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Clinical course of rhinitis and changes *in vivo* and *in vitro* of allergic parameters in old patients: a long-term follow-up study

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Commissione:

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If

"If you can keep your head
when all about you
Are losing theirs and
blaming it on you,
If you can trust yourself
when all men doubt you
but make allowance for
their doubting too,……...
If you can fill the
unforgiving minute
With sixty seconds¹ worth
of distance run
Yours is the Earth and
everything in it,
And, what is more, you¹ll
be a Man, my son!"

Rudyard Kipling

Il più sentito ringraziamento all'amico e mio "magister vitae" il Prof. Gabriele Di Lorenzo, che durante questi anni di formazione mi ha insegnato la nobile pratica dell'ars medica ed al Prof. Calogero Caruso Coordinatore del Dottorato.

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Similarity and differences in elderly patients with fixed airflow obstruction by asthma and by chronic obstructive pulmonary disease

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Summary
Background: Epidemiologic studies have demonstrated that elderly patients with fixed airflow obstruction can be affected by asthma or chronic obstructive pulmonary disease (COPD).
Methods: We studied 49 consecutive elderly outpatients, presenting fixed airflow obstruction, by clinical history (smoking), pulmonary function tests, blood gas analysis, and induced sputum.
Results: The age was not different in patients with COPD ($n = 28$) and asthma ($n = 21$) (70.2 ± 3.9 years vs. 69.6 ± 3.7 years), also the degree of fixed airflow obstruction was similar (FEV_1: $58.3 \pm 1.5\%$ vs. $59.0 \pm 1.4\%$ of predicted). Patients with asthma had significantly more eosinophils in peripheral blood ($0.43 \pm 0.05 \times 10^{-3}$ μL vs. $0.27 \pm 0.1 \times 10^{-3}$ μL, $P < 0.0001$), and in induced sputum (5.0% [(p25th and p75th) 5.0–6.0%] vs. 1.0% [(p25th and p75th) 0.01–1.0%]; $P < 0.0001$), as well as serum ECP (18.6 ± 4.9 ng/mL vs. 7.7 ± 4.7 ng/mL, $P < 0.0001$) and ECP in the induced sputum (31.6 ± 2.9 ng/mL vs. 5.6 ± 4.9 ng/mL, $P < 0.0001$). Finally, in induced sputum the eosinophils EG_2^+ were higher in patients with asthma than in patients with COPD (40.5 [(p25th and p75th) 39.3–44.3] MFI vs. 3.9 [(p25th and p75th) 0–11.4] MFI, $P < 0.0001$). They also had significantly higher

Abbreviations: COPD, chronic obstructive pulmonary disease; ROC, receiver operating characteristic; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; DLCO, diffusing capacity of carbon monoxide; PO_2 (mmHg), partial oxygen pressure; PCO_2 (mmHg), partial carbon oxide pressure; SaO_2 (%), saturation of oxygen; ECP, eosinophil cationic protein; EG_2, monoclonal antibody (mAb) anti-ECP

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diffusing capacity, and a greater reversibility to steroids, after 14-day course of therapy, whereas the reversibility to 400 μg of salbutamol was similar.
Conclusion: Despite similar fixed airflow obstruction, elderly patients with asthma have distinct characteristics compared with patients with COPD.

Introduction

Airway diseases are a significant problem for older subjects. They cause a large burden of illness in the community, and, in primary settings, they present particular problems for diagnosis and management. Despite this, much of what we already know and do for asthma in older subjects is based on studies conducted in young people with asthma.

Lung function is not routinely measured and airflow obstruction is largely underestimated, particularly in the elderly.[1–3] However, distinguishing between asthma and chronic obstructive pulmonary disease (COPD) is difficult and may be impossible in some older patients, specially in those with fixed airflow obstruction.[4,5] Many elderly patients are often diagnosed as having COPD, even if the differential diagnosis between asthma and COPD, in patients with fixed airflow obstruction, may be important as the responses to treatment are different, depending on whether fixed airflow obstruction is due to asthma or COPD.[6,7] Epidemiologic studies have demonstrated that up to 30% of patients with fixed airflow limitation have a history of asthma.[8]

The goals of treatment are similar in asthma and COPD: to reduce symptoms, maintain lung function and normal activity, prevent exacerbation, and minimize the adverse effects of treatment.[9,10] Asthma is usually treated with anti-inflammatory medications, and bronchodilators are used as needed.[9] COPD is usually treated with bronchodilators, which provide small symptomatic benefits, and inhaled corticosteroids, which can reduce exacerbations and improve quality of life.[10,11]

We planned this study to investigate if fixed airflow obstruction in elderly subjects, by asthma or by COPD, can be differentiated through clinical and functional characteristics or through the evaluation of the cells in induced sputum, or both.

Methods

Patients

From January 2000 to December 2004, we evaluated 80 patients, older than 64 years, who consecutively presented at *Dipartimento di Medicina Clinica e delle Patologie Emergenti* of the University of Palermo (Italy), with fixed airflow obstruction.

Fixed airflow obstruction was defined as post-bronchodilator (salbutamol) FEV_1/FVC less than 70%.[12]

None of the patients received regular anti-inflammatory treatment at the time of the sampling. Smoking status was checked during patient interview.[13]

We excluded patients who had an exacerbation requiring pharmacologic treatment in the 6 months before the study. The number and severity of exacerbations before the months preceding the study were not recorded.

Flow-volume curves were assessed at baseline and after 400 μg salbutamol by metered-dose inhaler, and diffusing capacity (diffusing capacity of carbon monoxide [DLCO]), and carbon monoxide transfer coefficient [KCO]) was measured. Equipment: Gould 2400 automated system (Bilthoven, Netherlands), and SensorMedics Vmax 229 V6200 Autobox Bodypletismograph with DLCO (Yorbalinda, CA, USA).

Atopic status was assessed by skin prick test (SPT) for pneumo-allergens in the Palermo area[14] (allergens used: Alk Abellò, Milan, Italy). The panel included the following extracts: pollens (grass [*Phleum pratense*], mugwort [*Artemisia vulgaris*], wall pellitory [*Parietaria judaica*], and trees [*Olea europea* and *Cupressus*]), house dust mites (*Dermatophagoides pteronyssinus* and *farinae*), molds (*Alternaria alternata* and *Aspergillus fumigatus*), animal danders (cat and dog), a negative (glycerinated saline), and a positive control (histamine, 10 mg/mL). A positive response was defined as any wheal with a diameter 3 mm greater than the negative control, 15 min after the application.[15]

Each patient also performed arterial blood gases analysis, eosinophils blood count, serum total IgE and ECP in serum and in induced sputum, according to the manufacturer's instructions. Equipment: pH/Blood Gas Analyzer, Instrumentation Laboratory 1306 (Lexington, MA, USA), Technicon-H1 blood cell counter (Bayer Leverkusen, Germany), and CAP™ SYSTEM (Phadia Diagnostics, Uppsala, Sweden).

In all patients were controlled the reversibility to corticosteroids (14-day course with oral prednisone, 50 mg/day).

Authorization of the study was not required according to our institutional policy and the ethical committees of our institution. However, written informed consent to the study was obtained from every patient, in compliance with our institutional policy.

All the measurements and clinical data collections were performed during the first visit.

Sputum induction and processing

After baseline FEV_1 and FVC measurements, salbutamol was given by inhalation (200 μg by metered-dose inhaler), and subjects then inhaled hypertonic (4.5%) saline nebulized solution for periods of progressively increasing length (1, 2, 4, 8, and 16 min). FEV_1 was measured 1 min after each inhalation. The hypertonic saline solution was administered with a MEFAR nebulizer (Markos, Monza, Italy). The collected sputum samples were examined within 2 h. Selected portions of the sputum sample originating from the lower respiratory tract were chosen through examination with an inverted

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microscope, were weighed, and then, processed using 1% dithiothreitol (Sigma Chemicals, Poole, UK). Total cell count and viability (Trypan blue exclusion method) were determined with a Burkers chamber hemocytometer. The cell suspension was placed in a Shandon cytocentrifuge (Shandon Southern Ltd., Runcorn, UK) and cytospin preparations were made at 450 rpm for 6 min. Cytospin slides were fixed with methanol, stained with May-Grunwald-Giemsa for an overall differential cell count of 500 nucleate nonsquamous cells, and examined, under oil immersion by light microscopy, at magnification of 400×, by an observer unaware of the clinical characteristics of the subjects. Only samples with a cell viability >50% and <20% squamous cell contamination were considered.[16]

EG_2^+ cells in induced sputum

A flow cytometric technique, based on fixation with formaldehyde and permeabilization with octyl-glucopyranoside of eosinophils from induced sputum, was used according to Hallden et al. with minor modifications, previous described.[17,18] The results were expressed as mean fluorescence intensity (MFI) ratio of positive cell populations.[17–19]

Statistical analysis

Data have been presented as mean±S.D. and as median and 25–75th percentile, and analyzed with Student's test for unpaired data, or with Mann–Whitney *U*-test, on the basis of the distribution of the data. For statistical analyses a value of $P<0.05$ was considered statistically significant.

Receiver operating characteristic (ROC) curve analysis was performed for all the functional/pathologic parameters that were thought to define the capability/power of each variable (predictive value) to recognize patients with a history of asthma within our study population. The area under the ROC curves was determined, and a value above 0.80 was considered a good discrimination.[20] ROC curve analysis also allowed (sensitivity vs. one minus specificity) selection of the best cut-off point of each variable for discriminating between the two groups.

Results

On the whole, the subjects were elderly, with fixed airflow obstruction. From the 80 patients recruited, we report the results obtained in the 49 patients who agreed to participate in the study. Each patient was characterized by medical history and physical examination. Of the 49 patients studied, 21 had a history of asthma and 28 had a history of COPD.

All asthma patients had a clear clinical history of recurrent wheezing or breathlessness episodes that reversed spontaneously or after treatment, and a familial history of asthma.[9] None of these patients was a smoker. All patients with COPD had a clear history of smoking, with more than 20 pack-years, chronic productive cough or sputum, no history of asthma, even in their familial, and no reported allergic diseases.[10]

In Table 1, we have been reported gender, age, duration of disease (years), smoking (pack-years), previous treatments, total serum IgE, and rate of SPT positivity. The patients with history of asthma differed from patients with history of COPD for smoking (no asthmatic was a smoker), previous treatments, total serum IgE (209 kU/L [162–331] vs. 36 kU/L [27.5–63.0], $P<0.0001$), and rate of SPT positivity (47.6 vs. 7.1, $P=0.001$).

In Table 2, we reported the pulmonary function and diffusing capacity. FEV_1, FVC, and FEV_1/FVC have been reported as value obtained and as percentage of theoretical value. These parameters did not differ between the 21 patients with asthma and the 28 patients with COPD. Patients with asthma had higher diffusing capacity (DLCO

Table 1 Demographic and clinical features of patients.

	Asthma group ($n=21$)	COPD group ($n=28$)	*P*-value
Gender (M/F)	10/11	16/12	0.5
Age (years)*	70.2±3.9	69.6±3.7	0.6
Duration of disease (years)*	11.9±3.7	11.7±4.3	0.9
Previous treatments			
Inhaled steroid (%)	71.4	60.7	0.4
β_2-short-acting (%)	100	100	
β_2-long-acting (%)	61.9	46.4	0.2
Oral steroids (%)	100	100	
Cromones (%)	52.0	3.5	<0.0001
Anticholinergic (%)	14.2	42.8	0.03
Mucolytic (%)	9.5	100.0	<0.0001
Antileukotrienes (%)	66.6	42.8	0.1
Ketotifen (%)	33.3	7.1	0.02
Serum total IgE (kU/L)†	209 (162–331)	36 (27.5–63)	<0.0001
Rate of skin prick test positivity (%)	47.6	7.1	0.001

*Data have been reported as mean±S.D.
†Data have been reported as median with lower quartile (25th) and higher quartile (75th) shown in parentheses.

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Table 2 Pulmonary function of patients.

Parameters	Asthma group ($n=21$)	COPD group ($n=28$)	P-value
DLCO (mL/min/mmHg)	23.2±1.5	15.7±1.5	<0.0001
KCO (mL/min/mmHg/L)	4.1±0.2	3.3±0.2	<0.0001
FEV_1 (L)	1.29±0.23	1.37±0.21	0.1
FEV_1 (%)	58.3±1.5	59.0±1.4	0.1
FVC (L)	2.13±0.37	2.23±0.35	0.2
FVC (%)	76.0±2.3	76.7±2.8	0.09
FEV_1/FVC (%)	60.5±2.1	61.3±4.1	0.9
FEV_1 after bronchodilator (400 μg of salbutamol) (L)	1.40±0.24	1.48±0.22	0.2
Increasing of FEV_1 (mL) after bronchodilator (400 μg of salbutamol)	106.4±16.5	112.5±16.8	0.09
Δ % of FEV_1 after bronchodilator (400 μg of salbutamol)	8.3±1.2	8.3±1.6	0.7
FEV_1 after steroid (50 mg of prednisone) (L)	1.47±0.05	1.51±0.04	0.4
Increasing of FEV_1 (mL) after steroid (50 mg of prednisone)	165.8±52.9.5	144.6±34.5	0.1
Δ % of FEV_1 after steroid (50 mg of prednisone)	13.1±5.0	10.7±3.0	0.04

Data have been reported as mean±S.D. Δ = change.

Table 3 The results of arterial blood gas analysis.

Parameters	Asthma	COPD	P-value
pH	7.43±0.02	7.43±0.01	0.7
PO_2 (mmHg)	86.9±1.2	85.5±2.0	0.006
PCo_2 (mmHg)	38.4±0.6	38.5±0.7	0.9
SaO_2 (%)	94.9±1.9	93.5±6.0	0.01

Data have been reported as mean±S.D.

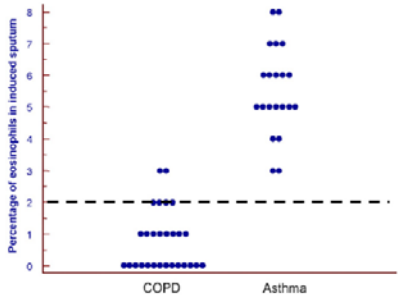

Figure 1 Percentage of eosinophils in induced sputum in patients with fixed airflow obstruction by COPD and asthma. The best cut-off points to discriminate between the two groups are >2.0% eosinophils in induced sputum.

and KCO). However, the patients with asthma differed from patients with COPD only for an increasing FEV_1 after steroids (14-day course), considered as Δ % of FEV_1 (13.1±5.0 vs. 10.7±3.0, $P=0.04$).

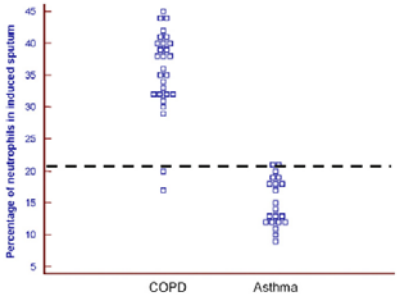

Figure 2 Percentage of neutrophils in induced sputum in patients with fixed airflow obstruction by COPD and asthma. The best cut-off points to discriminate between the two groups are ⩽21.0% neutrophils in induced sputum.

In Table 3, have been shown the results of ABG analysis. Both PO_2 (86.9±1.2 mmHg vs. 85.5±2.0 mmHg, $P=0.006$) and SaO_2 (94.9±1.9% vs. 93.5±6%, $P=0.01$) significantly differed in patients with COPD respect to patients with asthma.

ECP in the serum (18.6±4.9 ng/mL vs. 7.7±4.7 ng/mL, $P<0.0001$) and in the induced sputum (31.6±2.9 ng/mL vs. 5.6±4.9 ng/mL, $P<0.0001$) was higher in patients with asthma than in patients with COPD.

Also the number of eosinophils in the blood was higher in patients with asthma than in patients with COPD ($0.43\pm0.05\times10^{-3}$ μL vs. $0.27\pm0.1\times10^{-3}$ μL, $P<0.0001$). Compared with the patients with COPD, patients with asthma had more eosinophils (5.0% [(p25th and p75th) 5.0–6.0%] vs. 1.0% [(p25th and p75th) 0.01–1.0%]; $P<0.0001$), and fewer neutrophils in the induced sputum

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Table 4 Inflammatory cells in the induced sputum in patients with fixed airflow obstruction.

	Asthma group ($n = 21$)	COPD group ($n = 28$)	P-value
Macrophages (%)	33.0 (26.0–36.0)	34.0 (28.0–36.0)	0.8
Neutrophils (%)	9.0 (8.0–11.0)	36.0 (32.0–40.0)	<0.0001
Eosinophils (%)	5.0 (5.0–6.0)	1.0 (0–1.0)	<0.0001
Eosinophils EG_2^+ (MFI)	40.5 (39.3–44.3)	3.9 (0–11.4)	<0.0001

Data have been expressed as median with lower quartile (25th) and higher quartile (75th) shown in parentheses.

(9.0% [(p25th and p75th) 8.0–11.0] vs. 36.0% [(p25th and p75th) 32.0–40.0]; $P<0.0001$) (Figures 1 and 2). No difference was found between patients with asthma (33.0% [(p25th and p75th) 26.0–36.0]) and COPD (34.0% [(p25th and p75th) 28.0–36.0], $P = 0.8$) as regards to percentage of macrophages. Finally, in the induced sputum, the MFI of eosinophils EG_2^+ was higher in patients with asthma than in patients with COPD (40.5 [(p25th and p75th) 39.3–44.3] vs. 3.9 [(p25th and p75th) 0–11.4], $P<0.0001$) (Table 4).

ROC curve analysis

None of the functional pulmonary parameters were able to recognize patients with asthma among subjects with fixed airflow obstruction due to asthma or COPD. The values of the area under the ROC curves (0.53 for reversibility to bronchodilators, 0.55 for reversibility to steroids, 0.59 for KCO, 0.70 for SaO_2, and 0.71 for PO_2) were below 0.80, suggesting that these parameters are poor predictors of the diagnosis of asthma.

In contrast, the percentage of eosinophils in sputum was good predictors of asthma, whereas the percentage of neutrophils in sputum was good predictors of COPD. The area under the ROC curve was 0.99 (CI 95%, 0.92–1.00) for the percentage of eosinophils in sputum. For sputum eosinophils, the best cut-off point was 2.0% [(with a sensitivity of 1.00 (CI 95% 0.83–1.00) and a specificity of 0.92 (CI 95% 0.75–0.98)], indicating that values higher to 3.0% predicted asthma, whereas values lower than 2% predicted COPD, among subjects with fixed airflow obstruction. The area under the ROC curve was 0.99 (CI 95%, 0.89–0.99) for the percentage of neutrophils in sputum. For sputum neutrophils, the best cut-off point was $\leqslant$21% [(with a sensitivity of 1.00 (CI 95% 0.83–1.00) and a specificity of 92.9 (CI 95% 0.75–0.98)], indicating that values lower or equal to 21% predicted asthma, whereas value higher than 21% predicted COPD, among subjects with fixed airflow obstruction.

Discussion

In this study, we showed that, within a group of elderly patients with fixed airflow obstruction, those with asthma have distinct airway inflammation as compared with those with COPD and history of smoking-induced airway disease. This finding suggests that asthmatic airway inflammation does not change with the development of fixed airflow obstruction and thus does not become similar to the airway inflammation characteristic of COPD. Therefore, our results indicate that, even when fixed airflow obstruction is present, asthma should be diagnosed as asthma and not as COPD.

Previous studies have compared airway inflammation in asthma and COPD.[21,22] All those studies compared young patients with asthma, who had variable airflow obstruction, with older COPD patients, who had fixed airflow obstruction. Thus, they did not address whether the issue of the pathology of asthma changes with the development of fixed airflow obstruction and becomes similar to that characteristic of COPD. In another study, the authors compared 27 patients with late-onset asthma and 24 patients with COPD. The reported values for FEV_1(%), FVC(%), and FEV_1/FVC(%), in their patients with COPD (43.79 ± 20.08, 59.54 ± 18.21, and 56.08 ± 14.36, respectively), were lower that the values of our patients with COPD (59.0 ± 1.4, 76.7 ± 2.8, and 61.3 ± 4.1, respectively). Moreover, the characteristics of the asthmatic patients were different between the studies: their asthmatic patients were smoker, and the comparisons between patients with asthma and patients with COPD were statistical significant for FEV_1%, FVC%, and FEV_1/FVC(%). On the contrary, our asthmatic patients were never smoker and we found no differences between FEV_1(%), FVC(%), and FEV_1/FVC(%) between asthmatic patients and patients with COPD.[23]

Indeed, in this study, the patients examined were clearly identified as suffering from COPD, and the differential diagnosis with asthma has not been even previously considered.[24,25]

In this study, we investigated the characteristics of airway inflammation in elderly patients of similar age and similar degree of fixed airflow obstruction, but with a different clinical history, asthma or COPD.

The relationship between airway inflammation and airflow obstruction is poorly understood, both in asthma and in COPD. The increased number of eosinophils in asthma and neutrophils in COPD seems to be the major determinant of airflow obstruction, therefore it may be a marker of two different inflammatory cascades for two diseases, asthma and COPD, that result in the same functional abnormality, i.e. fixed airflow obstruction. One limitation of our study is that no patients have been submitted to bronchial biopsies. Our Ethic Committee did not consider ethical performing bronchial biopsies in elderly subjects with the diagnosis of asthma or COPD.

The differential diagnosis between fixed airflow obstruction due to asthma or COPD is important in clinical practice, because the response to treatment of the two diseases are different.[26] The results of our study show that measurement of lung volumes, responsiveness to steroids, and even

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diffusing capacity overlap considerably, making these tests of little use for distinguishing the two groups. Airway hyperresponsiveness to methacholine is with difficulty performing, considering the values of FEV_1 of these patients.[27] However, in previous study the airway hyperresponsiveness to methacholine was not significantly different between patients with asthma and with COPD, confirming that, once fixed airflow obstruction develops, measurement of airway responsiveness to methacholine is not useful for distinguishing asthma from COPD.[28]

Eosinophils in induced sputum are a well-established marker of airway inflammation in asthma, and also the most reliable objective measurement that helps to distinguish asthma from COPD once fixed airflow obstruction has developed.[28] Our results suggest that, in particular, the noninvasive measurements of eosinophils in induced sputum might be clinically useful in assessing the relative contributions of asthma.

Using the discriminating point of 2.0% sputum eosinophils, identified in our study, we found that only 6 of the 28 patients with COPD had sputum eosinophilia: 4 patients with 2% of eosinophils and 2 patients with 3%, respectively. These results confirm that eosinophilia in sputum may occur in only a minority of patients with COPD. Because these patients with COPD could be able to respond to steroids as asthma patients do, they should be properly identified and treated.[29,30] However, the eosinophils EG_2^+ and ECP in serum and sputum in patients with COPD were lower that in patients with asthma.

The diagnosis of asthma is more difficult in older patients and it could be responsible for a lower rate of asthma diagnosis in elderly subjects. Physicians may underdiagnose asthma, in older patients.[31,32] Therefore, it is a common misconception that adult-onset asthma is rare and that dyspnea is caused by aging.[23,31]

Considering the presented data, on the basis of a detailed clinical history, especially smoking habit, it should be possible to differentiate asthma from COPD. Whereas, it may not be possible to differentiate fixed airflow obstruction due to asthma or COPD, considering only pulmonary function examination, i.e. change of FEV_1 after 400 μg of salbutamol. In other words, common diagnostic tools are not helpful in elderly patients for discrimination between these two obstructive diseases. However, the results of our study demonstrate that, despite similar fixed airflow obstruction, subjects without history of smoking, i.e. with asthma, have distinct functional and pathologic characteristics compared with patients with a history of smoking, i.e. with COPD. These differences may explain the better response to steroids described in patients with fixed airflow obstruction due to asthma, compared with patients with fixed airflow obstruction due to COPD.[28]

Anyway, the principle limitation of our study is the small number of patients studied. Larger populations are needed to conclude more accurate interpretations. However, it is difficult to find elderly patients available to these kinds of investigations.

Finally, our study suggests that, in clinical practice, older patients with fixed airflow obstruction due to asthma should not be grouped under the general heading of COPD. Rather, they should be properly identified and treated. Our data shown that the atopy and the smoking predispose to chronic respiratory disease with a different effect on the prevalence of asthma and COPD, respectively.

