Original Article

Investigation of factors associated with difficult-to-control asthma*

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Abstract

Objective: To determine the prevalence of factors associated with difficult-to-control asthma. **Methods:** Patients with severe asthma were selected from the outpatient asthma clinic of the Ribeirão Preto School of Medicine *Hospital das Clínicas*. The patients were divided into two groups: controlled severe asthma and difficult-to-control severe asthma. After new attempts to optimize the severe asthma treatment, a questionnaire was applied, and additional tests for factors associated with difficult-to-control asthma, such as environmental exposure, occupational exposure, smoking history, social factors, rhinitis/sinusitis, gastroesophageal reflux disease (GERD), obstructive sleep apnea, congestive heart failure (CHF), pulmonary embolism, cystic fibrosis, vocal cord dysfunction, α-1 antitrypsin deficiency, and Churg-Strauss syndrome, were performed. **Results:** 77 patients with severe asthma were selected, of which 47 suffered from hard-to-control asthma, being 68.1% female, with mean age of 44.4 years (± 14.4), and forced expiratory volume in one second of 54.7% (± 18.3). The factors most often associated with difficult-to-control asthma were noncompliance with treatment (68%), rhinitis/sinusitis (57%), GERD (49%), environmental exposure (34%), occupational exposure (17%), smoking history (10%), obstructive sleep apnea (2%), and CHF (2%). At least one of these factors was identified in every case. **Conclusions:** Noncompliance with treatment was the factor most often associated with difficult-to-control asthma, underscoring the need to investigate comorbidities in the evaluation of patients with this form of the disease.

Keywords: Asthma; Smoking; Gastroesophageal reflux; Patient compliance; Rhinitis; Sinusitis.

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Introduction

Approximately 5% of asthma patients have severe asthma that is not clinically controlled, regardless of the prescription of appropriate doses of inhaled corticosteroids and long-acting bronchodilators. In these cases, the occurrence of frequent exacerbations requires the use of systemic corticosteroids.[1,2] These patients visit the emergency room 15 times more often and are hospitalized 20 times more often than are those with moderate asthma.[3] Several factors can contribute to the severity of this disease. Among such factors are occupational exposure, rhinosinusitis, gastroesophageal reflux disease (GERD), low compliance with treatment, and psychological problems.[1,4]

Currently, the Brazilian government provides medications for severe asthma, and this seems to have modified the pattern of treatment and compensation in these cases. However, objective measures of response to severe asthma treatment associated with Brazilian government directive no. 1318 have yet to be researched or published.[5] Therefore, knowing the frequency of cases that remain decompensated even after appropriate treatment is important, as is establishing means of investigating difficult-to-control asthma.

We formulated the hypothesis that difficult-to-control asthma is associated with factors that are possible to identify. The aim of this study was to research, using a diagnosis algorithm, the factors associated with difficult-to-control asthma.

Methods

Study sample

Between October of 2003 and October of 2004, all severe asthma patients treated at the asthma outpatient clinic of the Pulmonology Division of the Ribeirão Preto School of Medicine Clinical Hospital were selected. The diagnosis was based on the presence of partially or totally reversible airway obstruction and symptoms related to such obstruction. In order to classify the severity of the disease, were defined severe asthma as forced expiratory volume in one second (FEV_1) or peak expiratory flow (PEF) < 60% of the estimated value, together with continuous symptoms, use of bronchodilators ≥ twice a day, nocturnal symptoms > twice a week, or previous history of orotracheal intubation due to bronchospasm crisis according to the III Brazilian Consensus on Asthma Management.[6] A Koko pneumotachograph spirometer and the accompanying software (PDS Instrumentation, Inc., Louisville, CO, USA) were used for spirometry, and the measurements were analyzed based on the normality values described by other authors.[7] All patients were receiving medication provided by the Brazilian government, according to Directive no. 1318,[5] for the treatment of severe asthma. We divided the patients into two groups: controlled severe asthma and difficult-to-control asthma. Those patients who had used oral corticosteroid for at least 50% of the year or had used high doses of inhaled corticosteroids (≥ 800 µg/day of beclomethasone or equivalent) were initially classified as having difficult-to-control asthma. However, at least two of the following criteria also had to be met: daily use of a long-acting bronchodilator, theophylline or antileukotriene combined with an inhaled corticosteroid; daily use of a short-acting bronchodilator; persistent obstruction of the airway (FEV_1 < 80% of the estimated value; PEF variance > 20% of the estimated value); one or more visits per year to the emergency room due to asthma; three or more pulses of oral corticosteroid per year; rapid worsening with a reduction of 25% in the corticosteroid dose; and having had a near-fatal crisis.

