Original Article

Clinical phenotypes of severe asthma*

Fenótipos clínicos de asma grave

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Abstract

Objective: To characterize clinical phenotypes of severe asthma. **Methods:** A total of 111 patients were retrospectively evaluated at a specialized outpatient clinic. A systematic protocol for patient evaluation and follow-up was applied. Treatment compliance and control of the disease at the end of follow-up were defined by clinical and functional data. Patients who did not meet asthma control criteria after six months despite compliance with treatment and correct use of medication were characterized as treatment-resistant. Phenotypes were determined by factorial analysis and compared using various tests. **Results:** At the end of follow-up, 88 patients were considered treatment compliant and 23 were considered noncompliant. Factorial analysis of the compliant patients identified four phenotypes: phenotype 1 (28 patients) comprised patients who were treatment-resistant, more often presenting nocturnal symptoms and exacerbations, as well as more often using rescue bronchodilators; phenotype 2 (48 patients) comprised patients with persistent airflow limitation, lower ratios of forced expiratory volume in one second/forced vital capacity at baseline, more advanced age and longer duration of symptoms; phenotype 3 (42 patients) comprised patients with allergic rhinosinusitis who were nonsmokers and presented predominantly reversible airflow obstruction; and phenotype 4 (15 patients) comprised cases with a history of aspirin intolerance to acetylsalicylic acid associated with near-fatal asthma. **Conclusions:** A significant number of patients with severe asthma are noncompliant with treatment. Although many patients with severe asthma have persistent airflow obstruction, the most relevant clinical phenotype comprises patients who are resistant to the typical treatment.

Keywords: Asthma; Asthma/prevention & control; Asthma/treatment.

Resumo

Objetivo: Estabelecer os fenótipos clínicos em portadores de asma grave. **Métodos:** Foram estudados, retrospectivamente, 111 pacientes em um ambulatório especializado. Os pacientes foram avaliados e acompanhados de maneira sistemática, estabelecendo-se ao final do acompanhamento a adesão e o controle ou não da doença por dados clínicos e funcionais. A resistência ao tratamento foi definida como o não preenchimento, ao final do acompanhamento, por pelo menos seis meses, dos critérios de controle de asma, apesar do uso correto e adesão à medicação. Os fenótipos foram determinados por análise fatorial e comparados por testes diversos. **Resultados:** Ao final, 88 pacientes foram considerados aderentes e 23 não aderentes. Por análise fatorial do grupo aderente, quatro fenótipos foram determinados: o fenótipo 1 (28 pacientes), formado pelos pacientes resistentes ao tratamento, com maior freqüência de sintomas noturnos, maior número de exacerbações e uso mais freqüente de broncodilatador de resgate; o fenótipo 2 (48 pacientes), formado pelos pacientes com obstrução persistente, com menores valores de relação volume expiratório forçado no primeiro segundo/capacidade vital forçada na avaliação inicial, idade mais avançada e maior tempo de doença; o fenótipo 3 (42 pacientes), representa os pacientes com rinossinusite alérgica, sendo constituído de não fumantes com obstrução predominantemente reversível; e o fenótipo 4 (15 pacientes), formado por casos com história de intolerância à aspirina associado à asma quase fatal. **Conclusões:** Um número significativo de portadores de ama grave não adere ao tratamento. Muitos pacientes com asma grave têm obstrução irreversível, mas o fenótipo clínico mais relevante é constituído pelos pacientes resistentes ao tratamento habitual.

Descritores: Asma; Asma/prevenção & controle; Asma/tratamento.

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Introduction

Although severe asthma affects only 10% of individuals with asthma, mortality and health care costs are higher in this group.[1] There is a subgroup of patients who have severe asthma that is not controlled by the treatment regimens currently available and is denominated difficult-to-control asthma. Numerous factors influence the response to asthma treatment, including treatment compliance, accuracy of the diagnostic evaluation, exclusion of concomitant diseases, identification of aggravating factors and the correct use of medication.[2] In addition to these variables, phenotypical characteristics are associated with patients being refractory to treatment.

The determination of phenotypes of severe asthma is important in order to gain a better understanding of the pathophysiological mechanisms of the disease and response to treatment. However, the precise definition of phenotypes is still debatable.[1] Numerous phenotypes have been described: clinical, inflammatory and, recently, genetic.

The objective of this study was to characterize clinical phenotypes of severe asthma after standardized treatment and compare findings with those described in the literature.