Conflict of interest

The authors declare no competing interests.

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CHAPTER 3

Evaluation of serum s-IgE/total IgE ratio in predicting clinical response to allergen specific immunotherapy

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Evaluation of serum s-IgE/total IgE ratio in predicting clinical response to allergen-specific immunotherapy

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Background: To date, no predictive tests for the clinical response to allergen-specific immunotherapy (ASI) are available. Therefore an *in vivo* or *in vitro* test would be of great value.

Objective: We sought to evaluate pretreatment parameters used in diagnosing allergic rhinitis and determining serum specific IgE (s-IgE) levels, serum total IgE (t-IgE) levels, and blood eosinophil counts and to identify whether can be used to predict clinical improvement in monosensitized patients with allergic rhinitis with or without asthma treated with immunotherapy.

Methods: We analyzed 279 patients who had undergone 4 years of ASI administered either by means of the subcutaneous immunotherapy (76 patients) or sublingual immunotherapy (203 patients) routes. Serum t-IgE and s-IgE levels, blood eosinophil counts, and serum s-IgE/t-IgE ratios were calculated and tested for correlation with clinical response to ASI. Receiver operating characteristic curves were determined. Predicted probabilities and predictive areas under the curve were calculated.

Results: The clinical response to ASI was effective in 145 (52.0%) of 279 total patients, 42 (55.2%) of 76 patients treated with subcutaneous immunotherapy, and 103 (50.7%) of 203 patients treated with sublingual immunotherapy. A significant correlation was found between the serum s-IgE/t-IgE ratio and the clinical response to ASI, with high ratios (>16.2) associated with an effective response. The sensitivity and specificity of the area under the curve of the ratio were higher than those of serum s-IgE and t-IgE alone.

Conclusion: The calculation of the serum s-IgE/t-IgE ratio for predicting the clinical response to ASI offers an advantage over measuring t-IgE and s-IgE levels in monosensitized patients for the following allergens: grass, *Parietaria judaica*, *Olea europea*, and house dust mite. (J Allergy Clin Immunol 2009;123:1103-10.)

Key words: *Allergen-specific immunotherapy, total IgE, specific IgE, blood eosinophil counts, serum-specific IgE/serum total IgE ratio, receiver operating characteristic curve*

Allergen-specific immunotherapy (ASI) is the practice of administering gradually increasing doses of allergens (allergen extracts or vaccines) to reduce allergic symptoms and the need for medication resulting from exposure to a specific allergen.[1,2] Subcutaneous immunotherapy (SCIT) was introduced into clinical practice early in the 20th century.[3] In 1986, sublingual immunotherapy (SLIT) was introduced.[4,5] Double-blind placebo-controlled trials and meta-analyses confirm the efficacy, safety, and indications and contraindications of both SCIT and SLIT.[6-8] However, the efficacy of ASI is still debated, despite solid documentation. ASI, in practice, is indicated for patients for whom the causative role of the allergen is well documented. This is determined most commonly *in vivo* in skin tests (eg, skin prick testing) and *in vitro* in quantitative assays for serum specific IgE (s-IgE; eg, Unicap 100; Phadia, Uppsala, Sweden). It is unclear how serum total IgE (t-IgE) measurements, alone or in relation to s-IgE measurements, or blood eosinophil (b-eos) counts should be interpreted, as well as what role they should play in selecting patients for ASI in clinical practice. Furthermore, the significance of serum s-IgE levels might vary depending on the level of t-IgE.

In this study we report the clinical results of 279 patients who received 4 years of ASI in a clinical setting administered either by means of SCIT or SLIT. We retrospectively examined the relationship of the following parameters determined at the time of diagnosis: diameter of wheal induced by the allergen, serum t-IgE levels, serum s-IgE levels, b-eos counts, and clinical response to ASI. We used receiver operating characteristic (ROC) curves to determine the sensitivity, specificity, and predicted values for wheal diameter, serum s-IgE level, serum t-IgE level, serum s-IgE/t-IgE ratio, and b-eos count, all obtained at the time of diagnosis, in predicting one's response to ASI.

METHODS

Patients

We retrospectively analyzed monosensitized adult patients consecutively referred to the Outpatient Allergy Units of the Dipartimento di Medicina Clinica e delle Patologie Emergenti of the University of Palermo, Italy, and of the Dipartimento di Medicina Clinica e Medicina Sperimentale of the University of Verona, Italy, between January 1995 and December 2000 for evaluation of their allergic rhinitis with or without asthma symptoms. All patients underwent ASI as part of the therapy for allergic rhinitis. Patients did

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Abbreviations used
ASI: Allergen-specific immunotherapy
b-eos: Blood eosinophils
HDM: House dust mite
SCIT: Subcutaneous immunotherapy
s-IgE: Specific IgE
SLIT: Sublingual immunotherapy
SPT: Skin prick test
ROC: Receiver operating characteristic
t-IgE: Total IgE
VAS: Visual analog scale

not have other allergic diseases, such as atopic dermatitis, eczema, or nasal polyps.

A total of 279 subjects (120 male and 159 female subjects), with ages ranging between 18 and 56 years (mean age, 29.5 ± 8.1 years) were selected: 126 subjects from Palermo and 153 subjects from Verona, respectively.

All patients presented with a clinical diagnosis of allergic rhinitis with or without asthma based on patient-reported symptoms, physical examination, and a normal baseline lung function test (baseline $FEV_1 \geq 80\%$ of predictive value). All patients has positive skin test responses for 1 of 11 common airborne allergens, as determined by using the skin prick test method, with monosensitization to 1 of the following: grass, *Parietaria judaica*, *Olea europea*, or house dust mite (HDM). All were treated with ASI for at least 4 years administered either as SCIT or SLIT. At the time of diagnosis, blood was collected for analysis of serum t-IgE levels, s-IgE levels, and b-eos counts. Family history of atopy, as well as history of smoking and onset of respiratory symptoms, was obtained from each patient. Clinical evaluations were done at baseline and once a year for the 4-year period of ASI. Evaluations included rhinoscopy and spirometry (if asthmatic), symptom scoring with the visual analog scale (VAS), and medication use, referring to the previous year. Evaluations were conducted at the end of the season for the 3 outdoor allergens and at the end of February for *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*. More precisely, we performed a clinical evaluation and administered the VAS for symptoms in June for patients allergic to grass and *O europea* and in September for patients allergic to *P judaica*. For patients allergic to *D pteronyssinus* and *D farinae*, we performed a clinical evaluation and administered the VAS (in February) because the symptoms were worse in autumn, after vacations, and during winter (for more information, see the Methods section in this article's Online Repository at www.jacionline.org).

Because ASI is commercially available and was prescribed for indications that are recognized both nationally and internationally, our ethics committees required written informed consent for the diagnostic tests only, and this was obtained from each patient.[8-10]

Immunotherapy intervention

The route of administration of ASI (SCIT or SLIT) was chosen by the patient to ensure compliance. Each patient received the maximum tolerated dose, per the manufacturers' recommendations, for both SCIT and SLIT. All the patients in this study tolerated the maximum dose indicated by the manufacturers' recommendations as follows. For SCIT, the maintenance dose was 0.8 mL, which corresponds to 1.6 μg of the major allergen of grass, 0.4 μg of the major allergen of *P judaica*, 9.6 μg of the major allergen of *O europea*, and 3.84 μg of the major allergens of *D pteronyssinus* and *D farinae*. On the other hand, for SLIT, the maintenance dose was 60 drops (1 drop = 25 μL) administered 3 times a week on alternate days, which corresponds to 28.2 μg of the major allergen of grass, 6.6 μg of the major allergen of *P judaica*, 169.2 μg of the major allergen of *O europea*, and 67 μg of the major allergens of *D pteronyssinus* and *D farinae*. These doses were administered monthly. Immunotherapy with grass, *P judaica*, and *O europea* pollen was not interrupted during the spring, but the dose was halved (see the Methods section in this article's Online Repository).

TABLE I. Characteristics of cohort study patients examined in the 2 centers

No. of patients	279
Age (y)*	29.5 (28.6-30.5)
Male/female sex	120/159
SCIT/SLIT	76/203
Atopic family history (yes/no)	116/163
Passive smoking (yes/no)	123/156
Rhinitis/rhinitis plus asthma	152/127
Onset of symptoms (y)*	7.1 (6.4-7.7)
Pollens/HDM sensitization (no)	106/173
Response to ASI (effective/ineffective)	145/134
SPT to allergen (mm)†	5.4 (5.3-5.5)
Serum t-IgE level (kU/L)†	139.3 (121.4-159.9)
Serum s-IgE level (kAU/L)†	20.2 (17.6-23.0)
b-eos Counts (cells × 10^{-3} μL)†	0.35 (0.34-0.37)
Serum s-IgE/t-IgE* ratio	14.4 (12.3-16.9)

*Mean (95% CI).
†Geometric mean after logarithmic transformation (95% CI).

Assessment of symptoms and medication use

The effectiveness of ASI was evaluated on the basis of clinical response (reduction in nasal and pulmonary symptoms) and reduction of the pharmacotherapy taken on an as-needed basis (eg, oral second-generation H_1-antihistamine for rhinitis and inhaled short-acting β_2-agonist for asthma symptoms).[10,11] Patients were not previously treated with nasal or inhaled corticosteroids.

VAS. To evaluate symptom response to ASI and reduction of pharmacotherapy, we used a VAS sufficiently sensitive to detect changes in symptom severity (see the Methods section in this article's Online Repository).[12,13]

The response to ASI was determined clinically by asking the patient the following: "Do you feel better than you did before therapy?" The answer could be one of the following:

1. I have not noticed any improvement since I have used ASI.
2. I noticed a worsening of symptoms since I have used ASI.
3. I noticed that my symptoms improved since I have used ASI.

When we analyzed the 1624 ASI VAS responses throughout the 4-year study, we noticed that patients who stated improvement of symptoms during immunotherapy indicated a reduction in their rhinitis (or asthma) VAS values of at least 30% compared with their baseline VAS values before starting immunotherapy at the time of diagnosis. To be sure of the results, for each subject, we used all the ASI values obtained for each year, calculated the mean, and then subtracted the baseline VAS (VASb) from the mean of the VAS obtained over 4 years. Then we divided the result by the baseline VAS value and multiplied by 100, as shown by the following formula:

$$VAS\ decrease\ (\%) = \frac{(Mean\ VAS - VASb)}{VASb} \times 100$$

We evaluated the ASI as effective if the mean of the VAS scores for the 4 years showed a 30% decrease with respect to the value of the VAS score before ASI by using the formula reported above and if the values of the rescue medications indicated at the third and fourth years of ASI were 0 or 1. In all other cases, ASI was evaluated as ineffective. Symptom scoring and the medication used were reviewed by a physician (PM for Palermo and NM for Verona).

Spirometry. FEV_1 and forced expiratory vital capacity were measured with a Gould 2400 automated system (Sensormedics BV, Bilthoven, Netherlands) by using the highest of 3 successive measurements, provided that the difference between measurements was within 100 mL. Spirometric results were followed each year for 4 years. There was no significant change in FEV_1 or forced expiratory vital capacity (all >80% of predicted value) in any patient, irrespective of whether the patient responded clinically to ASI.

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TABLE II. Characteristics of the cohort study patients in respect to effective or ineffective clinical response to ASI

	All patients (n = 279)			Patients treated with SCIT (n = 76)			Patients treated with SLIT (n = 203)		
	Effective clinical response	Ineffective clinical response	*P* value	Effective clinical response	Ineffective clinical response	*P* value	Effective clinical response	Ineffective clinical response	*P* value
Patients, no. (%)	145 (52.0)	134 (48.0)		42 (55.2)	34 (44.8)		103 (50.7)	100 (49.3)	
Age (y)*	30.3 (28.9-31.7)	28.7 (27.4-30.1)	.1	29.8 (26.9-32.7)	29.6 (26.7-32.5)	.9	30.5 (28.9-32.0)	28.5 (26.9-30.0)	.06
Male/Female sex	52/93	68/66	.01	11/31	19/15	.01	41/62	49/51	.2
Male (%)	35.8	50.7		26.2	55.9		39.8	49.0	
Female (%)	64.1	49.2		73.8	44.1		60.2	51.0	
SCIT/SLIT	42/103	34/100	.5	NA	NA	NA	NA	NA	NA
SCIT group (%)	28.9	25.3							
SLIT group (%)	70.1	74.7							
Atopic family history (yes/no)	64/81	52/82	.4	36/6	22/12	.06	28/75	30/70	.7
Positive family history (%) group	44.1	38.8		85.7	64.7		27.2	30.0	
Negative family history group (%)	55.9	61.2		14.3	35.3		72.8	70.0	
Passive smoking (yes/no)	65/80	58/76	.8	16/26	14/20	.9	49/54	44/56	.7
Positive smoking group (%)	44.8	43.3		38.1	41.2		47.6	44.0	
Negative smoking group (%)	55.2	56.7		61.9	58.8		52.4	56.0	
Rhinitis/rhinitis plus asthma	72/73	80/54	.1	22/20	20/14	.7	50/53	60/40	.1
Rhinitis group (%)	49.7	59.7		52.4	58.8		48.5	60.0	
Rhinitis-asthma group (%)	50.3	40.3		47.6	41.2		51.5	40.0	
Onset of symptoms (y)*	6.6 (5.8-7.5)	7.5 (6.5-8.4)	.2	7.1 (5.4-8.7)	8.9 (6.6-11.2)	.1	6.5 (5.5-7.5)	7.0 (5.9-8.0)	.4
Pollens/HDM sensitization	97/48	76/58	.1	24/18	15/19	.3	73/30	61/39	.1
Pollens group (%)	66.9	56.7		57.1	44.1		70.9	61.0	
Grass, no. (%)	4 (2.7)	12 (8.9)		1 (2.4)	2 (5.9)		3 (2.9)	10 (10.0)	
P judaica, no. (%)	90 (62.1)	45 (33.6)		23 (54.7)	11 (32.3)		67 (65.1)	34 (34.0)	
O europea, no. (%)	3 (2.1)	19 (14.2)		0 (0)	2 (5.9)		3 (2.9)	17 (17.0)	
HDM, no. (%)	48 (33.1)	58 (43.3)		18 (42.9)	19 (55.9)		30 (29.1)	39 (39.0)	
SPT response to allergen (mm)†	5.4 (5.2-5.6)	5.4 (5.2-5.7)	.9	5.4 (5.1-5.8)	5.3 (4.9-5.7)	.9	5.5 (5.3-5.7)	5.4 (5.2-5.6)	.9
Serum t-IgE level (kU/L)†	84.2 (72.7-97.7)	240.2 (196.2-294.2)	<.0001	105.2 (80.8-137.1)	266.7 (177.4-401.0)	.0007	76.9 (64.3-91.9)	231.8 (182.9-293.9)	<.0001
Serum s-IgE level (kAU/L)†	30.5 (26.1-35.7)	12.9 (10.6-15.6)	<.0001	38.5 (28.6-51.9)	19.3 (12.7-29.2)	.01	27.7 (23.1-33.3)	11.2 (9.1-13.9)	<.0001
b-eos Counts (cells $\times 10^{-3}$ μL)†	0.31 (0.29-0.32)	0.46 (0.42-0.49)	<.0001	0.30 (0.27-0.34)	0.46 (0.39-0.53)	.0006	0.31 (0.29-0.34)	0.45 (0.42-0.49)	<.0001
Serum s-IgE/t-IgE* ratio	36.2 (33.3-39.5)	5.4 (4.4-6.6)	<.0001	36.6 (29.6-45.2)	7.2 (5.6-9.4)	<.0001	36.1 (33.1-39.3)	4.8 (3.7-6.2)	<.0001
Patient no. (%) with s-IgE/t-IgE ratio >16.2%	141 (97.2)	17 (12.7)	<.0001	41 (97.6)	2 (5.9)	<.0001	100 (97.1)	15 (15.0)	<.0001
Patient no. (%) with s-IgE/t-IgE ratio ≤16.2%	4 (2.8)	117 (87.3)		1 (2.4)	32 (94.1)		3 (2.9)	85 (85.6)	

NA, Not applicable.
*Mean (95% CI).
†Geometric mean after logarithmic transformation (95% CI).

Skin prick tests. Skin prick tests with a standard aeroallergen panel (Alk-Abelló, Milan, Italy) were performed and evaluated on the volar aspect of the forearm after withholding antihistamines for at least 5 days. The panel included the following extracts: pollens (grass *[Phleum pratense]*, mugwort *[Artemisia vulgaris]*, pellitory of the wall or sticky weed *[P judaica]*, and trees [*O europea* and *Cupressus species*]), HDM (*D pteronyssinus* and *D farinae*), molds (*Alternaria alternata* and *Aspergillus fumigatus*), and animal dander (cat and dog), as well as a negative control (glycerinated saline) and a positive control (histamine, 10 mg/mL). A positive response was defined as any wheal with a diameter 3 mm larger than that elicited by the negative control 15 minutes after application.[14] The wheal diameters were reported for each patient.

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TABLE III. Characteristics of patients with effective and ineffective responses to ASI in respect to symptoms

	Patients with rhinitis (n = 152)			Patients with rhinitis plus asthma (n = 127)		
	Effective clinical response	Ineffective clinical response	*P* value	Effective clinical response	Ineffective clinical response	*P* value
Patients, no. (%)	72 (47.4)	80 (52.6)		73 (57.5)	54 (42.5)	
Age (y)*	29.3 (27.5-31.2)	28.3 (26.6-30.0)	.4	31.3 (29.2-33.3)	29.4 (27.2-31.6)	.2
Male/female sex	25/47	41/39	.04	27/46	27/27	.1
Male (%)	34.7	51.2		37.0	50.0	
Female (%)	65.3	48.8		63.0	50.0	
SCIT/SLIT	22/50	20/60	.4	20/53	14/40	.9
SCIT group (%)	30.6	25.0		27.4	26.0	
SLIT group (%)	69.4	75.0		72.6	74.0	
Atopic family history (yes/no)	36/36	34/46	.4	28/45	18/36	.5
Positive family history group (%)	50.0	42.5		38.4	33.3	
Negative family history group (%)	40.0	57.5		61.6	66.7	
Passive smoking (yes/no)	30/42	33/47	.9	35/38	25/29	.8
Positive smoking group (%)	41.7	41.2		48.0	46.3	
Negative smoking group (%)	58.3	58.8		52.0	53.7	
Onset of symptoms (y)†	5.1 (4.2-6.0)	7.2 (5.9-8.5)	.01	8.1 (6.8-9.5)	7.9 (6.4-9.4)	.5
Pollens/HDM sensitization	45/27	46/34	.6	52/21	30/24	.1
Pollens group (%)	62.5	57.5		71.2	55.6	
HDM group (%)	37.5	42.5		28.8	44.4	
Grass, no. (%)	1 (1.4)	8 (10)		3 (4.1)	4 (7.4)	
P judaica, no. (%)	43 (59.7)	24 (30)		47 (64.4)	21 (38.9)	
O europea, no. (%)	1 (1.4)	14 (17)		2 (2.7)	5 (9.3)	
HDM, no. (%)	27 (37.5)	34 (43)		21 (28.8)	24 (44.4)	
SPT response to allergen (mm)†	5.3 (5.0-5.6)	5.3 (5.1-5.6)	.7	5.4 (5.1-5.6)	5.3 (5.0-5.6)	.8
Serum t-IgE level (kU/L)†	84.2 (68.7-103.2)	206.4 (161.5-263.8)	<.0001	84.2 (67.6-104.9)	300.8 (212.3-428.2)	<.0001
Serum s-IgE level (kAU/L)†	30.1 (24.6-37.5)	10.0 (7.9-12.7)	<.0001	30.9 (24.6-38.7)	18.6 (13.6-25.3)	.01
b-eos Counts (cells $\times 10^{-3}$ μL)†	0.31 (0.29-0.33)	0.40 (0.37-0.42)	<.0001	0.30 (0.28-0.33)	0.43 (0.40-0.47)	<.0001
Serum s-IgE/t-IgE* ratio	41.5 (36.9-48.1)	9.9 (7.6-12.2)	<.0001	39.8 (35.1-44.5)	8.1 (8.5-9.7)	<.0001
Patient no. (%) with s-IgE/t-IgE ratio >16.2%	70 (97.2)	10 (12.5)	<.0001	71 (97.3)	7 (13.0)	<.0001
Patient no. (%) with s-IgE/t-IgE ratio ≤16.2%	2 (2.8)	70 (87.5)		2 (2.7)	47 (87.0)	

*Mean (95% CI).
†Geometric mean after logarithmic transformation (95% CI).

Serum t-IgE and s-IgE levels

A blood sample was processed at the time of diagnosis and before ASI. Serum t-IgE and s-IgE levels were determined by using the Unicap 100 with the fluoroimmunoassay technique (Phadia, Uppsala, Sweden), according to the manufacturer's instructions. Results for both serum t-IgE and s-IgE measurements were expressed in kilounits per liter and equilibrated against the World Health Organization standard for IgE: 1 kU for t-IgE and 1 kAU for s-IgE was equal to 2.4 ng/mL, respectively. Serum t-IgE levels were determined with a detection limit of 2 kU/L and an upper limit of 5000 kU/L. Serum s-IgE levels were determined with a detection limit of 0.35 kAU/L and an upper limit of 100 kAU/L. In all patients the s-IgE level was measured for the same allergens used in the skin prick tests (11 allergens).[15,16] All patients were monosensitized (had a positive skin prick test response for only 1 allergen and presented with s-IgE for the same allergen). For the calculation of the ratio, we used the following formula:

$$s\text{-}IgE/t\text{-}IgE\ ratio = \frac{s\text{-}IgE}{t\text{-}IgE} \times 100$$

Peripheral b-eos counts. Absolute peripheral b-eos counts were determined before ASI with a Technicon-H1 blood cell counter (Bayer, Leverkusen, Germany), with the normal range being 0.10 to 0.40 cells/10^{-3} μL.[17]

Statistical analysis

Statistical analysis was performed with the SYSTAT 10 software package (Systat Software, Inc, San Jose, Calif). Data were reported as the arithmetic mean and 95% CI for the mean when the distribution of the data was normal. When normality was rejected, data were examined after logarithmic transformation and presented as the geometric mean and the 95% CI for the geometric mean. We used the Kolmogorov-Smirnov test to evaluate the normal distribution. Group comparison tests were performed with the 2-sided *t* test. Categorical variables between groups were compared by using the χ^2 test. An effective or ineffective response to ASI was assessed by examining the area under the ROC curves (c-statistic). Models with an ROC area of at least 0.80

TABLE IV. Multivariate regression using the response to ASI as variable-dependent

Independent variables	*r*	*P* value
Age (y)	0.095	NS
Male/female sex	−0.150	NS
SCIT/SLIT	0.040	NS
Atopic family history	0.054	NS
Rhinitis/rhinitis plus asthma	0.101	NS
Onset of symptoms (y)	−0.075	.007
Pollens/HDM sensitization	0.105	NS
Serum s-IgE/t-IgE ratio	0.723	<.0001
Serum t-IgE level	−0.342	NS
Serum s-IgE level	0.316	.007
b-eos Counts	−0.429	<.0001
SPT response to allergens (mm)	0.009	NS

NS, not significant.

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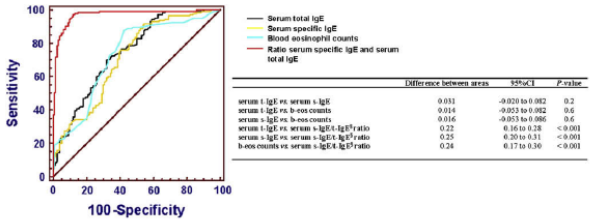

	Difference between areas	95%CI	P-value
serum t-IgE vs. serum s-IgE	0.031	-0.020 to 0.082	0.2
serum t-IgE vs. b-eos counts	0.014	-0.033 to 0.062	0.6
serum s-IgE vs. b-eos counts	0.016	-0.053 to 0.086	0.6
serum t-IgE vs. serum s-IgE/t-IgE^{2} ratio	0.22	0.16 to 0.28	< 0.001
serum s-IgE vs. serum s-IgE/t-IgE^{2} ratio	0.25	0.20 to 0.31	< 0.001
b-eos counts vs. serum s-IgE/t-IgE^{2} ratio	0.24	0.17 to 0.30	< 0.001

FIG 1. ROC curves obtained with serum t-IgE levels (decision point, ≤133 kU/L; sensitivity, 69.7%; and specificity, 67.9%), serum s-IgE levels (decision point, 9.5 kAU/L; sensitivity, 91.0%; specificity, 46.3%), b-eos counts (decision point, 0.43 cells × 10^{-3} μL; sensitivity, 87.6%; specificity, 57.5%), and serum s-IgE/serum t-IgE ratios (decision point, 16.2%; sensitivity, 97.2%; specificity, 88.1%) by plotting sensitivity in patients with an effective response to ASI versus 100-specificity in patients with an ineffective response to ASI.

were considered to have good predictive value.[18] For all analyses, a *P* value of less than .05 was considered statistically significant.