Study protocol

Prior to collecting the study data, we attempted to optimize the treatment. This consisted of re-educating the patients in relation to asthma, increasing the medication dose, and performing a preliminary evaluation of the compliance with treatment, which was performed by the physician who monitored the patient. This optimization was made following the outpatient clinic routine, by resident physicians who did not participate in the data collection for the study, and who reported patient compliance with the treatment in the clinical charts. The first phase of data collection was the application of a questionnaire completed during an interview carried out by the same pulmonologist, one of the authors of the study, in order to determine the occurrence of factors associated with difficult-to-control asthma, such as environmental exposure (pets, carpets, curtains, mold, and dust in the home) and occu-

pational exposure. In this case, PEF was evaluated on 15 workdays and on 15 holidays in patients reporting asthma onset upon entering the workplace or worsening of asthma associated with work.[8] The following factors were also studied: smoking, social factors, with evaluation of the correct use of prescribed medications, and low compliance with treatment. Until this phase, we presupposed that the patient used the prescribed medications correctly, and the revaluation was performed by the physician who carried out the study.

All selected patients were submitted to complementary investigation of the following:

- Rhinosinusitis: The diagnosis of rhinitis was based on symptoms of pruritus, nasal congestion, and rhinorrhea.
- Sinusitis: Sinusitis was investigated through symptoms, physical examination, and X-ray of the paranasal sinuses.
- GERD: Those patients who presented gastroesophageal reflux symptoms ≥ twice a week in a period of four to eight weeks, for whom endoscopy of the upper digestive tract showing esophagitis, or who tested positive in esophageal pHmetry testing (DeMeester score > 14.72) were considered cases of GERD.[9]
- Aspergillosis: In order to diagnose aspergillosis, specific serological testing (counterimmunoelectrophoresis) and a skin test (skin prick test), the latter consisting of the application of antigenic extract on the skin, followed by light excoriation, were carried out. As a criteria for aspergillosis, we also evaluated the serum concentration of total immunoglobulin E (IgE), measured by fluorescent enzyme immunoassay using the UniCAP 100 system (Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden).
- Diseases that mimic asthma: An additional investigation was carried out using high-resolution computed tomography scans of the chest in order to exclude alveolar infiltrate and other pulmonary diseases, such as emphysema and bronchiectasis. If the investigation was normal, specific investigations were carried out in order to identify obstructive sleep apnea (questionnaire and confirmation through polysomnography, the criterion being an apnea-hypopnea index above five events/h),[10] congestive heart failure (CHF, specific questionnaire and doppler echocardiogram), pulmonary embolism (investigation of triggering factors and confirmation through scintigraphy), cystic fibrosis (sweat chloride levels), vocal cord dysfunction (laryngoscopy), α-1 antitrypsin deficiency, and Churg-Strauss vasculitis.
- If none of the comorbidities listed above were identified, bronchoscopy was ordered.

The diagnostic investigation protocol is illustrated in Figure 1.[11]

Statistical analysis

Using the Microsoft Excel program, a database was created, into which all of the data were entered. The database was then translated to the GraphPad Prism program, version 3.02 (GraphPad Software, San Diego, CA, USA). The statistical comparison of the general characteristics of difficult-to-control asthma and controlled severe asthma patients was performed using unpaired, bicaudal Student's t-test, except for the use of formoterol and beclomethasone, which presented a negative normality test result. Therefore, the Mann-Whitney test was applied to that variable, and the comparison of concomitant diagnoses in both groups was made using Fisher's exact test. The proportion of women, as well as that of patients using systemic corticosteroids, was compared between the two groups using the chi-square test. The level of significance adopted was 5% ($p \leq 0.05$).

Results

During the one-year period defined, 77 patients with severe asthma were included in the study. Of those 77, 30 (39%) presented a satisfactory clinical response (minimum use of short-acting bronchodilators and systemic corticosteroids, reduction or elimination of visits to the emergency room) after the therapeutic doses for the treatment of severe asthma had been adjusted according to step IV of the III Brazilian Consensus on Asthma Management.[6] The remaining 47 patients (70%) were diagnosed with difficult-to-control asthma. There were no statistically significant differences when we compared difficult-to-control asthma patients and controlled severe asthma patients in terms of age, gender, weight, height, and FEV_1 (Table 1).

