

Respiratory pathophysiologic responses

Relationship between serum IgE and airway responsiveness in adults with asthma

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Background: General population studies have shown a relationship between total serum IgE levels and airway responsiveness, but this association has not been documented in patients with asthma.

Objective: The study assesses the cross-sectional relationship between IgE levels and airway responsiveness in 208 subjects who had had emergency department treatment for asthma at least 2 years earlier.

Methods: All participants completed a standardized respiratory questionnaire and underwent spirometry, allergy skin testing, and a dose-response methacholine challenge test.

Results: After adjusting for age and gender, the percentage of patients with asthma and airway responsiveness (provocative concentration causing a 20% fall in forced expiratory volume in 1 second [PC_{20}] ≤ 8 mg/ml) increased from 52% in the lower quintile of IgE to 72% in the upper quintile ($p < 0.01$). After adjusting for age, gender, baseline percent predicted forced expiratory volume in 1 second, and smoking, the association between IgE (both in quintiles and continuous) and PC_{20} appeared consistent and statistically significant ($p < 0.01$). This association was stronger in patients who were not given inhaled steroid (odds ratio for twice the concentration of IgE, 1.42; 95% confidence interval, 1.09 and 1.84), than in patients treated with inhaled steroid (odds ratio, 1.10; 95% confidence interval, 0.82 and 1.50). Eosinophilia and skin reactivity were associated with PC_{20} although to a lesser extent.

Conclusion: These findings strengthen the role played by IgE in facilitating the development of bronchial responsiveness in patients with asthma. (*J ALLERGY CLIN IMMUNOL* 1995;95:699-706.)

Key words: Asthma, bronchial responsiveness, IgE, methacholine challenge test, skin reactivity

Experimental and clinical studies have provided evidence for the role played by allergy in the development of airway responsiveness. Allergen inhalation has been shown to increase inflammatory cells in bronchoalveolar lavage.¹ Human long-lasting bronchial reactivity was provoked by allergens,^{2,3} whereas the avoidance of allergens was

Abbreviations used

CI:	Confidence interval
FEV ₁ :	Forced expiratory volume in 1 second
OR:	Odds ratio
PC ₂₀ :	Provocative concentration causing a 20% fall in FEV ₁

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followed by a reduction of bronchial responsiveness.⁴ Allergic seasonal rhinitis has also been associated with periodic occurrence of bronchial hyperresponsiveness.⁵ Epidemiologic studies in the general population have reinforced these observations. In a 4-year follow-up study, skin reactivity in early childhood was found to be a predictor of late appearance of bronchial hyperresponsiveness.⁶

In several cross-sectional studies⁷⁻¹³ in which different age groups were investigated, both serum

levels of IgE⁷⁻⁹ and skin reactivity⁸⁻¹³ were related to bronchial responsiveness. However, in cross-sectional studies in which populations were selected according to the presence of asthma or atopy, a lack of association between serum IgE levels and airway responsiveness has been reported.¹⁴⁻¹⁷ Study design drawbacks related to the selection of subjects and the small sample size¹¹ have been suggested as explanations for these findings.

The purpose of this study was to assess the relationship between total serum IgE levels and bronchial responsiveness in subjects with former or current symptoms of asthma.

METHODS

Study design

A cross-sectional study was conducted in 1989. The study population consisted of subjects over 14 years of age, living in the city of Barcelona, who required treatment in an emergency department because of an episode of acute asthma exacerbation at least 2 years earlier. Patients were selected from the medical records of emergency department admissions for treatment of asthma at four large urban hospitals (covering most of the emergencies in Barcelona) according to a standardized respiratory emergency department monitoring system, as previously described,^{18,19} and were those who had been included in a case-control study on the characteristics and risks of soybean epidemic asthma.¹⁹

Two groups of subjects were studied: a random sample of patients with asthma admitted during soybean asthma epidemics occurring in Barcelona from 1981 to 1987 ($n = 169$) and a random sample of patients with asthma admitted during a 3-month period after the cessation of epidemics who had not visited the emergency department during asthma epidemics ($n = 147$).