RESULTS

We examined a total of 120 male and 159 female subjects (mean age, 29.5 ± 8.1 years) meeting the criteria outlined above. One hundred fifty-two patients were affected by rhinitis alone, and 127 were affected by rhinitis plus asthma. Sixteen patients were monosensitized to grass, 135 to *P judaica*, 22 to *O europea*, and 106 to HDM. Two hundred three (72.8%) patients were treated with SLIT, and 76 (27.2%) were treated with SCIT. Response to ASI was considered effective in 145 (52.0%) patients: 4 sensitive to grass, 90 sensitive to *P judaica*, 3 sensitive to *O europea*, and 48 sensitive to HDM. ASI was considered clinically ineffective in 134 (48.0%) patients: 12 sensitive to grass, 45 sensitive to *P judaica*, 19 sensitive to *O europea*, and 58 sensitive to HDM.

Patient characteristics are reported in Table I. Table II compares patients with an effective clinical response to ASI with those with an ineffective response, both as a group and according to the type of ASI (SLIT and SCIT). When comparing all the study patients, those who had an effective response to ASI differed significantly from those with an ineffective response in the following characteristics: sex (female subjects better than male subjects, $P = .01$), serum t-IgE levels (low levels better than high levels, $P < .0001$), serum s-IgE levels (high levels better than low levels, $P < .0001$), b-eos counts (low counts better than high counts, $P < .0001$), and serum s-IgE/t-IgE ratios (high ratios better than low ratios, $P < .0001$). Between patients with effective and ineffective clinical responses to SCIT, significant differences were found with regard to the following characteristics: sex (female subjects better than male subjects, $P = .01$), serum t-IgE levels (low levels better than high levels, $P = .007$), serum s-IgE levels (high levels better than low levels, $P = .01$), b-eos counts (low counts better than high counts, $P < .0001$), and serum s-IgE/t-IgE ratios (high ratios better than low ratios, $P < .0001$). Significant differences were found between patients with effective and ineffective clinical responses to SLIT with regard to serum t-IgE levels (low levels better than high levels, $P < .0001$), serum s-IgE levels (high levels better than low levels, $P < .0001$), b-eos counts (low counts better than high counts, $P < .0001$), and serum s-IgE/t-IgE ratios (high ratios better than low ratios, $P < .0001$). We did not find a relationship among allergen dosing, total dose received, and clinical response because all the patients within each group received an equal dose.

Table III shows the characteristics of patients with rhinitis only and those with rhinitis and asthma symptoms. For patients with rhinitis only, significant differences were found between those with effective and ineffective clinical responses to ASI with regard to serum t-IgE levels (low levels better than high levels, $P \leq .0001$), serum s-IgE levels (high levels better than low levels, $P \leq .0001$), b-eos counts (low counts better than high counts, $P < .0001$), and serum s-IgE/t-IgE ratios (high ratios better than low ratios, $P < .0001$). For patients with rhinitis and asthma symptoms, significant differences were found between patients with effective and ineffective clinical responses to ASI with regard to serum t-IgE levels (low levels better than high levels, $P \leq .0001$), serum s-IgE levels (high levels better than low levels, $P \leq .01$), b-eos counts (low counts better than high counts, $P < .0001$), and serum s-IgE/t-IgE ratios (high ratios better than low ratios, $P < .0001$).

Serum t-IgE and s-IgE levels correlated with age (both showing), whereas the s-IgE/t-IgE ratio was not affected by age. Regression analysis showed that t-IgE levels ($r = -0.13$ [95% CI, −0.24 to −0.01], $P = .02$) and s-IgE levels ($r = -0.17$ [95% CI, −0.28 to −0.05], $P = .004$) were inversely related to age in years, whereas s-IgE/t-IgE ratios did not correlate with age ($P = .3$). In addition, using multivariate regression analysis, we found that response to ASI is independently related only to onset of symptoms, s-IgE/t-IgE ratios, s-IgE levels, and b-eos counts, again confirming that response to ASI is not related to age (Table IV).

Fig 1 shows the sensitivity and specificity obtained by calculating ROC curves for serum t-IgE levels, serum s-IgE levels, b-eos counts, and serum s-IgE/t-IgE ratios and the pairwise comparisons of the ROC curves. The area under the curve was 0.74 for serum t-IgE levels (95% CI, 0.69-0.79), 0.71 for serum s-IgE levels (95% CI, 0.65-0.76), 0.73 for b-eos counts (95% CI, 0.67-0.78), and 0.97 for serum s-IgE/t-IgE ratios (95% CI, 0.94-0.98). Significant differences were found between the s-IgE/t-IgE ratio and t-IgE levels alone ($P < .001$), s-IgE levels alone ($P < .001$), and b-eos counts ($P < .001$). No other significant differences were found.

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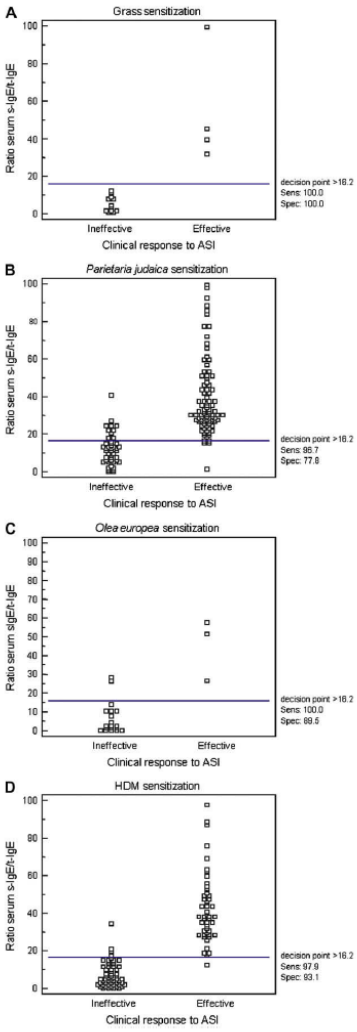

Our ROC analysis of the serum s-IgE/t-IgE ratio showed that a ratio of greater than 16.2% had the best sensitivity (97.2%) and specificity (88.1%) to predict effective ASI, regardless of whether SCIT or SLIT was used. The sensitivity and specificity of the decision point for a serum s-IgE/t-IgE ratio of greater than 16.2%, as obtained from the ROC, was examined for each allergen used for immunotherapy. Results are as follows: sensitivity and specificity of 100% for grass; 96.7% and 77.8%, respectively, for *P judaica*; 100% and 89.5%, respectively, for *O europea*; and 97.9% and 93.1%, respectively, for HDM. This is shown in Fig 2. Fig 3 shows the means (± SD) of VAS scores with regard to rhinitis and asthma symptoms, respectively. Of note, rescue medication use decreased with improvement in symptoms, as reflected in the VAS. Likewise, medication use increased with worsened symptoms per the VAS (Tables E1-E3).

DISCUSSION

Our investigation shows that the serum s-IgE/t-IgE ratio significantly correlates with the clinical response to ASI administered through both the SCIT and SLIT routes. We considered the result of ASI to 4 aeroallergens epidemiologically very important in our geographic area (ie, grass, *P judaica*, *O europea*, and HDM) in a total of 279 patients.[14] Tests to predict the outcome of ASI would be of tremendous help in daily practice, but data about this aspect of immunotherapy have not been reported. Therefore we evaluated clinical, functional, and laboratory characteristics evaluated at the time of clinical diagnosis and analyzed the variables that were statistically different between the patients with effective and ineffective clinical responses to ASI after 4 years. These were serum t-IgE levels, serum s-IgE levels, b-eos counts, and serum s-IgE/t-IgE ratios. We compared these variables, considering the clinical response to ASI, apart from the route of administration. We found that for all the allergens considered, a serum s-IgE/t-IgE ratio of greater than 16.2% correlated with an effective clinical response to ASI with a sensitivity of 97.2% and a specificity of 88.1%. Our analyses demonstrated that the serum s-IgE/t-IgE ratio is superior to both serum t-IgE and s-IgE levels alone in predicting clinical response to ASI. This is based on only 1 measurement of s-IgE and t-IgE levels, which is a limitation of the study. Both samples were drawn at the time of diagnosis when patients were manifesting symptoms and therefore during a time when the patient was presumed to have a high clinical exposure. Measurements were obtained uniformly for all subjects at the time of diagnosis, generally during peak allergen exposure, thus reflecting a real-life situation comparable with the usual clinical practice for the management of such patients. Certainly, these considerations might be too speculative, and further studies with serial evaluations of IgE concentrations, including measurements during the season to look for the ablation of the seasonal increase in allergen s-IgE levels, are needed to confirm our results. Measuring allergen-specific IgG levels would also be useful because these are classically used to demonstrate response to ASI. It has been reported that the percentage of allergen s-IgE is approximately 25% of t-IgE.[19] Allergic inflammation is initiated by allergen molecules cross-linking their corresponding

FIG 2. Sensitivity *(Sens)* and specificity *(Spec)* calculated for each allergen used for ASI by using the ratio of serum s-IgE/serum t-IgE of 16.2% as the decision point. **A**, grass; **B**, *Parietaria judaica*; **C**, *Olea europa*; **D**, house dust mites (HDM).

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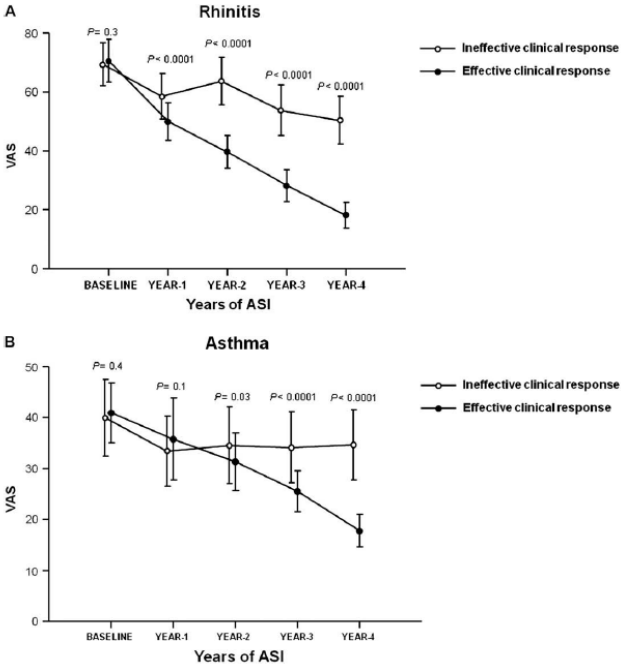

FIG 3. Graphic representation of means of VAS (± SD) with regard to **A**, rhinitis and **B**, asthma symptoms, respectively.

receptor-bound s-IgE on the mast cell and basophil surface.[20,21] Although it is possible to quantify both serum t-IgE and s-IgE levels, serum t-IgE levels are not measured because they are not useful in the clinical diagnosis of allergy to common aeroallergens.[15] Thus a higher s-IgE/t-IgE ratio might reflect a higher level of allergen s-IgE on the mast cell and basophil surface, whereas this probability is lower when the serum s-IgE/t-IgE ratio is low.

For this reason, it might be helpful to measure the serum t-IgE level and calculate the serum s-IgE/t-IgE ratio. In fact, as shown by the area under the curve values of the ROC, this ratio is at least as accurate, if not better, than serum t-IgE and s-IgE levels alone at predicting clinical response to ASI. Calculating a decision point for the ratio that represents a 95% predicted probability for an effective clinical response for all 4 allergens might improve the sensitivity and specificity compared with both serum s-IgE and t-IgE levels alone. The predicted probability, calculated for each allergen studied, demonstrated that the cutoff level of greater than 16.2% showed both high specificity (between 77.8% for *P judaica* and 100% for grass) and high sensitivity (between 96.7% for *P judaica* and 100% for grass and *O europea*).

The subjects in this study are monosensitized to the aeroallergens deemed most important in Italy.[14] We cannot completely exclude the possibility of sensitization to allergens not routinely tested, nor can we apply the findings to monosensitized patients. However, it is likely that the amount of s-IgE in the serum reflects the degree of environmental exposure to individual allergens. Thus it is conceivable that the higher the s-IgE/t-IgE ratio, the more clinically relevant the allergen is for a particular patient. Likewise, the more clinically relevant the allergens included in the ASI, the more successful ASI will be. A possible mechanism is that ASI generates allergen-specific regulatory T cells, and generating regulatory T cells specific to the patient's dominant and most relevant allergen might help generate sufficient regulatory T cells in the respiratory mucosa to suppress bystander IgE responses to other less relevant allergens, resulting in an overall decrease in mucosal allergic inflammation.[19]

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ASI has proved efficacy for a variety of inhalant allergens. However, the treatment is of long duration. Because not all patients benefit from treatment, it would be useful to be able to have specific criteria to determine those patients who might best benefit from this therapy. We found that the serum s-IgE/t-IgE ratio is the best predictor of clinical response to allergen-specific immunotherapy. Although the s-IgE/t-IgE ratio has been already described in the medical literature, to the best of our knowledge, this is the first study that demonstrates a possible role of s-IgE/t-IgE ratio as a predictor of clinical response to allergen-specific immunotherapy. Our results are applicable only to patients monosensitized to these 4 allergens studied. In addition, the lack of precise data about pollen counts might be another limitation. However, there is no reason to think there was an important difference between years because the local registries for pollen counts did not reflect this. In addition, patients with no response to ASI required more rescue medication compared with those patients who responded, providing indirect evidence of adequate pollen counts.

Finally, the lack of a placebo is a limitation of this study. However, the aim of this study was not to perform a clinical trial that might be addressed in the future but to search for a potential explanation for why patients who have received ASI could have very different response rates and thus to search for possible predictors of such varied responses. Our study has a retrospective design and, consequently, has the common limitations of such types of studies. Nonetheless, we believe that these limitations do not significantly confound the main finding of our study. However, this needs to be further investigated, preferably through studies with a double-blind design, which is the gold standard for determining the efficacy of any therapy.

Clinical implications: The s-IgE/t-IgE ratio significantly correlated with the clinical response to ASI in monosensitized patients. This suggests that the s-IgE/t-IgE ratio can be used as a predictor of clinical response to immunotherapy.

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METHODS

Immunotherapy intervention

Dose administered of SCIT and SLIT. All the patients in this study tolerated the maximum dose indicated by the manufacturers' recommendations as follows. For SCIT, the maintenance dose was 0.8 mL, which corresponds to 1.6 μg of the major allergen of grass, 0.4 μg of the major allergen of *P judaica*, 9.6 μg of the major allergen of *O europea*, and 3.84 μg of the major allergens of *D pteronyssinus* and *D farinae*. For SLIT, the maintenance dose was 60 drops (1 drop = 2.5 μL) administered 3 times a week on alternate days, which corresponds to 28.2 μg of the major allergen of grass, 6.6 μg of the major allergen of *P judaica*, 169.2 μg of the major allergen of *O europea*, and 67.7 μg of the major allergens of *D pteronyssinus* and *D farinae*. These doses were given monthly. Immunotherapy with grass, *P judaica*, and *O europea* pollen was not interrupted during the spring, but the dose was halved.

The use of a perennial schedule with grass, *P judaica*, and *O europea* pollen was well tolerated in our patients, as shown by the absence of side effects associated with administration during the spring, the peak period of these pollens, both in Sicily and in Veneto.

We did not find a relationship between allergen dosing, total dose received, and clinical response because all the patients received an equal dose.

Assessment of symptoms and medication use. For clinical control, with regard to the 3 outdoor allergens, we performed clinical control and evaluation of the VAS for symptoms at the end of the season, specifically in June for patients allergic to grass and *O europea* and in September for patients allergic to *P judaica*. For patients allergic to *D pteronyssinus* and *D farinae*, we performed clinical control and evaluation of the VAS for symptoms at the end of February because they are typically increased in autumn, after vacations, and during winter.

In Sicily, however, there is not a well-defined season for grass and *P judaica*. Thus the use of medication and, perhaps, symptom scoring might be outside the pollen season and therefore might be relevant to the assessment of the efficacy of immunotherapy.

Evaluation of clinical response. The clinical response to ASI was evaluated with separate VASs for rhinitis and asthma. For rhinitis, the patients assessed their total nasal symptom scores (sneezing, rhinorrhea, nasal congestion, and nasal pruritis) yearly for 4 years with the VAS. Subjects were instructed that 0 indicated "nasal symptoms not at all bothersome" and that 100 indicated "nasal symptoms extremely bothersome." For asthma, the patients did the same, marking the VAS for all asthma symptoms yearly for 4 years (shortness of breath, chest tightness, cough, and wheezing). Each VAS was 100 mm horizontal with 0 and 100 on the left and right ends, respectively. Subjects were instructed that 0 indicated "no complaints of respiratory sensation, such as shortness of breath, chest tightness, and breathlessness" and 100 indicated "the worst complaints of respiratory symptoms imaginable." The distance between 0 and the marks the subjects made on the scale was measured with a Digimatic caliper (Mitutoyo, Kawasaki, Japan).

Rescue medication included an H_1-antagonist for relief of rhinitis symptoms (loratadine [Claritin], 10 mg; Schering-Plough, Segrate, Italy) and a short-acting β_2-agonist for relief of asthma symptoms (salbutamol [Ventolin], 100 μg per actuation of a metered-dose inhaler; GlaxoSmithKline, Naples, Italy). We asked patients to indicate the number of packages of loratadine tablets (20 tablets per package) taken in each year and the number of salbutamol inhalers used in each year. The scale of rescue medication was between 0 and 3. The subjects were instructed that 0 indicated no rescue medication; 1 indicated a maximum of 1 package of loratadine ($\leq$20 tablets per year; see Table E1) and 1 salbutamol inhaler ($\leq$ 20 mg/y); 2 indicated a maximum of 3 packages of loratadine ($\leq$60 tablets per year) and a maximum of 4 salbutamol inhalers ($\leq$ 80mg/y); and 3 indicated 4 or more packages of loratadine and 5 or more salbutamol inhalers (Table E2).

Comparison between SCIT and SLIT in patients with effective clinical responses to ASI. The comparison between SCIT and SLIT in patients with an effective clinical response to ASI is shown in Table E3. Significant differences were noted only for atopic family history ($P < .0001$) and serum s-IgE levels ($P = .02$).

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TABLE E1. Short-acting β_2-agonist used as rescue medication for asthmatic symptoms

	No. of patients			
	Ineffective clinical response (n = 54)		Effective clinical response (n = 73)	
Rescue medication	Before ASI	After ASI	Before ASI	After ASI
0 (no rescue medication)	0	0	0	68
1 (mild use)	10	13	9	5
2 (moderate use)	22	30	35	0
3 (major use)	22	11	29	0

TABLE E2. H_1-antagonist used as rescue medication for symptoms of rhinitis

	No. of patients			
	Ineffective clinical response (n = 80)		Effective clinical response (n = 72)	
Rescue medication	Before ASI	After ASI	Before ASI	After ASI
0 (no rescue medication)	0	0	0	0
1 (mild use)	0	0	0	70
2 (moderate use)	22	30	21	2
3 (major use)	58	50	51	0

TABLE E3. Patients with effective clinical responses to ASI: Comparison between SCIT and SLIT

	SCIT	SLIT	*P* value
Patients, no. (%)	42	103	
Age (y)*	29.8 (26.8-32.7)	30.5 (28.9-32.1)	.6
Male/female sex	11/31	41/62	.1
Male subjects (%)	26.2	39.8	
Female subjects (%)	73.8	60.2	
Atopic family history (yes/no)	36/6	28/75	<.0001
Positive family history group (%)	85.7	27.2	
Negative family history group (%)	14.3	72.8	
Passive smoking (yes/no)	16/26	49/54	.3
Positive smoking group (%)	38.1	47.6	
Negative smoking group (%)	61.9	52.4	
Rhinitis/rhinitis plus asthma	22/20	50/53	.8
Rhinitis group (%)	52.4	48.5	
Rhinitis-asthma group (%)	47.6	51.5	
Onset of symptoms (y)*	7.1 (5.4-8.7)	6.5 (5.5-7.5)	.5
Pollens/HDM sensitization	24/18	73/30	.6
Pollens group (%)	57.1	70.9	
HDM group (%)	42.9	29.1	
Grass, no. (%)	1 (2.3)	3 (2.9)	
P judaica, no. (%)	23 (54.8)	67 (65.0)	
O europea, no. (%)	0	3 (2.9)	
HDM, no. (%)	18 (42.9)	30 (29.1)	
SPT response to allergen (mm)†	5.4 (5.2-5.6)	5.4 (5.2-5.6)	.8
Serum t-IgE level (kU/L)†	105.2 (80.8-137.1)	76.9 (64.4-91.8)	.09
Serum s-IgE level (kAU/L)†	38.5 (28.5-51.9)	27.7 (23.1-33.3)	.02
b-eos Counts (cells $\times 10^{-3}$ μL)†	0.30 (0.27-0.36	0.31 (0.29-0.33)	.5
Serum s-IgE/t-IgE* ratio	36.6 (29.6-45.2)	36.1 (33.1-39.3)	.4
Patient no. (%) with s-IgE/t-IgE ratio >16.2%	41 (97.6)	100 (97.1)	.8
Patient no. (%) with s-IgE/t-IgE ratio ≤16.2%	1 (2.4)	3 (2.9)	

SPT, Skin prick test.
*Mean (95% CI).
†Geometric mean after logarithmic transfomation (95% CI).

CHAPTER 4

SENESCENZA ED ALLERGIA RESPIRATORIA

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SENESCENZA ED ALLERGIA RESPIRATORIA

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RIASSUNTO

Le malattie allergiche respiratorie, come la rinite e l'asma, sono relativamente comuni nei bambini e nei giovani adulti. Queste patologie possono essere, comunque, presenti, anche, in pazienti di età superiore ai 65 anni. I dati della letteratura indicano che fra il 4 ed 13% e fra il 3 ed 12% dei soggetti di questa fascia d'età sono affetti, rispettivamente, da rinite allergica ed asma bronchiale.

Si ritiene, comunque, che queste percentuali siano, probabilmente, molto più elevate, perché le malattie allergiche respiratorie non vengono, spesso, prese in considerazione nella popolazione anziana. La diagnosi di rinite e di asma allergico nei pazienti anziani è più difficile che nei pazienti più giovani, perché si deve porre una diagnosi differenziale con altre malattie che presentano sintomi simili. Inoltre, la terapia delle allergie respiratorie nell'anziano è più difficile, per le possibili interazioni farmacologiche con altri eventuali farmaci assunti per altre patologie, per i possibili effetti collaterali dei trattamenti e, infine, per la mancanza di studi clinici controllati, mirati su pazienti anziani con rinite allergica ed asma.

INTRODUZIONE

La rinite allergica e l'asma bronchiale sono considerate malattie infiammatorie croniche dei bambini e dei giovani adulti; esse, comunque,

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possono manifestarsi in individui di tutte le età. Molti anziani sono affetti da malattie che possono mimare le patologie allergiche respiratorie, eppure la diagnosi di rinite e di asma è spesso trascurata in questa particolare fetta di popolazione. La terapia delle malattie allergiche respiratorie nella popolazione anziana è più difficile, per la presenza, in molti di questi soggetti, di altre patologie che richiedono altri farmaci. Un ulteriore problema è che la terapia delle malattie allergiche, o di qualsiasi altra malattia cronica, nei pazienti anziani, può presentare anche, problematiche legate alla scarsa comprensione di come e quando assumerla e ad alterazioni fisiche (visive o motorie, o a difficoltà della deglutizione), che possono renderne difficile e problematica l'assunzione (1-3).

