

Influence of upper airway abnormalities on the control of severe asthma: a cross-sectional study

Francisco Soares Nascimento-Sampaio, MD, PhD^{1,2}, Mylene dos Santos Leite, MD¹, Donald Arthur Leopold, MD³, Suzam Guedes Oliva da Silva¹, Paulo Adriano Schwingel, BSS, PhD⁴, Carlos Maurício Cardeal Mendes, MD, PhD⁵, Adelmir Souza-Machado, MD, PhD^{1,6} and Régis de Albuquerque Campos, MD, PhD²

Background: A better understanding of severe uncontrolled asthma (UA) in the upper airways is needed. The aims of this study were to assess the prevalence of upper airway abnormalities and their associations with UA.

Methods: An observational study enrolled individuals with severe asthma. Sociodemographic and clinical questionnaires regarding asthma, rhinosinusitis, and laryngopharyngeal reflux (LPR) were administered. Skin-prick tests and fiber optic nasolaryngoscopies were also performed. Descriptive statistical analysis was performed, using a multiple Poisson regression model to obtain adjusted prevalence ratios (PRs) and to identify the clinical profiles associated with the highest and lowest percentages of the dependent variable, lack of asthma control.

Results: The sample consisted of 64 participants who were divided into 2 groups according to asthma control. Thus, group I comprised 27 individuals with severe controlled asthma (CA), and group II consisted of 37 individuals with UA. Women represented 87.5% of the study population. The median age was 54 years, and 86% of the sample had rhinosinusitis. Relevant associations were detected

between UA and hyposmia (PR = 2.04), hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) (PR = 1.45), arytenoids hyperemia (PR = 1.45), LPR (PR = 1.37), a positive family history of asthma (PR = 1.35), onset of asthma at age 10 years or older (PR = 0.59), and swelling of the vocal cords (PR = 0.54).

Conclusion: This study found a very high prevalence of rhinosinusitis in patients with severe asthma as well as associations between UA and hyposmia, hypersensitivity to NSAIDs, arytenoids hyperemia, and LPR. Clinical profiles prone to UA were identified. © 2015 ARS-AAOA, LLC.

Key Words:

laryngopharyngeal reflux; sinusitis; olfaction disorders; aspirin; dyspnea

How to Cite this Article:

Nascimento-Sampaio FS, dos Santos Leite M, Leopold DA, et al. Influence of upper airway abnormalities on the control of severe asthma: a cross-sectional study. *Int Forum Allergy Rhinol.* 2015;5:371-379.

Asthma is currently estimated to affect approximately 300 million people worldwide.¹ It is a heterogeneous

disease that is characterized by chronic airway inflammation and a clinical history of wheezing, shortness of breath, chest tightness, and coughing that vary in time and intensity and are accompanied by variable expiratory airflow limitations.¹

Although severe asthma affects only approximately 10% of the asthmatic population,² it accounts for more than 50% of the global cost of asthma.³ Severe asthma can be defined as “uncontrolled asthma which can result in risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidity (including impaired lung function or reduced lung growth in

¹Program for Asthma Control in Bahia (PROAR), Bahia School of Medicine (FMB), Federal University of Bahia (UFBA), Salvador, BA, Brazil; ²Post-Graduate Program in Health Sciences (PPgCS), FMB, UFBA, Salvador, BA, Brazil; ³Department of Surgery, College of Medicine, University of Vermont, Burlington, VT; ⁴Department of Nutrition, University of Pernambuco (UPE), Petrolina, PE, Brazil; ⁵Post-Graduate Program in Interactive Processes of Organs and Systems, Institute of Health Sciences (ICS)UFBA, Salvador, BA, Brazil; ⁶Department of Biomorphology, ICSUFBA, Salvador, BA, Brazil

Correspondence to: Francisco Soares Nascimento-Sampaio, MD, PhD, Rua das patativas 400, casa 4, Imbui, 41720100, Salvador - BA, Brazil; e-mail: yfsampaio@yahoo.com.br

Funding sources for the study: F.S.N.S. was awarded a PhD scholarship by the Research Support Foundation of the State of Bahia Government (FAPESB), grant number: BOL2176/2011. Potential conflict of interest: None.

