

## Evaluation of diagnostic criteria for severe asthma described in a public health directive regulating the free distribution of medications for the maintenance treatment of asthma\*

Avaliação dos descritores de asma grave em pacientes incluídos na portaria de saúde pública que regulamenta a distribuição gratuita de medicamentos para o tratamento de manutenção da asma

Maria Amélia Carvalho da Silva Santos, Ana Luisa Godoy Fernandes, Mara Marta Amorim, Patrícia Bueno Lima, Sonia Maria Faresin, Ilka Lopes Santoro

### Abstract

**Objective:** To evaluate the capacity of the criteria described in Complementary Directive SAS/MS 12, issued on November 12, 2002, to identify patients with severe asthma, describing and comparing clinical, functional and treatment data of such patients. **Methods:** This was a nested case-control study using a structured database for adult asthma outpatients. We defined cases as asthma patients who met the inclusion criteria described in the directive, defining controls as those who did not. We collected and compared data related to the following: demographic characteristics; history of asthma; medications in use; comorbidities; history of tobacco use; number of exacerbations within the last 12 months, asthma-related hospitalizations and intensive care unit admissions within the last 12 months; spirometry; and sputum cytology. **Results:** The case and control groups consisted of 29 and 31 patients, respectively. The number of asthma exacerbations and emergency room visits within the last 12 months, as well as the number of patients that received at least one pulse of oral corticosteroids, was significantly higher in the case group than in the control group. In addition, prebronchodilator FVC was lower among the cases than among the controls. Furthermore, cytology revealed that eosinophil counts were significantly higher in the induced sputum of cases than in that of controls. **Conclusions:** The criteria described in the directive are suited to stratifying patients with severe asthma.

**Keywords:** Asthma; Budesonide; Combined modality therapy.

### Resumo

**Objetivo:** Avaliar a capacidade dos critérios descritos na Portaria Complementar SAS/MS nº 12, de 12 de novembro de 2002, em identificar pacientes asmáticos graves, bem como descrever e comparar dados clínicos, funcionais e de tratamento destes pacientes. **Métodos:** Estudo caso-controle aninhado em um banco de dados estruturado de atendimento ambulatorial de asmáticos. Foram considerados casos os pacientes asmáticos que preencheram os critérios de inclusão determinados na portaria e considerados controles os que não preencheram os mesmos critérios. Foram coletados e comparados dados demográficos; história pregressa da asma; medicamentos em uso; presença de comorbidades; história de tabagismo; presença, no último ano, de exacerbações, de hospitalizações e de admissões em unidades de terapia intensiva devido à asma; e resultados de espirometria e de citologia de escarro. **Resultados:** Foram incluídos 29 e 31 pacientes, respectivamente, nos grupos caso e controle. O grupo caso apresentou maior número de exacerbações e maior número de visitas ao pronto-socorro no último ano, maior porcentagem de pacientes que receberam pelo menos um pulso de corticosteroide oral, assim como menores valores de CVF pré-broncodilatador em relação ao grupo controle. O grupo caso também apresentou um aumento significativo de eosinófilos na citologia do escarro induzido. **Conclusões:** Os critérios de inclusão descritos na portaria são adequados para estratificar pacientes com asma grave.

**Descritores:** Asma; Budesonida; Terapia combinada.

\* Study carried out under the auspices of the Postgraduate Program in Pulmonology, Pulmonology Section of the Department of Internal Medicine, *Universidade Federal de São Paulo* – Unifesp, Federal University of São Paulo – São Paulo, Brazil.

Correspondence to: Ilka Lopes Santoro. Rua Botucatu, 740, Disciplina de Pneumologia, 3º andar, Vila Clementino, CEP 04023-062, São Paulo, SP, Brazil.

Tel 55 11 5549-1830. E-mail: [ilkasantoro@uol.com.br](mailto:ilkasantoro@uol.com.br) or [ilka@pneumo.epm.br](mailto:ilka@pneumo.epm.br)

Financial Support: None.

Submitted: 7 August 2008. Accepted, after review: 7 September 2008.