In questa revisione dell'argomento affronteremo, brevemente, l'epidemiologia e la fisiopatologia della rinite allergica e dell'asma bronchiale in persone anziane, quindi tratteremo le problematiche legate alla diagnosi ed alla terapia di queste malattie, in questa particolare tipologia di soggetti.

Abbiamo effettuato una ricerca sul PubMed per identificare gli articoli ed i case report pubblicati tra 1985 ed il 2008, utilizzando le seguenti parole chiave: rinite, asma, pazienti anziani, anziani, invecchiamento, diagnosi e terapia.

RINITE ALLERGICA

Fisiopatologia e prevalenza negli anziani

Come è noto, le IgE svolgono un ruolo cruciale nella patogenesi delle malattie allergiche e, quindi, anche, nella rinite allergica. Dopo l'esposizione ad allergeni, gli individui si sensibilizzano, sintetizzando immunoglobuline della classe delle IgE, che presentano una peculiare caratteristica biologica, che è quella di aderire, attraverso il frammento Fc dell'immunoglobulina ai recettori ad alta affinità (FCεRI), presenti sulla superficie dei mastociti e dei basofili, ed a bassa affinità (FCεRII), questi ultimi presenti invece, sulla superficie degli eosinofili, delle plasmacellule, dei macrofagi e delle cellule epiteliali. L'interazione tra l'allergene e due molecole di IgE allergene-specifiche contigue, presenti sulla membrana dei mastociti, determina il rilascio di mediatori preformati e neoformati, quali l'istamina, le prostaglandine, il fattore di attivazione piastrinica (PAF) e le chinine. Questa fase iniziale della flogosi allergica è denominata 'early phase', o fase immediata. L'istamina agisce, prevalentemente, sull'endotelio vasale, in-

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ducendo vasodilatazione ed edema delle mucose, che sul piano clinico si riflette nei sintomi 'congestione nasale' e 'rinorrea' e, stimolando i recettori irritativi, provoca starnuti e prurito nasale. Alla 'early phase' segue, dopo 4-8 ore, la 'late phase', o fase tardiva della reazione allergica, che si caratterizza per il reclutamento di altre cellule infiammatorie, quali eosinofili, neutrofili, linfociti e macrofagi. Queste cellule sono responsabili dell'infiammazione nasale minima persistente, propria dei pazienti affetti da rinite allergica, che induce la persistenza dei sintomi nasali anche in assenza di stimolazione allergenica, e del cosiddetto effetto 'priming' che determina la pronta ricomparsa dei sintomi nasali, anche in presenza di stimolazioni allergeniche minime. Gli eventi che caratterizzano la rinite allergica sono riportati in dettaglio in un volume pubblicato dalla Società Italiana di Allergologia ed Immunologia Clinica (4).

La rinite allergica è una patologia molto comune, che interessa tra il 15% e il 45% della popolazione mondiale. Sebbene alcuni studi abbiano dimostrato che le IgE specifiche diminuiscono con l'età, pazienti di età avanzata possono ugualmente sensibilizzarsi. Studi più recenti, comunque, non hanno dimostrato, nei soggetti anziani, una diminuzione delle IgE sieriche, rispetto ai soggetti giovani .

La rinite allergica interessa il 3-12% dei pazienti di età > 65 anni. Essa non è una patologia banale, ha un considerevole impatto sulla qualità della vita e sullo stato di salute globalmente considerato, può aggravare l'asma, indurre una sinusite ed un'otite media catarrale, ed infine, essere responsabile della formazione di polipi nasali (5).

Diagnosi

Il sospetto clinico della presenza di una rinite è facilmente deducibile ed intuibile dalla storia clinica raccontata dal paziente. La rinite allergica si presenta con starnuti, rinorrea, prurito e congestione nasale e si associa spesso a congiuntivite. In un recente passato, la rinite allergica è stata classificata come 'stagionale' (se dovuta a pollini) o 'perenne' (se dovuta ad allergeni diversi dai pollini, ma presenti tutto l'anno, come gli acari della polvere di casa e gli epiteli di animali domestici, quali cane e gatto). Oggi, la rinite allergica è stata riclassificata in 'rinite allergica intermittente' (quando i sintomi nasali hanno una durata < 4 giorni a settimana o < 4 settimane all'anno) e 'persistente' (quando i sintomi hanno una durata maggiore di 4 giorni a settimana o di 4 settimane all'anno). In base alla gravità dei sintomi, la rinite è stata ulteriormente classificata in 'lieve' e

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'moderata/grave', a seconda se i sintomi interferiscono o meno con le normali attività quotidiane ed il sonno del paziente (5).

Quando ci si trova di fronte ad un paziente di età > 60 anni, con una possibile diagnosi di rinite allergica, si devono escludere altre patologie con sintomi simili. Innanzitutto, i pazienti anziani sono a rischio di rinite per i cambiamenti strutturali del tessuto connettivo e del sistema vascolare nasale. In particolare, la riduzione del flusso ematico nasale nell'anziano può essere responsabile di un'atrofia della mucosa nasale che, clinicamente, si riflette in congestione nasale, presenza sulla mucosa nasale di croste, e può essere responsabile, anche di alitosi. Numerosi farmaci antipertensivi possono indurre congestione nasale come effetto collaterale. Ricordiamo tra questi, gli agonisti selettivi dei recettori α_2-adrenergici (la clonidina), i β-bloccanti, gli α-bloccanti (prazosina), i vasodilatatori arteriosi diretti (idralazina) ed i diuretici (idroclorotiazide). Anche l'uso degli estrogeni coniugati può indurre congestione nasale. La 'rinite medicamentosa' è dovuta all'uso, da parte del paziente, per lunghi periodi di tempo di α-adrenergici nasali, che hanno un azione decongestionante e che, in tali condizioni, inducono una congestione nasale 'paradossa'. La 'rinite vasomotoria' è una condizione clinica nella quale i pazienti presentano sintomi simili a quelli della rinite allergica, dopo l'esposizione a sostanze irritanti, come profumi, aria fredda e spezie, ma nei quali non vi è alcuna evidente sensibilizzazione nei confronti dei più importanti allergeni ambientali. Il meccanismo fisiopatologico della rinite vasomotoria non è completamente noto, anche se si ritiene che essa possa essere secondaria ad un'iperattività del sistema parasimpatico delle vie respiratorie superiori e delle fibre C. La 'rinite non allergica con eosinofilia' (NARES) presenta sintomi simili a quelli della rinite allergica persistente. Gli strisci nasali mostrano un elevato numero di eosinofili, ed anche in questo caso non vi è alcuna evidente sensibilizzazione nei confronti dei più importanti allergeni ambientali.

Nella diagnosi differenziale della rinite allergica devono essere infine considerati, nei pazienti anziani con disturbi nasali, anche l'ipotiroidismo, la malattia granulomatosa di Wegener e la sarcoidosi.

In pazienti con sintomi unilaterali, in particolare quando il sintomo riferito è l'ostruzione nasale, deve essere sospettata anche, la possibilità della presenza di una neoplasia. Infine, in pazienti anziani che riferiscono una sensazione di 'dolce in bocca', accompagnata ad una rinorrea acquosa e chiara, il cui flusso aumenta con la tosse o con i cambiamenti di posizione del capo, deve essere considerata anche, una perdita di liquido cerebrospinale (6).

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Valutazione allergologica

Il primo passo per determinare se la rinite di un paziente anziano è di natura allergica, è quello di valutare se il soggetto presenta IgE sieriche specifiche per i comuni aeroallergeni presenti nell'ambiente di vita 'outdoor' e 'indoor'. La presenza di una sensibilizzazione IgE ad uno specifico allergene può essere determinata con i test cutanei [skin prick test (SPT) o test per puntura] o con la ricerca, nel siero, delle IgE allergene-specifiche. I vantaggi del test cutaneo sono che i risultati sono disponibili entro circa 15 minuti e che il test è più sensibile rispetto al dosaggio, nel siero, delle IgE allergene-specifiche. Il principio su cui si basa lo SPT è che gli allergeni si legano agli anticorpi IgE allergene-specifici presenti sulla membrana dei mastociti cutanei con la stessa modalità con cui l'allergene, durante l'esposizione naturale, interagisce con i mastociti della mucosa nasale. Un test cutaneo è positivo se si evidenzia una reazione nella sede dove si effettua la prova con l'allergene. Tale reazione, descritta come 'pomfo ed eritema', è del tutto simile a quella secondaria alla puntura di una zanzara. Tuttavia, con l'invecchiamento, vi sono cambiamenti della cute e del sottocutaneo che possono influenzare negativamente la risposta del test cutaneo. Queste comprendono una riduzione del numero dei vasi sanguigni e del numero dei mastociti cutanei, nonché le alterazione da esposizione alla luce solare. Una diminuzione della risposta cutanea all'istamina (che è la sostanza utilizzata durante l'esecuzione dello SPT come controllo positivo) è stata descritta in soggetti di età > 50 anni. Pertanto, i risultati dello SPT potrebbero non essere attendibili, qualora il controllo positivo, l'istamina, risultasse negativo, ed in questi casi si dovrà ricorrere al dosaggio *in vitro*, delle IgE allergene-specifiche (7-9).

Il test di provocazione nasale è, il più delle volte, usato solo negli studi clinici, per confermare la diagnosi di rinite allergica, mentre non è stato finora usato, se non in casi eccezionali, nella pratica clinica. Infine, la rinomanometria, che misura i cambiamenti del flusso dell'aria nasale durante la respirazione, e che potrebbe essere d'aiuto nella diagnosi di rinite allergica, è impiegata anch'essa, solo per scopi di ricerca. Infine, l'endoscopia nasale e la tomografia computerizzata non sono metodiche utilizzate routinariamente per la diagnosi di rinite allergica, pur essendo fondamentali per l'esclusione di altre cause che possono determinare congestione nasale, come i difetti strutturali delle fosse nasali o la presenza di sinusite cronica o di neoplasie (9).

Chapter 4

Terapia

Prevenzione ambientale

Il primo approccio terapeutico per la rinite allergica, come per tutte le malattie allergiche, è quello di evitare l'esposizione all'allergene verso cui il paziente è sensibilizzato e che è, quindi, responsabile dei sintomi. Anche se è importante evitare l'esposizione allergenica, è spesso concretamente difficile attuarla, e la maggioranza dei pazienti necessita di una terapia medica per il controllo dei sintomi. Nella tabella 1 sono indicate alcune misure di prevenzione ambientale che sono, comunque, difficilmente applicabili al paziente geriatrico, che spesso non vive in casa propria ma in una struttura sociale. Alcuni prodotti industriali come, ad esempio, il copri-materasso anti-acaro si sono dimostrati efficaci nel ridurre l'esposizione a questi allergeni e, quindi, nel migliorare i sintomi del paziente, mentre gli agenti chimici, gli acaricidi, non sembrano produrre effetti duraturi e non sono pertanto, raccomandati (10, 11).

Tabella 1
Misure di igiene ambientale

ALLERGENE	MISURE AMBIENTALI
Allergeni indoor Acari della polvere di casa	Utilizzare copricuscini e copri materassi anti acaro. Lavare frequentemente a 55°C lenzuoli e pigiami Eliminare la moquette Ridurre l'umidità ambientale
Epiteli animali	Evitare di avere l'animale in casa Pulire accuratamente i divani e i tappeti Evitare che l'animale entri in camera da letto
Micofiti	Eliminare le possibili sorgenti di micofiti Ridurre l'umidità Evitare gli scantinati
Allergeni outdoor Pollini	Chiudere bene le finestre nel periodo di pollinazione Evitare le gite in campagna Usare l'aria condizionata

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Terapia farmacologica

1) Corticosteroidi nasali

I corticosteroidi nasali (CN) sono i farmaci di prima scelta per la terapia della rinite allergica persistente moderata/grave. Essi riducono tutti i sintomi della rinite, congestione nasale, rinorrea, starnuti e prurito nasale, hanno anche effetto seppur minore sui sintomi oculari. I CN forniscono una concentrazione elevata di steroide nella mucosa dell'organo d'applicazione (il naso) evitando, in tal modo, gli eventuali effetti sistemici. Tuttavia, se il paziente ha un'ostruzione nasale persistente, i CN, specie in età geriatrica, possono risultare poco efficaci. Pertanto si consiglia, in questi pazienti, di effettuare un breve periodo di trattamento con steroidi sistemici (4-7 giorni) prima di iniziare i CN. L'azione anti-infiammatoria dello steroide sistemico consentirebbe, infatti, una migliore deposizione del CN sulla mucosa nasale. In tali situazioni, però, lo steroide sistemico deve essere immediatamente sospeso se compaiono alterazioni del tono dell'umore. È importante anche, ricordare che, per valutare gli effetti terapeutici dei CN, si devono attendere fino a 2 settimane di terapia consecutiva. Le diverse molecole di CN usati nella terapia della rinite allergica sono efficaci e quasi tutte sono disponibili in soluzione acquosa. Gli effetti collaterali dovuti all'uso dei CN sono per la maggior parte locali, comprendono secchezza nasale, bruciore nasale ed epistassi, e si presentano con una frequenza del 5-10%. L'epistassi con Mometasone furoato ha un'incidenza del 2%. Uno studio con il mometasone fuorato utilizzato per 12 mesi ha dimostrato che l'uso prolungato di queste molecole non induce atrofia della mucosa nasale. Sono stati segnalati pochi casi di alterazioni della funzione del surrene in adulti che usano i CN alla dose consigliata dall'industria produttrice. Vi è invece un rischio teorico che i CN, usati ad alte dosi, per lunghi periodi di tempo, possano indurre osteoporosi, sebbene non vi sono studi che abbiano dimostrato un aumentato rischio di fratture o un'alterazione del turnover osseo in questi pazienti. Comunque la biodisponibilità di questi farmaci è molto bassa, e per alcuni come il mometasone furoato è quasi assente (minore di 0.1%) e l'incidenza di effetti collaterali sistemici è molto bassa. Uno studio condotto in pazienti anziani (età media 81 anni) non ha dimostrato un aumentato rischio di fratture con l'uso dei CN. Attualmente, non vi sono dati sufficienti per escludere che i trattamenti con CN possano aumentare la pressione intraoculare. A tal proposito, in letteratura, sono disponibili 2 studi: uno condotto in 34 soggetti di sesso maschile, di età media di 71 anni e l'altro condotto in 12

pazienti, di età media di 66 anni che descrivono un aumento della pressione intraoculare dopo trattamento con CN e, successivamente, un calo della stessa con l'interruzione del trattamento (12, 13). Tuttavia, anche se i dati sono certamente inadeguati si consiglia, nel paziente anziano che deve essere trattato con CN, di controllare la pressione oculare prima di intraprendere la terapia. Questa raccomandazione va estesa, anche ai pazienti anziani asmatici. Il ruolo infine dei CN nella formazione della cataratta, soprattutto in pazienti anziani, è ancora poco chiaro. Un ampio studio, che ha esaminato se vi era un rapporto tra l'uso di CN e la formazione di cataratta, in soggetti < 70 anni di età, non ha riscontrato alcuna associazione rilevante.

2) Gli antistaminici

L'istamina, come accennato precedentemente, è il mediatore più importante rilasciato dai mastociti durante l''early phase' della reazione allergica. La sua azione farmacologica sui recettori H_1 induce i classici sintomi della rinite allergica: starnuti, rinorrea, congestione e prurito nasale (4, 5).

Gli antistaminici sono classificati in generazioni, in base alle loro diverse caratteristiche farmacologiche (Tab. 2). Gli H_1 antagonisti di prima generazione sono lipofili, attraversano facilmente la barriera ematoencefalica, si legano ai recettori H_1 del sistema nervoso centrale, ed inducono sedazione, riduzione della vigilanza, vertigini e confusione mentale, tutti effetti collaterali che sono particolarmente accentuati nei pazienti più anziani. Gli H_1 antagonisti di prima generazione, per la mancanza di specificità per i recettori H_1, hanno anche, effetti dopaminergici, serotoninergici, colinergici e muscarinici. Il legame non specifico con questi recettori può essere causa di altri effetti iatrogeni, soprattutto nei pazienti anziani, tra cui: ritenzione urinaria, stipsi, aritmie ed ipotensione posturale. Poiché molti di questi H_1 antagonisti di prima generazione sono disponibili come prodotti da banco, anche in associazione con altre molecole, la comparsa improvvisa di questi sintomi, in pazienti anziani, deve essere sempre considerata attentamente durante la raccolta dell'anamnesi farmacologica (5).

Gli H_1 antagonisti di seconda generazione (desloratadina, fexofenadina, cetirizina e loratadina) hanno una ridotta capacità di attraversamento della barriera ematoencefalica ed una maggiore specificità per il recettore H_1. Tra gli antistaminici di seconda generazione, la cetirizina è la molecola con la più elevata incidenza di sedazione, come effetto collaterale, alla dose indicata come terapeutica (5).

Tabella 2
Classificazione degli antistaminici

PRIMA GENERAZIONE	SECONDA GENERAZIONE
clorfenamina (Trimeton, Dirahist, Fienamina) ciproeptadina (Periactin) d-clorferamina (Polaramin) prometazina (Fargan, Farganesse)	azelastina (Allergodil) cetirizina (Zirtec, Formestin) desloratadina (Aerius) ebastina (Kestine) fexofenadina (Telfast) ketotifene (Zaditen, Totifen) levocabastina (Livostin, Levostab) levocetirizina (Xyzal) loratadina (Clarityn, Fristamin) oxatomide (Tinset) mizolastina (Mizollen) rupatidina (Rupafin, Pafinur)

Per alcuni H_1 antagonisti di seconda generazione sono state segnalate, anche, proprietà anti-infiammatorie (14). Sebbene gli H_1 antagonisti di seconda generazione siano più specifici per il recettore H_1, e in generale hanno dimostrato una migliore tollerabilità, devono essere sempre somministrati con cautela nei pazienti di età geriatrica. La somministrazione di ketoconazolo, insieme con la fexofenadina o con rupatadina 20 mg, può aumentare la loro concentrazione plasmatica di 2-3 volte e di 10 volte, rispettivamente. Nei pazienti con insufficienza renale, le dosi di fexofenadina devono essere adeguate al grado di insufficienza, mentre la cetirizina non dev'essere somministrata (5).

Inolte Ebastina deve essere utilizzata con cautela in pazienti in cui sia noto un rischio cardiaco e Rupatadina deve essere utilizzata con cautela nei pazienti con prolungamento del tratto QT21.

I farmaci antistaminici sono utilizzati in monoterapia in pazienti con rinite intermittente o rinite lieve persistente. Possono, inoltre, essere usati, unitamente ai CN, in pazienti nei quali questi farmaci, da soli, non sono in grado di controllare tutti i sintomi, oppure in pazienti che non sono in grado di eseguire la somministrazione nasale dei CN. Gli antistaminici sono disponibili, anche come spray nasali (azelastina e levocabastina), che possono essere utilizzati da soli o in combinazione con gli antistaminici orali, evitando di aumentare la dose di questi ultimi.

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3) Decongestionanti nasali

In molti pazienti con rinite allergica, la congestione nasale è il sintomo più fastidioso. In pazienti in cui il sintomo congestione nasale è importante e persistente, nonostante l'utilizzo di antistaminici e CN, si possono prendere in considerazione i decongestionanti nasali per via orale. La pseudoefedrina, un α-agonista, è il più usato, in associazione con gli antistaminici orali. I decongestionanti orali devono essere, però, usati con cautela nei pazienti anziani, perchè possono aumentare la frequenza cardiaca e la pressione arteriosa, e possono causare ansia, insonnia, irritabilità e secchezza della mucosa orale. Per tali motivi, non devono essere somministrati in pazienti con cardiopatia ischemica ed ipertensione arteriosa (5).

L'uso prolungato dei decongestionanti nasali per via topica (spray) presenta molti effetti collaterali, che abbiamo già descritto a proposito dei decongestionanti nasali assunti per via orale. I decongestionanti nasali per via topica dovrebbero essere utilizzati solo per brevi periodi di tempo (5-7 giorni) perché possono causare, se usati più a lungo, la rinite medicamentosa. In Italia ne è vietato l'uso ai bambini fino a 12 anni.

4) Altri trattamenti farmacologici

I leucotrieni sono sintetizzati dai mastociti dopo l'esposizione all'allergene, ed aumentano la permeabilità vascolare, la produzione di muco e l'ostruzione nasale. Gli antileucotrieni sono stati approvati per la terapia dell'asma e, successivamente, sono stati usati anche nella terapia della rinite allergica, con risultati non univoci. Il montelukast, usato in associazione con i CN o con gli antistaminici, non ha dimostrato un effetto terapeutico aggiuntivo sui sintomi nasali (5).

L'utilizzo dell'omalizumab, un anticorpo monoclonale anti-IgE, si è dimostrato efficace, in diversi studi clinici, nel ridurre i sintomi nasali e l'uso degli antistaminici in pazienti con rinite allergica. Ad oggi però la terapia con omalizumab è stata approvata solo per l'asma bronchiale (5).

L'ipratropio bromuro è un antimuscarinico topico nasale che diminuisce la secrezione del muco. Esso può essere utile nella rinite con ipersecrezione di muco, ed è da considerarsi relativamente sicuro, se assunto alle dosi indicate dall'industria produttrice.

I cromoni, infine, inibiscono la degranulazione dei mastociti, ma richiedono almeno 4 somministrazioni nasali al giorno. Hanno un'azione preventiva e non agiscono sui sintomi. Questo ne limita notevolmente l'uso, nonostante l'eccellente tollerabilità e l'assenza di effetti collaterali (5).

Chapter 4

Immunoterapia Allergene-Specifica

Nei pazienti più giovani, che hanno sintomi nasali persistenti nonostante le cure mediche, può essere consigliata l'immunoterapia allergene-specifica (ITS). L'immunoterapia può essere somministrata per via sottocutanea o per via sublinguale. Studi clinici controllati hanno dimostrato che 3-4 anni di trattamento con ITS può ridurre i sintomi rinitici, e che tale effetto può durare per un massimo di 3 anni dopo l'interruzione del trattamento. La maggior parte degli studi sulla sicurezza ed efficacia dell'ITS per il trattamento della rinite allergica non sono stati condotti in pazienti anziani per due ordini di motivi: a) vi è un'alta percentuale di pazienti anziani che assume β-bloccanti, che, quindi, in caso di anafilassi (effetto collaterale possibile dell'ITS), impedirebbero all'organismo di rispondere prontamente all'adrenalina somministrata in muscolo; b) la risposta immunitaria, nel soggetto anziano, è spesso deficitaria, e quindi, anche quella all'ITS. Due studi hanno tuttavia dimostrato che l'immunoterapia, in pazienti non immunocompromessi di età > 60 anni, è sicura ed efficace.

Ricordiamo che l'ITS richiede frequenti visite ambulatoriali per la sua somministrazione e che, purtroppo, non è efficace in tutti i pazienti. Inoltre, ha altre limitazioni che devono essere attentamente considerate prima di iniziarla, soprattutto in un paziente anziano: a) è più probabile che l'ITS abbia successo in un paziente monosensibile; b) i pazienti sono a rischio di sviluppare una reazione sistemica, che richiede la somministrazione di adrenalina in muscolo; c) non tutti i pazienti migliorano con l'ITS e, ad oggi, è difficile determinare *a priori* quali pazienti ne avranno un reale vantaggio (5, 15).

ASMA BRONCHIALE

Patogenesi

Il National Heart Lung e Blood Institute (NHLBI) ha definito l'asma come una malattia infiammatoria cronica delle vie respiratorie, caratterizzata da una ostruzione bronchiale reversibile e da iperreattività bronchiale. Gli eventi che caratterizzano questa specifica infiammazione sono riportati in dettaglio in un volume pubblicato dalla Società Italiana di Allergologia ed Immunologia Clinica (16). In generale, l'infiammazione asmatica è caratterizzata da un aumento dei linfociti CD4+, in particolare linfociti con

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caratteristiche T helper 2 (T_H2), eosinofili, mastociti e basofili. A seguito di uno stimolo specifico, ad esempio l'allergene responsabile della sensibilizzazione, o da uno non specifico, ad esempio un'infezione delle alte vie respiratorie, le cellule infiammatorie delle vie aeree vengono attivate. Queste cellule (mastociti ed eosinofili) rilasciano mediatori ed i linfociti le citochine, che favoriscono il reclutamento di altre cellule infiammatorie. Questa infiammazione è responsabile della broncocostrizione e della secrezione di muco e quindi della comparsa dei tipici sintomi dell'asma: tosse, dispnea e respiro sibilante (11, 16, 17).