Received: 17 September 2014; Revised: 2 December 2014; Accepted: 6 January 2015
DOI: 10.1002/alr.21501
View this article online at wileyonlinelibrary.com.

children).^{3,4} According to the Global Initiative for Asthma (GINA) criteria,¹ severe asthma is characterized by continuous symptoms, limitations in physical activity, frequent exacerbations, night awakenings, and daily use of bronchodilators for the relief of symptoms.

Since 2010, the World Health Organization (WHO) has categorized severe asthma into untreated severe asthma, difficult-to-treat severe asthma, and treatment-resistant severe asthma. The last category consists of asthma for which control can only be maintained with the highest level of recommended treatment and those cases for which control is not achieved despite the highest level of recommended treatment (refractory asthma and corticosteroid-resistant asthma).⁴

The upper airways are the initial anatomical portion of the airways and include the nasal cavity, paranasal sinuses, pharynx, and larynx. These structures influence the physiological function of breathing; alterations of the upper airways may thus contribute to asthma control. In addition, various studies have supported the theory of united airway disease; according to this theory, rhinitis and asthma are manifestations of the same disease process.⁵ The most common upper airway disorders include allergic rhinitis (AR), chronic rhinosinusitis (CRS), and laryngopharyngeal reflux (LPR). AR is defined as immunoglobulin E (IgE)-mediated inflammation of the nasal mucosa, and it presents with the 3 cardinal symptoms of sneezing/nasal itch, nasal obstruction, and rhinorrhea.⁵ Ponte et al.⁶ showed that moderate/severe AR was associated with a lack of asthma control. CRS is defined as inflammation of the nose and paranasal sinuses characterized by the presence of two or more symptoms, one of which must be nasal obstruction or rhinorrhea. Other manifestations include facial pain and hyposmia. Polyps and rhinorrhea can be identified during nasal endoscopy or paranasal sinus computed tomography (CT) scan abnormalities such as mucoperiosteal thickening or opacifications.⁷ LPR is defined as reflux of the gastric contents into the larynx and pharynx.⁸

The aims of this study were as follows: (1) to assess the prevalence of upper airway abnormalities, such as LPR, AR, and CRS, in patients with severe asthma; (2) to assess the associations of these upper airway abnormalities with severe uncontrolled asthma (UA); and (3) to identify the clinical profiles (phenotypes) exhibiting the lowest and the highest percentages of UA.

Patients and methods

Program for asthma control in bahia at the federal university of bahia

This study was conducted at the Program for Asthma Control in Bahia (ProAR) referral center at the Federal University of Bahia (UFBA). The ProAR includes 4 referral centers for the multidisciplinary care of patients. The outpatient referral clinics provide care and medication free of charge to all nonsmoking patients. ProAR prioritizes the

treatment of severe cases of asthma, for which patients are regularly treated with the medications offered by the Brazilian government: a combination of inhaled formoterol and corticosteroids (beclomethasone or budesonide) and a beta 2-agonist (salbutamol or fenoterol) as a rescue medication, in compliance with current guidelines for the treatment of asthma.¹ Before admission to ProAR, a clinical evaluation and a pulmonary function test are routinely performed to confirm the diagnosis of asthma.

Participants and study design

This cross-sectional study was part of a ProAR cohort; it assessed adults (aged 18 years and older) of both genders, all nonsmokers, who had been diagnosed with untreated severe asthma according to WHO 2010.⁴ After at least 1 year of receiving the highest level of recommended treatment,¹ participants completed the 6-question Asthma Control Questionnaire (ACQ).⁹

All of the participants responded to sociodemographic and clinical questionnaires regarding asthma, AR, CRS, and the presence of other comorbidities. Data on a variety of clinical factors were collected, including family history of asthma, hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs), and currently used medications. As in other studies,^{10–12} hyposmia was evaluated by asking a simple clinical question: “Can you smell?” AR was defined according to the guidelines of Allergic Rhinitis and its Impact on Asthma (ARIA).⁵

All of the participants signed an consent form approved by the Ethics Committee on Human Research of the Professor Edgar Santos University Hospital Complex at the UFBA, ruling/additive resolution number 217/2010. Refusal to participate did not alter patients’ treatment.