## Introduction

Asthma is a chronic inflammatory disease and, according to the multicenter International Study of Asthma and Allergies in Childhood, the mean worldwide prevalence is 11.6% among schoolchildren aged 6-7 years and 13.7% among adolescents aged 13-14 years.<sup>(1)</sup> In Brazil, asthma prevalence rates remain elevated, approximately 20% for those same two age brackets.<sup>(2-4)</sup>

Most cases present with mild or intermittent clinical expression, although 25-30% of patients have moderate asthma and 5-10% have severe asthma.<sup>(4)</sup> Although patients with severe asthma are the minority, they account for a significant portion of the health care resources allocated.<sup>(3)</sup>

One of the first definitions of "severe asthma" was given by the American Thoracic Society (ATS),<sup>(5)</sup> which recommended that patients who presented at least one major criterion and two minor criteria be considered patients with severe asthma. The major criteria are using high doses of inhaled corticosteroids or using oral corticosteroids on a continuous basis (or during at least 50% of the preceding year). The minor criteria include aspects of pulmonary function, exacerbations, stability of the disease and the use of one or more additional medications (long-acting bronchodilator, theophylline or leukotriene antagonists) in order to obtain control.<sup>(5)</sup>

Since the recent advent of effective management for the control of the disease, the term "controlled asthma" has been used. The concept of controlled disease is different from the concept of severity, although some variables be included in the definition of both.<sup>(6)</sup> Patients with uncontrolled severe asthma are likely to experience frequent exacerbations and to contribute disproportionately to the total costs of the treatment.<sup>(7)</sup> In a study evaluating the economic cost of asthma, carried out at our facility, it was observed that patients with controlled asthma accounted for lower health care expenditures than did those with uncontrolled asthma, due to a decrease in the number of emergency room visits as well as in the number of hospitalizations.<sup>(3)</sup> It is known that 80% of the users of emergency rooms who are frequently hospitalized due to asthma are those who did not comply with treatment and maintenance recommendations.<sup>(5,8,9)</sup> In addition, one of the obstacles to asthma maintenance treatment adherence in

Brazil is limited access to medication, especially for low-income populations.<sup>(4)</sup>

On 23 July, 2002, the Brazilian Federal Government approved Directive 1318/GM, published in the Official Federal Government Gazette, which ordered the distribution of medication at no charge to patients diagnosed with severe asthma.<sup>(4,10)</sup> The criteria for the inclusion and exclusion of patients in this program are set forth in the Complementary Directive of the *Secretaria de Atenção à Saúde/Ministério da Saúde* (SAS/MS, Health Care Department/National Ministry of Health) no. 12, issued on 12 November, 2002.<sup>(4,10)</sup>

The present study was aimed at evaluating the capacity of the aforementioned directive criteria in identifying this population of asthma patients, as well as at describing and comparing clinical, functional and treatment data for the monitoring of a sample of adult asthma patients.

## Methods

This was an observational nested case-control study, using a database structured for the monitoring of adult asthma patients.

In the period between January of 2005 and February of 2007, regularly monitored and treated patients were consecutively interviewed, as recommended by the ATS,<sup>(5)</sup> in the *Hospital São Paulo Asthma Research Outpatient Clinic, Universidade Federal de São Paulo* (Unifesp, Federal University of São Paulo), in the city of São Paulo, Brazil.

This study was approved by the Unifesp Ethics in Research Committee and was conducted in accordance with the ethical principals established in the Declaration of Helsinki.

The inclusion criteria were as follows: being aged between 16 and 80 years, being diagnosed with asthma according to the 2004 Global Initiative for Asthma (GINA) criteria<sup>(11)</sup>; agreeing to participate in the study; undergoing spirometry with bronchodilator test during the initial evaluation (at inclusion); and having had at least three documented evaluations in the year preceding the inclusion date.

Cases were defined as patients who met the inclusion criteria to receive the benefit granted by the directive with the completion of the "Exceptional Medication Request" (EMR) form. Controls were defined as asthma patients who

did not meet the same criteria and therefore were not granted the benefit (non-EMR).<sup>(4)</sup>

The criteria for being granted the benefit are as follows: presenting continuous, daily asthma symptoms; requiring the use of a short-acting bronchodilator at least twice per day; presenting a PEF or FEV<sub>1</sub> < 60% of predicted, prior to bronchodilator use, on spirometry tests<sup>(10)</sup>; and presenting nocturnal symptoms at least twice per week.