La prevalenza dell'asma nelle persone anziane è stata stimata tra il 4% e il 13%. Comunque, questi dati sembrano essere più bassi rispetto a quelli reali, perché l'asma, in questi pazienti è spesso sottovalutata, perché non diagnosticata. Nei pazienti anziani vi è, inoltre, un aumento di morbilità e mortalità associate all'asma. In particolare, uno studio ha documentato che, in pazienti anziani con asma insorto in età giovanile, vi è un rischio 3 volte più elevato di morte per asma. Negli USA è stato documentato che, tra il 2001 ed il 2003, oltre la metà dei 4.210 decessi per asma erano di pazienti di età > a 65 anni. I pazienti anziani con asma sono più facilmente ospedalizzati rispetto ai pazienti più giovani. Le ragioni di questo dato sono molto probabilmente multi-fattoriali. Una possibile spiegazione è che i pazienti anziani hanno condizioni di comorbilità. La cardiopatia ischemica, il diabete mellito, l'ipertensione arteriosa ed i tumori sono fattori di rischio per le visite d'emergenza e le ospedalizzazioni. Un'altro motivo è che il paziente anziano ha una maggiore probabilità di non essere adeguatamente trattato con i farmaci 'controller' rispetto ai pazienti più giovani.

Nonostante l'aumento di morbilità e mortalità nei pazienti anziani con asma, la patogenesi dell'asma, in questa particolare fascia d'età, non è ben caratterizzata. L'asma dell'anziano può essere dovuto: 1) alla persistenza dell'asma infantile; 2) al ritorno della malattia nella fase avanzata della vita, dopo un periodo di remissione nell'età adulta; 3) più raramente si tratta di un'asma che si è sviluppata nella senescenza, il cosiddetto 'asma ad esordio tardivo'. Mentre la sensibilizzazione ad allergeni è influenzata da fattori genetici ed ambientali, ed essi sono cruciali per lo sviluppo dell'asma infantile, il loro ruolo nell'asma in età avanzata e nell'asma ad esordio tardivo è meno certo. Nel 60% e nell'80% dei bambini e dei giovani adulti con asma, è facilmente dimostrabile una sensibilizzazione. Al contrario, per molti anni, vi è stata la convinzione che l'asma dei pazienti anziani non presentasse una componente allergi-

ca. Tuttavia, alcuni gruppi hanno successivamente dimostrato che elevati livelli di IgE sieriche totali e allergene-specifiche si possono presentare anche in età geriatrica, ed uno studio ha evidenziato che il 72% dei pazienti anziani asmatici presentavano una nuova diagnosi di asma. La sensibilizzazione agli scarafaggi è associata con i casi più gravi di asma in pazienti anziani che vivono nelle città americane (18). In una popolazione giapponese, l'associazione tra il polimorfismo del recettore ad alta affinità per le IgE ed il promoter del gene per la RANTES (Regulated on Activation Normal T Cell Expressed and Secreted), un chemoattrattante per le cellule T, gli eosinofili, i basofili e i mastociti, è risultata un potente fattore di rischio per lo sviluppo di asma dopo i 40 anni d'età. Comunque, questa associazione, cioè asma ad insorgenza tardiva-polimorfismi del recettore per le IgE, non è stata ulteriormente confermata da parte di un gruppo inglese.

Anche se una storia familiare di asma rappresenta un'importante fattore di rischio per l'insorgenza dell'asma infantile, il suo ruolo nella senescenza non è certo. Alcuni studi hanno ipotizzato che una storia familiare di asma costituisce un fattore di rischio anche per lo sviluppo di asma ad insorgenza tardiva, mentre altri studi non hanno evidenziato questo rapporto. In uno studio sono stati confrontati pazienti asmatici tra i 50 ed i 59 anni di età, con una storia familiare positivo per asma, con pazienti asmatici, del medesimo range di età, con un'anamnesi familiare negativa per asma: il primo gruppo risultava avere un'iperreattività bronchiale ed un numero di linfociti nel liquido di lavaggio bronchiale superiori rispetto al secondo gruppo. Le infezioni virali dell'apparato respiratorio, sia del tratto superiore che di quello inferiore, in particolare le infezioni dovute ai rinovirus ed al virus respiratorio sinciziale, possono predisporre i pazienti più giovani a sviluppare asma. Altri studi hanno, poi, evidenziato che le infezioni respiratorie sostenute da virus o da *Chlamydia pneumoniae* possono svolgere un ruolo più importante dell'atopia nello sviluppo dell'asma ad insorgenza tardiva. Infine, il fumo di sigaretta, principalmente responsabile della broncopatia cronica ostruttiva, è stato indicato da alcuni autori, come un fattore di sviluppo di asma ad insorgenza tardiva in pazienti anziani.

Le modificazioni delle vie aeree dovute all'invecchiamento

L'invecchiamento è associato a diversi cambiamenti della struttura e della funzione polmonare, che possono a loro volta, influenzare la

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morbilità e la mortalità di individui anziani affetti da asma bronchiale. Con l'avanzare dell'età, la matrice polmonare si altera, determinando un calo del ritorno elastico. Ciò è causa di una minore elasticità del polmone e, quindi, del calo del flusso espiratorio e dell'aumento della broncostruzione durante un'esacerbazione asmatica. Anche la forza dei muscoli respiratori diminuisce con l'invecchiamento, ed è stato osservato che la forza del diaframma diminuisce di circa il 25% con l'età (11, 17, 18).

Diagnosi di asma bronchiale nei pazienti anziani

Storia clinica

I sintomi tipici dell'asma, come ad esempio la tosse, la difficoltà respiratoria e la dispnea, sono simili nei pazienti giovani e negli anziani. Ad ogni modo, nella diagnosi differenziale dell'asma bronchiale di un paziente geriatrico, bisogna considerare un maggior numero di malattie. L'insufficienza cardiaca congestizia, l'angina pectoris, la bronchite cronica ostruttiva, l'enfisema polmonare, l'embolia polmonare, le aspirazioni ricorrenti, i tumori delle vie respiratorie, il reflusso gastro-esofageo e la disfunzione della laringe, sono tutte patologie che possono mimare, per comportamento clinico e sintomi, l'asma bronchiale (Tab. 3) (18).

Ottenere da un paziente anziano un'anamnesi positiva per sintomi asmatici può essere più difficile che in un paziente giovane. I pazienti anziani possono avere una bassa percezione dei sintomi ostruttivi delle vie aeree e, di conseguenza, essere meno propensi a riferirli. Inoltre, i pazienti anziani possono attribuire i sintomi asmatici all'invecchiamento, piuttosto che ad una condizione clinica come l'asma. E' fondamentale chiedere al paziente se ha modificato la sua attività fisica per problemi di tosse, difficoltà respiratoria o altri sintomi riferibili all'asma.

In età geriatrica si deve eseguire un'attenta raccolta dell'anamnesi farmacologia, per identificare eventuali farmaci, come gli ACE-inibitori, che possono indurre una tosse che mima la tosse asmatica. La storia clinica deve, altresì, considerare l'anamnesi familiare e personale del paziente per quanto riguarda le malattie allergiche, e tra queste, l'eczema, la rinite allergica, l'allergia alimentare e l'allergia a farmaci, perché queste forme cliniche possono essere più frequenti negli anziani con asma allergico.

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Tabella 3
Diagnosi differenziale in pazienti anziani con sospetta asma bronchiale

Patologia	**Caratteristiche cliniche ed esami di laboratorio che possono aiutare nella diagnosi**
Anemia	Emocromo
Cardiopatia congestistia	Rx torace Elettocardiogramma Elevati livelli sierici di peptide natruretico cerebrale Edemi declivi Ortopnea
Embolia polmonare	d-dimero Equilibrio acido-base Elettocardiogramma Improvvisa insorgenza dei sintomi
Aritmie cardiache	Elettocardiogramma
Broncopatia cronica ostruttiva	Rx torace (aumento della trama vasculo-bronchiale) Aumento della diffusione del monossido di carbonio (DL_{CO})
Polmonite	Rx torace Febbre
Neoplasia polmonare	Rx torace Calo ponderale
Malattia da reflusso gastro-esofageo	Ph-metria 24 ore Miglioramento dei sintomi con la terapia anti-reflusso
Vocal cord dysfunction	Alterazione della fase inspiratoria della curva spirometrica Video-laringoscopia
Post-nasal drip	Storia clinica Video-laringoscopia

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Misurazioni obiettive

I pazienti con sintomi clinici suggestivi per asma dovrebbero essere valutati con la spirometria, determinando il volume espiratorio forzato in 1 secondo (FEV_1) e la capacità vitale forzata (FVC) (11,17,18). Un rapporto del $FEV_1/FVC < 0.7$ o $FEV_1 < 80\%$ del predittivo suggerisce una patologia polmonare ostruttiva, senza distinzione però, tra asma e BPCO.

Spesso la spirometria è un esame non eseguito/non richiesto dal medico di medicina generale e, pertanto, la terapia è empirica. Solo dopo molto tempo il paziente viene avviato ad uno specialista allergologo o pneumologo per eseguire un iter diagnostico più completo. Se la spirometria dimostra la presenza di un quadro ostruttivo, è fondamentale eseguire un test di reversibilità con un broncodilatatore β_2-agonista 'short acting': in genere 400 µg di salbutamolo. Se la somministrazione del farmaco aumenta il FEV_1 del 12% o di 200 ml rispetto ai valori ottenuti con la spirometria basale, questo incremento è indicativo di malattia ostruttiva delle vie respiratorie 'reversibile', che può essere migliorata con i farmaci broncodilatatori. Tuttavia, negli anziani, alcune funzioni del sistema nervoso simpatico e parasimpatico possono diminuire con l'età, diminuendo in tal modo, anche la reversibilità bronchiale. Inoltre, le vie respiratorie degli asmatici di vecchia data possono essere sede di alterazioni permanenti ('remodelling'), come la fibrosi, la presenza di bronchiectasie e l'instabilità tracheale, che sono, a loro volta, causa di riduzione della reversibilità dell'ostruzione bronchiale (19).

Esiste comunque, una certa convinzione che la spirometria non sia eseguibile dai soggetti anziani. Tuttavia, alcuni studi hanno dimostrato che un'elevata percentuale di pazienti anziani (82%-93%) sono in grado di eseguire una buona spirometria. Spesso l'incapacità di eseguire correttamente la spirometria è dovuto ad un disturbo cognitivo, piuttosto che ad una patologia respiratoria; questo dato, comunque, non è stato confermato da altri autori. Nei pazienti che non sono in grado di eseguire la spirometria, si può eseguire una pletismografia, che permette ai pazienti di respirare più 'normalmente' rispetto alla spirometria, che prevede un'adeguata coordinazione respiratoria ed una respirazione forzata. L'oscillazione forzata è un altro metodo per misurare l'ostruzione delle vie aeree. Tuttavia, questo metodo non è ben standardizzato per la diagnosi di asma e, attualmente, è usato solo per la ricerca clinica.

In un paziente in cui la storia clinica di asma sia molto suggestiva, ma la spirometria è normale, deve essere eseguito un test di provocazione bronchiale aspecifico, per valutare la presenza ed il grado dell'iperreattività bronchiale aspecifica. Il test di provocazione bronchiale aspecifico è eseguito con

la somministrazione, per via aerosolica, di metacolina o istamina (stimoli diretti) o di adenosina-5'-monofosfato o agenti osmotici (stimoli indiretti), utilizzando dosi crescenti dello stimolo al fine di determinare la dose che induce broncocostrizione. Mentre nella maggioranza degli individui le vie aeree presentano una risposta broncocostrittiva solo ad alte dosi, nei pazienti con asma, ed in alcuni pazienti con BPCO, le vie aeree presentano un'ostruzione a dosi più basse della sostanza utilizzata, quindi, l'assenza di una broncocostrizione con l'uso di queste particolari sostanze farmacologiche escluderebbe la diagnosi di asma. La sostanza più comunemente usata è la metacolina. Spesso, comunque, il test di provocazione bronchiale non è eseguito nei pazienti anziani, anche se molti studi hanno dimostrato che il test può essere effettuato, con sicurezza, anche nei pazienti di questa fascia di età. Ricordiamo, comunque, che il test di provocazione bronchiale con metacolina non dovrebbe essere eseguito in pazienti con un $FEV_1 < 70\%$, in pazienti con ipertensione arteriosa non controllata od in pazienti con un recente episodio anginoso o un pregresso ictus. Nei pazienti più giovani, la definizione di iperreattività bronchiale è quella di un calo del 20% nel FEV_1 ad una dose di metacolina compresa tra 8 e 16 mg/ml. Nei pazienti anziani è stato suggerito di fissare il cut-off di metacolina a 4 mg/ml, dopo correzione per grado basale di ostruzione delle vie aeree, fumo e presenza di atopia.

Come abbiamo accennato, la spirometria non permette di distinguere l'asma dalla BPCO e viceversa. Per distinguere queste due malattie polmonari ostruttive, oltre alla spirometria, si dovrebbe eseguire anche la diffusione alveolo-capillare del CO. Nei pazienti con BPCO, la diffusione è ridotta, mentre in quelli con asma rimane normale o è addirittura aumentata (19).

Altre indagini

Lo studio radiologico del torace dovrebbe essere sempre eseguito nei pazienti anziani, alla prima diagnosi di asma, per escludere la presenza di altre malattie. La radiografia del torace è di solito normale nell'asma controllata, anche se può rivelare una modesta iperinflazione durante le esacerbazioni. L'esecuzione di un ECG può aiutare ad escludere malattie cardiache, che possono presentarsi con un quadro clinico simile a quello dell'asma bronchiale, e permette di individuare quei pazienti che possono essere potenzialmente a rischio per un eccesso di terapia con β_2-agonisti. Generalmente, l'ECG nell'asma ben controllato non evidenzia alcuna particolare alterazione, mentre durante gli episodi acuti di broncospasmo può comparire un quadro di tachicardia sinusale.

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L'esecuzione di un emocromo può essere utile per valutare se un'eventuale anemia può essere la causa della dispnea del nostro paziente. I soggetti asmatici possono presentare un'eosinofilia. La conta degli eosinofili ematici è importante nei pazienti con asma difficile da controllare, nell'asma steroido-resistente, ed infine nella diagnosi differenziale con la sindrome di Churg-Strauss.

La misurazione dell'ossido nitrico nell'aria espirata è ampiamente usata sia in sede diagnostica che per monitorare la terapia dell'asma bronchiale. Elevati livelli di ossido nitrico nell'aria espirata hanno dimostrato un'importante correlazione con l'iperreattività bronchiale, l'eosinofilia delle vie aeree ed il grado di sensibilizzazione allergica del paziente con asma, rivestendo, anche, secondo alcuni autori, una buona capacità predittiva del rischio di esacerbazione asmatica (11, 18, 19).

La terapia dell'asma bronchiale

Nei primi anni '90, due diversi comitati scientifici, il NHLBI ed il GINA hanno definito le Linee Guida per la diagnosi ed il trattamento dell'asma, che sono state poi, periodicamente aggiornate. Dal momento che entrambe le Linee Guida sono rivolte alla popolazione asmatica giovanile, un gruppo di esperti nel trattamento dell'asma nei pazienti anziani ha pubblicato nel 1996, un addendum alle prime Linee Guida NHLBI, inerente proprio, alla gestione dei pazienti asmatici anziani. Gli Autori di questa pubblicazione hanno concluso che le Linee Guida scritte per l'asma nella popolazione giovanile potrebbero essere applicate anche a pazienti anziani, considerando però, con particolare attenzione l'istruzione all'uso dei farmaci (11, 17, 18).

Valutazione e monitoraggio

L'obiettivo della terapia dell'asma è quello di ridurre i sintomi e migliorare la funzionalità polmonare e la qualità di vita dei pazienti. Durante la prima visita deve essere valutata la gravità dell'asma. E' bene fare questa valutazione prima di iniziare una terapia, e ci si deve basare sulla frequenza dei sintomi e sulle misure obiettive della funzionalità polmonare. Se i pazienti sono già in trattamento, la gravità dell'asma è determinata dalle terapie necessarie per controllare adeguatamente i sintomi.

Tutti i pazienti con asma dovrebbero essere controllati da uno specialista almeno ogni 6 mesi, per valutare il controllo dell'asma. Quando si apportano variazioni allo schema terapeutico è bene effettuare un controllo entro 6 settimane dalla variazione. Nella tabella 4 riportiamo alcuni suggerimenti per le

visite di follow-up (11,18). Il controllo dell'asma può essere valutato, anche, con la somministrazione di questionari standardizzati, come le Four Questions Asma Control Test, o ponendo specifiche domande rapportate allo stile di vita (20). Spesso, si osserva come i pazienti asmatici giovani difficilmente riconoscono un peggioramento dei loro sintomi e questo fenomeno è ancora più evidente nell'asmatico anziano. La spirometria e soprattutto, il picco di flusso espiratorio (PEF) al domicilio forniscono parametri oggettivi e dovrebbero essere utilizzati in tutti i pazienti, ma spesso accade che, dopo un'iniziale entusiasmo, la misurazione del PEF domiciliare non viene poi più eseguita.

Tabella 4
Valutazione del paziente asmatico

Valutazione dei sintomi	Chiedere se vi sono risvegli notturni per tosse o mancanza d'aria Chiedere al paziente se la mattina ha tosse e/o espettorato Chiedere se vi è dispnea (a riposo o dopo esercizio fisico) Chiedere se vi è stato un cambiamento nella tolleranza all'esercizio fisico
Valutazione dei farmaci assunti	Chiedere al paziente se la terapia prescritta è stata assunta correttamente Chiedere se, e quante volte, ha avuto bisogno di β2-short acting Chiedere al paziente di elencare i farmaci e gli orari in cui sono assunti
Esame fisico del paziente	Osservare la respirazione del paziente Contare il numero di atti respiratori al minuto Ascultare il torace
Dati obiettivi	Visionare le misurazioni del PEF Visionare il diario dei sintomi Eseguire una spirometria
Valutazione della capacità del paziente	Osservare l'esecuzione dell'erogazione del farmaco con MDI o con diskus o con altro sistema
Condivisione del piano terapeutico	Rileggere con il paziente il piano terapeutico

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Informazione del paziente

Informare i pazienti asmatici sulla loro malattia, su come valutarla e come gestire eventuali esacerbazioni ridurrà il numero delle visite al Pronto Soccorso, diminuirà la spesa sanitaria asma-correlata e migliorerà lo stato di salute, la qualità della vita e l'adesione alla terapia.

L'approccio educazionale nei centri di geriatria è una delle operazioni terapeutiche più importanti. Durante la prima visita, si dovrebbe valutare se il paziente avrà bisogno, o ha già, un'assistenza per la somministrazione dei farmaci, e se questa è data da membri della famiglia o da assistenti sociali. Molti dei farmaci per l'asma vengono somministrati per inalazione ed i pazienti più anziani hanno, spesso, problemi tecnici ad eseguire correttamente l'inalazione. Questo può dipendere da una ridotta funzione cognitiva, come è stato appurato dall'esecuzione dei Mini-Mental test, o da una concomitante menomazione fisica (21).

Si è visto che il paziente anziano può avere, comunque, problemi ad usare correttamente il sistema di erogazione del farmaco. Per valutare se i pazienti possono assumere autonomamente i farmaci, è utile utilizzare inalatori che non contengano il farmaco. Sulla base della capacità del paziente ad utilizzare l'inalatore, il medico potrà decidere di prescrivere una terapia per via inalatoria o per via orale.

Controllo dei fattori scatenanti e le condizioni di comorbilità nell'asma

Quando si effettua la valutazione iniziale del paziente è fondamentale cercare di identificare i fattori che possono peggiorare l'asma o scatenarne una riacutizzazione, in modo da intervenire su questi. Tra i fattori ambientali ricordiamo gli allergeni, le infezioni virali (più frequentemente) e quelle batteriche (più raramente), e gli irritanti ambientali aspecifici, come l'esposizione al fumo di sigaretta, i profumi, l'aria fredda e l'inquinamento. Anche i fattori psicosociali, come la depressione e l'isolamento sociale, possono essere causa di morbilità e mortalità per asma, ed è fondamentale determinare se questi fattori svolgono un ruolo importante nella storia clinica degli asmatici anziani.

Tutti i pazienti con asma persistente dovrebbero essere sottoposti a test allergologici, valutando, con particolare attenzione, gli allergeni 'indoor', visto che la maggioranza dei pazienti passa la maggior parte della propria giornata in ambienti chiusi. Nei pazienti allergici ad allergeni 'indoor' dovrebbero essere prese in considerazioni le misure per ridurre l'esposi-

zione ad essi già precedentemente descritte nella tabella 1. Il NHLBI raccomanda che, in tutti i pazienti con asma e con test allergologici positivi, debbano essere intraprese misure di prevenzione ambientale (5), anche se una recente revisione della Cochrane ha dimostrato che le misure di controllo ambientali non hanno un effetto rilevante sull'asma bronchiale. Un ulteriore studio ha però dimostrato che gli adulti più anziani con asma allergico, che non hanno instaurato un adeguato controllo ambientale, hanno una maggiore probabilità di essere ricoverati per esacerbazione della malattia.

Tutti i pazienti anziani con asma dovrebbero essere sottoposti alla vaccinazione per lo *Pneumococcus pneumoniae* ed alla vaccinazione annuale contro il virus dell'influenza. La vaccinazione per lo pneumococco deve avere una frequenza non superiore ai 5 anni, perché, con l'invecchiamento, le IgG opsonizzanti e la risposta vaccinale al polisaccaride tendono a diminuire (22).

Molti dei farmaci usati per la terapia dell'insufficienza cardiaca congestizia, per il glaucoma e per i dolori articolari possono aggravare l'asma. L'asma dei pazienti anziani è, quindi, a più elevato rischio di esacerbazioni, anche perché i pazienti possono assumere, per le loro comorbilità cardio-vascolari (ipertensione arteriosa e coronaropatie), β-bloccanti, come il propranololo, il nadololo e l'esmololo. Questi farmaci, per la mancanza di una adeguata selettività recettoriale, possono agire anche sui recettori β_2 del muscolo liscio delle vie aeree. Pertanto, nei pazienti che necessitano di una terapia con un β-antagonista, è meglio utilizzare un β_1-antagonista selettivo (metoprololo o atenololo), somministrando il dosaggio più basso possibile. In ogni caso, è sempre consigliabile valutare la funzione polmonare prima della prima somministrazione del farmaco, rivalutandola poi, dopo 2-3 ore. Spesso, comunque, accade che le terapie sono prescritte e gestite da diversi specialisti d'organo e non sono mai valutate collegialmente. Per esempio, l'uso di un β-bloccante come il timololo utilizzato per la terapia medica del glaucoma, può essere causa di un peggioramento dell'asma, fino al male asmatico. L'asma di alcuni pazienti può essere dovuto ad una ipersensibilità all'acido acetilsalicilico (ASA) o ai FANS. E' importante, in questi pazienti, scegliere terapie alternative, utilizzando, come antiaggregante, in alternativa all'ASA, la ticlopidina e, per il dolore osteo-articolare, il paracetamolo.

Altre malattie possono, infine, aggravare l'asma e dovrebbero, pertanto, essere attentamente considerate come la malattia da reflusso gastro-esofageo (GERD), spesso clinicamente silente. E' stato, infatti, riporta-

to che l'80% dei pazienti con asma hanno anche un GERD, e che nel 50% di questi il GERD è del tutto asintomatico. Anche l'obesità si associa ad un aumento della prevalenza e gravità dell'asma; in questi soggetti, la riduzione del peso corporeo si è dimostrata capace nel migliorare i sintomi dell'asma (23).

Terapia farmacologica

I farmaci usati per la terapia dell'asma nei pazienti anziani non sono diversi da quelli utilizzati nei pazienti più giovani. Tuttavia, bisogna fare alcune importanti considerazioni, soprattutto in merito al dosaggio dei farmaci, tenendo conto delle diverse vie metaboliche, alle interazioni farmacologiche, agli effetti collaterali, ai costi ed alle modalità di somministrazione.