Asthma control

Asthma control was assessed using the ACQ,⁹ which has been validated for use in Brazil.¹³ The questionnaire covers nocturnal and daytime symptoms, limitation of daily activities, dyspnea, wheezing, and the use of rescue beta 2-agonists. The score of each item ranges from 0 (well controlled) to 6 (extremely poorly controlled); scores >1.5 indicate UA.

Reflux Symptom Index

To diagnose LPR, the Reflux Symptom Index (RSI) was used. This validated index of LPR symptoms, formulated at the University of California, Davis,¹⁴ consists of 9 items that assess the occurrence of the following symptoms over the previous 30 days: hoarseness, clearing of the throat, excess throat mucus, dysphagia, coughing after eating or lying down, troublesome or annoying coughing, dyspnea, feeling of a lump in the throat, and dyspepsia. The score of each item ranges from 0 (no problem) to 5 (severe problem); when the total score is >13, the RSI indicates the presence of LPR.¹⁴

Body mass index

The body mass index (BMI) was used to access the relevance of obesity and overweight as confounders. It was calculated by dividing the total body weight in kilograms (kg) by the square of the height in meters (m²). BMI values of 18.5 to 24.9 kg/m² were considered normal weight, whereas results between 25 and 29.9 kg/m² were defined as overweight, and values equal to or greater than 30 kg/m² indicated obesity.

Skin-prick test

Atopy was diagnosed by a positive skin-prick test (SPT). The participants were subjected to the aeroallergens most commonly detected in our geographical area: *Blomia tropicalis*, *Dermatophagoides pteronyssinus*, *Aspergillus spp.*, *Cladosporium herbarum*, cockroach mix, and cat and dog dander. Histamine and saline were tested as the positive and negative controls, respectively. A test was considered positive if any wheal at least 3 mm in diameter appeared 20 minutes after the skin was pricked with one of the tested aeroallergens, indicating IgE-mediated inflammation (atopy).

Fiber optic nasolaryngoscopy

Fiber optic nasolaryngoscopy was used to detect abnormalities in the nasal fossa, pharynx, and larynx. To reduce sensitivity and avoid swelling of the nasal mucosa, a thin piece of cotton with topical decongestant (0.05% oxymetazoline) and an anesthetic solution (10% lidocaine) were placed in each nasal cavity in the middle meatus and removed after 20 minutes. Then, the fiber optic nasolaryngoscope was carefully introduced through the nasal fossa, rhinopharynx, and larynx to detect changes in the color of the nasal mucosa and the presence of septal deviation, nasal polyps, purulent rhinorrhea, laryngeal secretions, or hyperemia/swelling of the arytenoids, interarytenoid area, or vocal cords. The tests were videotaped. According to the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2012),⁷ abnormalities on nasal endoscopy contribute to the diagnosis of rhinosinusitis. In such cases, patients may also complain of nasal obstruction and/or rhinorrhea, facial pain/pressure, and hyposmia. Changes may also be observed by CT of the paranasal sinuses.⁷ According to Vaezi et al.¹⁵ laryngoscopic findings associated with LPR include: erythema and/or edema of the arytenoids, vocal cords, and lingual tonsils; obliterated laryngeal ventricles; postcricoid hyperplasia; and vocal cord nodules. The mucosa was considered to be erythematous if it was graded as 2 or 3 on a subjective scale of red color intensity ranging from 0 to 3.

Statistical analysis

Descriptive statistical analysis was performed using the multiple Poisson regression model to directly calculate the adjusted prevalence ratios.¹⁶ Inferential statistical analysis was not performed, because of the lack of a probability-sampling plan for appropriate estimation of the standard

error.¹⁷ The initial model included 29 independent dichotomous variables; control of asthma was the dependent variable. Next, unbalanced variables were removed from the model. As a criterion for retaining variables in the model, a prevalence ratio (PR) greater than 30% was arbitrarily selected. Following an interactive process, in which variables considered to be relevant were removed or reintroduced, 18 variables were retained in the model. At this point, the model was assessed as a function of the clinical relevance of the independent variables, the adjusted coefficient of determination, and Mallows's C_p, which were used to select the best model. On those grounds, the final model included 7 independent variables. The presence of collinearity and goodness of fit were assessed next using residual analysis and the Akaike information criterion (AIC). To assess the assumption of non-overdispersion, the residual deviance was divided by its degrees of freedom.¹⁸ Finally, the probability of UA was calculated based on the combination of the profiles of the independent variables included in the final model. The statistical analyzes were performed using the R statistical package (version 3.0.2; R Foundation, Vienna, Austria)¹⁹ in the Ubuntu operating system, version 13.10 (Canonical Ltd, Isle of Man, UK).