Methods

The study was carried out from 1999 to 2004 at the Severe Asthma Outpatient Clinic of the São Paulo Hospital for State Civil Servants, located in São Paulo, Brazil.

A retrospective analysis was conducted using standardized forms, with complete data, which were used in the treatment, both in the initial medical appointment and during follow-up. Diagnosis and follow-up treatment were performed by a pulmonologist. Data regarding disease control criteria were obtained after a minimum of three consultations, scheduled at least three months apart. For patients with uncontrolled asthma, the follow-up period was at least 12 months. For patients with controlled asthma, the follow-up period was defined as the time to obtaining control, although the follow-up period extended for longer periods.

Patients diagnosed with severe asthma, as defined by the criteria suggested by the Brazilian Thoracic Association,[1,3] were included in the study. Severe asthma patients were defined as those who presented continuous symptoms that impaired their performance of activities of daily living, sleep disturbance caused by asthma more than twice a week, peak expiratory flow (PEF) < 75% of best personal value (basal PEF), daily use of rescue bronchodilator and a history of one or more episodes of near-fatal asthma.

The criteria for exclusion were as follows: current or previous smoking within the last 15 years or a smoking history of ≥ 15 pack-years; concomitant lung disease (allergic bronchopulmonary aspergillosis or bronchiectasis); a history of lung surgery; and concomitant chronic obstructive pulmonary disease (COPD). The diagnosis of COPD was made through clinical evaluation and complementary tests.

In the initial evaluation, we collected information on disease duration, evolution, current symptoms, concomitant diseases and medication used, triggering factors (dust, mold, pets, emotions, exposure to irritants, menstrual cycle, a change of climate and aspirin use) hospitalizations due to asthma and classification of the severity of asthma.

Aggravating factors rhinosinusitis, gastroesophageal reflux disease (GERD) and nasal polyposis were evaluated on the basis of clinical symptoms/signs and confirmed through complementary tests with referral to specialists. Treatment of aggravating factors was carried in the usual manner.

Prior to each medical appointment, a trained nurse instructed patients in how to use inhaler devices for delivering medication and evaluated treatment compliance. Patients who failed to take any of the medications prescribed at any time during the follow-up period were considered treatment noncompliant.

Over the course of the disease, we evaluated current medication and the dose used, as well as the persistence of aggravating factors, reports by other specialists consulted, complementary test results and control criteria. Lack of control was defined as presenting one or more of the following: persistent daily symptoms; daily bronchodilator use; impaired activities of daily living; asthma-related sleep disturbance > once a week, PEF < 70% of basal value; and mild to severe persistent obstruction measured by spirometry.[3]

Doses of inhaled corticosteroids were expressed in equivalent doses of beclomethasone (fluticasone = 2× beclomethasone; and budesonide = beclomethasone).

All patients were submitted to spirometry, performed using a Koko spirometer (v4.2.24.4; Ferraris Respiratory, Louisville, CO, USA) in the initial evaluation and during follow-up. Tests were repeated after the administration of salbutamol spray, 4 jets (400 μg), through a device coupled to a large volume spacer. At follow-up appointments, PEF was evaluated using Assess equipment (Health Scan, Cedar Grove, NJ, USA). Measurements are expressed as absolute values, as percentages of predicted and as percentages of basal PEF.

Initially, general characteristics of the sample as a whole (compliant and noncompliant patients) were analyzed. In a second stage, only compliant patients were evaluated, and patients were classified into phenotypes by factorial analysis based on clinical data and on pulmonary function. Data regarding age, gender, disease duration, pulmonary function, symptom score at admission, concomitant rhinosinusitis, GERD and treatment were compared in the various phenotypes.

In the various follow-up evaluations, patients who did not meet the asthma control criteria described above were characterized as treatment-resistant despite correct use of medication and compliance with treatment using inhaled corticosteroids combined with a long-acting bronchodilator, oral corticosteroids or both.[1,4] Persistent obstruction was characterized by greater PEF value (<75% of predicted in serial evaluations), postbronchodilator forced expiratory volume in one second (FEV_1) <80% of predicted or postbronchodilator FEV_1/forced vital capacity (FVC) ratio <70% of predicted.

Table 1 - General characteristics of treatment compliant patients (n = 88).