Farmaci antinfiammatori

1) Corticosteroidi

Essendo l'asma una malattia infiammatoria cronica, tutti i pazienti, classificati come affetti da asma persistente, dovrebbero ricevere, quotidianamente, farmaci ad attività antinfiammatoria (11, 17, 18). I corticosteroidi sono i farmaci più efficaci per la terapia dell'asma. L'infiammazione delle vie aeree induce cambiamenti strutturali delle stesse ('remodelling') che, dal punto di vista funzionale, sono responsabili dell'ostruzione fissa, dimostrabile in molti asmatici, soprattutto di vecchia data. La mancata reversibilità dell'ostruzione bronchiale suggerirebbe che le modificazioni anatomiche delle vie aeree siano permanenti. In questi pazienti, i vantaggi derivanti dagli steroidi topici per via inalatoria possono essere ridotti. Per determinare, quindi, se i corticosteroidi inalatori avranno efficacia clinica, in questi particolari pazienti, essi vanno trattati, prima con corticosteroidi per via orale, alla dose di 0,3-0,5 mg/kg per 2 settimane, eseguendo, dopo tale periodo, una nuova spirometria ed un test di reversibilità con β_2-agonista short acting, valutando, quindi, se l'ostruzione bronchiale sia o meno reversibile.

I corticosteroidi possono essere somministrati per via inalatoria (ICS), attraverso un nebulizzatore, o per via orale o per via parenterale (i.m. o e.v.). Le ultime due vie sono utilizzate, in genere, per il trattamento delle esacerbazioni acute, tuttavia, in alcuni pazienti con asma grave, può essere necessaria la somministrazione quotidiana di corticosteroidi orali. Negli asmatici anziani, in genere, gli ICS sono prescritti con notevole difficoltà.

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Alcuni autori hanno rilevato che ben il 40% dei pazienti di età <65 anni viene dimesso dall'ospedale, dopo una esacerbazione acuta di asma, senza la prescrizione di un ICS. Altri gruppi hanno segnalato che meno di 1/3 dei pazienti asmatici con asma moderato-severo usa ICS e che il 39% di essi non assume alcun farmaco per l'asma.

La maggior parte degli studi che hanno valutato l'efficacia del trattamento con ICS sono stati eseguiti in pazienti giovani, e questo fa sì che i geriatri siano meno disponibili a prescrivere gli ICS nei pazienti asmatici più anziani. Inoltre, i pazienti asmatici anziani, per la presenza di un maggior numero di comorbidità, presentano una più bassa probabilità di avere una prescrizione di ICS. Le ragioni per la mancata prescrizione degli ICS possono, comunque, essere dovute, anche ad una scarsa conoscenza dell'importanza di questi farmaci nel trattamento dell'asma bronchiale.

Gli ICS sono somministrabili o attraverso un inalatore-dosatore (MDI) o attraverso inalatori di polvere secca. La tecnica di utilizzazione degli MDI è piuttosto impegnativa per molti pazienti anziani. L'utilizzazione dell'MDI con una camera da inalazione può rendere un po' più facile l'assunzione di questi farmaci con questo particolare sistema di erogazione. Alcuni ICS vengono dispensati mediante dispositivi erogatori di polvere secca, e tale sistema di erogazione può risultare più facile proprio nelle persone anziane. Se i pazienti non sono in grado di gestire gli ICS, si ricorrerà alla loro somministrazione per via aerosolica con nebulizzatori.

Gli ICS possono avere effetti collaterali locali, quali raucedine e candidiasi del cavo orale, che possono essere prevenute con i distanziatori e con il risciacquo della bocca dopo l'erogazione dell'ICS. Per dosi elevate di ICS, in genere > 1000 µg/die, aumenta la probabilità di assorbimento sistemico, con la possibilità degli stessi effetti collaterali dei corticosteroidi orali. Gli effetti avversi sistemici dei corticosteroidi comprendono: le ecchimosi, la debolezza muscolare, l'osteoporosi (con aumento del rischio di fratture), la depressione, la cataratta, il glaucoma, la perdita di denti, l'aumento della pressione sanguigna e l'intolleranza al glucosio. Dosi elevate di ICS possono, infine, sopprimere l'asse ipotalamo-ipofisi-surrene (HPA), ed aumentare il rischio di infezioni. Il rischio di osteoporosi è tra i più temuti nei pazienti anziani, per l'aumento del rischio di fratture ossee. Diversi studi suggeriscono che, nelle donne in periodo pre-menopausale, l'uso di ICS diminuisce la densità minerale ossea (BMD) in modo dose-dipendente.

E' quindi pleonastico sottolineare che devono essere privilegiati gli ICS a bassa biodisponibilità orale. Budesonide, fluticasone propionato, mo-

metasone hanno una biodisponibilità orale > 1%, mentre la biodisponibilità orale di beclometasone, triamcinolone e flunisolide è > 10%. I pazienti dovrebbero assumere la dose più bassa di ICS necessaria per controllare la loro malattia, preferibilmente < 1600 µg/die di dose equivalente di beclometasone. Infine, per ridurre gli effetti degli ICS sul riassorbimento osseo, i pazienti dovrebbero evitare l'assunzione eccessiva di alcol e prendere, ogni giorno, un supplemento di calcio con vitamina D. Il ruolo dei bifosfonati, nella prevenzione delle fratture in pazienti che assumono ICS, è tuttora controversa e gli studi hanno finora riportato risultati non univoci. Ogni paziente, quindi, che assume alte dosi di ICS è sottoposto a steroidoterapia per via orale, deve essere valutato misurando la BMD all'inizio del trattamento, e quindi dopo 6 mesi. Infine, pazienti che assumono alte dosi di ICS o corticosteroidi per via orale dovrebbero sottoporsi ad una visita oculistica ogni 6 mesi, per ridurre al minimo il rischio di cadute e, quindi di fratture.

Il rapporto tra cataratta e utilizzo di ICS sembra essere correlato all'età del paziente, ma non vi sono studi controllati e randomizzati in tal senso. Negli asmatici giovani, il rischio di cataratta non sembra secondario all'uso di ICS. Studi osservazionali condotti negli anziani hanno, invece, suggerito che l'uso di ICS è associato ad un significativo rischio di cataratta nucleare e subcapsulare. Di conseguenza, è prudente monitorare i pazienti anziani che assumono ICS con la lampada a fessura, esaminandoli almeno una volta ogni anno. Studi osservazionali hanno inoltre suggerito che i pazienti anziani, trattati con ICS, hanno un rischio maggiore di sviluppare il glaucoma, ma sono necessari ulteriori ricerche in tal senso.

E' riportata, infine, la comparsa di depressione, secondaria all'uso di corticosteroidi per via orale ma, ad oggi, non del tutto dimostrata (24).

2) Antileucotrieni

In pazienti con asma grave, il ricorso all'uso dei corticosteroidi per via orale è difficilmente evitabile. In questi pazienti bisogna tentare di: a) ottimizzare la terapia con ICS; b) mantenere i corticosteroidi per via orale a basso dosaggio, a giorni alterni; c) aggiungere risparmiatori di corticosteroidi. In questo senso, gli antileucotrieni sono una classe di farmaci antinfiammatori che, diversamente dai corticosteroidi, agiscono solo sui leucotrieni. Gli effetti farmacologici dei leucotrieni, sono molteplici: sono potenti broncocostrittori, hanno effetto chemiotattico sulle cellule infiammatorie reclutate nelle vie respiratorie, ed inducono ipersecrezione di muco. Le

azioni farmacologiche degli antileucotrieni sono: (a) inibire la formazione degli stessi a partire dall'acido arachidonico, inibendo la 5-lipossigenasi (zileuton), oppure (b) prevenire le azioni dei leucotrieni C_4 e D_4, antagonizzando il recettore dei cysteinyl-leukotrieni (zafirlukast e montelukast). Questi farmaci sono assunti per via orale, che rappresenta, sicuramente, una via facile di somministrazione, ma sia zileuton che zafirlukast e montelukast vengono metabolizzati a livello epatico, e questo può interferire con il metabolismo di altri farmaci, frequentemente utilizzati nei pazienti anziani, come il warfarin. Confrontando gli ICS con gli antileucotrieni, i primi risultano più efficaci. Gli antileucotrieni sono quindi, raccomandati come terapie alternative per i pazienti che non tollerano gli ICS. Solo due studi hanno esaminato il ruolo degli antileucotrieni in pazienti asmatici di età diverse ed hanno concluso che l'efficacia di questi farmaci è limitata nei pazienti anziani rispetto ai pazienti più giovani (25).

3) Teofillina

La teofillina aumenta i livelli intracellulari di adenosina monofosfato ciclico, dilatando le vie aeree e, a dosi più basse, presenta anche proprietà antinfiammatorie. L'utilizzo della teofillina nell'asma, specialmente nei pazienti più anziani, è limitato per il minore effetto broncodilatatore rispetto ai β-agonisti, e per i molti effetti collaterali e le interazioni farmacologiche. Di conseguenza, l'uso della teofillina nei pazienti anziani è, nel tempo, notevolmente diminuito. Se ad un paziente anziano è somministrata la teofillina, è fondamentale, nella gestione del farmaco, usare la dose più bassa possibile, monitorando i livelli sierici di teofillina, con l'obiettivo di raggiungere una concentrazione ematica compresa tra 8-12 μg/mL, inferiore a quella prevista nei pazienti più giovani (10-20 μg/mL).

Superando il range terapeutico, un paziente di età > 75 anni ha un rischio più elevato di presentare segni di tossicità del farmaco: cefalea, nausea, vomito, aritmie, agitazione e convulsioni. Il metabolismo della teofillina può essere diminuito nell'insufficienza cardiaca congestizia, nelle malattie epatiche croniche o con l'uso concomitante di farmaci, come la cimetidina, i calcio-antagonisti, l'eritromicina, i fluorochinoloni e l'allopurinolo (26).

4) Altri farmaci

Tra gli altri farmaci ad azione antinfiammatoria ricordiamo i cromoni (sodio cromoglicato e nedocromil sodico). Tuttavia, i benefici derivanti da questi farmaci sembrano maggiori nei pazienti asmatici giovani.

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Farmaci broncodilatatori

I β_2-agonisti sono classificati in 'a breve durata di azione' ('short acting', SABA), da usare al bisogno, in caso di difficoltà respiratoria acuta (SABA) e 'a lunga durata d'azione' ('long acting', LABA), adoperati come 'controller' dei sintomi ed in genere in associazione con gli ICS. Il numero dei β_2-recettori diminuisce con l'età, e quindi, i β_2-agonisti possono essere meno efficaci nei pazienti asmatici anziani; tuttavia, questi risultati non sono definitivi. I SABA sono relativamente sicuri nei pazienti anziani, se utilizzati per il trattamento delle esacerbazioni, ma, anche se il loro assorbimento è basso, ad alti dosaggi possono indurre tachicardia e tremori. Sia i SABA che i LABA devono essere usati con cautela nei pazienti con malattie cardiache e con ipertensione arteriosa, perché il loro sovradosaggio può causare aritmie pericolose per la vita ed anche ipokaliemia, soprattutto se usati contemporaneamente ai diuretici non risparmiatori di potassio, quali i tiazidici. I LABA dovrebbero essere utilizzati solo in aggiunta ai ICS, poiché, in monoterapia, potrebbero, nel lungo periodo, determinare un peggioramento dell'asma (27).

Gli anticolinergici (disponibili in forma nebulizzata), anche se indicati, soprattutto per il trattamento della BPCO, possono offrire alcuni vantaggi terapeutici nei pazienti anziani con asma, specialmente in quelli con una spiccata componente ipersecretiva. Tuttavia, l'uso dell'ipratropio bromuro, in pazienti anziani asmatici, è stato associato ad un lieve aumento della mortalità, probabilmente secondario al fatto che questi pazienti presentano, di per sé, un asma più grave. Comunque, gli anticolinergici, per i loro effetti atropino-simili, possono indurre diversi effetti collaterali, soprattutto nelle persone anziane: secchezza delle fauci, ritenzione urinaria, stipsi ed esacerbazione del glaucoma (28).

Anti-IgE (omalizumab)

La molecola anti-IgE omalizumab è stata approvata dalla FDA e dall'EMEA per il trattamento dell'asma allergico grave, non controllato dalle terapie convenzionali. Le sperimentazioni cliniche sono state condotte in pazienti d'età inferiore ai 75 anni. L'uso di anti-IgE diminuisce il numero delle esacerbazioni asmatiche e l'uso dei corticosteroidi sistemici, migliorando la qualità della vita. La terapia con anti-IgE rappresenta un trattamento molto costoso e può essere indicato solo in pazienti che necessitano spesso di corticosteroidi per via orale, in aggiunta all'associazione

ICS + LABA, per il controllo dell'asma. Sebbene negli studi clinici l'omalizumab abbia un profilo di sicurezza comparabile a quello del placebo, il suo uso è stato associato con l'insorgenza di tumori maligni (0,5% vs 0,2% con placebo). Sono state riportate, anche rare reazioni anafilattiche. Le anti-IgE possono essere usate in pazienti con un peso corporeo < 150 kg e con una concentrazione sierica di IgE < 700 UI/ml (29).

CONCLUSIONI

Anche se la rinite allergica e l'asma bronchiale sono, prevalentemente, malattie pediatriche e dei soggetti giovani, esse non sono rare in pazienti di età geriatrica, dove sono spesso non diagnosticate ed adeguatamente trattate. Il primo passo, infatti, per porre la diagnosi di una malattia allergica in pazienti anziani è quello, innanzitutto, di prenderla in considerazione. Le tecniche diagnostiche sono uguali nei pazienti giovani e anziani, ma in questi ultimi devono essere considerate più malattie nel processo diagnostico differenziale. Il trattamento, sia della rinite allergica che dell'asma, in pazienti anziani, è complicato dalla potenziale presenza di altre patologie e dalle possibili interazioni farmacologiche. Gli studi sulla diagnosi e la terapia delle malattie allergiche respiratorie nei pazienti anziani sono limitati, rendendone più difficile la gestione complessiva. Sia la rinite che l'asma possono interferire con la qualità della vita del paziente, e l'asma può causare una significativa morbilità e mortalità. Pertanto, poiché la nostra popolazione invecchia, è fondamentale redigere protocolli diagnostici e terapeutici per la rinite allergica e l'asma, mirati proprio sulla popolazione dei pazienti anziani.

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CHAPTER 5

CLINICAL lMPORTANCE OF EOSINOPHIL COUNT IN NASAL FLUID IN PATIENTS WITH ALLERGIC AND NON-ALLERGIC RHINITIS

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CLINICAL lMPORTANCE OF EOSINOPHIL COUNT IN NASAL FLUID IN PATIENTS WITH ALLERGIC AND NON-ALLERGIC RHINITIS

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Eosinophil count in nasal ftuid (ECNF) was used to differentiate nasal pathologies. Receiver Operating Characteristic (ROC) curve analysis and the area under the curve (AVC) were performed to evaluate the ECNF's accuracy in distinguishing allergie rhinitis (AR) from non-allergie rhinitis (NAR). We also evaluated the accuracy of ECNF in recognizing patients with mild and severe symptoms of rhinitis and patients with ineffective and effective clinical responses to antihistamines. 1,170 consecutive adult patients with a clinical history of rhinitis were studied. ECNF's median in AR was 6.0 and 2.0 in NAR and the best cut-offvalue was > 3.0,AVC = 0.75. ECNF's median inAR with mild nasal symptoms was 3.0 and 7.0 with severe symptoms, and the best cut-offvalue was 4.0, AVC =0.90. ECNF's median in NAR with mild nasal symptoms was 2.0 and 8.5 with severe symptoms, and the best cut-off value was > 4.0, AVC = 0.86. ECNF's median in AR with effective clinical response to antihistamines was 4.0 and 8.0 with ineffective response, the best cut-off value was :5 5.0, AVC = 0.94. ECNF's median in NAR with an effective clinical response to antihistamines was 1.0 and 2.0 with ineffective response, and the best cut-off value was :5 3.0, AVC =

0.64. Our results suggest an interesting practical use of ECNF data as evaluator of the clinical severity both AR and NAR. As predictor of the clinical response to antihistamines, ECNF is accurate only in patients with AR. The ECNF's performance was moderately accurate in distinguish patients with AR and NAR.

Key words: eosinophil count in nasal fluid, allergy rhinitis, non-allergic rhinitis, receiver operating characteristic curve

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Chapter 5

The most common diagnostic tests for allergic rhinitis are the Skin Prick Test (SPT) and the determination of serum allergen-specific IgE. A less common diagnostic tool is nasal cytology. Nasal cytology is generally employed by subspecialists or in research, but does not play a role in the routine evaluation of rhinitis (1). The techniques for obtaining cells for cytology in lavage, or brushings, have not been standardized as the criteria for evaluating cell counts (2). Nasal lavage is the reference method among adult patients (3). Brushing was compared to lavage among adults by Juliusson et al. They found a strong correlation between the two methods regarding the percentage of eosinophils (4). Therefore, the use of nasal cytology to evaluate mucosal cellular patterns has the potential to distinguish inflammatory from non-inflammatory nasal conditions, to follow the course of an allergic disease and to evaluate the response to the treatment (5-6). Previously, we evaluated the importance of eosinophil count in nasal fluid (ECNF) (7-11), hence, we use ECNF routinely, integrating it in diagnostic tests: i.e. SPT and total and allergen-specific IgE assays.

Other investigators have studied nasal cytology in relationship to various upper respiratory diseases (2, 12-13). However, few prospective studies evaluating the diagnostic utility of nasal cytology in allergic rhinitis have been performed (14-17).

The accuracy of a diagnostic test is characterized by its sensitivity and specificity. However, the sensitivity and specificity of a test depends on the level that has been chosen as the cut-off to distinguish two conditions, i.e. normal or abnormal. Therefore, if the results of a clinical test, i.e. ECNF, are quantitative and provided on a continuous scale, the Receiver Operating Characteristic (ROC) curve is widely accepted as a method for selecting an optimal cut-off point for the test (18-20). The ROC curve is also important because the area under the curve (AUC) is a reflection of how good the test is to distinguish between the presence or the absence of a clinical characteristic. The greater the AUC, the better the test (20-21).

The characteristics of the ROC curve was used to evaluate the discriminating value of ECNF between patients with AR and patients with NAR, between patients with mild and severe nasal symptoms, and between patients with effective and ineffective response to antihistamines.

MATERIALS AND METHODS

Patients

Between March 2001 and October 2005, 1,170 consecutive adult patients with a clinical history of rhinitis were tested at the Outpatient Allergy Unit of the Department of Clinical Medicine and Emerging Diseases, University of Palermo, Italy. At the time of the first visit all the included patients had been symptomatic for rhinitis symptoms for at least two years. Patients with nasal polyps, and/or symptoms of asthma, urticaria, or eczema were excluded from the study. All the study patients had taken antihistamines in the past. However, no patient had taken any medication for at least 5 days before the first visit.

Diagnostic process

A detailed questionnaire, concerning the history of rhinitis and the severity of nasal symptoms, was filled out by the patients, under the supervision of the authors (GDL and PM). The questionnaire used in this study was the same used for the selection of the patients in a randomized control trial study that compared placebo, an intranasal H1-antihistamine and an intranasal steroid in patients with AR (8). Nasal symptoms were judged mild if they did not interfere with work and sleep, and severe if they did (1). Nasal appearance was examined by anterior rhinoscopy. Special attention was directed to the occurrence of nasal secretion and changes in the mucosa of the *conchae* (3). We performed the SPT and nasal cytology, using nasal lavage. All these tests were performed at the first visit. During the diagnostic process, patients were also asked to state if the rhinitis symptoms were controlled by antihistamines, indicating 'Yes' or 'No' (22).

The Institutional Review Board approved the study, which was conducted according to the Declaration of Helsinki. Authorization of the study was not required according to our institutional policy and the ethical committee of our institution because ENCF was used routinely among the diagnostic tests. However, written informed consent to the study was obtained from each patient in compliance with our institutional policy.

Skin Prick Test

Patients performed the SPT using standard aeroallergens panels (Alk Abellò, Milan, Italy) that are present in our geographical area. The SPT was performed and evaluated on the volar aspect of the forearm. The panel included the following extracts: grass (*Phleum pratense, Dactila glomerara, Festuca elator, Lolium perenne, Poe pratensis)*; weeds [mugwort (*Artemisia vulgaris*), pellitory-of- the-wall or sticky weed [(*Parietaria judaica)* and *Salsola kali*]; trees [birch (*Olea europea* and *Cupressus)*]; house dust mite (HDM, *Dermatophagoides pteronyssinus* and *farinae*); moulds (*Alternaria alternata, Cladosporium erbarium* and *Aspergillus fumigatus*); animal dander (cat and dog), plus a negative (glycerinated saline) and a positive control (histamine, 10 mg/mL). Positive responses were defined as any wheal with a diameter 3 mm greater than the negative control, 15 min after application. The wheal diameters were reported for each patient (23-24).

Eosinophil Count in Nasal Fluid

Nasal lavage was performed using a disposable metered-dose nasal inhaler (Markos, Monza, Italy) filled with sterile, room-temperature, normal saline solution. The

device consists of a plastic cup with two compartments. The central compartment was filled with sterile saline solution while the external compartment collected the liquid after washing. Total input of saline solution was approximately 8 mL (4 mL in each nostril for 5 min). To collect the nasal washings, the subjects were instructed to actively breathe during a Valsalva maneuver in order to harvest nasal fluid in the cup. The samples obtained were stored on ice and centrifuged at 400 *g* for 10 min at 4°C. The individual variation in the recovered *vs.* introduced volume was 86% ± 8%. Nasal eosinophil counts were performed on nasal lavage. One cytospin slide for each sample ($1x10^{-4}$ cells in 170 mL per slide) was centrifuged at 10 *g* for 10 min in a Shandon cytocentrifuge (Shandon Southern Ltd, Runcorn, Cheshire, UK). The slides were immediately fixed in 95% ethyl alcohol, dipped in Wright-Giemsa stain, and examined under oil immersion by light microscopy at a magnification of 400x. Eosinophils were expressed as a percentage of 300 cells counted (7, 10-11).

All specimens were examined by the same blinded microscopist (VD), without knowing the clinical histories, the results of the SPT, the severity of the rhinitis symptoms, or the subjects' clinical responses to antihistamines.

Statistical analysis

In order to distribute the data, the results are presented as an arithmetic mean (normally distributed) and a confidence interval of 95% (95%CI) and analyzed using Student's *t* test. If the normal distribution of data was rejected, the results are presented as median and 25th and 75th percentiles (P25th and P75th), and analyzed using the Mann-Whitney U-test. For statistical analyses a value of P = 0.05 was considered statistically significant. To define sensitivity, specificity, positive likelihood ratio (LR+), and negative likelihood ratio (LR-) of ECNF we analyzed the ROC curve analysis.

The ROC curve is a graphical technique for assessing the ability of the ECNF to discriminate between subjects with AR and subjects with NAR. ROC curves allow visual analyses of the trade-offs between the sensitivity and the specificity of a test with regard to the various cut-off values that may be used. The curve is obtained by calculating the sensitivity and specificity of the test at every possible cut-off point, and plotting sensitivity against 100-specificity.

One way of interpreting the area under the ROC curve is that an AUC $\geq$ 0.90 indicates high accuracy, while between 0.89 to 0.70 indicates moderate accuracy, between 0.69 to 0.51 low accuracy, and $\leq$ 0.50 a chance result (20-21, 25-26).

RESULTS

The study population comprised 1,170 adult patients, 651 females and 519 male, aged 18 to 81 years [mean age 34.6 years (95%CI 33.8-35.3)] (Fig. 1). All 1,170 patients referred symptoms of rhinitis going back at least two years. The mean of the years of the onset of nasal symptoms was 7.08 (95%CI 6.68-7.48). Patients reported at least two of the following symptoms of rhinitis: sneezing, watery and/or mucous rhinorrhea, nasal itch, and nasal obstruction. All the patients had previously taken antihistamines for their nasal symptoms and 163 also decongestants, 115 anti-cholinergics, 88 nasal corticosteroids, 53 oral corticosteroids, and 47 systemic corticosteroids. The SPT was positive in 827 patients (70.7%) and negative in 343 patients (29.3%). The SPT was positive to pollens in 348 patients (grass and/or *Artemisia vulgaris* and/or *Parietaria judaica* and/or *Olea Europea* and/or *Cupressus*), in 108 patients to perennial allergens (HDM and/or cat and/or dog dander), and in 371 patients to both pollen and perennial allergens. The frequency of the distributions of the ECNF in AR and in NAR patients are reported in Fig. 2 and it show an important overlap between AR and NAR.

