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Trajectory of the response to bronchodilator and respiratory outcomes in adults with asthma-like symptoms

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Abstract

In the real world, health professionals need to care for individuals with asthma-like symptoms who have a persistently negative bronchodilator response (BDR). Little is known about the evolution of symptoms and lung function of these individuals because they are usually excluded from studies on asthma. The aim of this study was to evaluate whether individuals with asthma-like symptoms but with a persistently negative BDR have a different evolution of symptoms and lung function compared to individuals with asthma proven by positive BDR. This prospective cohort study included adults with asthma-like symptoms. Individuals participated in two visits, 12 months apart. They responded to questionnaires and underwent a spirometry test. In individuals without airway obstruction in the first visit, those with asthma-like symptoms and persistently negative BDR were less likely to lose forced expiratory volume in the first second during follow-up or progress to airway obstruction at the final visit compared to individuals with asthma proven by positive BDR. Among individuals with airway obstruction at baseline, those with asthma-like symptoms and persistently negative BDR were less likely to resolve the airway obstruction during follow-up compared to individuals with asthma proven by positive BDR. In individuals with proven asthma, the emergence or persistence of positive BDR during follow-up was accompanied by a worsening of asthma outcomes compared to the remission of positive BDR. Thus, BRD is an accessible marker of disease progression in individuals with asthma-like symptoms. In individuals with asthma proven by positive BDR, the trend in BDR was associated with the evolution of symptoms and lung function.

Key words: airway inflammation, bronchial hyperresponsiveness, airway remodeling, airway smooth muscle, bronchodilator response.

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Introduction

Studies indicate that the intrinsic contractility of human airway smooth muscle (ASM) cells is not different between individuals with asthma and healthy individuals [1], but inflammatory mediators produced in the airways of asthmatic individuals stimulate these cells to proliferate [2,3]. The consequences of ASM hyperplasia and hypertrophy are bronchial hyper-responsiveness (BHR), loss of lung function, and irreversible airway obstruction [4].

Guidelines require evidence of BHR or bronchodilator response (BDR) for the diagnosis of asthma [5]. More than 200 mL and 12% increase of forced expiratory volume in the first second (FEV₁) after bronchodilator in the spirometry test is evidence of BDR, but 36 to 83% of individuals with asthma have negative BDR in a single test [6-8]. Studies have shown that asthmatics with negative BDR have less eosinophilic airway inflammation [9,10]. In these individuals, the guidelines recommend repeating spirometry later to try to detect the presence of immediate BDR or performing a bronchoprovocation test with methacholine to investigate BHR, but this last test is rarely available in clinical practice.

In the real world, health professionals need to care for individuals with asthma-like symptoms who have a persistently negative BDR on repeated spirometry. Little is known, however, about the evolution of symptoms and lung function of these individuals, because they are usually excluded from studies on asthma. Therefore, the primary objective of this study was to evaluate whether individuals with asthma-like symptoms but with a persistently negative BDR have a different evolution of symptoms and lung function compared to individuals with asthma proven by positive BDR. The secondary objective was to evaluate, in individuals with asthma proven by a positive BDR, if the evolution of BDR during follow-up is associated with the variation in the symptom score and lung function.

Materials and Methods

We conducted this prospective cohort study in Jundiaí, a 400,000-inhabitant city in southeast Brazil. We screened consecutive individuals attending a scheduled spirometry test requested



by physicians from any of the 42 public health facilities in the municipality; therefore, the sample is representative of the population of users of the public health service. The recruitment period was from January 2021 to July 2022.

We included individuals aged 18 years or older reporting typical asthma symptoms for 2 years or more. We excluded current smokers, smoking history above 5 pack-years, pregnant women, history of tuberculosis treatment, thoracic surgery, exposure to indoor air pollution, occupational risk factors for chronic obstructive pulmonary disease (COPD) or pneumoconiosis, and those unable to achieve American Thoracic Society (ATS) requirements in the spirometry test. All individuals included in the study signed the informed consent. The institutional review board of the Jundiaí School of Medicine approved the study, approval number 5.221.754.