Patients diagnosed with COPD were excluded from the present study, as were patients with severe concomitant pulmonary disease and smokers or former smokers with a smoking history of more than five pack-years.

### Study protocol

Demographic data (age, race, gender, weight and height) were obtained at the time of inclusion.

In relation to history of asthma, we evaluated the age at onset of asthma symptoms, duration (date of diagnosis), trigger factors and asthma control. We also recorded the frequency and number of episodes of exacerbation, which was defined as an increase of diurnal and nocturnal symptoms requiring the use of quick-relief bronchodilator, more than 8 times per day, consecutive nighttime awakenings or treatment with systemic corticosteroids given as pulse therapy.<sup>(12,13)</sup> We registered the number of emergency room visits in the preceding year and the lifetime/previous-year incidence of hospi-

talizations, as well as the lifetime/previous-year incidence of admission to the intensive care unit (ICU).

We obtained the following information as for the use of asthma medications: dose of inhaled corticosteroid for maintenance treatment in the preceding three months, the use of oral corticosteroid in the preceding year; use of short-acting and long-acting bronchodilator; and use of methylxanthines, antileukotrienes, anticholinergics or chromones.

The evaluation of asthma control, at the time of inclusion, was based on the standardized algorithm on the patient chart, in compliance with the 2006 GINA criteria.<sup>(2)</sup> Therefore, as a conclusion of the evaluation, the patient was classified according to the level of control of the disease: controlled, partially controlled, uncontrolled or exacerbated.<sup>(2)</sup>

We also evaluated the systemic presence of the following comorbidities: rhinitis, gastroesophageal reflux, systemic arterial hypertension and obesity.

In the case of former smokers, we collected information on the history of smoking: age at smoking onset; tobacco intake, expressed as pack-years; and the date of smoking cessation. Nonsmokers were defined as individuals with tobacco exposure of less than one pack-year. Former smokers were defined as individuals who had quit smoking more than five years prior.

Spirometry and bronchodilator response test were performed at the time of inclusion of patient in the protocol. The functional evalua-

**Table 1** - Spirometry of the studied patients at the time of inclusion.

Parameter	Total	EMR	Non-EMR	p*
	(n = 60)	(n = 29)	(n = 31)	
Pre-BD				
FVC, L	3.13 ± 0.88	2.89 ± 0.84	3.34 ± 0.87	0.04
FEV <sub>1</sub> , L	1.93 ± 0.66	1.59 ± 0.49	2.24 ± 0.66	NA
FEV <sub>1</sub> , %	62.18 ± 16.57	49.04 ± 9.25	74.5 ± 11.7	NA
FEV <sub>1</sub> /FVC	61.58 ± 10.90	56.01 ± 10.52	66.79 ± 8.50	NA
Post-BD				
FVC, L	3.43 ± 0.88	3.30 ± 0.9	3.55 ± 0.85	0.33
FEV <sub>1</sub> , L	2.23 ± 0.72	1.96 ± 0.66	2.47 ± 0.70	NA
FEV <sub>1</sub> , %	71.50 ± 17.53	58.55 ± 13.54	83.42 ± 11.15	NA
FEV <sub>1</sub> /FVC	64.71 ± 11.08	59.82 ± 11.69	69.20 ± 8.45	NA
ΔFEV <sub>1</sub> BD L	19.01 ± 18.47	24.4 ± 22.15	14.05 ± 12.83	0.06

EMR: group of patients accepted into the Exceptional Medication Request Program; non-EMR: group of patients not accepted into the Exceptional Medication Request Program; BD: bronchodilator; and NA: not applicable. \*Unpaired t-test.

tion consisted of spirometry, with conventional bronchodilator response test. Spirometry was performed in accordance with the norms of the "Pulmonary Function Test Guidelines" issued in 2002.<sup>(14)</sup>

When available, sputum cytology results were registered in order to evaluate airway inflammation. These examinations were performed in the Unifesp Department of Pulmonology Laboratory for Airway Inflammation Research. The procedures for the collection and processing of the sputum were performed in accordance with methods previously described.<sup>(15)</sup> The total number of cells was evaluated, as were the percentages of macrophages, neutrophils, lymphocytes and eosinophils.