ECNF and AR and NAR

The medians of ECNF were significantly different between patients with AR [6.0 (P25th and P75th 4.0-8.0)] and patients with NAR [2.0 (P25th and P75th 1.0-4.7)] ($P < 0.0001$). The ECNF was not significantly different among patients with SPT positive only to pollens [6.0 (P25th and P75th 4.0-8.0)], only to HDM and/or cat and/or dog dander [5.0 (P25th and P75th 4.0-8.0)], and both to pollens and to HDM and/or cat and/or dog dander [6.0 (P25th and P75th 4.0-8.0)] ($P = 0.7$).

The ROC curve is shown in Fig. 3a. The best cut-off point between patients with AR and NAR was > 3.0 [sensitivity 0.79 (95%CI 0.76-0.82) and specificity 0.66 (95%CI 0.61-0.71), LR+ 2.37 (95%CI 2.20-2.60) and LR- 0.31 (95%CI 0.30-0.40)], and the AUC was 0.75 (95%CI 0.72-0.77). Fig. 3b shows the number of patients with positive and negative SPT in respect to the best cut-off (> 3.0) of ECNF. Considering that the ECNF was moderately accurate for distinguishing AR from NAR patients, we examined ECNF in respect to the severity of nasal symptoms (mild vs severe) and the clinical response to antihistamines (effective vs

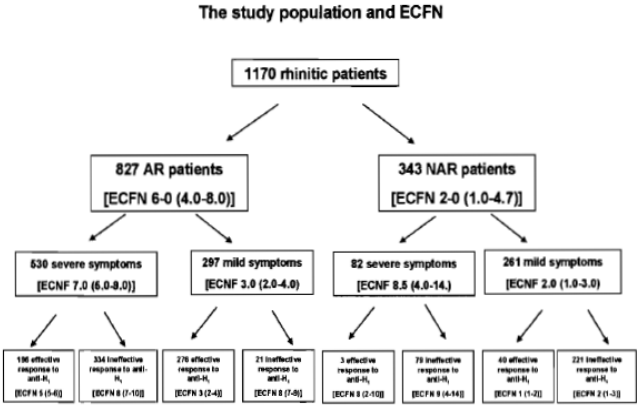

Fig. 1. *Diagram flow chart of schematic characteristics of the patients and medians (25th and 75th percentiles) of ECNF.*

ineffective) separately, in patients with AR and with NAR.

ECNF and the severity of nasal symptoms

Among AR patients, 530 (64.0%) indicated their rhinitis as severe and 297 (36.0%) as mild, while among NAR patients 261 (76.0%) defined their rhinitis as mild and 82 (24%) as severe ($P < 0.0001$). We found a significant difference in the ECNF between patients with nasal symptoms indicated as severe [7.0 ($P25^{th}$ and $P75^{th}$ 5.0-9.0)] and as mild [3.0 ($P25^{th}$ and $P75^{th}$ 2.0-4.0)] in patients with AR ($P < 0.0001$). Fig. 4a shows the ROC curve obtained from patients with AR. The best cut-off point of ECNF was > 4.0 [sensitivity 0.90 (95%CI 0.88-0.93) and specificity 0.84 (95%CI 0.79-0.88), LR+ 5.73 (95%CI 5.40-6.10) and LR- 0.11 (95%CI 0.08-0.20)]; the AUC was 0.90 (95%CI 0.88-0.92). Fig. 4b shows the number of patients with mild and severe symptoms in respect to the best ECNF cut-off (> 4.0).

Similarly, we found a significant difference in the ECNF between patients with nasal symptoms indicated as severe [8.5 ($P25^{th}$ and $P75^{th}$ 4.0-14.0)] and as mild [2.0 ($P25^{th}$ and $P75^{th}$ 1.0-3.0)] in patients with NAR ($P < 0.0001$). The ROC curve obtained from patients with NAR is shown in Fig. 5a. The best cut-off point of ECNF was > 4.0 [sensitivity 0.74 (95%CI 0.63-0.83) and specificity 0.90 (95%CI 0.86-0.93), LR+ 7.77 (95%CI 6.80-8.90) and LR- 0.28 (95%CI 0.20-0.50)]; the AUC was 0.86 (95%CI 0.82-0.90). Fig. 5b shows the number of patients with mild and severe symptoms in respect to the best ECNF cut-off (> 4.0).

We did not find statistical differences between the ECNF in severe AR [7.0 ($P25^{th}$ and $P75^{th}$ 5.0-9.0)] and in severe NAR [8.5 ($P25^{th}$ and $P75^{th}$ 4.0-14.0)] ($P = 0.2$). On the contrary, we found statistical differences between mild AR [3.0 ($P25^{th}$ and $P75^{th}$ 2.0-4.0)] and mild NAR [2.0 ($P25^{th}$ and $P75^{th}$ 1.0-3.0)] ($P < 0.0001$).

ECNF and the clinical response to antihistamines

Of the 472 (57.0%) patients with AR, 196 (37%) with severe symptoms and 276 (97%) with mild symptoms, judged the clinical response to antihistamines as effective, and 355 (43.0%) as ineffective, of whom 334 (63%) with severe symptoms and 21 (3%) with mild symptoms. While among patients with NAR only 43 (12.5%), 3 (3.7%) with severe symptoms and 40 (15.3%) with mild symptoms, judged the clinical response to

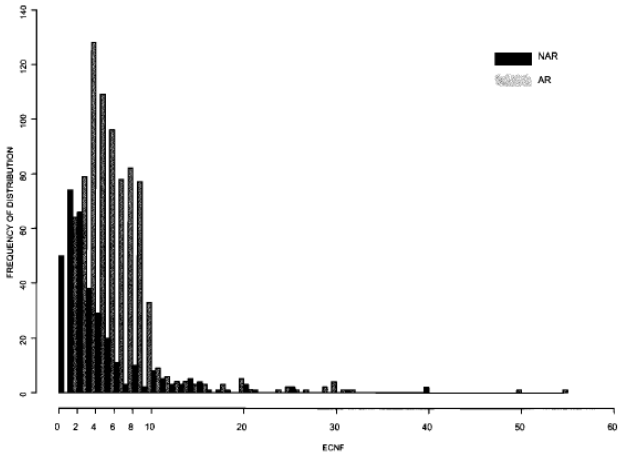

Fig. 2. *Distribution of ECNF values in patients with AR and in patients with NAR. In patients with AR the lower value was 1.0 and the higher value was 55.0, the coefficient of Skewness and the coefficient of Kurtosis were 4.1 and 28.1, respectively. In patients with NAR the lower value was 0.0 and the higher value was 40.0, the coefficient of Skewness and the coefficient of Kurtosis were 3.2 and 14.6, respectively.*

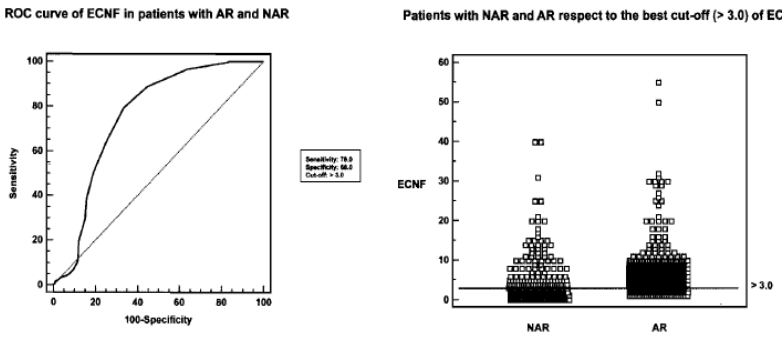

Fig. 3. ***a)*** *The ROC curve obtained in patients with AR and NAR (Nº patients = 1170). The best cut-off point of ECNF between patients with AR and NAR was > 3.0 [sensitivity 0.79 (95%CI 0.76-0.82) and specificity 0.66 (95%CI 0.61-0.71), LR+ 2.37 (95%CI 2.20-2.60) and LR- 0.31 (95%CI 0.30-0.40)], and the AUC was 0.75 (95%CI 0.72-0.77).* ***b)*** *Number of patients with positive and negative SPT in respect to the best cut-off (> 3.0) of ECNF.*

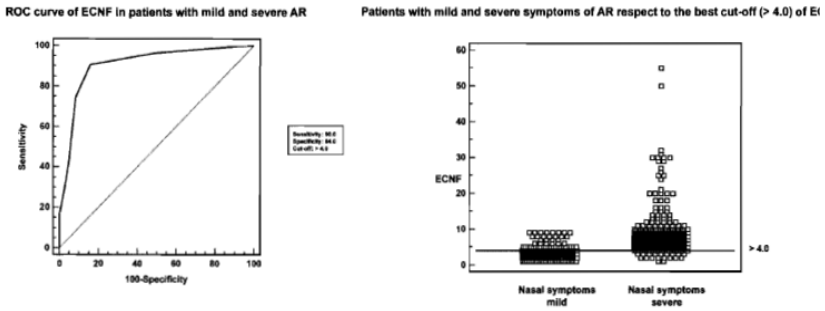

Fig. 4. ***a)*** *The ROC curve obtained in patients with AR and mild and severe nasal symptoms (N° patients with AR = 827). The best cut-off point of ECNF between patient with mild and severe nasal symptoms was > 4.0 [sensitivity 0.90 (95%CI 0.88-0.93) and specificity 0.84 (95%CI 0.79-0.88), LR+ 5.73 (95%CI 5.40-6.10) and LR- 0.11 (95%CI 0.08-0.20)]; the AUC was 0.90 (95%CI 0.88-0.92).* ***b)*** *Number of patients with mild and severe symptoms in respect to the best ECNF cut-off (> 4.0).*

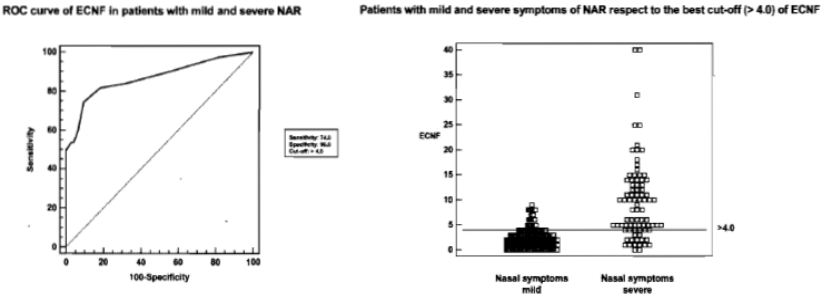

Fig. 5. ***a)*** *The ROC curve obtained in patients with NAR and mild and severe nasal symptoms (N° patients with NAR = 343). The best cut-off point of ECNF between patient with mild and severe nasal symptoms was > 4.0 [sensitivity 0.74 (95%CI 0.63-0.83) and specificity 0.90 (95%CI 0.86-0.93), LR+ 7.77 (95%CI 6.80-8.90) and LR- 0.28 (95%CI 0.20-0.50)]; the AUC was 0.86 (95%CI 0.82-0.90).* ***b)*** *Number of patients with mild and severe symptoms in respect to the best ECNF cut-off (> 4.0).*

antihistamines as effective compared to 300 (87.5%) as ineffective, of whom 79 (96.3%) with severe symptoms and 221 (84.7%) with mild symptoms (P < 0.0001).

There was a significant difference in the ECNF between patients with an effective [4.0 ($P25^{th}$ and $P75^{th}$ 3.0-5.0)] and an ineffective response to antihistamines [8.0 ($P25^{th}$ and $P75^{th}$ 7.0-9.0)] in patients with AR (P < 0.0001). Fig. 6a shows the ROC curve obtained in patients with AR and effective and ineffective clinical response to antihistamines. The best cut-off point of ECNF was ≤ 5.0 [sensitivity 0.83 (95%CI 0.79-0.86) and specificity 0.95 (95%CI 0.92-0.97), LR+ 18.43

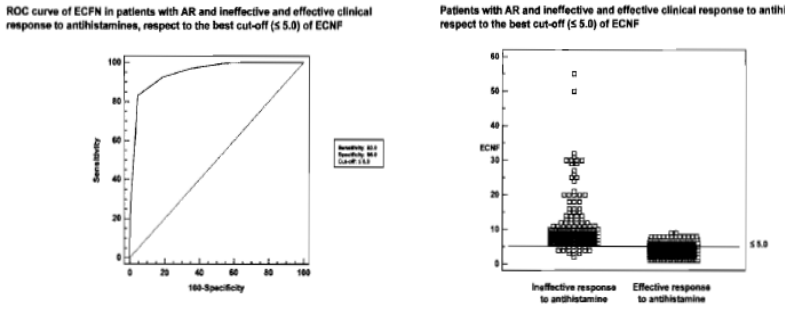

Fig. 6. ***a)*** *The ROC curve obtained in patients with AR and ineffective and effective clinical response to antihistamines (N° patients with AR = 827). The best cut-off point of ECNF was ≤ 5.0 [sensitivity 0.83 (95%CI 0.79-0.86) and specificity 0.95 (95%CI 0.92-0.97), LR+ 18.43 (95%CI 17.60-19.30) and LR- 0.18 (95%CI 0.10-0.30)]; the AUC was 0.94 (95%CI 0.93-0.96).* ***b)*** *Number of patients with effective and ineffective clinical response to antihistamine in respect to the best cut-off (≤ 5).*

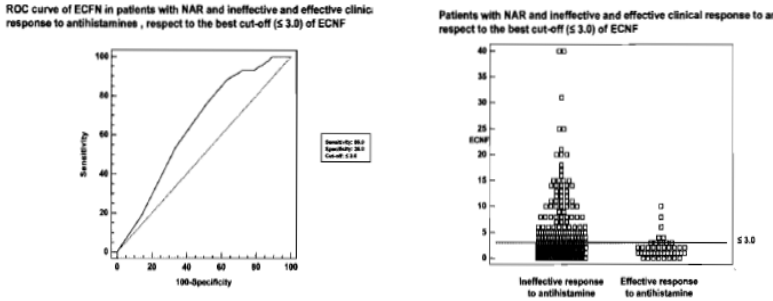

Fig. 7. ***a)*** *The ROC curve obtained in patients with AR and ineffective and effective clinical response to antihistamines (N° patients with NAR = 343). The best cut-off point was ≤ 3.0 [sensitivity 0.88 (95%CI 0.74-0.96) and specificity 0.36 (95%CI 0.31-0.42), LR+ 1.40 (95%CI 1.20-1.70) and LR- 0.32 (95%CI 0.10-0.70)]; the AUC was 0.64 (95%CI 0.59-0.69).* ***b)*** *the number of patients with effective and ineffective clinical response to antihistamine in respect to the best cut-off (≤ 3).*

(95%CI 17.60-19.30) and LR- 0.18 (95%CI 0.10-0.30)]; the AUC was 0.94 (95%CI 0.93-0.96). Fig. 6b shows the number of patients with ineffective and effective clinical response regarding the best ECNF cut-off (≤ 5.0).

With regard to patients with NAR, we found a significant difference of ECNF between patients with an effective [1.0 ($P25^{th}$ and $P75^{th}$ 1.0-2.0)] and an ineffective response to antihistamines [2.0 ($P25^{th}$ and $P75^{th}$ 1.0-5.0)] (P = 0.001). The ROC curve obtained in the patients with NAR and effective and ineffective clinical response to antihistamines is shown in Fig. 7a. The best cut-off point was ≤ 3.0 [sensitivity 0.88 (95%CI 0.74-0.96) and specificity

0.36 (95%CI 0.31-0.42), LR+ 1.40 (95%CI 1.20-1.70) and LR- 0.32 (95%CI 0.10-0.70)]; the AUC was 0.64 (95%CI 0.59-0.69). Fig. 7b shows the number of patients with ineffective and effective clinical response in respect to the best ECNF cut-off (≤ 3.0).

DISCUSSION

Our results demonstrate that the ECNF's performance was moderately accurate in distinguishing patients with AR and NAR. However, ECNF showed high accuracy in distinguishing patients with mild rhinitis from patients with severe rhinitis, both in patients with AR and with NAR. Finally, the ECNF had high accuracy in identifying patients with an effective clinical response to antihistamines from patients with an ineffective response, only in patients with AR. The low accuracy of the ECNF in patients with NAR can be traced to several factors. NAR is a heterogeneous disease, and the diagnosis is more problematic than AR because it is made after the exclusion of the IgE-mediated causes. Basically, NAR presents both with and without eosinophilia of nasal mucosa. NAR without the eosinophilia syndrome include vasomotor rhinitis, hormonal rhinitis, occupational rhinitis (irritant subtype), gustatory rhinitis, rhinitis *medicamentosa*, and drug-induced rhinitis. NAR with eosinophilia syndrome (NARES) presents with signs and symptoms that mimic allergic disease, but the patients do not have an identifiable allergen and have negative skin test results. When these patients are symptomatic, a nasal smear with 5-25% of eosinophils confirms the diagnosis.

These considerations might explain why the ECNF present a moderate accuracy (AUC = 0.75) in discriminating AR patients from NAR patients, and a low accuracy (AUC = 0.64) in identifying NAR patients with an effective clinical response to antihistamines.

In AR the tissue recruitment of eosinophils is a hallmark of the natural history of the disease and of untreated allergic inflammation with nasal steroids (7, 27-28). In NARES the cause of eosinophilia is unclear. However, both AR and NAR with eosinophilia have more severe symptoms, particularly nasal obstruction and rhinorrhea (7-11). Eosinophilia, both in patients with AR and with NAR, may contribute to nasal mucosal dysfunction, through the granules released from eosinophil (i.e. the major basic protein and eosinophil cationic protein) that are capable of damaging the nasal epithelium and prolonging mucociliary clearance (9-11). Intranasal steroid therapy has been employed to reduce the recovery of eosinophils in nasal lavage, when used on a regular basis (27) or on an as-needed basis (28). Some studies have shown that intranasal corticosteroids are particularly effective in the treatment of NAR when nasal eosinophilia is present (29). The options in the treatment of NAR patients who have few or no eosinophilia in nasal smears include either non-specific, broad-based therapy aimed at multiple symptoms or, alternatively, therapy tailored to treat specific symptoms (30-31). The effectiveness of intranasal corticosteroid therapy in NAR without eosinophils has not been clearly demonstrated (12, 29, 31-33). Nonetheless, there is a clinical impression that intranasal corticosteroids are not as effective in NAR without eosinophils, as in NARES (29, 34). With regard to the treatment with antihistamines, currently there are only few studies that have evaluated the effectiveness of these drugs in patients with NAR, with and without eosinophilia. Our results showed that the antihistamines were judged less effective by patients suffering from NAR in respect to those with AR, and that the ECNF have a low predictive power of effective clinical response to antihistamines, in respect to that of ECFN in AR patients.

The monitoring of nasal airway inflammation and cell recruitment, in clinical trials and in real-life medical practice, might provide insight into the mechanism of action of the therapeutic intervention, and in monitoring clinical severity of the disease and/or the response to the prescribed therapy (1).

Nasal lavage is relatively non-invasive, is easy and rapid to perform, is well tolerated, and is repeatable over relatively short periods. Nasal brushing is easy to perform and is well tolerated in general, although some find that the procedure causes a transient unpleasant sensation. However, nasal lavage offers the advantage of providing considerably greater information from the sample. Finally, nasal biopsy is a considerably more invasive procedure and requires expertise, not only in tissue

sampling but also in biopsy processing. Therefore, it is applicable only in specialist centers (1-3, 5-6). Although these approaches have been widely used in the limited research setting, they have been less widely applied as a means of objectively monitoring nasal disease in the clinical trial and/or in real-life clinical practice setting (14-17).

Our study demonstrates that ECNF might be of practical utility in real-life clinical allergology and found that the areas under the ROC curves of the ECNF presented a high accuracy as regards the severity of nasal symptoms (mild *vs.* severe) and the response to antihistamines (effective *vs* ineffective), 0.90 and 0.94, respectively, in patients with AR, while in patients with NAR only the AUC of the severity of the nasal symptoms was of moderate accuracy (AUC = 0.86). This result seems to be due to the fact that patients with NAR may or may not have eosinophilia in their nasal fluid (35).

In conclusion, our results suggest an interesting practical use of ECNF data as an evaluator of the clinical severity of rhinitis, both allergic and non-allergic. As predictor of the clinical response to antihistamines, ECNF is accurate only in patients with positive SPT and, finally, the ECNF's performance was moderately accurate in distinguishing patients with AR and NAR.

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CHAPTER 6

Differences and Similarities between Allergic and Nonallergic Rhinitis in a Large Sample of Adult Patients with Rhinitis

Chapter 6

Symptoms

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Differences and Similarities between Allergic and Nonallergic Rhinitis in a Large Sample of Adult Patients with Rhinitis Symptoms

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Key Words
Allergic rhinitis · Non allergic rhinitis · Skin prick test · Peak nasal inspiratory flow · Blood eosinophil · Nasal eosinophil · Visual analog scale · Receiver operating characteristic

Abstract
Background: Allergic rhinitis (AR) and nonallergic rhinitis (NAR) may present with different clinical and laboratory characteristics. ***Methods:*** A total of 1,511 consecutive patients, aged 18–81 years, diagnosed with rhinitis, 56% females and 44% males, underwent complete allergic evaluation including skin prick test, blood eosinophil counts, nasal eosinophil counts, peak nasal inspiratory flow (PNIF) measurement and evaluation of nasal symptoms using a visual analog scale (VAS). ***Results:*** A total of 1,107 patients (73%) had AR, whereas 404 (27%) had NAR. Patients with NAR were older and predominantly female. A higher nasal eosinophils count was associated with AR and a lack of clinical response to antihistamines. AR patients had more sneezing and nasal pruritus, whereas NAR was characterized mainly by nasal obstruction and rhinorrhea. AR patients had more severe symptoms and recurrent conjunctivitis, whereas NAR patients had slightly more frequent episodes of recurring headaches as well as olfactory dysfunction. PNIF, blood eosinophil counts and VAS of nasal symptoms were higher in patients with AR. In a final logistic regression model, 10 variables were statistically different between AR and NAR: age [OR 0.97 (95% CI 0.96–0.98)], sneezing [OR 4.09 (95% CI 2.78–6.00)], nasal pruritus [OR 3.84 (95% CI 2.60–5.67)], mild symptoms [OR 0.21 (95% CI 0.09–0.49)], intermittent/severe nasal symptoms [OR 3.66 (95% CI 2.06–6.50)], VAS [OR 1.06 (95% CI 1.04–1.08)], clinical response to antihistamines [OR 22.59 (95% CI 13.79–37.00)], conjunctivitis [OR 4.49 (95% CI 2.86–7.05)], PNIF [OR 1.01 (95% CI 1.00–1.01)] and nasal eosinophil counts [OR 1.14 (95% CI 1.10–1.18)]. Receiver operating characteristic analysis showed high predictive accuracy for a model including these variables independently of the diagnosis of AR/NAR (cutoff <0.74). ***Conclusions:*** We showed that the several clinical and laboratory parameters reported above may help to reinforce or exclude the diagnosis of AR obtained with skin prick test.

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Chapter 6

Introduction

Rhinitis is an inflammation of nasal mucosa resulting in nasal secretions that are nonpurulent and watery. In noninfectious rhinitis the eosinophils are the predominant inflammatory cell type found [1]. Noninfectious rhinitis includes both allergic rhinitis (AR) and nonallergic rhinitis (NAR). AR is further divided into two groups: seasonal and perennial. An alternative classification system based on the severity of the nasal symptoms and frequency has been proposed by the Allergic Rhinitis and Its Impact on Asthma (ARIA) trial [2, 3].

NAR is a less well-defined condition oftentimes being a diagnosis of exclusion, considered when a patient is found to have negative skin tests or serum specific IgE, in the absence of any sign of infection [4]. Despite having different characteristics, such as skin test reactivity, AR and NAR may share several common features. Few previous studies have addressed the similarities and differences between AR and NAR in a clinical setting [5, 6].