Variable	
Gender (female/male), n (%)	64 (73%)/24 (27%)
Smoking, n (%)	11 (12%)
Age (years), mean ± SD	56 ± 12
FEV_1/FVC (%), mean ± SD	53 ± 14
Disease duration (years), median (variation)	28 (1-60)
Inhaled corticosteroids ≥ 1.200 μg beclomethasone, n (%)	59 (67%)
Oral corticosteroids, n (%)	26 (30%)
Long-acting β_2 agonists, n (%)	77 (88%)
Follow-up period (months), median (variation)	14 (3-72)

FEV_1/FVC: forced expiratory volume in one second/forced vital capacity ratio.

The statistical analysis was carried out using the Statistical Package for the Social Sciences, version 13.0 for Windows (SPSS Inc., Chicago, IL, USA). Demographic data are presented as mean ± standard deviation or as median. Phenotypes were determined by factorial analysis. Groups were compared using the Student's t-test for continuous variables, the chi-square test ($p < 0.05$) for dichotomous variables and the Mann-Whitney test for nonparametric variables. Factors associated with final control were determined by logistic regression.

Table 2 - Factorial analysis of a sample of 88 patients with severe asthma.

Factor	Phenotype 1	Phenotype 2	Phenotype 3	Phenotype 4
Treatment resistance	0.884	-	-	-
Nocturnal symptoms	0.873	-	-	-
Nondaily use of rescue bronchodilator	–0.816	-	-	-
Frequent exacerbations	0.719	-	-	-
Disease duration	-	0.716	-	-
Fixed obstruction	-	0.699	–0.383	-
Prebronchodilator inspiratory time	-	–0.678	-	-
Age	-	0.465	-	-
Rhinitis	-	-	0.672	-
Gastroesophageal reflux disease	-	-	0.619	-
Sinusitis	-	-	0.598	-
Smoking	-	-	–0.590	-
Near-fatal episode	-	-	-	0.786
Aspirin	-	-	-	0.766

Phenotype 1: treatment-resistant asthma; Phenotype 2: asthma with persistent obstruction; Phenotype 3: asthma with rhinitis ("atopic"); and Phenotype 4: near-fatal asthma.

Results

A total of 111 patients were included: 88 were considered treatment compliant, and 23 were considered noncompliant with treatment. There was no difference between the two groups regarding gender, age, FEV_1/FVC ratio and disease duration. The female gender prevailed in both groups (73% in the noncompliant group and 72% in the compliant group). Mean age was similar (53 ± 11 years in the noncompliant group and 56 ± 14 years in the compliant group), and there were no statistical differences between the two groups in terms of mean FEV_1/FVC ratio (47 ± 11 *vs.* 53 ± 14, p = 0.07). As expected, we observed a significant difference between the compliant and noncompliant group regarding control criteria.

There was no difference between the noncompliant and compliant group regarding the median dose of inhaled corticosteroids prescribed—1,750 µg (range, 800-3,000 µg) *vs.* 1,800 µg (range, 800-3,000 µg), p = 0.67—and regarding the frequency of oral corticosteroid prescription—10 of 23 (43%) *vs.* 26 of 88 (30%), p = 0.38. There was no significant difference between the two groups regarding the frequency of the various aggravating and triggering factors.

The remaining results refer to treatment compliant patients. General data are shown in Table 1. The typical patient was female, in the fifth decade of life, reported a nearly 30-year history of adult onset asthma and presented mild airway obstruction in the initial evaluation. Approximately two thirds of the patients used inhaled corticosteroids at a dosage of ≥1,200 µg of beclomethasone or equivalent, nearly 90% used long-acting bronchodilator, and one third used oral corticosteroids. The mean follow-up period after the first medical appointment was 14 months.

Concerning aggravating factors, we observed rhinitis in 51% of the patients, sinusitis in 22% and GERD in 19%. Worsening after exposure to dust and irritants, as well as after temperature variations, was observed in 78, 92 and 88% of those cases, respectively. Fourteen patients (16%) described worsening during menstruation, and 15 patients (17%) reported worsening after ingesting aspirin.

After the treatment, 49 patients (56%) came to use bronchodilator on a nondaily basis, 53 patients (60%) reached PEF ≥ 70% of basal PEF, 62 patients (70%) presented normal activities of daily living/normal sleep, 24 patients (27%) stopped visiting the emergency room, and 26 (30%) presented no nocturnal symptoms.

Table 3 - General characteristics of the treatment-resistant asthma and treatment-sensitive asthma phenotypes.

