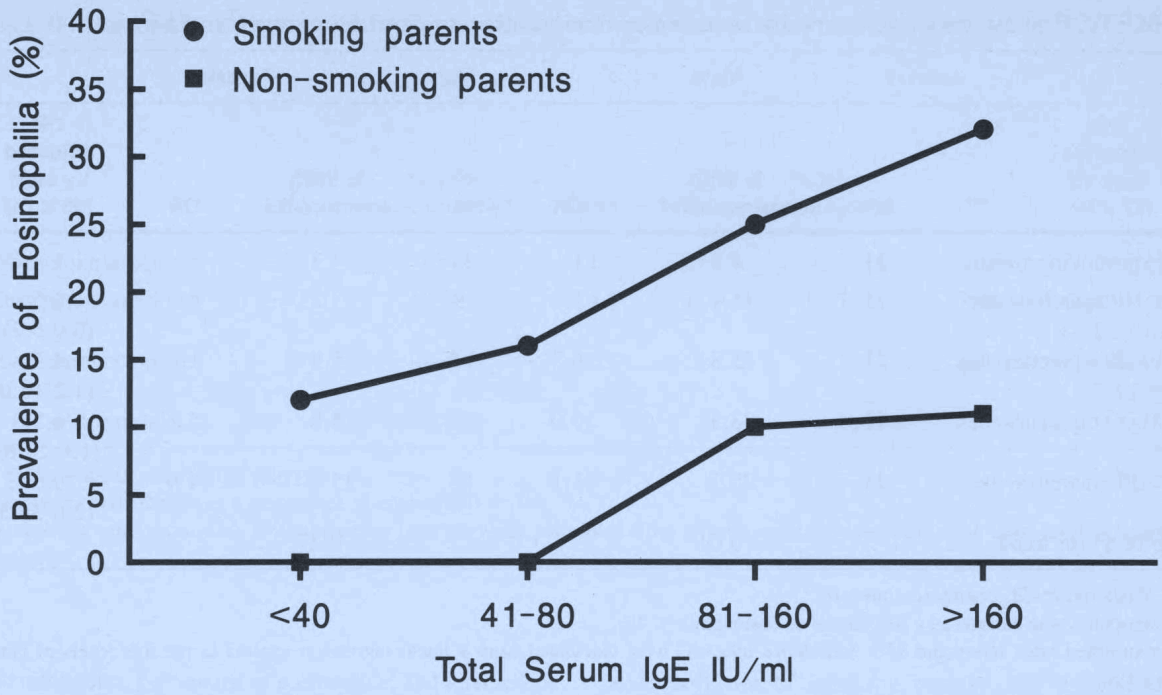

FIG. 1. Prevalence of eosinophilia (percent eosinophils ≥4) by total serum IgE levels in children of smoking parents and in children of nonsmoking parents. Prevalence of eosinophilia was significantly higher ($p = 0.01$) in children of smoking parents independently of serum IgE levels.

were reported. Conversely, Ownby and McCullough[13] found no significant increase in total or allergen-specific IgE in children aged 1 to 19 years exposed to their parents' cigarette smoke, compared to children of nonsmoking parents and of similar age. As these authors acknowledged, however, the age range of their sample covers a period of life during which total serum IgE levels first increase dramatically and, subsequently, start decreasing.[14] In these circumstances, it may be difficult to compare group means, even after controlling for the effect of age with standard, linear-regression methods. In addition, 62% of all subjects in the sample of Ownby and McCullough[13] had serologic signs of atopy, and thus, true controls were probably not adequately represented in their sample.

Several articles have dealt with the relationship of voluntary smoking with serum IgE levels and eosinophil counts in adults. Smokers have almost invariably been revealed to have higher total serum IgE levels,[1, 2, 15-18] higher eosinophil blood counts,[3, 19] and increased prevalence of eosinophilia.[4] Since smokers are known to be more likely to give up smoking if they are atopic,[19] self-selection may decrease the estimation of this effect in smoking adults. There was no evidence in our data of a significant clustering between active smoking and lower reported prevalence of allergic disorders in parents; 50% of atopic fathers (that is, fathers who said they had asthma or allergic rhinitis) were smokers compared to 63% of nonatopic fathers ($p = 0.9$), and 21.4% of atopic mothers were smokers compared to 36.5% of nonatopic mothers ($p = 0.4$). In addition, 9-year-old children have no control over their parent's smoking habits, and therefore, the most sensitive part of the population was probably not excluded by self-selection from our smoke-exposed subjects, as could be suspected to happen among voluntary, adult smokers.