We report the demographic and clinical similarities and differences between AR and NAR. The primary objective of this study was to find clinical and objective parameters that, in addition to the result of the skin prick test (SPT), were predictive of allergic rhinitis. The second was to identify patient characteristics in accordance with the ARIA classification system.

Methods

All patients over the age of 18 years with a diagnosis of rhinitis were consecutively seen and evaluated in the outpatient allergy office of the Dipartimento di Medicina Clinica e delle Patologie Emergenti of the University of Palermo, Italy. This evaluation consisted of the following: skin test (SPT), blood eosinophil count (b-eos) and a nasal lavage with eosinophil count (n-eos). Assessment symptoms were: sneezing, rhinorrhea, nasal pruritus and nasal obstruction. These were graded with the following scale: 0 = absent, 1 = mild (symptoms were present but not troublesome), 2 = moderate (symptoms were present but did not interfere with normal activity) and 3 = severe (symptoms were troublesome and interfered with normal activity) [7]. The severity of all nasal symptoms was evaluated by patients using a visual analog scale (VAS) [8] and was classified, in accordance with ARIA guideline, as severe if there was one or more of the following items: sleep disturbance; impairment of daily activities, leisure or sport; impairment of school or work; or troublesome symptoms. Rhinitis in the absence of all these qualifiers was classified as mild. The nasal symptoms were also classified as intermittent or persistent with intermittent symptoms defined as the presence of symptoms <4 days a week or <4 weeks per year and persistent symptoms defined as symptoms more frequent than this [3]. Other symptoms reported by patients that correlated with rhinitis were headache, olfactory dysfunction and dysphonia. Headache and dysphonia were dichotomized and reported as present or absent. Olfactory dysfunction was graded as 0 = normal function, 1 = hyposmia and 2 = anosmia.

The study was approved by the Institutional Review Board of the Dipartimento di Medicina Clinica e delle Patologie Emergenti of the University of Palermo, Italy, and it was conducted according to the Declaration of Helsinki. Authorization of the study was not required according to our institutional policy and the ethical committee of our institution, as procedures done were part of routine diagnostic testing. However, written informed consent for the study was obtained from each patient in compliance with our institutional policy.

Skin Prick Test

Patients underwent SPT on the volar aspect of the forearm, using a standard panel of aeroallergens present in our geographic area (Alk Abellò, Milan, Italy). The panel consisted of the following extracts: grass *(Phleum pratense, Dactila glomerara, Festuca elator, Lolium perenne* and *Poe pratensis)*; weeds [mugwort *(Artemisia vulgaris)*], pellitory of the wall or sticky weed *(Parietaria judaica* and *Salsola kali)*; trees [birch *(Olea europea* and *Cupressus)*]; house dust mite *(Dermatophagoides pteronyssinus* and *D. farinae);* moulds *(Alternaria alternata, Cladosporium erbarium* and *Aspergillus fumigatus)*; animal dander (cat and dog); negative control (glycerinated saline) and positive control (histamine, 10 mg/ml).

Positive responses were defined as any wheal with a diameter 3 mm greater than the negative control, 15 min after application. The diameter was assessed by measuring the minimal + maximal diameter/2. The wheal diameters were reported for each patient [9, 10].

Eosinophil Counts in Nasal Fluid

Nasal lavage was performed using a disposable metered-dose nasal inhaler (Markos, Monza, Italy) filled with sterile normal saline solution at room temperature. The device consists of a plastic cup with two compartments. The central compartment was filled with sterile saline solution, while the external compartment collected the liquid after washing. Total input of saline solution was approximately 8 ml (4 ml in each nostril for 5 min). To collect the nasal washings, the subjects were instructed to actively breathe during a Valsalva maneuver in order to harvest nasal fluid in the cup. The samples obtained were stored on ice and centrifuged at 400 *g* for 10 min at 4°C. The individual variation in the recovered versus introduced volume was 86 $\pm$ 8%. Nasal eosinophil counts were performed on the nasal lavage. One cytospin slide for each sample (1×10^{-4} cells in 170 ml per slide) was centrifuged at 10 *g* for 10 min in a Shandon cytocentrifuge (Shandon Southern Ltd., Runcorn, UK). The slides were immediately fixed in 95% ethyl alcohol, dipped in Wright-Giemsa stain, and examined under oil immersion by light microscopy at a magnification of $\times$400. Eosinophils were expressed as a percentage of 300 cells counted [7, 11, 12].

All specimens were examined by the same blinded microscopist (V.D.), who did not know the clinical histories, the results of the SPT, the severity of the rhinitis symptoms or the subjects' clinical responses to antihistamines.

Peripheral Blood Eosinophil Counts

Absolute peripheral blood eosinophil counts were determined with a Technicon-H1 blood cell counter (Bayer, Leverkusen, Germany), with the normal range being 0.10–0.40 cells/10^{-3} ml [11].

Visual Analog Scale

To evaluate nasal symptoms we used a VAS. The patients assessed their total nasal symptom scores (sneezing, rhinorrhea, nasal obstruction and nasal itching). Subjects were instructed that 0 indicated 'nasal symptoms not at all bothersome' and that 100 indicated 'nasal symptoms extremely bothersome'. The distance between 0 and the mark the subjects made on the scale was measured with a Digimatic caliper (Mitutoyo, Kawasaki, Japan) [8].

Measurements of Peak Nasal Inspiratory Flow

An In-check™ peak nasal inspiratory flow meter (Clement Clarke International Ltd., Harlow, UK) was used to measure peak nasal inspiratory flow (PNIF). After blowing their nose, patients forcefully inspired with mouth closed. All measurements were made while sitting and with a good seal around soft facemask. The PNIF was reported as a mean of three consecutive recordings and expressed as liter per minute.

Statistical Analysis

Noncontinuous data are reported as percentages. Continuous variables normally distributed are reported as means ± standard deviation. Data that are not normally distributed data are reported as medians (with interquartile ranges in parentheses) or with the entire distribution for variables with limited number of categories. Comparisons between groups were done by χ^2 test, Student's t test or the Mann-Whitney U test for nominal, continuous normally distributed and continuous nonnormally distributed variables, respectively. Moreover, a multivariate analysis by backward stepwise logistic regression was carried out to determine variables significantly associated with AR. All variables that did differ between subjects with AR ($p < 0.10$, with χ^2, Student's t test or Mann-Whitney analysis) were initially entered in the model, and the least significant variable was removed one at a time. Goodness of fit of the logistic models was assessed using the Hosmer and Lemeshow test. Several multiple logistic regression models were tested in order to determine the most significant and simplest model with the best available fit for the data available. Based on the regression coefficients obtained for each significant factor chosen by logistic regression, a predictive probability equation was used to generate predicted probability of AR for each individual. Therefore, the probability of having allergic rhinitis (p) was calculated using the following equation:

$$p = e^y/(1 + e^y),$$

where y = constant + x1 × variable 1 + x2 × variable 2 + x3 × variable 3 …

Subsequently, we assessed the performance of the algorithm by calculating its sensitivity, specificity, positive likelihood ratio, negative likelihood ratio and area under curve.

All analyses were repeated with sneezing, rhinorrhea, nasal pruritus and nasal obstruction as categorical variables. Analyses were done using the statistical package MedCalc® (version 2.7.2) and R statistical software package (version 2.10.0). Probability values less than 0.05 were considered significant.

Table 1. Results of SPT in patients with nasal symptoms

Allergens	Patients mono-sensitized	Patients polysensitized		Total
		to other pollens	to other indoor allergens	
Pollens				
Grass	26	142	255	423
Weeds				
Mugwort	10	83	121	214
Pellitory	152	190	329	671
Trees				
Olea europea	15	153	225	393
Cupressus	15	56	150	221
Indoor allergens				
House dust mite[1]	128	457	25	610
Cat dander	5	85	20	110
Dog dander	2	65	9	76

[1] *D. pteronyssinus* and *D. farinae*. All patients with SPT positive to *D. pteronyssinus* had SPT positive to *D. farinae*. We considered these positivities as one positivity.

Results

Our study population consisted of 1,511 patients: 847 (56%) women and 664 (44%) men, with a mean age of 35.0 years. 1,107 patients, 73% of the whole study population, had a diagnosis of AR by clinical history, physical examination and positive SPT for one or more allergens, reflecting that these patients were referred for allergic evaluation by specialists (table 1). The mean number of allergens to which subjects with AR were sensitized was 2.48. A total of 353 patients (31.8%) were monosensitized. The clinical characteristics of the study population divided into AR and NAR subgroups are summarized in table 2.

Demographic Data

The mean age of patients with AR was significantly lower than that of patients with NAR (33.3 vs. 39.8 years, $p < 0.0001$). The frequency of NAR in women was twice than that of men (67.0 vs. 33.0%, $p < 0.0001$). The duration of nasal symptoms was similar in the two groups (7.0 vs. 7.4 years, $p = 0.3$). The prevalence of other respiratory complications in the upper respiratory tract (i.e., sinusitis, nasal polyposis, laryngitis and otitis) was not significantly different between AR and NAR patients (30.9 vs. 26.1%, $p = 0.07$).

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Table 2. Characteristics of the patients (n = 1,511) with AR and NAR

Variable	AR (n = 1,107)	NAR (n = 404)	p
Demographics			
Mean age, years	33.3 ± 11.7	39.8 ± 15.0	<0.0001
Males/female	531/576	133/271	<0.0001
Years of rhinitis	7.0 (6.8)	7.4 (7.0)	0.3
Familiarity	377 (34.0)	106 (26.2)	0.004
Seasonal/perennial nasal symptoms	214/893	70/334	0.4
Smoking			
Active smoker	226 (20.4)	81 (20.0)	0.9
Ex-smoker	103 (9.3)	36 (8.9)	0.8
Passive smoker	255 (23.0)	103 (25.4)	0.3
Nasal symptoms in the last 8 weeks			
Sneezing	997 (90.0)	153 (37.8)	<0.0001
Sneezing[a]	3 (2–3)	0 (0–1)	<0.0001
Rhinorrhea	1,028 (92.8)	377 (93.3)	0.8
Rhinorrhea[a]	2 (1–3)	2 (1–2)	0.0009
Nasal pruritus	974 (87.9)	186 (46)	<0.0001
Nasal pruritus[a]	2 (1–3)	0 (0–1)	<0.0001
Nasal obstruction	1,001 (90.4)	392 (97.0)	<0.0001
Nasal obstruction[a]	2 (1–3)	2 (2–3)	0.001
Total symptoms score[a]	8 (6–10)	5 (4–6)	<0.0001
Nasal symptoms according to the ARIA classification			
Intermittent/persistent	676/431	226/178	0.08
Mild/severe	415/692	272/132	<0.0001
Mild/intermittent	298 (26.9)	198 (49.0)	<0.0001
Severe/intermittent	378 (34.1)	28 (6.9)	<0.0001
Mild/persistent	117 (10.1)	74 (18.3)	<0.0001
Severe/persistent	314 (28.3)	104 (25.7)	0.3
VAS[a]	75 (39–85)	41 (27–73.5)	<0.0001
Medication taken in the last 8 weeks			
Effective response to antihistamines	560 (50.5)	44 (10.8)	<0.0001
Concurrent disorders			
Conjunctivitis	409 (36.9)	54 (13.3)	<0.0001
Complications of upper airway			
Presence of complications	289 (26.1)	125 (30.9)	0.07
Sinusitis	264 (23.8)	123 (30.4)	0.01
Nasal polyposis	152 (13.7)	55 (13.6)	0.9
Laryngitis	187 (16.8)	55 (13.6)	0.1
Otitis media with effusion	52 (4.6)	29 (7.1)	0.07
Other Symptoms			
Recurrent headache	272 (24.5)	124 (30.6)	0.01
Smell	264 (23.8)	120 (29.7)	0.02
Smell[a]	1 (1–1)	0 (0–1)	0.04
Dysphonia	264 (23.8)	101 (25.0)	0.6
Objective tests			
PFIN[a]	110 (80–130)	90 (60–120)	<0.0001
Blood eosinophil counts[a], cells × 10^{-3} µl	0.34 (0.26–0.40)	0.33 (0.20–0.40)	0.06
Nasal eosinophil counts[a]	6 (4–9)	2 (1–5)	<0.0001

Figures in parentheses are percentages unless indicated otherwise.
[a] Medians with 25th–75th percentiles in parentheses.

Chapter 6

Cigarette Smoke Exposure

There was no difference in cigarette exposure found between AR and NAR patients. Specific results are as follows: active smoker (20.4 vs. 20.0%, p = 0.9), ex-smoker (9.3 vs. 8.9%, p = 0.8) and passive smoker (23.0 vs. 25.4%, p = 0.3).

Conjunctivitis

AR was characterized by more frequent episodes of conjunctivitis (36.9 vs. 13.3%, $p < 0.0001$).

Nasal Symptoms

When considering specific symptoms of rhinitis, both sneezing (90.0 vs. 37.8%, $p < 0.0001$) and nasal itching (87.9 vs. 46.0%, $p < 0.0001$) were more frequent in patients with AR, whereas the percentage of patients with rhinorrhea (92.8 vs. 93.3%) was similar in the two groups. On the other hand, the percentage of patients with nasal obstruction was greater among patients with NAR (97.0 vs. 90.0%, $p < 0.0001$).

Nasal Symptoms According to the ARIA Classification

Using the ARIA criteria for classification of rhinitis we found a total of 44% of the subjects with NAR had had persistent symptoms within the last 8 weeks as compared to 38.9% of the subjects with AR (p = 0.08), however, a greater proportion of AR patients had severe symptoms (62.5 vs. 32.6%, $p < 0.0001$). The percentage of patients with nasal symptoms indicated as mild intermittent or mild persistent was higher in the patients with NAR (49.0 vs. 26.9%, $p < 0.0001$, and 18.1 vs. 10.1%, $p < 0.0001$, respectively), whereas the percentage of patients with severe intermittent nasal symptoms was higher in patients with AR (34.1 vs. 6.9%, $p < 0.0001$). We found no difference in the percentage of AR and NAR patients who reported severe persistent symptoms (28.3 vs. 25.7%, p = 0.3).

Medication Use in the Previous 8 Weeks

All patients had taken oral antihistamines (i.e., cetirizine, loratadine, desloratadine, levocetirizine, terfenadine, rupatadine, mizolastine and ebastine) in the previous 8 weeks. A higher percentage of patients with AR reported an effective response to antihistamines as compared to NAR patients (50.5 vs. 10.8%, $p < 0.0001$). However, the lack of clinical response to antihistamines seemed to correlate with greater numbers of eosinophils both in AR and NAR patients.

Complications of Upper Airway

Upper airway complications diagnosed on physical exam were found in 414 patients (27.3%). Particularly, nasal polyps were noted in 207 patients (13.7%), sinusitis in 387 patients (25.6%), laryngitis in 242 patients (25.6%) and otitis in 81 patients (5.4%). Of these patients, 127 had only one complication (100 sinusitis only, 27 laryngitis only), 124 patients presented with two complications (56 sinusitis + nasal polyposis, 49 sinusitis + laryngitis, 12 sinusitis + otitis and 7 laryngitis + otitis), 131 patients presented with three complications (108 sinusitis + nasal polyposis + laryngitis, 19 sinusitis + laryngitis + otitis and 4 sinusitis + nasal polyposis + otitis) and 39 patients presented with all four complications. Of the 414 patients presenting with one or more complications only 27 (6.5%) did not present with sinusitis and only 2 of these 27 patients were SPT negative. Sinusitis was the only upper airway complication found more frequently in patients with NAR compared to patients with AR (30.4 vs. 23.8%, p = 0.01).

Other Symptoms

Recurring headaches and olfactory dysfunction were more common in NAR than AR patients (30.6 vs. 24.5%, p = 0.01, and 29.7 vs. 23.8%, p = 0.02, respectively). However, there was no difference in the frequency of recurrent dysphonia (23.8 vs. 25.0%, p = 0.6).

Objective Tests

We evaluated PNIF, b-eos, n-eos, as well as nasal symptoms measured by VAS. PNIF and n-eos were found to be higher in AR patients compared to NAR patients, and these results were highly statistically significant (all $p < 0.0001$), while no difference was found between AR and NAR regarding the blood eosinophil counts (p = 0.06).

Logistic Regression

All variables found to be significantly different between AR and NAR were subsequently analyzed with backward stepwise logistic regression. All variables that differed between these 2 groups ($p < 0.05$ with χ^2 or Mann-Whitney analysis) were initially entered in the model, and the least significant variable was removed one at a time. Goodness of fit of the logistic models was assessed using the Hosmer and Lemeshow test. Table 3 shows the results of logistic regression retaining only the significant covariates in this model. The presence of conjunctivitis, a clinical response to antihistamines, high n-eos, the presence of sneezing, the presence of nasal pru-

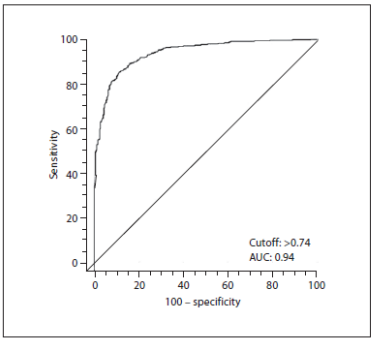

Fig. 1. Receiver operating characteristic curve of the predictive model obtained by applying backward stepwise logistic regression.

Table 3. Factors that significantly distinguish subjects with AR from subjects with NAR by backward stepwise logistic regression

Variable	OR	95% CI	p
Age	0.97	0.96–0.98	<0.0001
Presence of sneezing	4.09	2.78–6.00	<0.0001
Presence of nasal pruritus	3.84	2.60–5.67	<0.0001
Nasal symptoms			
Mild	0.21	0.09–0.49	0.0003
Intermittent/severe	3.66	2.06–6.50	<0.0001
VAS	1.05	1.03–1.07	<0.0001
Conjuntivitis	4.49	2.86–7.05	<0.0001
Effective response to antihistamines	22.59	13.79–37.00	<0.0001
PNIF	1.01	1.00–1.01	<0.0001
Nasal eosinophil counts	1.14	1.10–1.18	<0.0001

ritus, intermittent/severe nasal symptoms and a high VAS score were associated with AR. However, older age, mild nasal symptoms and a lower value of PFIN were associated with NAR.

Subsequently, we performed receiver operating characteristic analysis for all variables that were found to be independently associated with the diagnosis of AR and NAR in order to identify the optimal cutoff point useful in predicting AR. For the optimal cutoff point useful in predicting AR, based on the above-mentioned logistic regression model, the following equation was generated and used in order to calculate predicted probability (p_i) of having AR:

$$\ln [p_i/(1 - p_i)] = -5.8262 - 0.02808 \times (\text{age in years}) + 1.4088 \times (\text{presence of sneezing}) + 1.3465 \times (\text{presence of nasal pruritus}) - 1.5220 \times (\text{mild nasal symptoms}) + 1.2997 \times (\text{intermittent/severe nasal symptoms}) + 0.05312 \times (\text{VAS score}) + 3.1178 \times (\text{effective response to antihistamines}) + 1.5040 \times (\text{presence of conjunctivitis}) + 0.01371 \times (\text{PNIF}) + 0.1367 \times (\text{n-eos}).$$

This algorithm resulted in a high predictive accuracy, considering as the best cutoff >0.74: sensitivity 86.2 (95% CI 84.0–88.2), specificity 88.1 (95% CI 84.6–91.1), positive likelihood ratio 7.2 (95% CI 6.9–7.6), negative likelihood ratio 0.16 (95% CI 0.1–0.2) and area under curve 0.94 (95% CI 0.93–0.95) (fig. 1).

Discussion

In the present study, we found that the proportion of patients with AR in an adult population with symptoms of rhinitis is about 70%. This data is in line with the European Community Respiratory Health Survey [13] and with the National Rhinitis Classification Task Force (USA) [14].

The patients with AR have more sneezing and nasal pruritus, whereas the patients with NAR were characterized mainly by nasal obstruction and rhinorrhea. This is similar to results found in other studies [6, 15, 16].

Eighty percent of men with rhinitis symptoms have AR [17]. In general, patients with AR have more severe but equally persistent nasal symptoms when compared to patients with NAR. These data contradict the findings of Mølgaard et al. [6]. In a large sample of adolescents and adults with AR and NAR, they found that NAR patients suffer from more persistent symptoms and that severe symptoms were equally frequent in both AR and NAR patients. However, Bachert et al. [5] found in a questionnaire-based survey in Belgium that AR patients had both more persistent and more severe symptoms than NAR patients.

According to our results, comorbidities also differed in the two groups. Patients with NAR suffered more from sinusitis, whereas patients with AR suffer more frequently from conjunctivitis. The presence of nasal polyposis, laryngitis and otitis was similar in the two groups but re-

curring headaches and olfactory dysfunction were increased in NAR patients, whereas the presence of recurrent headache and olfactory dysfunction in patients with NAR could be partially explained by their having more sinusitis. Recurring headaches are subjective and therefore quite loosely defined. However, our data demonstrate that the frequency of recurring headaches in patients without sinusitis was very low and that the patients with recurring headaches had more severe nasal obstruction as measured by PNIF. These data are consistent with the finding of other authors [18].

It is important to underscore the correlation of nasal eosinophilia with all associated complications (sinusitis, nasal polyposis, laryngitis and otitis) in both AR and NAR patients alike. This data indirectly confirms the importance of nasal cytology for the correct clinical classification of rhinitis and in the pathogenesis of complicated forms of rhinitis.

There are at least two limitations to our study. First, since this study was done with rhinitis patients it may not be possible to generalize the data to the population as a whole. However, our focus was the population seen daily by allergists and otolaryngologists in clinical practice. The results are therefore consistent with the high prevalence of AR and NAR in the general population. Second, we classified the rhinitis only by the presence or absence of a positive SPT. However, in practice, the diagnosis of AR is based only on SPT [3, 19].

However, the study has some important aspects to consider in diagnosing rhinitis. It is important to objectively evaluate possible causes of subjective signs and symptoms such as the nasal obstruction. Not only is it important to inspect the nasal cavity for the presence of nasal polyps, turbinate sizes and condition of the nasal mucosa, but it is also important to objectively measure nasal obstruction using PNIF as a parameter. PNIF can be measured with an inexpensive device. However, based on our data we think nasal cytology is the most important objective measurement. In our opinion a correct diagnosis of rhinitis cannot be made without nasal cytology. Our conclusion is based on the fact that only 50% of AR patients, generally those with few eosinophils found in their nasal secretions, controlled their nasal symptoms only with the antihistamines and that all patients with complications of the upper airway, whether allergic and nonallergic, had higher nasal eosinophil counts in their secretion. Getting this objective data may help in better management of rhinitis in all patients.

This study shows that rhinitis is not a trivial disease. Patients with both AR and NAR presented with coexisting sinusitis, nasal polyposis, laryngitis and otitis, suggesting that there may be a common pathophysiological pathway causing severe rhinitis resulting in complications, such as rhinitis with nasal eosinophilia, and that this is common in both AR and NAR.

Our results underline several clinical and demographic differences between patients with AR and NAR and emphasize the need of a correct diagnosis and medical treatment. This large cross-sectional study shows that AR is a prevalent condition, which is characterized both by intermittent and severe symptoms, most prominently sneezing and nasal pruritus. The majority of patients with AR are young men, while the patients with NAR are middle-aged women who have a tendency to suffer from recurring headaches and recurrent sinusitis as well.

Receiver operating characteristic curves are used in biomedical research to evaluate the effectiveness of biomarkers for distinguishing individuals with the disease from those without that disease, in our study patients with AR from patients with NAR. Future research needs to include closer investigation of subjects with AR and NAR. In particular, more attention should be paid to accurately distinguish between different subtypes of AR and NAR in relation to treatment and to presence of eosinophils in the nasal mucosa.

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CHAPTER 7

Clinical course of rhinitis and changes *in vivo* and *in vitro* of allergic parameters in old patients: a long-term follow-up study

Chapter 7

Autori

gruppo

Key words:

Summary

Introduction

Materials and Methods

Subjects

Statistical Analysis

Results

Discussion

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References

Figure

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SUMMARY AND GENERAL DISCUSSION

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CHAPTER 10

CURRICULUM VITÆ

Chapter 10

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