Results

A total of 73 individuals with severe asthma participated in the study between January and June 2012. We excluded 9 individuals because their chest radiographs were not normal. The sample thus consisted of 64 participants, none of whom were current smokers (9 were former smokers), who were divided into 2 groups according to the level of asthma control as assessed by the ACQ.

Group I consisted of 27 individuals with severe controlled asthma (CA), and group II consisted of 37 individuals with severe UA. The lung function characteristics were similar between the 2 groups (forced expiratory volume in 1 second [FEV1]: 59 ± 17 [% predict, mean ± SD] vs 59 ± 15; forced vital capacity [FVC]: 76 ± 18 vs 78 ± 14; and Tiffeneau-Pinelli index [FEV1/FVC, %]: 78 ± 12 vs 76 ± 11, respectively). The main characteristics of the sample are described in Table 1. Most of the sample consisted of women (56; 87.5%). The median age of the sample was 54 years (interquartile range [IQR], 45–60), and 48 (75%) participants were older than 45 years (Table 1).

There was a higher percentage of hypersensitivity to NSAIDs in the UA group; these patients were also more likely to have LPR than the CA group (Table 2).

There was an 86% prevalence of rhinosinusitis clinically diagnosed in the sample.⁷ Participants in the UA group consistently reported more CRS-related symptoms (Table 2).

Nasal endoscopy showed no difference between the groups in terms of the color of the nasal mucosa or the presence of a deviated nasal septum, nasal polyps, or purulent nasal secretions. Of the entire sample, nasal polyps

TABLE 1. Distribution of individuals with severe asthma relative to demographic and clinical variables (n = 64)

Variables	Total	Group I (CA)	Group II (UA)
Severe asthma, n (%)	64	27	37
Age, years, median	54	58	51
More than 54 years old, n (%)	30 (47 ^a)	16 (59 ^a)	14 (38 ^a)
Gender, female, n (%)	56 (88 ^a)	22 (81 ^a)	34 (92 ^a)
BMI, kg/m ² , median	28	28	28
BMI > 30 kg/m ² , n (%)	21 (33 ^a)	8 (30 ^a)	13 (35 ^a)
Age at onset of asthma, years, median	10	16	5
Onset of asthma at age <10 years old, n (%)	31 (48 ^a)	10 (37 ^a)	21 (57 ^a)
Positive family history of asthma, n (%)	47 (73 ^a)	19 (70 ^a)	28 (76 ^a)

^aValues are percentages related to their column grouping (Total, CA or UA).

ACQ = Asthma Control Questionnaire; BMI = body mass index; CA = severe controlled asthma according to the ACQ; UA = severe uncontrolled asthma according to the ACQ.

TABLE 2. Distribution of individuals with severe asthma relative to specified symptoms*

Variables	Total n (%)	Group I (CA) n (%)	Group II (UA) n (%)
Severe asthma relative to allergy symptoms, allergy skin testing, and diagnosis of laryngopharyngeal reflux			
Hypersensitivity to NSAIDs (positive history)	10 (18)	3 (14)	7 (21)
Diagnosis of AR	61 (97)	24 (92)	37 (100)
Persistent AR	48 (79)	18 (75)	30 (81)
Moderate/severe AR	50 (82)	19 (79)	31 (84)
Positive skin prick test (atopy)	34 (57)	13 (57)	21 (57)
Laryngopharyngeal reflux (as assessed by RSI)	37 (59)	14 (52)	23 (64)
Severe asthma relative to symptoms of rhinosinusitis ^a			
Facial pain/pressure	52 (81)	18 (67)	34 (92)
Headache	53 (84)	19 (70)	34 (94)
Nasal obstruction	55 (86)	20 (74)	35 (95)
Rhinorrhea	52 (83)	21 (78)	31 (86)
Hyposmia	44 (69)	15 (56)	29 (78)
Rhinosinusitis	55 (86)	20 (74)	35 (95)

*The obtained results percentages are related to their columns; total, group I; group II.