There was a clear sex heterogeneity in the relationship of IgE and eosinophils with parental smoking habits: male children were more susceptible than female children. This confirms our previous observation in this same population[6] that the prick skin test index is significantly correlated with the number of cigarettes smoked by parents, but only in male children. A similar discrepancy between sexes in the effect of involuntary tobacco smoke inhalation on serum IgE levels in children was reported by Wagner et al.[11] Interestingly, active smoking in adults is associated with increased levels of serum IgE[14] and with higher eosinophil counts,[4] but only in male subjects. This finding suggests that the mechanism by which tobacco smoke increases serum IgE levels and eosinophil counts may be similar for voluntary and involuntary smoke inhalation.

Evidence in this same sense is provided by the finding that, as in the Tucson study,[20] boys in our study had higher mean eosinophil counts than girls

TABLE V. Eosinophil counts by number of cigarettes smoked by parents and by sex

	Male		Female	
	No.	Eosinophils/cu mm	No.	Eosinophils/cu mm
Both parents smokers	21	115.2* (87.1-152.3)	23	132.7 (104.7-168.2)
1-10 cigarettes/day	13	151.6 (113.2-203.0)	9	97.2 (48.2-196.0)
11-20 cigarettes/day	21	156.7 (116.6-210.7)	17	115.3 (78.1-170.4)
21-30 cigarettes/day	12	211.4 (146.6-304.9)	16	135.4 (91.3-200.7)
>30 cigarettes/day	14	225.2 (165.1-307.2)	13	95.6 (50.6-180.5)
Kendall's tau		0.25		0.08
p		0.003		0.31

*Values are geometric mean of number of eosinophils/cu mm of blood (95% confidence interval of geometric mean).

(Table I). This difference was not statistically significant when male and female children of nonsmoking parents were compared (Table II). No evidence from the Tucson study are available on the effect of passive smoking on eosinophil counts, but in adults from that same study, male-female differences in percentages of eosinophils were largely explained by the increase in eosinophils in smoking men.[4]

There is no explanation available for the differences in the effects of tobacco-smoke inhalation between sexes. For passive smoking in children, differences in life-style between boys and girls could be adduced as an explanation, but (if anything) it would be expected that boys would be more active and more prone to play outdoors than girls, and thus to be *less* affected (and not more affected, as we found) by their parents' smoke than girls. More detailed questionnaires on parental smoking habits (including questions on where and when cigarettes are smoked) may help elucidate this issue. However, the consistency of findings for passive and active smoking suggests the existence of differences in susceptibility to tobacco-smoke inhalation between sexes.

The causes of the increase in IgE levels and in eosinophils in voluntary or involuntary smokers are unknown. The specificity of the excess IgE has not been determined.[19] Lehrer et al.[21] detected IgE specific for tobacco antigens in a small group of subjects, but this was independent of smoking habits. We found that male children of smoking parents present an increased risk of having at least one positive skin test to any of several common aeroallergens, which did not include tobacco smoke extract.[6] The intensity of the reaction to these aeroallergens (as measured by the sum of the diameters of the skin prick test wheals elicited by these aeroallergens) was directly correlated with the number of cigarettes smoked by parents in these same male children. Therefore, cigarette smoke inhalation appears to influence indirectly the production of IgE specific for other antigens. This is also confirmed by the finding of increased mite-specific IgE in children of smoking parents.[12]

In adults, Zetterstrom et al.[16] demonstrated that smoking workers are at increased risk of having specific IgE and allergy skin reactivity to agents with which they are in direct contact, compared with non-smoking workers. They hypothesized that this specific sensitization was due to an increased mucosal permeability elicited by tobacco smoke.[16] Indeed, active smoking in adults has been found to be associated with a marked increase in mucosal clearance of aerosolized technetium-labeled ^{99m}diethylenetriamine-pentaacetic acid.[22] Lung clearance of ^{99m}diethylenetriamine-pentaacetic acid is a function of the permeability of the alveolar-capillary membrane.[23] Witten et al.[24] confirmed this increased clearance in rabbits exposed to cigarette smoke. Cigarette-smoke exposure may thus disrupt alveolar-capillary membrane function, and this may in turn facilitate sensitization to aeroallergens. We can only speculate that similar mechanisms of sensitization may be present in involuntary smoke inhalation.