Variable	Resistant (n = 28)	Sensitive (n = 60)	p
Age (years), mean ± SD	56 ± 13	56 ± 12	0.97*
FEV_1/FVC (%), mean ± SD	54 ± 12	53 ± 15	0.92*
Response to bronchodilator, yes/no (%)	17/7 (71%)	38/4 (90%)	0.04**
Gender (female/male), n	19/9	45/15	0.61**
Disease duration (years), median (variation)	29.5 (1-44)	27 (2-60)	0.60***
Greater PEF (% of basal), mean ± SD	65 ± 20	68 ± 22	0.49*
Sinusitis, yes/no	5/23	14/46	0.56**
Gastroesophageal reflux disease, yes/no	9/19	8/52	0.037**
Aspirin, yes/no	6/22	9/51	0.45**
Menstrual cycle, yes/no	5/23	9/51	0.73**
Exposure to dust, yes/no	23/5	46/14	0.56**
Exposure to irritants, yes/no	26/2	55/5	0.85**
Δ temperature, yes/no	25/3	52/8	0.73**
Smoking, yes/no	3/25	8/52	0.73**
Nocturnal symptoms, yes/no	23/5	28/32	0.002**
Impaired ADLs, yes/no	16/12	15/45	0.003**
Oral corticosteroids, yes/no	16/12	10/50	0.000**
Inhaled corticosteroids,[a] yes/no	23/5	36/24	0.04**

FEV_1/FVC: forced expiratory volume in one second/forced vital capacity ratio; PEF: peak expiratory flow; and ADLs: activities of daily living. [a]dose ≥ 1,200 µg beclomethasone. *Student's t-test. **Chi-square test. ***Mann-Whitney test.

At the end of follow-up, 24 patients (27%) maintained fixed obstruction. Treatment resistance was observed in 28 of the cases (32%). A total of 39 patients (44%) maintained daily symptoms, and 26 patients (30%) continued to use > four daily doses of rescue bronchodilator. Treatment-resistant patients were monitored for a significantly longer time than were those in the treatment-sensitive group (median, 72 months *vs.* 24 months, $p < 0.001$)

The factorial analysis (Table 2) identified four distinct phenotypes: phenotype 1 (n = 28) comprised patients who were treatment-resistant, more often presenting nocturnal symptoms and exacerbations, as well as more often using rescue bronchodilators; phenotype 2 (n = 48) comprised patients with persistent airflow limitation, lower FEV_1/FVC ratios in the initial evaluation, more advanced age and longer duration of the disease; phenotype 3 (n = 42) comprised patients with allergic rhinosinusitis who were nonsmokers and presented predominantly reversible airflow obstruction (this group was denominated atopic asthma); and phenotype 4 (n = 15) comprised patients with aspirin intolerance associated with near-fatal asthma episodes.

Compared with the other patients, treatment-resistant patients presented general characteristics similar to those of patients who were treatment-sensitive in the initial evaluation (Table 3). However, GERD was more frequent and rate of response to bronchodilator was lower. In relation to initial severity score, the treatment-resistant group presented more often nocturnal symptoms and impaired activities of daily living. We did not observe any differences in relation to daily symptoms, frequency of daily bronchodilator use or frequency of near-fatal episodes. In the treatment-resistant asthma group, a greater number of patients used oral corticosteroid therapy, daily inhaled corticosteroid therapy at a dosage ≥1,200 μg of beclomethasone or equivalent, and the inhaled/oral corticosteroid combination.

Mean age in the group with persistent obstruction (Table 4) was higher than that observed in the remaining patients, as was disease duration. In relation to aggravating factors, previous smoking was reported by 18% of the patients with persistent obstruction and by 5% of those with reversible obstruction ($p = 0.052$). The rate of bronchodilator response was similar between groups, and the presence of allergic rhinitis was less frequent in the group with persistent obstruction. The classification of initial severity was similar between groups, as was the treatment prescribed. Despite persistent obstruction, there were no differences between groups in relation to the control obtained in the final post-treatment evaluation.

The group with atopic asthma presented higher FEV_1/FVC ratios in the initial evaluation, as well

Table 4 - General characteristics of the asthma with persistent obstruction and asthma with reversible obstruction phenotypes.