The study protocol was approved by the ethical committees of the participating hospitals, and written informed consent was obtained from all patients. They were invited to come to a central office where a standardized American Thoracic Society respiratory questionnaire²⁰ was completed; forced spirometry, allergy skin testing, and methacholine bronchial challenge tests were also carried out. The two random samples of patients with asthma were reviewed in blinded fashion by two interviewers at the same center. The American Thoracic Society questionnaire was administered with some additional questions from the International Union Against Tuberculosis questionnaire²¹ concerning symptoms present in the last year. Current asthma was defined as a positive response to any of the following questions: "Have you awakened with a feeling of tightness in your chest at any time in the last 12 months?" "Have you been awakened by an attack of shortness of breath at any time in the last 12 months?" and "Have you had an attack of asthma in the last 12 months?"

These symptoms were selected for their validity in predicting bronchial reactivity.²²

Bronchial responsiveness

Subjects underwent spirometry (Sibel 2002 spirometer; Sibel, S.A., Barcelona, Spain), performing at least three acceptable (repeatable within 5% or 100 ml) maneuvers to measure forced expiratory volume in 1 second (FEV₁).²³ Bronchial responsiveness was measured by means of a methacholine inhalation challenge.²⁴ After subjects inhaled nebulized saline solution, five deep breaths of each methacholine dose were administered with a Hudson nebulizer (Hudson Respiratory Care, Inc., Temecula, Calif.) at 4-minute intervals as follows: 0.1, 0.5, 1, 2, 5, 10, and 25 mg/ml. The challenge was terminated when FEV₁ fell by more than 20% from baseline value or after the maximal concentration of methacholine was given. The challenge was not performed when FEV₁ after administration of saline solution was 20% lower than baseline. Subjects with a baseline FEV₁ lower than 40% of predicted value were excluded. The provocative concentration of methacholine causing a 20% fall in FEV₁ (PC₂₀) was calculated by interpolation on a logarithmic scale. To calculate relative risks, a binary definition of bronchial responsiveness was accepted (PC₂₀ ≤ 8 mg/ml).²⁵

Atopy

Total serum IgE levels were assessed by paper radioimmunosorbent test (Pharmacia Diagnosis AB, Barcelona, Spain), and values are expressed in international units per milliliter. Because IgE values are concentrations that typically exhibit skewed distribution, IgE was transformed to a logarithmic scale. To standardize log IgE by age and gender, a standard multiple linear regression of log IgE on age as a continuous variable and gender as a binary variable (0 = female, 1 = male) was fitted. Residuals of that regression were then used, to which overall mean of IgE (i.e., 4.83) was added to obtain a standardized IgE on a scale similar to that of the original values. Standardized values by age and gender were calculated with the following equation:

$$4.83 + [\log(\text{IgE}) - (4.6337 + (-0.0403 \text{ age} - 44.46) + (0.4831 \text{ male gender}))]$$

Cutaneous hypersensitivity to common local airborne allergens found in the geographic area of Barcelona was assessed by means of the standard prick technique with a battery of 16 allergens (C.B.F. Leti S.A., Barcelona, Spain)¹⁹ including house dust; *Dermatophagoides pteronyssinus*; *D. pharinae*; danders from cat, horse, cow, and dog; tree mix I (*Cupressus*, *Olea*, *Pinus*, *Salix*, and *Thuja* spp.); tree mix II (*Fagus*, *Platanus*, *Populus*, *Quercus*, and *Ulmus* spp.); grass mix (*Anthoxanthum*, *Cynodon*, *Agrostis*, *Dactylis*, *Lolium*, *Festuca*, *Holcus*, *Phleum*, *Poa*, and *Secale* spp.); weed mix (*Amaranthum* spp., *Artemisia* abs., *Plantago*, spp., and *Parietaria officinalis*); mold mix I

TABLE I. Age and gender distribution of 214 participants and 50 nonparticipants

Gender	Age group (yr)	Nonparticipants					
		Participants		FEV ₁ < 40% predicted		Refusal	
		No.	Percent	No.	Percent	No.	Percent
Male	15-34	30	33.3			4	19.0
	35-54	27	30.0	8	34.8	9	42.9
	>54	33	36.7	15	65.2	8	38.1
	All ages	90	—	23	—	21	—
Female	15-34	36	29.0	1	3.7	7	28.0
	35-54	47	37.9	7	25.9	8	32.0
	>54	41	33.1	19	70.4	10	40.0
	All ages	124	—	27	—	25	—

(*Alternaria*, *Aspergillus*, *Cladosporium*, *Mucor*, *Penicillium* spp.); mold mix II (*Fusarium*, *Phoma*, *Rhizopus*, and *Curvularia* spp.); mold mix III (*Candida* and *Trichoderma* spp.); cotton; and wool. Wheals of 3 mm in diameter and larger than histamine control were considered positive reactions. Eosinophilia was measured as a proportion of the total white blood cell count.