Smoke-induced changes in the immune system, and particularly in T cell function, could also explain our findings. Studies differ widely, however, with respect to the effects of cigarette smoke on the cell-mediated immune responses with both decreases and increases in T-lymphocyte-mediated responses reported.[25-28] As explained earlier, self-selection of voluntary smokers may bias the results of these studies. Animal models

of immune responses to active[29] and passive smoking may yield new, useful information in this regard.

In children of smoking parents, both absolute number of eosinophils per cubic millimeter and prevalence of eosinophilia were increased independently of serum IgE levels; children of smoking parents had increased eosinophil counts and increased risk of having eosinophilia even when subjects of equal serum IgE levels were compared (Fig. 1). This is very similar to the findings of Halonen et al.[4] concerning the effects of voluntary smoking in adults. They postulated that the eosinophilic response to smoke inhalation may be more sensitive than the IgE response to smoke.[4] This appears to be confirmed by our data. The effect of passive smoking on IgE levels was no longer significant when a log-linear analysis was used to control for the effect of passive smoking on eosinophils, whereas the latter was still highly significant after controlling for the former.

Eosinophil counts have been associated with significant reductions in FEV_1[3] and with an increase in respiratory symptom rates, especially in subjects with positive skin tests.[21] Since passive smoking also enhances skin test reactivity,[5, 6] we hypothesize that the increased prevalence in chronic respiratory symptoms usually reported for children of smoking parents[10] may be mediated at least in part by an enhancement of these markers of the atopic state.

In addition, these data offer new evidence in favor of our hypothesis that sex differences in prevalence of asthma observed in schoolage children may be due, at least partially, to a greater immunologic susceptibility of male children to environmental noxious stimuli.[6]

It remains to be elucidated if the effects we have described are reversible and transient or if, conversely, they may play a role in the development of chronic airflow limitation in adult life. In any case, our findings support strongly the increasing medical and public concern with the health consequences of involuntary smoking.

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Risk of systemic reactions in patients taking beta-blocker drugs receiving allergen immunotherapy injections

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To learn whether patients taking beta-blocker (BB) drugs were at increased risk of having systemic reactions (SRs) from allergen immunotherapy, we prospectively studied 56,105 injection visits in 3178 patients during a 1-year interval. A total of 166 SRs occurred in 144 patients (4.5% of all patients) or 3.0 SRs occurred per 1000 injection visits. Sixty-eight patients were taking BB drugs throughout the year, and only one patient had an SR. By chance, 3.08 patients were expected to have had SRs. We conclude that BB drugs did not increase the frequency of SRs in the patients studied who were receiving immunotherapy ($p > 0.95$). Patients taking BB drugs may still be at increased risk, however, from more severe SRs or their SRs may be more refractory to therapy. (J Allergy Clin Immunol 1990;86:407-11.)

Recently, concern has been raised about the safety of allergen IT in patients taking BB drugs.[1] This concern can be separated into three components: (1) patients taking BB drugs may be at increased risk of having SRs from IT injections, (2) patients taking BB drugs may develop more severe symptoms during SR, and (3) patients taking BB drugs may not respond normally to medications used to treat SR.

Abbreviations used
BB: Beta blocker
SR: Systemic reaction
IT: Immunotherapy
AgE: Antigen E (*Amb a* I)

Several case reports and experimental evidence from animal studies leave little doubt that beta blockade will adversely affect the response to epinephrine, the first-line drug in the treatment of anaphylaxis.[2-5] Similarly, the few case reports available suggest that the symptoms of anaphylaxis may be more severe in patients taking BB drugs.[4, 5] The other critical issue, concerning the frequency of SR in patients taking BB drugs compared to patients not receiving these drugs, requires a systematic survey of a large number of patients receiving IT, as noted by Toogood.[1]

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