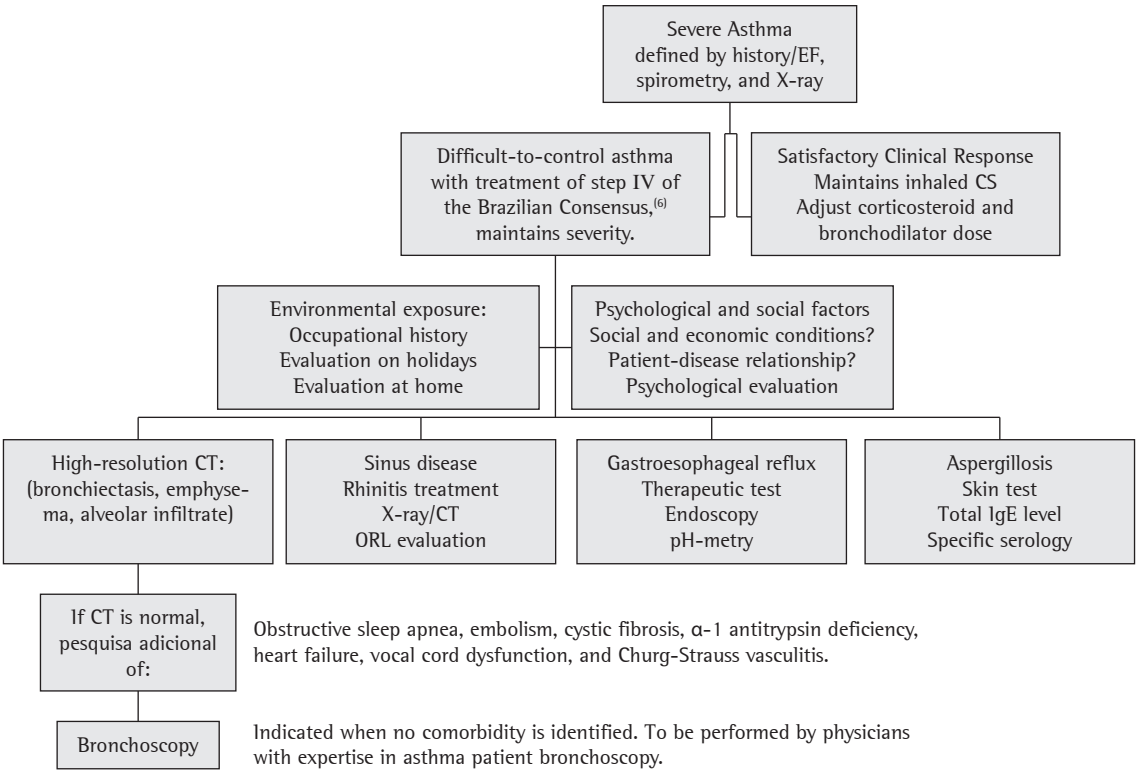

Figure 1 - Suggestion of algorithm for the investigation of difficult-to-control asthma. EF: expiratory flow; CS: corticosteroid; CT: computed tomography; and ORL: otorhinolaryngological. Vianna E., 2003

The frequency of the diagnoses associated with the difficult clinical control of these patients is illustrated in Figure 2. Low compliance with treatment, detected in 68% of the cases (32 patients), was the main factor that contributed to the development of difficult-to-control asthma. In addition, it was the only factor presenting a significant difference between the two groups (p = 0.036). Rhinosinusitis was present in 27 patients (57%) and GERD in 23 (49%). Occupational asthma was identified in 8 patients (17%), and deleterious environmental exposure was reported by 16 asthma patients (34%). One patient was diagnosed with obstructive sleep apnea, and another patient was diagnosed with CHF. All patients presented at least one diagnosis associated with difficult-to-control asthma. In total, 20 patients had two associated factors, 12 had three, 2 had four, and 2 had five. In the controlled severe asthma group, there were 3 patients that presented no factors associated with asthma severity, 7 that presented one, 10 that presented two, 9 that presented three, and 1 that presented four.