Variable	Persistent obstruction (n = 48)	Reversible obstruction (n = 48)	p
Age (years), mean ± SD	58 ± 13	53 ± 11	0.035*
FEV_1/FVC (%), mean ± SD	48 ± 13	60 ± 13	0.000*
Response to bronchodilator, yes/no (%)	28/7 (80%)	27/4 (87%)	0.44**
Gender (female/male), n	12/36	12/28	0.60**
Disease duration (years), median (variation)	34 (5-58)	12 (1-60)	0.001***
Rhinitis, yes/no	18/30	27/13	0.005**
Gastroesophageal reflux disease, yes/no	9/39	8/32	0.88**
Aspirin, yes/no	10/38	5/35	0.30**
Menstrual cycle, yes/no	7/41	7/33	0.71**
Exposure to dust, yes/no	37/11	32/8	0.74**
Exposure to irritants, yes/no	44/4	37/3	0.021**
Δ temperature, yes/no	42/6	35/5	1.00**
Smoking, yes/no	9/39	2/38	0.052**
Sinusitis, yes/no	5/41	12/40	0.08**

FEV_1/FVC: forced expiratory volume in one second/forced vital capacity ratio. *Student's t-test. **Chi-square test. ***Mann-Whitney test.

Table 5 - General characteristics of nonsmoking patients with and without rhinitis.

Variable	With rhinitis (n = 42)	Without rhinitis (n = 35)	p
Age (years), mean ± SD	54 ± 12	58 ± 14	0.26*
FEV_1/FVC (%), mean ± SD	57 ± 16	50 ± 13	0.047*
Response to bronchodilator, yes/no (%)	28/4 (66%)	18/6 (51%)	0.23**
Gender (female/male), n	31/11	24/11	0.61**
Disease duration (years), median (variation)	30 (1-60)	26 (2-60)	0.75***
Gastroesophageal reflux disease, yes/no	13/29	4/31	0.040**
Aspirin, yes/no	10/32	2/33	0.029**
Menstrual cycle, yes/no	8/34	5/30	0.31**
Exposure to dust, yes/no	32/10	28/7	0.16**
Exposure to irritants, yes/no	38/4	34/1	0.24**
Δ temperature, yes/no	37/5	31/4	0.95**
Sinusitis, yes/no	15/27	4/31	0.014**

FEV_1/FVC: forced expiratory volume in one second/forced vital capacity ratio. *Student's t-test. **Chi-square test. ***Mann-Whitney test.

as a higher frequency of sinusitis and GERD. We observed aspirin intolerance in 10 patients (23%) in this group, compared to 2 patients (5%) in the nonatopic group (Table 5). Over the course of the disease, atopic patients presented better control level with greater PEF in relation to that of the others (73 ± 21% *vs.* 62 ± 20%, p = 0.017). No significant differences were observed in terms of the classification of initial severity or the treatment given.

Among the 15 patients with aspirin intolerance, near-fatal episodes occurred in 7 (47%), compared to only 9 among the remaining 63 cases (14%; χ^2 = 8.68, p = 0.003).

Classification criteria of the severity of asthma in the initial evaluation were submitted to logistic regression in order to predict final control. Only the frequency of nocturnal symptoms (p = 0.02) presented such predictive value. The presence of GERD was related to worse final control (p = 0.012). Of the 51 patients with nocturnal symptoms in the initial evaluation, 23 (45%) did not obtain control at the end of the treatment, whereas this occurred in only 5 cases (13.5%, p = 0.002) in the group without nocturnal symptoms. Of the 17 patients with GERD, 9 (53%) were treatment-resistant, compared to 19 (27%) of the 71 patients without GERD (p = 0.037).

Discussion

Differences in phenotype can explain the variety of clinical presentations of severe asthma.[4] Clinical, inflammatory and genetic phenotypes have been described.[5]

We found four distinct phenotypes: treatment-resistant asthma, asthma with persistent obstruction, atopic asthma and aspirin-intolerant asthma. Among these, the treatment-resistant asthma, or, definitively, difficult-to-control asthma, phenotype should be highlighted. It implies no response to the use of corticosteroids.

Reduced responsiveness to corticosteroids results from numerous mechanisms.[6] In our study, 32% of the patients had treatment-resistant asthma. Treatment resistance was related to lower response to bronchodilator, higher frequency of exacerbations and higher frequency of nocturnal symptoms, as well as to greater prevalence of GERD. Treatment-resistant patients used higher doses and longer courses of corticosteroids. New treatments such as the use of omalizumab and bronchial thermoplasty should be better studied in this group of patients.

In our study, the presence of nocturnal symptoms in the initial evaluation was related to treatment resistance and worse final control, therefore being a marker of asthma severity. In addition, we found that GERD was associated with the presence of nocturnal symptoms. Numerous mechanisms are implied in nocturnal asthma.[7]

Inflammation and airway remodeling result in structural alterations, which seem to explain the permanent reduction in airway diameter.[8-10] These alterations clinically manifest as fixed airway obstruction. In the present study, this phenotype was not related to greater difficulty in control.