^aRhinosinusitis: clinical diagnosis according to European Position Paper on Rhinosinusitis and Nasal Polyps 2012.

ACQ = Asthma Control Questionnaire; AR = allergic rhinitis; CA = severe controlled asthma according to the ACQ; NSAID = nonsteroidal anti-inflammatory drug; RSI = Reflux Symptom Index; UA = severe uncontrolled asthma according to the ACQ.

were found in 18 (28.1%) participants, 17 of whom had clinical evidence of rhinosinusitis (Table 3). Of the 55 participants with a clinical diagnosis of rhinosinusitis, 17 of 18 had nasal polyps, and 15 of 18 had purulent nasal secretions.

On laryngeal endoscopy, the following signs of inflammation were observed more frequently in the CA group than in the UA group: swelling in the arytenoids, interarytenoid area, and vocal cords; hyperemia in the interarytenoid area; and secretions in the vocal cords (Table 3).

A total of 29 independent dichotomous variables were included in the initial Poisson regression model; asthma control was used as the dependent variable. Following the removal of unbalanced variables, namely variables with PRs less than 30% (an arbitrary value), and the interactive process of removing and reintroducing the most relevant variables, the initial model included 18 variables (Table 4). The criteria used to establish the final regression model were as follows: clinical relevance, adjusted coefficient of determination, and Mallows's C_p . On

TABLE 3. Distribution of individuals with severe asthma relative to findings on fiber optic nasolaryngoscopy*

Variables	Total n (%)	Group I (CA) n (%)	Group II (UA) n (%)
Pale nasal mucosa	22 (34)	11 (41)	11 (30)
Deviated nasal septum	34 (53)	15 (56)	19 (51)
Nasal polyps	18 (28)	8 (30)	10 (27)
Purulent nasal secretion	18 (28)	7 (26)	11 (30)
Swelling of arytenoids	34 (55)	16 (62)	18 (50)
Hyperemia in arytenoids	13 (21)	6 (22)	7 (19)
Swelling of interarytenoid area	31 (53)	18 (67)	13 (41)
Hyperemia in interarytenoid area	18 (30)	12 (46)	6 (18)
Swelling of vocal cords	15 (25)	8 (30)	7 (21)
Hyperemia in vocal cords	5 (8)	2 (7)	3 (8)
Secretions in vocal cords	21 (34)	11 (41)	10 (29)

*The obtained results percentages are related to their columns; total, group I; group II.

ACQ = Asthma Control Questionnaire; CA = severe controlled asthma according to the ACQ; UA = severe uncontrolled asthma according to the ACQ.

those grounds, 7 independent variables with higher PRs (Table 4, in bold) were identified and selected for the best final model, with high credibility according to the AIC: hyposmia (PR = 2.04), hyperemia of the arytenoids (PR = 1.45), hypersensitivity to NSAIDs (PR = 1.45), LPR (PR = 1.37), a positive family history of asthma (PR = 1.35), age at onset of asthma of 10 years or older (PR = 0.59), and swelling of the vocal cords (PR = 0.54) (Table 4). According to the final model, the PR of UA individuals with an onset of asthma of age 10 years or older was 41% lower than in individuals who were younger than 10 years when their asthma started. The PR of UA participants with a positive family history of asthma was 35% higher than that in participants without a positive family history. A history of hypersensitivity to NSAIDs increased the PR of severe UA by 45%. LPR was associated with a 37% increase in the PR of severe UA. Hyposmia presented the greatest PR with severe UA (2.04) (Table 4). Swelling of the vocal cords exhibited a negative association (PR = 0.54) with severe UA (Table 4).

The probability of severe UA was calculated based on all of the possible combinations of the 7 relevant variables. Because these variables were dichotomous, only two options were possible in each case, resulting in a total of 128 profiles or phenotypes ($1 \times 2^7 = 128$). In Figure 1, we highlight the 4 clinical profiles (CLPs) associated with the lowest percentages of severe UA and the 4 CLPs associated with the highest percentages of severe UA. Although the CLPs with the lowest percentages of UA were less likely to exhibit the Poisson regression final model variables, the CLPs with the highest percentage of UA had these signs or symptoms in most cases. The exception was the variable "swelling of the vocal cords," which had an inverse association with UA.