Descriptive statistical methods were used in order to profile of the studied population. The chi-square test (together with the partition chi-square test, when necessary) was used to compare the two groups in terms of the frequency of the categorical variables. The unpaired t-test was used to compare the two groups as for the continuous variables with normal distribution. The nonparametric Mann-Whitney test was used to compare the two groups in terms of the continuous variables with non-normal distribution. We adopted a value of 5% in order to reject the null hypothesis in all tests.

In order to calculate the ideal size of the sample to be obtained, we took into account

the fact that that the prevalence of one annual pulse of oral corticosteroids per year is 60% in patients regularly monitored at the *Hospital São Paulo Asthma Research Outpatient Clinic*. If this event occurred in 75% of the group with mild asthma (the study group) and in 15% in the control group, we would need 29 patients in each group in order to observe this difference, with an  $\alpha = 0.05$  (two-tailed) and statistical power of the test of 80% ( $\beta = 0.2$ ).<sup>(16)</sup>

The data were tabulated using Microsoft Excel 2000. The tool used to conduct the statistical calculation was the Statistical Package for the Social Sciences, version 13.0 (SPSS Inc., Chicago, IL, USA).

## Results

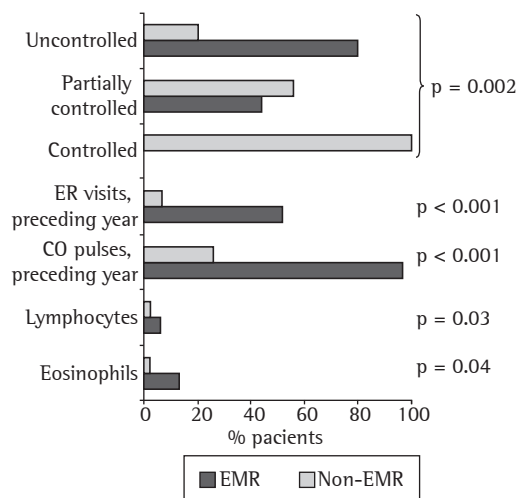
Sixty patients were included in the study. The group of patients who received free medication (EMR group) presented lower prebronchodilator FVC values, and this difference was statistically significant. The variable FEV<sub>1</sub> was not statistically evaluated, since it was not related to any of the inclusion criteria. The two studied groups were homogeneous in relation to postbronchodilator  $\Delta$ FEV<sub>1</sub> (Table 1).

There no statistically significant difference between the groups in terms of age, body mass index, gender, race, time since diagnosis, history of smoking, rhinitis, gastroesophageal reflux,

**Table 2** - Demographic characteristics, asthma history, comorbidities and control of patients at the time of inclusion.

Characteristic	Total (n = 60)	EMR (n = 29)	Non-EMR (n = 31)	p*
Age, <sup>a</sup> years	41.88 ± 13.25	40.83 ± 13.16	42.87 ± 13.47	0.55
BMI, <sup>a</sup> kg/m <sup>2</sup>	26.75 ± 6.17	26.17 ± 7.08	27.28 ± 5.23	0.49
Female, % (n)	61.7 (37)	58.6 (17)	64.5 (20)	0.64
Caucasian, % (n)	67.8 (40)	79.3 (23)	54.8 (17)	0.14
Onset of asthma symptoms (> 12 years)	51.7 (31)	44.8 (13)	51.6 (16)	0.59
Rhinitis, % (n)	86.7 (52)	86.2 (25)	87.1 (27)	0.91
GERD, % (n)	15 (9)	13.8 (4)	16.1 (5)	0.80
SAH, % (n)	23.3 (14)	13.8 (4)	32.2 (10)	0.09
Obesity, % (n)	20 (12)	13.8 (4)	25.8 (8)	0.24
Former smoker, % (n)	10 (6)	13.8 (4)	6.5 (2)	0.34
Asthma control, % (n)				
Uncontrolled	25 (15)	80 (12)	20 (3)	
Partially controlled	65 (39)	44 (17)	56 (22)	0.002
Controlled	10 (6)	0 (0)	100 (6)	