Individuals participated in two study visits 12 months apart. In each study visit, they attended a consultation with a chest physician, responded to study questionnaires, and underwent a spirometry test. Between study visits, individuals had one intermediate consultation with their referring physician. The researchers did not inform the referring physician about the hypothesis and purpose of the research.

Study procedures and definitions

In both study visits, the chest physician in charge of the research interviewed the volunteers, obtained clinical and demographic information, reviewed prescriptions, and inspected medicines to record the drugs that individuals were taking during the preceding 8 weeks. The record of pharmacological treatment considered the drugs and the quantity actually used. We instructed in advance that individuals bring to the study visit the prescriptions and medications so that the chest physician in charge of the research could confirm the patient's report. A trained healthcare professional applied the Asthma Control Test (ACT). This questionnaire measures the severity of asthma symptoms on a scale from five to 25, with the highest values indicating less symptomatology. The 19-point score discriminates between controlled and uncontrolled symptoms [11]. In each study visit, individuals underwent a spirometry test with a Koko PDS® (nSpire Health, USA) equipment and repeated the test twenty minutes after 400 mcg of salbutamol administration to measure the immediate BDR. Salbutamol was administered through a spacer. We advised individuals to discontinue bronchodilators in the 24 hours prior to carrying out the study spirometry. The spirometer was calibrated daily with a 3 L syringe. Trained respiratory therapists executed the spirometry tests according to the ATS protocol. Briefly, all tests had at least three reproducible curves; all curves would need to have retro-extrapolated volume below 5% and end of the curve in a plateau. The researcher in charge evaluated all spirometry exams for quality. Individuals who were unable to perform spirometry according to ATS criteria were excluded from the study. The criteria for positive BDR in the spirometry test were FEV₁ variation after bronchodilator greater than 12% and 200 mL.

The chest physician in charge of the research identified individuals with asthma-like symptoms through an in-depth interview, physical examination, and review of medical records. Some clinical evidence of asthma-like symptoms was recurrent wheezing, cough, or dyspnea lasting longer than 2 years, lability of symptoms, improvement of symptoms after inhaled corticosteroid maintenance therapy, and relief of symptoms after bronchodilator. It was crucial for the individual's inclusion in the

study that there was evidence of typical asthma-like symptoms for at least 2 years.

Individuals with asthma-like symptoms and a positive BDR in at least one of the two spirometry tests performed during the study were labeled as "asthma". Individuals with a negative BDR in both spirometry tests performed during the study were named "asthma-like symptoms". To meet the main objective of the study, we compared the evolution of symptoms and lung function between these two groups.

Subsequently, individuals with "asthma" were grouped according to the evolution of their BDR during follow-up in the study. Individuals with a positive BDR at the first study visit but a negative BDR at the second study visit were named "remission of BDR". Individuals with negative BDR on the first study visit who presented positive BDR on the second visit were labeled "emergence of BDR". Individuals with positive BDR at both study visits were called "persistently positive BDR". To meet the secondary objective of the study, we compared the evolution of symptoms and lung function between the group "remission of BDR" and the other two groups.

We computed comorbidities whenever the individual reported current use of any pharmacological therapy for the referred illnesses [12].

Statistical analyses

The primary outcome was loss of lung function. Loss of more than 200 mL in FEV₁ between the first and last study visits defined loss of lung function because this amount of loss is large enough to ensure that it is not random, according to data from two Brazilian cohorts. [13,14]. Secondary outcomes were variation in the intensity of respiratory symptoms (any improvement or worsening of the ACT score) and airway obstruction at the final study visit. The criterion of airway obstruction was an FEV₁/forced vital capacity ratio below the lower limit of normality.