Discussion

In our study, all difficult-to-control asthma patients had at least one diagnosis associated with the difficult-to-control form of the disease. We investigated 16 factors in our study, including poor environmental conditions (34%), occupational asthma (17%), smoking (10%), poor social conditions, low treatment compliance with the treatment (68%), rhinosinusitis (57%), GERD (49%), chronic obstructive pulmonary disease, bronchiectasis, aspergillosis, obstructive sleep apnea (2%), CHF (2%), pulmonary embolism, cystic fibrosis, vocal cords dysfunction, a-1 antitrypsin deficiency, and Churg-Strauss vasculitis. The only factor that presented a significant difference between difficult-to-control asthma patients and controlled severe asthma patients was low compliance with the prescribed treatment.

One group of authors studied 73 patients with difficult-to-control asthma and found that 34% had another diagnosis associated with respiratory symp-

Table 1 - General characteristics of the patients evaluated (n = 77).

Variable	Difficult-to-control asthma (n = 47)	Controlled asthma (n = 30)	p value
Age (years)[a]	44.4 ± 14.4	40.1 ± 15.4	0.846
Gender (% female)	68.1	60	0.302
Weight (kg)[a]	71.2 ± 16.3	69.4 ± 14.5	0.639
Height (m)[a]	1.61 ± 0.1	1.60 ± 0.1	0.695
FEV_1 before treatment (% of estimated value)[a]	54.7 ± 18.3	62.4 ± 18.1	0.081
Beclomethasone dose (μg/day)[a,b]	1312 ± 503.7	773 ± 143.6	<0.001
Formoterol dose (μg/day)[a,b]	18.6 ± 9.5	10.4 ± 11.9	<0.01
Use of systemic CS > 50% of the year	29 (61.7%)	0	<0.001
Patients using aminophylline	11 (23.4%)	2 (6.6%)	0.109

[a]Data presented as mean ± standard deviation; [b]The doses refer to the prescribed medication; and FEV_1: forced expiratory volume in one second; CS: corticosteroid.

toms. The frequency of GERD (57%), rhinosinusitis (95%), and psychiatric comorbidities (49%) did not differ between the groups. After treating these comorbidities, more than 50% of patients achieved clinical control of the disease.[4] The patients with difficult-to-control asthma, as in our study, received significantly higher doses of inhaled corticosteroids in relation to those with controlled severe asthma. This probably reflects the low compliance with treatment and the gradual increase in the dosage of anti-inflammatory medication in an attempt to control the disease.[4]

Low compliance with the prescribed treatment was the main factor that contributed to the difficult control of asthma (68%). Although this was the factor most often implicated in our sample, this number might have been even higher if there were laboratory tests available that were designed to verify compliance.

In other studies, suspected noncompliance with treatment is the factor most strongly associated with the difficult control of the disease.[11] Another similar study investigated GERD, lack of inhaled corticosteroid in the treatment, environmental/occupational factors, incorrect inhalation technique, other diagnosis (chronic obstructive pulmonary disease and CHF), rhinosinusitis, psychological factors, smoking, and isoproterenol abuse. The authors associated therapeutic success with the addition of inhaled corticosteroid, and with the response to GERD treatment.[12]

In one study of compliance with asthma maintenance treatment conducted in Brazil,[13] the result of other studies of treatment compliance in cases of asthma were confirmed.[14] That study identified low compliance with the prescribed treatment in 52% of 131 patients with moderate to severe asthma who received medication for the treatment of the disease for three months. Higher rates of compliance were seen among the severe asthma patients (63.9%).[13]

In the present study, the second leading diagnosis associated with difficult-to-control asthma was rhinosinusitis, corresponding to 57% of the cases. Other authors have stated that chronic sinusitis and symptomatic GERD are the independent factors most strongly associated with severe asthma.[15] In that study, the GERD diagnosis was based on symptoms only. Neither endoscopy of the upper digestive tract nor esophageal pHmetry were performed. Therefore, the number of patients with GERD might have been overestimated.

The relationship between chronic sinusitis and severe asthma has been widely studied. However, the results remain conflicting, as shown by one group of authors,[16] who did not find a relationship between chronic sinusitis and corticosteroid-dependent severe asthma in adults. Those authors also overestimated the GERD frequency because they did not perform additional examinations.