Analysis

The association between airway responsiveness measured as a binary outcome (i.e., whether PC₂₀ was 8 mg/ml or less) and total serum IgE was calculated by the odds ratio (OR) with standard methods of logistic regression.²⁶ Total serum IgE was assessed both as age- and gender-standardized log IgE, categorized into quintiles, and as a continuous variable. For the categorized variable, the antilogs of the regression coefficients represent the OR with respect to the reference categories; and for the continuous variable in the log scale, k raised to the power given by the regression coefficient corresponds to the OR of two groups of individuals, one with k times the IgE concentration of the other. Potential confounders were variables related to bronchial responsiveness that may also be correlated with IgE, such as basal FEV₁, smoking, and treatment. Of primary importance was the determination of variables that modify the association between IgE and bronchial reactivity. This was accomplished by testing the significance of interactions in the logistic regression model. For those variables that significantly modified the association between IgE and airway responsiveness, ORs according to the categories of the modifier effect are presented separately. The association of skin reactivity, peripheral blood eosinophilia, and bronchial responsiveness was analyzed with the same standard methods of logistic regression used for IgE.

RESULTS

Six of the 316 patients with asthma were excluded because they did not report symptoms of

asthma and were thus considered to be nonasthmatic individuals. Of the remaining 310 patients, 50 (15%) did not undergo methacholine challenge testing because of severe baseline airway obstruction (FEV₁ predicted <40%), and 46 (14%) refused to be tested or interrupted the test (Table I).

The study population consisted of 214 patients with asthma. The percentage of men among participants (90 of 214, 42%) and nonparticipants (44 of 96, 46%) was similar. As expected, nonparticipants with severe airway obstruction were older than either patients included in the study or subjects who refused to participate. The age distribution of the participants and those who refused to participate did not differ significantly ($p > 0.1$) for both men and women. The study of the association between serum IgE levels and bronchial responsiveness was limited to 208 subjects, because IgE data were not available for six patients.

Figs. 1 and 2 show the age and sex distribution of both PC₂₀ of 8 mg/ml or less and IgE. A total of 135 (63.1%) patients had a PC₂₀ value of 8 mg/ml or less. The prevalence of PC₂₀ value of 8 mg/ml or less increased slightly with age and was significantly ($p < 0.01$) higher in women (Fig. 1). Serum IgE levels showed a marked decreasing trend with age ($p < 0.01$). Men showed greater ($p < 0.01$) levels of IgE than women at all ages (Fig. 2).

The relationships between bronchial responsiveness and the selected confounder variables adjusted by age and gender are shown in Table II. A positive association was found with the use of inhaled steroid during the previous year and baseline FEV₁ less than 60% of predicted value, whereas a negative association with smoking was detected. No relationship was found with history of