We calculated a minimum sample of 93 individuals in each group, considering that 70% of individuals in the "asthma" group would lose lung function over 1 year of follow-up, and 50% in the "asthma-like symptoms" group. The basis for this estimate comes from a Brazilian cohort, which showed that 70% of adults with asthma lose lung function over 1 year [13]. The α -error was set at 0.05, and the power was 80%. It is relevant that the descriptive and comparative analyses were stratified by the presence of pre-BD airway obstruction at baseline, because individuals with airway obstruction are more likely to have positive BDR [15]. We applied the Chi-Square test to compare nominal variables between two groups, while the Mann-Whitney test compared ordinal and continuous variables. We used binary logistic regression analyses to measure the risk of loss of lung function (dependent variable) in individuals with "asthma-like symptoms" compared to individuals with "asthma" (independent variable). A similar model was used to assess whether the independent variable was associated with the variation of symptoms score during follow-up (V_2 ACT score - V_1 ACT score) and airway obstruction at the last study visit (SPSS 25, IBM, Armonk, New York). We adjusted the analyses for age, gender, lung function at baseline, symptoms score at baseline, and asthma maintenance therapy at baseline because these covariates might modify the relationship between the dependent and independent variables [16-19]. In individuals with "asthma", binary logistic regressions assessed whether the groups with "persistence" or "emergence" of BDR



had worse asthma outcomes compared to the group with “remission of BDR”.

The method of data entry into the regression model was the Backward Likelihood Ratio. The level of significance required for a given variable to remain in the model was 0.10. We used the Hosmer-Lemeshow (HL) test to measure goodness-of-fit, and the tolerance test (Tol) and variance inflation factor (VIF) to measure collinearity. Data and model fitted together (HL>0.05), and we observed no collinearity (Tol>0.10 and VIF<10).

Results

We screened 3,626 individuals referred for a spirometry test during the recruitment period. Various respiratory and non-respiratory morbidities justified the request for spirometry by the referring physician. We did not enroll 1,891 individuals without asthma-like symptoms and 341 individuals aged below 18 years old. A total of 512 individuals were not included because they met any exclusion criteria. Thus, we enrolled 882 individuals, but we lost the follow-up of 182. A total of 700 individuals completed all study visits, of which 437 had no airway obstruction in the first study visit (110 individuals with “asthma” and 327 with “asthma-like symptoms”), and 263 had airway obstruction (133 individuals with “asthma” and 130 with “asthma-like symptoms”).

Table 1 shows baseline characteristics of individuals without airway obstruction. Individuals with “asthma-like symptoms” had higher pre-BD lung function values compared to individuals with “asthma”, whilst all other characteristics were similar between groups. Table 2 shows that, among individuals with airway obstruction, those with “asthma-like symptoms” were older, had more comorbidities, used a greater amount of asthma maintenance therapy, and had a lower post-bronchodilator FEV₁ value at baseline compared to individuals with “asthma”.

Among individuals without airway obstruction, the dose variation of inhaled corticosteroids maintenance therapy from the first to the second study visit was similar (p: 0.34) between individuals with “asthma-like symptoms” [0 (-320, 0) mcg per day] and those with asthma proven by positive BDR [0 (-240, 200) mcg per day]. In individuals with airway obstruction, the variation in inhaled corticosteroid dose was also similar between the groups [0 (0, 400) and 0 (0, 400) mcg per day; p: 0.86].

Table 3 presents the longitudinal data of individuals without airway obstruction at baseline. Compared to individuals with “asthma”, those with “asthma-like symptoms” were less likely to lose FEV₁ during follow-up or evolve to pre-BD airway obstruction at the final study visit. Table 4 describes that, among individuals with airway obstruction at baseline, those with “asthma-like symptoms” were less likely to resolve the airway obstruction during follow-up compared to individuals with “asthma”.

In individuals with “asthma”, the emergence or persistence of positive BDR during follow-up was accompanied by worsening of asthma outcomes compared to the remission of positive BDR (Table 5).