EMR: group of patients accepted into the Exceptional Medication Request Program; non-EMR: group of patients not accepted into the Exceptional Medication Request Program; BMI: body mass index; GERD: gastroesophageal reflux disease; and SAH: systemic arterial hypertension. <sup>a</sup>Mean ± SD. \*Chi-square test.



**Figure 1** – Asthma control, number of emergency room (ER) visits in the preceding year and corticosteroid (CO) pulses in the preceding year, together with the percentage of lymphocytes and eosinophils in the induced sputum of patients accepted or not accepted into the Exceptional Medication Request Program (EMR group and non-EMR group, respectively).

arterial hypertension or obesity. Most patients in the EMR group presented uncontrolled asthma, whereas most patients in the non-EMR group presented controlled asthma, and this difference was statistically significant (Table 2 and Figure 1).

The EMR group presented a higher number of exacerbations in the preceding year, with a higher number of emergency room visits, as well as a higher percentage of patients who received at least one pulse of oral corticosteroids in the same period. These differences were statistically significant. As for the number of lifetime/previous-year hospitalizations and ICU admissions, no statistically significant differences were observed between the groups (Table 3 and Figure 1).

The EMR group presented significantly greater numbers of lymphocytes and eosinophils in the induced sputum samples collected prior to the time of inclusion, in relation to the non-EMR group (Table 4 and Figure 1).

## Discussion

The criteria for patient acceptance into the EMR program, outlined in Complementary Directive SAS/MS 12, issued on 12 November, 2002,<sup>(4,10)</sup> were appropriate for the identification of the patients presenting the greatest disease severity. Those criteria stratified patients based on the frequency at which they used health care resources. The patients selected to receive medication from the EMR presented a higher number of emergency room visits in the preceding year, a higher number of exacerbations and a more frequent need for corticosteroid pulses. It is known that patients with severe asthma who achieve control of the disease visit the emergency room less frequently and are less likely to receive oral corticosteroid pulses, although these severity markers present no significant association with corticosteroid dependency.<sup>(17)</sup>

In the present study, we observed that the emergency room visits did not result in hospitalization or admission to the ICU; therefore, the attacks presented good response to the emergency treatment, which characterizes mild to moderate bronchospasm attacks,<sup>(2)</sup> as well as characterizing patients likely to have received insufficient maintenance treatment. Therefore, the EMR directive criteria were efficacious in identifying patients with frequent exacerbations and uncontrolled asthma, who are those that would potentially benefit most from the adequate and continuous use of medication.

**Table 3** – Clinical characteristics of asthma at the time of inclusion.

Characteristic	Total	EMR	Non-EMR	p
	(n = 60)	(n = 29)	(n = 31)	
Exacerbations in the preceding year, <sup>a</sup> n	1.13 ± 1.73	1.55 ± 2.08	0.74 ± 1.24	0.04*
Visits to the ER in the preceding year, % (n)	28.3 (17)	51.7 (15)	6.5 (2)	< 0.001**
Hospitalizations throughout life, % (n)	48.3 (29)	51.7 (15)	45.2 (14)	0.61**
Hospitalizations in the preceding year, % (n)	10 (6)	17.2 (5)	3.2 (1)	0.07**
ICU admissions throughout life, % (n)	16.7 (10)	20.7 (6)	12.9 (4)	0.42**
OC pulse in the preceding year, % (n)	60 (36)	96.6 (28)	25.8 (8)	< 0.001**

EMR: group of patients accepted into the Exceptional Medication Request Program; non-EMR: group of patients not accepted into the Exceptional Medication Request Program; R: emergency room; ICU: intensive care unit; and OC: oral corticosteroid. <sup>a</sup>Mean ± SD. \*Unpaired t-test, and \*\*Chi-square test.