Discussion

This study found that individuals with severe asthma had a very high frequency of rhinosinusitis (86%), particularly compared with the 5.5% prevalence of rhinosinusitis in the Brazilian population (Sao Paulo city).²⁰ Nasal obstruction and rhinorrhea were also highly prevalent, particularly among individuals in the UA group (Table 2).

Neither atopy (Table 2) nor rhinosinusitis (Table 2) was associated with asthma control. Additionally, nasal polyps were common among both CA and UA participants; 18 (28%) participants in the total sample had nasal polyps. This represents a 7-fold increase relative to the expected values for the overall population.^{21,22} Almost the same distribution was found for purulent nasal secretions. In contrast to what was expected, neither variable was associated with asthma control (Table 3). One possible explanation for this finding is that the treatment for severe asthma, which involves high doses of inhaled steroids, may down-regulate inflammatory mediators from both nasal polyps and nasal secretions.

Strong associations were found between severe UA and hyposmia, LPR, and hypersensitivity to NSAIDs (Table 4). The observed association between severe UA and hyposmia (PR = 2.04) may indicate a type of CRS regardless of the presence of nasal polyps, because both conditions have been strongly associated with a loss of the sense of smell.^{12,23,24} A direct relationship between mucosal thickening in the sinuses and bronchial inflammation has already been identified.¹¹

Patients with asthma exhibit an increased risk of anosmia.²⁵ Loss of smell impairs quality of life (QoL), because patients may have difficulty distinguishing flavors, and may pose a risk of decreased or inadequate dietary intake as well as exposure to unnoticed gas leaks.¹² Special

TABLE 4. Adjusted coefficients and PRs in the IM and FM Poisson regression model for UA

Variables	Coefficient IM	PR_IM	Coefficient FM	PR_FM
Older than 54 years old	−0.05	–	–	–
No	–	1	–	–
Yes	–	0.95	–	–
BM >29 kg/m ²	−0.32	–	–	–
No	–	1	–	–
Yes	–	0.73	–	–
Asthma onset <10 years old	−0.6	–	−0.52	–
Yes	–	1	–	1
No	–	0.55	–	0.59
Family history of asthma	0.12	–	0.3	–
No	–	1	–	1
Yes	–	1.13	–	1.35
Hypersensitive to NSAIDs	0.11	–	0.37	–
No	–	1	–	1
Yes	–	1.12	–	1.45
Allergic rhinitis (frequency)	0.23	–	–	–
No	–	1	–	–
Yes	–	1.26	–	–
Allergic test (prick)	0.06	–	–	–
Negative	–	1	–	–
Positive	–	1.06	–	–
Laryngopharyngeal reflux (RSI)	0.38	–	0.32	–
No	–	1	–	1
Yes	–	1.46	–	1.37
Hyposmia	0.48	–	0.71	–
No	–	1	–	1
Yes	–	1.62	–	2.04
Mucosal hyperemia	0.09	–	–	–
No	–	1	–	–
Yes	–	1.09	–	–
Nondeviated septum	−0.2	–	–	–
No	–	1	–	–
Yes	–	0.82	–	–
Nasal polyps	−0.16	–	–	–
No	–	1	–	–
Yes	–	0.85	–	–
Purulent nasal secretions	0.25	–	–	–
No	–	1	–	–
Yes	–	1.29	–	–

(Continued)

TABLE 4. Continued

Variables	Coefficient IM	PR_IM	Coefficient FM	PR_FM
Swelling in arytenoids	−0.39	–	–	–
No	–	1	–	–
Yes	–	0.68	–	–
Hyperemia in arytenoids	0.33	–	0.37	–
No	–	1	–	1
Yes	–	1.39	–	1.45
Swelling of interarytenoid area	0.24	–	–	–
No	–	1	–	–
Yes	–	1.27	–	–
Swelling of vocal cords	−0.67	–	−0.62	–
No	–	1	–	1
Yes	–	0.51	–	0.54
Secretions in vocal cords	0.2	–	–	–
No	–	1	–	–
Yes	–	1.22	–	–

*AIC: IM: 111.2; FM: 102. Bold values: relevant PRs second this Poisson regression model.