The European Network For Understanding Mechanisms Of Severe Asthma (ENFUMOSA) study compared severe asthma patients with moderate asthma patients.[17] The study revealed that being of the female gender is associated with the development of severe asthma, whereas atopy is not. In women, there was a higher incidence of sinusitis, symptoms increased in intensity during the premenstrual period, and symptoms were more often

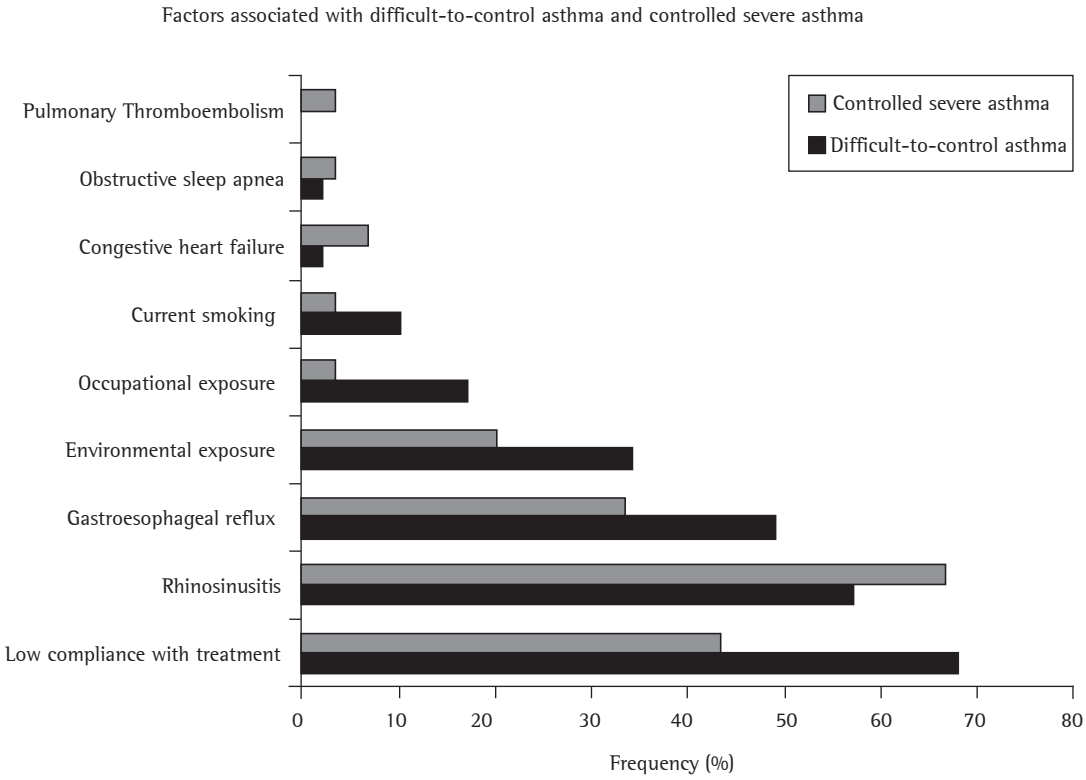

Figure 2 - Frequency of diagnosis associated with controlled severe asthma (n = 30) and difficult-to-control asthma (n = 47) in the studied population.

related to the use of aspirin, physical exercises, or the work environment. In addition, women presented a predominance of neutrophils in the sputum. However, in the present study, there was no significant difference in the proportion of female gender between the group with refractory asthma and the group without. In the literature, controversy remains regarding the hormonal effects or effects related to the female gender in the evolution of asthma.[17]

The administration of the European Community questionnaire to evaluate respiratory health, completed by participating ENFUMOSA study patients, showed that sharing the bedroom until the age of 5 years is associated with a higher risk of severe asthma. There was no risk relation with personal or family history of allergy, occurrence of respiratory infections and the period in preschool were not found to be related to the risk of severe asthma. Most severe asthma patients in the ENFUMOSA study reported asthma symptoms at work (and having changed jobs for this reason) and changes in dietary habits, such as reducing their consumption of snacks and sweets.[18]

Therefore, data such as those described in our study are fundamental for us to plan strategies for managing the disease, including those that involve the use of treatments that have a higher cost or carry a greater risk.

Studies involving larger patient samples could allow the identification of different factors, although several of the factors detected in the present study should be part of the pulmonology routine. Among those factors, low compliance with treatment merits urgent studies in order to identify its causes and devise methods for its detection. Preconceptions and lack of knowledge regarding inhaled medication are factors that are still relevant to low compliance with treatment. Further studies are also necessary to monitor these patients and to evaluate the advantages (cost-benefit ratio) of detecting associated factors.