**Table 4** – Comparison of the median values of the total and differential count of the cells of the induced sputum of the patients who underwent sputum cytology prior to the time of inclusion.

Count	Total	EMR	Non-EMR	p*
	(n = 60)	(n = 29)	(n = 31)	
Total number of cells × 10 <sup>6</sup>	0.28	0.24	0.60	0.43
Macrophages, %	26.38	25.75	33.00	0.82
Neutrophils, %	56.87	50.00	60.50	0.92
Lymphocytes, %	4.87	6.00	2.25	0.03
Eosinophils, %	3.63	13.00	2.00	0.04

EMR: group of patients accepted into the Exceptional Medication Request Program; and non-EMR: group of patients not accepted into the Exceptional Medication Request Program. \*Mann-Whitney test.

One limitation of the present study was the potential bias related to the registration of the use of the health care resources, although we were able to confirm the occurrence of emergency room visits and exacerbations using the data contained in the emergency room medical charts.

Strategies have recently been developed to evaluate the complexity of the treatment and monitoring of asthma patients as well as to identify phenotypes, especially that of difficult-to-control severe asthma. Therefore, the underuse of preventive medication, especially of inhaled corticosteroids, as well as inappropriate management—which includes exposure to trigger factors, inefficacious use of medication administered through inhalation and failure to identify the early signs of exacerbation—contribute to the collection of disparities in compliance with the consensus recommendations established for asthma patients.<sup>(18-20)</sup> Studies suggest that the lack of adherence to treatment due to costs or patient failure to appropriately prioritize treatment can contribute to sub-optimal use of medication.<sup>(21-24)</sup>

A reduction in the proportion of eosinophils in the induced sputum is to be expected in patients with controlled asthma.<sup>(25)</sup> In the present study, the inflammatory characteristics, evaluated by induced sputum cytology, differed between the two groups evaluated. Patients in the EMR group presented an increase in the number of eosinophils, which suggests a lack of disease control in this group. In the non-EMR group, the median number of eosinophils in the sputum was within the normal range, due to the greater proportion of controlled patients in this group (Tables 2 and 4).<sup>(24)</sup> Therefore, induced sputum cell counts can be used as a marker and add quality to the monitoring of the asthma

treatment, as well as correlating with the use of inhaled corticosteroid.<sup>(27)</sup> The higher number of lymphocytes in the sputum of patients in the non-EMR group was not a significant difference and has no clinical relevance.

It is known that the minority populations (Blacks, Hispanics and low-income individuals) in developed countries use less anti-inflammatory medication and, consequently, more frequently evolve to uncontrolled asthma.<sup>(22)</sup> However, genetic studies have shown that Black patients present alterations that explain the greater disease severity.<sup>(28)</sup> In both groups, there was a predominance of female patients and Caucasian patients; the groups were homogenous in terms of age and presence of comorbidities (rhinitis, gastroesophageal reflux, systemic arterial hypertension, obesity and smoking). Although no statistically significant differences for these variables were observed between the two groups, many of them have been associated with asthma severity.<sup>(9,29)</sup>

The variations observed in the functional study of our patients are related to the inclusion criteria applied for each group. Therefore, as expected, the patients who met the EMR acceptance criteria were the most functionally severe (Table 1). The FEV<sub>1</sub>/FVC ratio is considered the gold standard measurement for the identification of airway obstruction, whereas FEV<sub>1</sub> is used to grade this obstruction. The advantage of using FEV<sub>1</sub> as an asthma severity marker is the objectivity and the reproducibility of this variable.<sup>(14)</sup>

The control of asthma influences the value of the total cost by reducing expenses related to the use of health care resources.<sup>(3)</sup> Therefore, the distribution of asthma medication at no cost leads to a decrease in the number of exacerbations of the disease and, consequently, to a

lower number of emergency room visits, due to the improved control of the disease. This has been proven, in our group, through a randomized study which evaluated the distribution of asthma maintenance medication at no cost.<sup>(30)</sup> Therefore, we confirm the relevance of evaluating the EMR criteria to identify patients who overload treatment facilities and contribute to increasing emergency room costs.