ACQ = Asthma Control Questionnaire; AIC = Akaike information criterion; BMI = body mass index; FM = final model; IM = initial model; NSAID = nonsteroidal anti-inflammatory drug; PR = prevalence ratio; RSI = Reflux System Index; UA = severe uncontrolled asthma according to the ACQ.

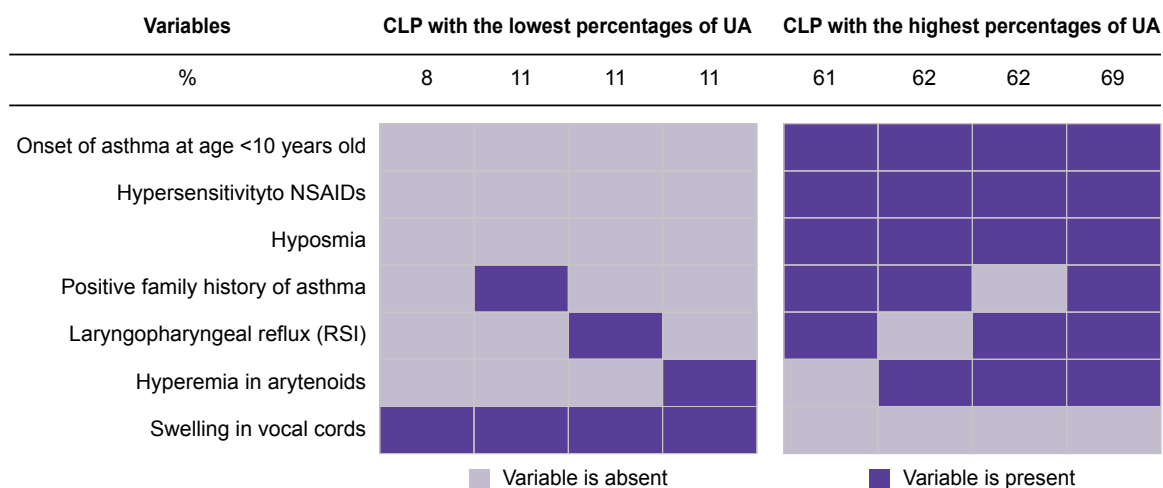


FIGURE 1. The 7 most relevant variables from CLPs with the lowest or highest percentage of UA. The 4 profiles with the lowest and the 4 profiles with the highest percentage of severe uncontrolled asthma are displayed below. CLP = clinical profiles; NSAID = nonsteroidal anti-inflammatory drug; RSI = Reflux System Index; UA = severe uncontrolled asthma.

attention must be paid to the loss of the sense of smell, because this symptom can be distressing and may be associated with insufficient asthma control.

Although the association between asthma and rhinitis symptoms worsen the patients' QoL,²⁶ treatment with intranasal corticosteroids seems to improve the patients' QoL.²⁷

The analysis of PRs found that UA was significantly associated with hypersensitivity to NSAIDs (PR = 1.45)

(Table 4), lending further support to the hypothesis that a hypersensitivity to NSAIDs tends to exacerbate asthma.²⁸

The exacerbation of asthma by NSAIDs is believed to be a result of a reflexive increase in arachidonic acid released from the cell membrane wall, resulting in the increased release of leukotrienes, which stimulate bronchoconstriction, among other effects.²⁹ Because none of these patients were taking antileukotriene drugs, it could be speculated that, at least in this subgroup of patients, using this class

of drugs may result in clinical benefits and better control of asthma symptoms.

The positive associations of severe UA with LPR as assessed by the RSI (PR = 1.37) and with hyperemia of the arytenoids on laryngoscopy (PR = 1.45) (Table 4) found in this study are consistent with prior reports.^{30,31} Several mechanisms have been suggested, but none has yet been proven. According to 1 hypothesis, beta 2 agonists reduce the tone of the lower esophageal sphincter³²; however, this idea is controversial.³³ The bronchi may be directly irritated by retrograde flow of the gastric contents, because pepsin has been found in the lung.³⁴ According to another hypothesis, the presence of gastric acid at the proximal third of the esophagus can stimulate a vagal reflex.³⁵ Some studies have demonstrated improvement in bronchial hyperresponsiveness following treatment for gastroesophageal reflux disease (GERD),³⁶ whereas other studies have consistently shown that treating GERD did not improve asthma.^{37,38} Therefore, many questions regarding the relationship of asthma to LPR and GERD remain unanswered.