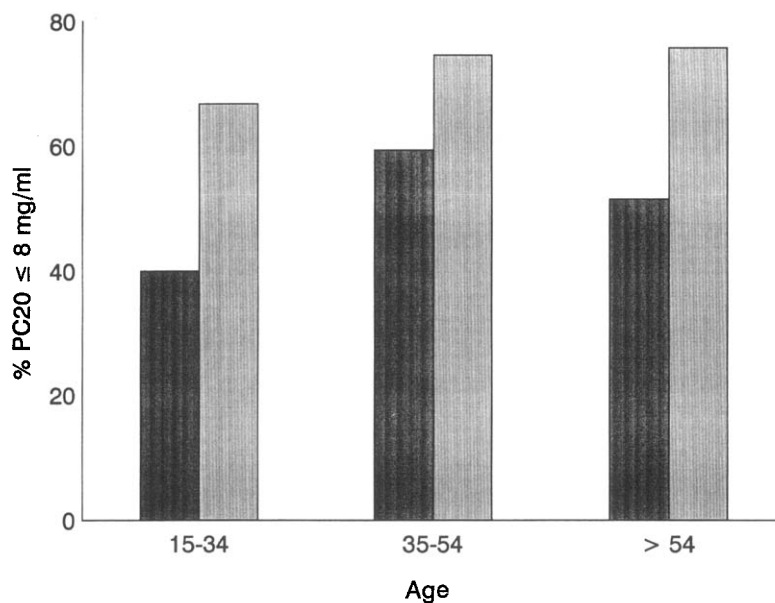


FIG. 1. Proportion of subjects with a PC₂₀ of 8 mg/ml or less by age groups and gender (male subjects: first column of each age group).

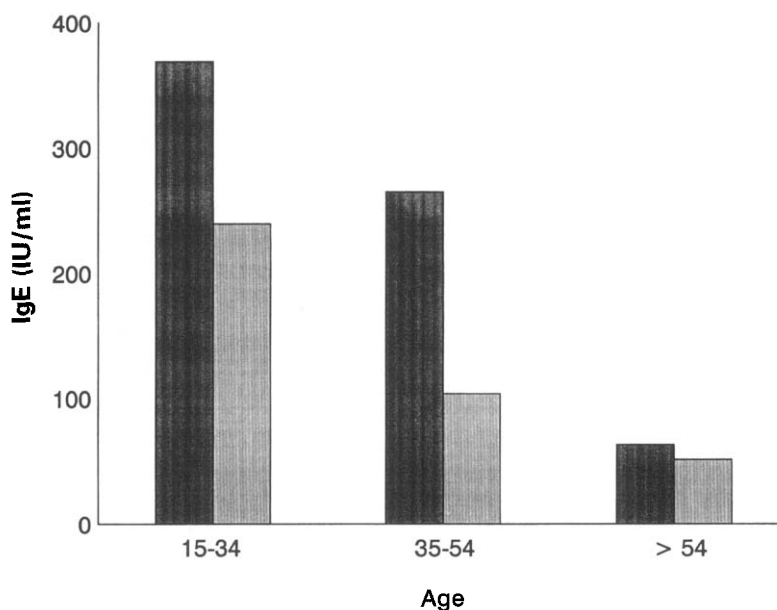


FIG. 2. Geometric mean of IgE according to age groups and gender (male subjects: first column of each age group).

current asthma ($p > 0.1$). The proportion of patients with a PC₂₀ value of 8 mg/ml or less was augmented with increasing quintiles of total serum IgE ($p < 0.01$) and was also elevated in those with positive skin reactivity or eosinophilia (Table II). Continuous IgE showed a positive linear relationship with bronchial responsiveness, whereas the

continuous number of skin reactions did not show such a relationship ($p > 0.1$). The association between PC₂₀ of 8 mg/ml or less and skin reactivity increased according to the number of positive test results up to three allergens. (Above this number, the association was invariable.) With regard to specific allergens, only *D. pteronyssinus* and cat

TABLE II. Airway responsiveness ($PC_{20} \leq 8$ mg/ml) according to symptoms, smoking, treatment, and variables measuring atopy

Variable	Airway responsiveness		OR†	95% CI
	No.*	Percent		
History of asthma‡				
Previous	64	60.9	1	
Current	150	64.0	1.13	0.60-2.10
FEV ₁ predicted				
>80%	98	50.5	1	
60%-80%	70	71.4	1.69	0.65-4.35
<60%	40	77.5	5.88	2.17-16.67
Smoking§				
Nonsmoker	118	72.0	1	
Former	54	53.7	0.64	0.31-1.33
Current	42	40.0	0.49	0.22-1.06
Inhaled steroids				
No	127	56.7	1	
Yes	87	72.4	1.89	1.02-3.53
Total IgE (IU/ml)				
<50	44	52.3	1	
50-99	35	62.9	1.77	0.69-4.59
100-199	51	60.8	1.52	0.65-3.54
200-349	38	71.1	2.95	1.11-7.89
≥350	40	72.5	2.42	0.96-6.08
Double concentration	—	—	1.18	1.00-1.41
No. of positive skin reactions				
0	48	56.3	1	
1-3	61	62.2	1.33	0.54-3.22
>3	99	67.7	2.04	1.03-4.01
Eosinophilia (%)				
<5	128	59.4	1	
≥5	68	75.0	2.14	1.09-4.22

*Total figures of the subgroups may not reach the total of 214 because of missing data.