Discussion and Conclusions

This study shows that, in the absence of airway obstruction at baseline, individuals with asthma-like symptoms and persistently negative BDR had more favorable outcomes compared to individuals with asthma proven by positive BDR. We are unaware of research that has investigated the disease progression of these individuals, who are not usually included in studies on asthma. We did not perform a methacholine bronchoprovocation test to confirm the diagnosis of asthma; therefore, we preferred to label individuals with persistently negative BDR as “asthma-like symptoms”. It is meaningful that only individuals with typical asthma symptoms, according to the careful assessment of experi-

Table 1. Baseline characteristics of individuals without pre-bronchodilator airway obstruction in the first study visit grouped according to the trajectory of immediate bronchodilator response.

	Asthma* (n=110)	Asthma-like symptoms** (n=327)	p
Age in years – median (IQ)	56 (44-67)	56 (42-66)	0.39
Female gender – n (%)	88 (80)	265 (81)	0.76
Body mass index – median (IQ)	31 (27-35)	30 (26-34)	0.14
Smoking history, pack-years – median (IQ)	0 (0-0)	0 (0-0)	0.65
Diabetes mellitus and/or systemic arterial hypertension – n (%)	53 (48)	165 (51)	0.64
Depression – n (%)	18 (16)	49 (15)	0.74
Asthma maintenance therapy according to the GINA – n (%)			
Step 1 or 2	36 (33)	93 (28)	
Step 3 or 4	56 (51)	165 (51)	0.47
Step 5	18 (16)	69 (21)	
Controlled symptoms of asthma, ACT>19 – n (%)	48 (44)	154 (48)	0.45
FVC % predict, pre-BD – median (IQ)	84 (75-95)	90 (80-101)	<0.01
FVC % predict, post-BD – median (IQ)	92 (83-103)	91 (81-103)	0.85
FEV ₁ % predict, pre-BD – median (IQ)	80 (70-90)	85 (76-99)	<0.01
FEV ₁ % predict, post-BD – median (IQ)	88 (78-102)	89 (78-103)	0.59

IQ, interquartile; GINA, Global Initiative Against Asthma; ACT, Asthma Control Test; BD, bronchodilator; FVC, forced vital capacity; FEV₁, forced expiratory volume in the first second. *Individuals with asthma-like symptoms and positive bronchodilator response (BDR) in any of the spirometry tests performed during the study. **Individuals with asthma-like symptoms and persistently negative BDR on spirometry performed during the study.



enced pulmonologists, were included in the study; even so, we cannot rule out the possibility that a few of them might have another illness simulating asthma. This limitation does not reduce the importance of the results and conclusions, as the intention of the study was to evaluate the disease progression of a population that frequently presents to healthcare professionals. We believe this information will help plan the management of the disease in these individuals.

In individuals with airway obstruction at baseline, those with asthma-like symptoms and persistently negative BDR had worse

lung function and greater use of maintenance therapy at the initial study visit compared with individuals with asthma proven by positive BDR. During follow-up, individuals with persistently negative BDR had a lower chance of resolving their airway obstruction. We hypothesize that the persistently negative BDR in these individuals results from the control of eosinophilic inflammation due to the use of a high dose of inhaled corticosteroids, while the persistence of airway obstruction during follow-up might be due to underlying airway remodeling. This hypothesis is supported by studies that demonstrated less

Table 2. Baseline characteristics of individuals with pre-bronchodilator airway obstruction in the first study visit, grouped according to the trajectory of immediate bronchodilator response.