The present study unexpectedly identified an inverse association between severe UA and vocal cord swelling (PR = 0.54) (Table 4). Reports in the literature have indicated a positive association between asthma and swelling of the vocal cords.³³ Upon reassessing our data, we found that at the time of the interview, participants in the UA group were more likely to be using proton-pump inhibitors and oral corticosteroids than were participants in the CA group (54% vs 33% and 22% vs 4%, respectively). These differences may account for this paradoxical finding (an inverse association between severe UA and vocal cord swelling).

Two variables corresponding to the participants' histories deserve special attention as functions of their associations with severe UA, namely a positive family history of asthma (PR = 1.35) and onset of the disease at the age of 10 years or older (PR = 0.59) (Table 4). Although a positive family history of asthma is commonly useful for the diagnosis of asthma in children,¹ we show here that it might also be associated with a lack of control of severe asthma. Participants who were younger than 10 years old at the time of asthma onset were more likely to have UA than patients who were older when they developed asthma. Wenzel²⁸ found that asthma tended to be more severe when it began at an early age. A longer history of asthma and the strong association between AR and the childhood onset of asthma³⁹ might explain why these patients had severe UA.

Figure 1 describes the 4 CLPs associated with the highest probability and the 4 CLPs associated with the lowest probability of the occurrence of severe UA, based on the 7 variables found to be most relevant using the multiple Poisson regression model. Figure 1 shows that these variables remained relevant when they were represented together as profiles. When the CLPs included more variables derived from the Poisson regression model, higher percentages of UA were found. In contrast, as the CLPs included fewer of these variables, lower percentages of UA were found. The only exception was "swelling of the vocal cords," which was inversely associated with asthma control. To determine

whether these profiles could be used in clinical settings to predict the possibility of controlling asthma and adjusting treatment, it would be necessary to study a larger sample of asthma patients and to include patients with different levels of asthma severity.

Certain limitations of this study are deserving of mention. The first is associated with its cross-sectional design, which is widely used due to its practicality and viability but does not allow for the identification of causal factors or for the control of potential confounding factors. One additional and patent limitation was that the study did not include individuals with moderate, mild, or no asthma. The inclusion of such groups would have enriched the comparisons and the understanding of the relationship between RS and asthma. However, it should be observed that small differences become more relevant when similar groups, such as those used in this study, are compared.

According to the European Network for Understanding Mechanisms of Severe Asthma (ENFUSOMA),⁴⁰ the much higher prevalence of cases with severe UA in women reflects the actual population treated in outpatient clinics. Because the asthma prevalence in both sexes in the general population is similar,⁴¹ this selection bias occurs because, in general, women take better care of their health.⁴²

CT of the paranasal sinuses uses high doses of ionizing radiation and is the best method of assessing sinus disease; however, the high costs of CT prevented it from being used in this study. Thus, we performed nasal endoscopy, which has been shown to have strong correlations with CT results.⁴³ Therefore, assessments of the sinuses were performed based on the clinical questionnaires regarding AR and CRS and nasal endoscopy.

For the detection of pharyngeal reflux events, 24-hour pH impedance monitoring would be helpful. However, this technology is still not available in our city. Furthermore, pharyngeal pH alone is not reliable for the detection of pharyngeal reflux.⁴⁴ Therefore, the RSI, a validated questionnaire,¹⁴ was used instead.

Conclusion

This study found a very high prevalence of rhinosinusitis (86%) in patients with severe asthma; in addition, associations between uncontrolled severe asthma and hyposmia, hypersensitivity to NSAIDs, hyperemia of the arytenoids, and LPR were observed. A probabilistic model might have the potential to identify CLPs of patients who are more prone to UA, which could improve clinical decision-making and asthma control. Further studies are needed to better understand the role of the upper airways in the control of severe asthma. 

Acknowledgments

F.S.N.S. was awarded a PhD scholarship by the Research Support Foundation of the State of Bahia (FAPESB), grant number BOL2176/2011.

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