†OR and 95% CI are adjusted by age and gender.

‡Symptoms during last 12 months.

§At least one cigarette per day, during 1 month.

dander (OR, 1.10; 95% CI, 1.00 and 1.29) showed a significant age- and gender-adjusted association with bronchial responsiveness as compared with patients with negative skin test responses to these two allergens.

After controlling for variables related to bronchial responsiveness (Table III), the relationship between IgE and bronchial responsiveness became more consistent and stronger with increasing quintiles of IgE, as well as with continuous IgE. In contrast, the adjusted relationships of skin reactivity and peripheral blood eosinophilia with bronchial responsiveness, developed in separate models, were attenuated and became insignificant ($p > 0.1$). The relationship between IgE and bronchial responsiveness was modified according to whether patients had received inhaled steroid treatment

during the previous year. Patients not treated with steroids showed a stronger adjusted association between IgE and bronchial responsiveness than patients treated with inhaled steroids. For the latter group, the relation was not significant ($p > 0.1$) (Table IV). In the group of patients not given inhaled steroid therapy, the adjusted relationship between IgE and PC_{20} of 8 mg/ml or less was slightly varied according to the history of current asthma. The relationship was stronger for patients with asthma symptoms during the last year (OR, 1.44) than for those without symptoms (OR, 1.17).

DISCUSSION

Total serum IgE levels were found to be related to PC_{20} in subjects with asthma. This finding coincides with results of studies in the general

TABLE III. Adjusted OR and 95% CI of airway responsiveness ($PC_{20} \leq 8$ mg/ml) for atopic variables assessed in separate models

Model*	OR	95% CI
Total serum IgE (IU/ml)		
<50	1	
50-99	1.72	0.64-4.62
100-199	2.18	0.80-5.90
200-349	3.17	1.13-8.93
≥ 350	3.42	1.23-9.55
Double concentration	1.27	1.06-1.51
No. of skin reactions		
0	1	
1-3	1.21	0.52-3.42
>3	1.77	0.86-3.63
Eosinophilia		
<5%	1	
$\geq 5\%$	1.90	0.90-3.98

*Adjusted by age, gender, percent predicted FEV₁, inhaled steroid, and smoking. When bronchial responsiveness was expressed as a continuous variable, each increase in 1 unit of log (IgE) reduced 0.23 mg/ml (± 0.11 mg/ml) the log (concentration) of methacholine required to produce a PC_{20} .

population but not with those based exclusively on patients with asthma. Some possible explanations for this positive finding that contrast with previous studies of patients with asthma¹⁵⁻¹⁷ are outlined below. First of all, the association between IgE and PC_{20} was stronger in subjects who were not receiving inhaled steroid than in patients given inhaled steroid. A different proportion of subjects receiving steroids could lead to different findings. Only one of the previous studies controlled for steroid treatment.¹⁷ Second, the correction of IgE by age and gender allowed us to control adequately for the decrease of IgE with age, whereas previous studies did not perform such a correction. This study also has greater statistical power in comparison with previous studies (208 vs 83 subjects in the study with the greater sample size).¹⁵ Moreover, our study population included a higher proportion of patients with current asthma symptoms than did a previous one.¹⁶ Finally, the exclusion of patients with asthma and severe airway obstruction may not explain the positive findings because this type of selection is common to all the studies.

Allergy is usually defined in terms of skin test positivity or increased levels of serum IgE.²⁶ Prevalence studies from the Tucson cohort²⁷ and the Normative Aging study cohort²⁸ have suggested that skin reactivity may be a less valid marker for

TABLE IV. Adjusted* OR and 95% CIs of airway responsiveness ($PC_{20} \leq 8$ mg/ml) for twice the concentration of total serum IgE according to inhaled steroid therapy

Inhaled steroids	OR	95% CI
No	1.42	1.09-1.84
Yes	1.10	0.81-1.50

*By age, gender, percent predicted FEV₁, and smoking.

atopy in patients with asthma than serum IgE levels or peripheral blood eosinophilia. We found an association between eosinophilia and bronchial responsiveness, although the relationship was shown less strong than that for IgE. Skin reactivity to common allergens was also related to bronchial responsiveness, although to a lesser extent.