Therefore, we have presented national data for a clinical entity, difficult-to-control asthma, research into which is limited by the heterogeneity of the disease and the difficulty in obtaining large patient samples. That is why there are so few studies, even in developed countries. Taking these characteristics into account, the medical instructions/indications can not be simplified, as they are for mild to moderate asthma, for which the treatment is standardized. In conclusion, patients with severe or difficult-to-control should receive individualized treatment, since, as we have demonstrated, other diagnoses are associated with therapeutic difficulty. The factor most commonly associated with therapeutic difficulty was low compliance with the treatment prescribed, which was also the only factor that differentiated the controlled severe asthma group from the difficult-to-control asthma group.

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References

1. 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.
2. Barnes PJ, Woolcock AJ. Difficult asthma. Eur Respir J. 1998;12(5):1209-18.
3. Serra-Batlles J, Plaza V, Morejon E, Comella A, Brugues J. Costs of asthma according to the degree of severity. Eur Respir J. 1998;12(6):1322-6.
4. Heaney LG, Conway E, Kelly C, Johnston BT, English C, Stevenson M, et al. Predictors of therapy resistant asthma: outcome of a systematic evaluation protocol. Thorax. 2003;58(7):561-6.
5. Secretaria de Estado de Saúde do Estado do Mato Grosso do Sul [Homepage on the Internet]. Campo Grande: Secretario de Estado de Saúde do Estado do Mato Grosso do Sul. [cited 2006 Mar 15]. Portaria 1318 do Mistério da Saúde. Available from: http://www.saude.ms.gov.br/
6. Sociedade Brasileira de Pneumologia e Tisiologia. III Consenso Brasileiro no Manejo da Asma. J Pneumol. 2002;28(Supl 1):S1-S28.
7. Polgar G, Promadhat V. Pulmonary function testing in children: techniques and standards. Philadelphia: WB Saunders; 1971.
8. Chan-Yeung M. Assessment of asthma in the workplace. ACCP consensus statement. American College of Chest Physicians. Chest. 1995;108(4):1084-117.
9. Moraes-Filho J, Cecconello I, Gama-Rodrigues J, Castro L, Henry MA, Meneghelli UG, et al. Brazilian consensus on gastroesophageal reflux disease: proposals for assessment, classification, and management. Am J Gastroenterol. 2002;97(2):241-8.
10. Sociedade Brasileira de Sono. I Consenso Brasileiro em Ronco e Apnéia do Sono. Hypnos: J Clin Experiment Sleep Res. 2001;2(Suppl 1).
11. Vianna EO. Asma grave: uma questão de prescrição ou de diagnóstico? J Pneumol. 2003;28(4):248.
12. Irwin RS, Curley FJ, French CL. Difficult-to-control asthma. Contributing factors and outcome of a systematic management protocol. Chest. 1993;103(6):1662-9.
13. Chatkin JM, Cavalet-Blanco D, Scaglia NC, Tonietto RG, Wagner MB, Fritscher CC. Adesão ao tratamento de manutenção em asma (estudo ADERE). J Bras Pneumol. 2006;32(4): 277-83.
14. Williams LK, Pladevall M, Xi H, Peterson EL, Joseph C, Lafata JE, et al. Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. J Allergy Clin Immunol. 2004;114(6):1288-93.
15. Liou A, Grubb JR, Schechtman KB, Hamilos DL. Causative and contributive factors to asthma severity and patterns of medication use in patients seeking specialized asthma care. Chest. 2003;124(5):1781-8.
16. Ishioka S, Terada M, Haruta Y, Hiyama K, Hozawa S, Yamakido M. Multiple logistic regression analysis of risk factors for the development of steroid-dependent asthma in the elderly: a comparison with younger asthmatics. Respiration. 2001;68(1):35-40.
17. The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. European Network for Understanding Mechanisms of Severe Asthma. Eur Respir J. 2003;22(3):470-7.
18. Gaga M, Papageorgiou N, Yiourgioti G, Karydi P, Liapikou A, Bitsakou H, et al. Risk factors and characteristics associated with severe and difficult to treat asthma phenotype: an analysis of the ENFUMOSA group of patients based on the ECRHS questionnaire. Clin Exp Allergy. 2005;35(7):954-9.