The EMR acceptance criteria (presenting continuous, daily asthma symptoms; requiring the use of a short-acting bronchodilator at least twice per day; presenting a PEF or FEV<sub>1</sub> < 60% of the predicted, prior to bronchodilator use, on spirometry tests; and experiencing nocturnal symptoms at least twice per week) allowed the identification of patients who had visited the emergency room more often, presented a higher number of exacerbations/oral corticosteroid pulses, as well as a greater degree of airway inflammation, as evidenced by the greater proportion of eosinophils in the induced sputum.

## Acknowledgments

This study was conducted as part of a Masters degree dissertation presented via the Unifesp Postgraduate Program in Pulmonology, Pulmonology Section of the Department of Internal Medicine.

## References

1. Rees J. ABC of asthma. Prevalence. *BMJ*. 2005;331(7514):443-5.
2. GINA Executive Committee; GINA Science Committee. Global Strategy for Asthma Management and Prevention. 2006 [cited; 2008 Aug 7]. Available from: <http://www.ginasthma.com>
3. Santos LA, Oliveira MA, Faresin SM, Santoro IL, Fernandes AL. Direct costs of asthma in Brazil: a comparison between controlled and uncontrolled asthmatic patients. *Braz J Med Biol Res*. 2007;40(7):943-8.
4. Sociedade Brasileira de Pneumologia. IV Diretrizes Brasileiras para o Manejo da Asma. *J Bras Pneumol*. 2006;32(Suppl 7):S447-S74.
5. Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions. American Thoracic Society. *Am J Respir Crit Care Med*. 2000;162(6):2341-51.
6. Sullivan SD, Rasouliyan L, Russo PA, Kamath T, Chipps BE; TENOR Study Group. Extent, patterns, and burden of uncontrolled disease in severe or difficult-to-treat asthma. *Allergy*. 2007;62(2):126-33.
7. Wenzel SE. Severe asthma in adults. *Exp Lung Res*. 2005;31 Suppl 1:22.
8. Wenzel S. Severe asthma in adults. *Am J Respir Crit Care Med*. 2005;172(2):149-60.
9. Wenzel S, Szefer SJ. Managing severe asthma. *J Allergy Clin Immunol*. 2006;117(3):508-11.
10. Stribulov R. Asma e Recursos legais Disponíveis. In: Gomes M, Faresin SM, editors. 7th ed. São Paulo: ROCA; 2007. p. 35-8
11. Masoli M, Fabian D, Holt S, Beasley R; Global Initiative for Asthma (GINA) Program. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy*. 2004;59(5):469-78.
12. Partridge MR. What do the words "asthma control" and "exacerbation" really mean? *Prim Care Respir J*. 2004;13(4):179-80.
13. Pauwels RA, Löfdahl CG, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. *N Engl J Med*. 1997;337(20):1405-11. Erratum in: *N Engl J Med*. 1998;338(2):139.
14. Sociedade Brasileira de Pneumologia e Tisiologia. Diretrizes para Teste de Função Pulmonar. *J Pneumol*. 2002;28(Suppl 3):S2-S238.
15. Pizzichini E, Pizzichini MM, Kidney JC, Efthimiadis A, Hussack P, Popov T, et al. Induced sputum, bronchoalveolar lavage and blood from mild asthmatics: inflammatory cells, lymphocyte subsets and soluble markers compared. *Eur Respir J*. 1998;11(4):828-34.
16. Browner WS, Newman T, Cummings SR, Hulley SB. Estimating Sample Size and Power: The Nitty-gritty In: Hulley SB, Cummings SR, Browner WS, Grady DG, Hearst N, Newman TB, editors. Designing clinical research. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 65-91
17. Calfee CS, Katz PP, Yelin EH, Iribarren C, Eisner MD. The influence of perceived control of asthma on health outcomes. *Chest*. 2006;130(5):1312-8.
18. de Oliveira MA, Bruno VF, Ballini LS, BritoJardim JR, Fernandes AL. Evaluation of an educational program for asthma control in adults. *J Asthma*. 1997;34(5):395-403.
19. de Oliveira MA, Faresin SM, Bruno VF, de Bittencourt AR, Fernandes AL. Evaluation of an educational programme for socially deprived asthma patients. *Eur Respir J*. 1999;14(4):908-14.
20. Sociedade Brasileira de Pneumologia e Tisiologia. I Consenso Brasileiro de Educação em Asma. *J Pneumol*. 1996;22(Suppl 1):S1-S24.
21. Halterman JS, Aligne CA, Auinger P, McBride JT, Szilagyi PG. Inadequate therapy for asthma among children in the United States. *Pediatrics*. 2000;105(1 Pt 3):272-6.
22. Lieu TA, Lozano P, Finkelstein JA, Chi FW, Jensvold NG, Capra AM, et al. Racial/ethnic variation in asthma status and management practices among children in managed Medicaid. *Pediatrics*. 2002;109(5):857-65.
23. Ortega AN, Gergen PJ, Paltiel AD, Bauchner H, Belanger KD, Leaderer BP. Impact of site of care, race, and Hispanic ethnicity on medication use for childhood asthma. *Pediatrics*. 2002;109(1):E1.
24. Warman KL, Silver EJ, Stein RE. Asthma symptoms, morbidity, and antiinflammatory use in inner-city children. *Pediatrics*. 2001;108(2):277-82.
25. Jayaram L, Pizzichini MM, Cook RJ, Boulet LP, Lemièrè C, Pizzichini E, et al. Determining asthma treatment by