Smoking has been found to be inversely related to bronchial responsiveness. This finding is not in agreement with general population-based studies in which smoking was generally reported to be associated with bronchial responsiveness, although this observation has not been confirmed in all studies.²⁹ The fact that we selected a population of patients with asthma may explain the negative relationship between smoking and bronchial responsiveness.

Serum IgE levels were both age- and gender-dependent. To standardize for age and gender, Burrows et al.²⁷ transformed log IgE values into Z scores. Z scores indicated the number of standard deviations by which each subject differed from the mean of his or her age-gender-specific group. In this study we used a different procedure to adjust IgE values by age and gender, that is, fitting a least-squares regression model and correcting IgE mean-centered values by the estimated age and gender coefficients. This method has been used in nutrition epidemiologic studies to adjust the concentration nutrient by calorie intake.³⁰ With this method, IgE values were expressed in international units per milliliter, and the correction was performed with age as a continuous variable instead of categories. We have presented the results with the latter method because it produces models with a better goodness of fit and narrower CI. However, whatever the method used, the conclusions seem to be similar. On the other hand, bronchial responsiveness may be assessed with different indexes. Although a standard measure of airway responsiveness was used, the analysis considering continuous PC_{20} was carried out and

similar findings were obtained. Each increase in 1 unit of log IgE reduced 0.23 mg/ml (SD = 0.11 mg/ml) the log concentration of methacholine required to produce PC₂₀.

We performed measurements of IgE levels and bronchial responsiveness 2 years after patients with asthma had been initially registered in the Barcelona respiratory emergency department admissions system,¹⁸ so that some patients have not experienced asthma symptoms for the past year. Subjects with former asthma symptoms showed a weaker association between IgE and bronchial reactivity than subjects with current symptoms, which may be because serum IgE could persist longer than bronchial responsiveness after remission.^{5,31} Therefore the inclusion of subjects with former asthma symptoms may have reduced the actual association between IgE and PC₂₀, which would be found if only subjects with current asthma symptoms had been included.

In this study, subjects were selected according to the diagnosis of asthma established during emergency department admissions. The validity of the diagnosis of asthma in emergency departments was evaluated, revealing that 94% of these subjects showed criteria compatible with asthma.³² In addition, we excluded from this analysis six subjects who reported that they had never had symptoms of asthma, although their inclusion did not substantially change the results.

Two groups of patients with asthma were selected according to their visits to emergency departments during soybean asthma epidemic days and after soybean epidemics has been controlled, 2 years before this study was carried out.³³

Subjects admitted during epidemics had, at the time of this study, higher levels of total IgE than subjects admitted during nonepidemic days (geometric age and sex adjusted means = 154 vs 103 IU/ml). However, the association between total serum IgE and bronchial responsiveness was positive in both groups and even higher in subjects selected during nonepidemic days (OR for twice the concentration of IgE, 1.39) than in those selected during the epidemics (OR, 1.22). This finding indicates that the possible bias of including patients affected by the epidemics, if any, would have to be in the direction of diluting the association between serum IgE levels and bronchial responsiveness.

Another selection bias may have resulted from patients who did not undergo methacholine challenge testing. These subjects were older than the participants, indicating that caution is necessary to

generalize our results for those patients older than 64 years of age. However, the relation between IgE and PC₂₀ was similar throughout the different age groups, suggesting that the exclusion of the older subjects probably did not influence the estimated association between IgE and PC₂₀. In addition, the relationship between IgE and bronchial responsiveness did not vary according to basal FEV₁ values.

In contrast to the evidence that inhaled steroid treatment slightly reduces airway responsiveness,³⁴ patients receiving inhaled steroid showed higher bronchial responsiveness than those not receiving inhaled steroid. It should be noted, however, that subjects given inhaled steroid were probably those who had more severe asthma. On the other hand, the antiinflammatory effect of steroids³⁵ might be the reason for a less strong association between IgE and bronchial hyperresponsiveness found in subjects treated with inhaled steroid as compared with those not given corticosteroid treatment.

Although the mechanisms of bronchial responsiveness are not well understood, our findings in patients with asthma confirm the role of IgE in the development of bronchial responsiveness.

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