Regarding persistent airway obstruction, we observed longer duration of the disease and lower

atopy level, suggested by the lower frequency of rhinitis in these patients, as seen in the literature.[11]

Persistent airway obstruction in asthma is more common in males, as well as being associated with more advanced age, prolonged disease, adult onset, lower IgE levels, lower response to environmental allergens, eosinophilia and thickened bronchial walls at high-resolution computed tomography, indicating a greater degree of inflammation and structural alterations, as well as a nonallergic phenotype.[11,12] The mechanisms that result in this obstruction differ from those found in COPD.[13]

Atopic asthma is the clinical phenotype most often described in the literature, is more common in childhood and is less associated with severe asthma.[10] The frequency of atopy is higher among patients with asthma and rhinitis. Our study identified a clinical phenotype comprising nonsmoking patients with severe asthma, rhinitis, greater functional response to bronchodilator use, more frequent association with aspirin intolerance, better pulmonary function and better final control.

A clinical history of a near-fatal episode is considered one of the defining criteria for difficult-to-control asthma. In 2 to 23% of adults with asthma, the use of aspirin and nonsteroidal anti-inflammatory drugs can cause exacerbations. The pathogenetic mechanism of aspirin-induced asthma has yet to be defined.[14] We identified a small subgroup of patients in whom aspirin intolerance and near-fatal asthma were associated, corresponding to a previously described phenotype of aspirin-induced asthma, with greater incidence of severe events. Some studies suggest that (upper and lower) airway remodeling is a severity factor in such cases.[15,16]

In our group of patients with severe asthma, treatment resistance was observed in 32% of the cases. We observed that many patients obtain control after long follow-up periods, suggesting that the six-month follow-up period currently proposed[17] to determine asthma refractory to treatment should be reevaluated.

There is currently a tendency to define difficult-to-control asthma as that which is treatment-resistant. However, some factors should be considered, principally noncompliance and comorbidities or aggravating factors.

Noncompliant cases are common and should not be considered as difficult-to-control asthma. Causes of noncompliance are complex.[18]

Numerous conditions can cause respiratory symptoms and coexist with asthma, leading to the diagnostic confusion with treatment resistance.[19] In severe asthma, alternative diagnoses or associated factors are present in one third of the cases.[20,21] Since all of our patients were submitted to systematic evaluation, the cases with alternative diagnoses were excluded.

Among asthma patients, GERD is a common comorbidity.[22] The effect of the treatment for GERD is controversial.[23] However, a recent study involving asthma patients treated with high doses of lansoprazole demonstrated reduced exacerbations and improved quality of life, with no impact on pulmonary function.[24] In our study, reflux was more common in the treatment-resistant and atopic asthma phenotypes. Reflux treatment was not related to better final control. However, the presence of GERD symptoms in the initial evaluation was associated with worse control at the end of the follow-up and to the presence of nocturnal symptoms.

Chronic rhinosinusitis frequently coexists with severe asthma. It is related to bronchial inflammation[25] and can contribute to poor control of the disease.[26] The treatment for rhinosinusitis can result in clinical and functional improvement and in reduced asthma inflammation.[27] In our study, the presence of rhinosinusitis was not associated with treatment resistance.

In the present study, all patients diagnosed with COPD and current smokers were excluded. Some asthma patients can develop persistent obstruction,[11] and numerous factors can contribute to this finding such as adult onset disease, bronchial hyperresponsiveness and persistent sputum eosinophilia.[12,28]

We found previous smoking in 12% of the patients. They had all stopped smoking for more than 10 years, and were smokers for less than 15 pack-years. The consumption of cigarettes among asthma patients is related to persistent obstruction, accelerated decrease of pulmonary function and lower response to corticosteroids.[11,29,30]

Determining clinical phenotypes can help as a tool to improve understanding and to manage cases of severe asthma. We suggest that the follow-up period to identify asthma refractory to treatment

be extended to approximately one year, aiming at controlling triggering and aggravating factors, as well as the inflammation itself, before considering asthma resistant. We observed that the initial classification of asthma severity remains limited, principally concerning prediction of final control. Nocturnal asthma and GERD correlate with poor post-treatment control.

A significant number of patients with severe asthma do not comply with treatment. Although many patients with severe asthma have irreversible obstruction, the most relevant clinical phenotype consists of patients resistant to the usual treatment, which includes the use of corticosteroids.

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