- monitoring sputum cell counts: effect on exacerbations. *Eur Respir J*. 2006;27(3):483-94.
26. Belda J, Leigh R, Parameswaran K, O'Byrne PM, Sears MR, Hargreave FE. Induced sputum cell counts in healthy adults. *Am J Respir Crit Care Med*. 2000;161(2 Pt 1):475-8.
27. Jayaram L, Pizzichini E, Lemièrre C, Man SF, Cartier A, Hargreave FE, et al. Steroid naive eosinophilic asthma: anti-inflammatory effects of fluticasone and montelukast. *Thorax*. 2005;60(2):100-5.
28. Wenzel SE, Balzar S, Ampleford E, Hawkins GA, Busse WW, Calhoun WJ, et al. IL4R alpha mutations are associated with asthma exacerbations and mast cell/IgE expression. *Am J Respir Crit Care Med*. 2007;175(6):570-6.
29. Bel E. Severe Asthma. *Breathe*. 2006;3(3):129-39.
30. Santos LA. Tratamento de manutenção da asma moderada: influência nos custos diretos e efetividade da concessão medicamentosa na obtenção do controle [thesis]. São Paulo: Universidade Federal de São Paulo; 2007.

## ***About the authors***

---

### ***Maria Amélia Carvalho da Silva Santos***

Masters Student in Sciences. Postgraduate Program in Pulmonology, Pulmonology Section of the Department of Internal Medicine, *Universidade Federal de São Paulo* – Unifesp, Federal University of São Paulo – São Paulo, Brazil.

### ***Ana Luísa Godoy Fernandes***

Tenured Associate Professor. Pulmonology Section of the Department of Internal Medicine, *Universidade Federal de São Paulo* – Unifesp, Federal University of São Paulo – São Paulo, Brazil.

### ***Mara Marta Amorim***

Biomedical Professional. Pulmonology Section of the Department of Internal Medicine, *Universidade Federal de São Paulo* – Unifesp, Federal University of São Paulo – São Paulo, Brazil.

### ***Patrícia Bueno Lima***

Masters Student in Sciences. Postgraduate Program in Pulmonology, Pulmonology Section of the Department of Internal Medicine, *Universidade Federal de São Paulo* – Unifesp, Federal University of São Paulo – São Paulo, Brazil.

### ***Sônia Maria Faresin***

Affiliate Professor. Pulmonology Section of the Department of Internal Medicine, *Universidade Federal de São Paulo* – Unifesp, Federal University of São Paulo – São Paulo, Brazil.

### ***Ilka Lopes Santoro***

Affiliate Professor. Pulmonology Section of the Department of Internal Medicine, *Universidade Federal de São Paulo* – Unifesp, Federal University of São Paulo – São Paulo, Brazil.