	Asthma* (n=133)	Asthma-like symptoms** (n=130)	p
Age in years – median (IQ)	53 (40-63)	59 (47-71)	<0.01
Female gender – n (%)	95 (71)	83 (64)	0.19
Body mass index – median (IQ)	28 (24-34)	28 (24-31)	0.23
Smoking history, pack-years – median (IQ)	0 (0-0)	0 (0-0)	0.14
Diabetes mellitus and/or systemic arterial hypertension – n (%)	47 (35)	66 (51)	0.01
Depression – n (%)	21 (16)	19 (15)	0.79
Asthma maintenance therapy according to the GINA – n (%)			
Step 1 or 2	34 (26)	19 (15)	
Step 3 or 4	64 (48)	51 (39)	<0.01
Step 5	35 (26)	60 (46)	
Controlled symptoms of asthma – n (%)	52 (40)	58 (46)	0.38
FVC % predict, pre-BD – median (IQ)	81 (68-96)	86 (71-100)	0.12
FVC % predict, post-BD – median (IQ)	91 (80-103)	89 (74-102)	0.10
FEV1 % predict, pre-BD – median (IQ)	59 (46-74)	63 (51-77)	0.30
FEV1 % predict, post-BD – median (IQ)	73 (58-86)	66 (53-81)	0.03

IQ, interquartile; GINA, Global Initiative Against Asthma; BD, bronchodilator; FVC, forced vital capacity; FEV1, forced expiratory volume in the first second. *Individuals with asthma-like symptoms and positive bronchodilator response (BDR) in any of the spirometry tests performed during the study. **Individuals with asthma-like symptoms and persistently negative BDR on spirometry performed during the study.

Table 3. Binary logistic regression is used to evaluate whether the trajectory of immediate response to bronchodilator (BDR) is associated with respiratory outcomes during the follow-up, in individuals without pre-bronchodilator (BD) airway obstruction at baseline.

	Odds ratio (95 confidence interval)			
	Crude	p	Adjusted	p
Worsening of ACT score*				
Asthma ^a	-	0.45	-	0.39
Asthma-like symptoms ^b	0.80 (0.46-1.41)		0.78 (0.44-1.38)	
>200 mL FEV ₁ decline - pre-BD**				
Asthma ^a	-	0.02	-	<0.01
Asthma-like symptoms ^b	0.60 (0.39-0.93)		0.41 (0.25-0.66)	
>200 mL FEV ₁ decline – post-BD**				
Asthma ^a	-	0.02	-	<0.01
Asthma-like symptoms ^b	0.60 (0.39-0.93)		0.52 (0.32-0.84)	
Emergence of pre-BD airway obstruction**				
Asthma ^a	-	<0.01	-	<0.01
Asthma-like symptoms ^b	0.30 (0.16-0.57)		0.42 (0.21-0.83)	
Emergence of post-BD airway obstruction**				
Asthma ^a	-	0.47	-	0.74
Asthma-like symptoms ^b	0.67 (0.22-1.99)		0.81 (0.24-2.77)	

ACT, Asthma Control Test; BD, bronchodilator; FEV₁, forced expiratory volume in the first second. *Adjusted for age, gender, ACT score at baseline, and asthma maintenance therapy at baseline. **Adjusted for age, gender, equivalent lung-function parameter at baseline and asthma maintenance therapy at baseline. ^aIndividuals with asthma-like symptoms and positive bronchodilator response (BDR) in any of the spirometry tests performed during the study. ^bIndividuals with asthma-like symptoms and persistently negative BDR on spirometry performed during the study.



eosinophilic inflammation and greater concentration of biomarkers of airway remodeling in the airways of asthmatic individuals with little response to BD when compared to asthmatic individuals with an intense response to BD [9,10,15].

A cross-sectional study by Denlinger *et al.* observed that the intensity of BDR in individuals with severe asthma was associated with self-reported exacerbations in the previous year [20]. We

observed, in individuals with asthma proven by positive BDR, that the “emergence” or “persistence” of positive BDR during follow-up was accompanied by worsening of asthma outcomes compared to the remission of positive BDR. Compared to Denlinger’s study, our study has the quality of its prospective design and greater external validity, as it included individuals from all spectrums of asthma severity. Studies would need to

Table 4. Binary logistic regression is used to evaluate whether the trajectory of immediate response to bronchodilator (BDR) is associated with respiratory outcomes during the follow-up, in individuals with pre-bronchodilator (BD) airway obstruction at baseline.

	Odds ratio (95 confidence interval)			
	Crude	p	Adjusted	p
Worsening of ACT score*				
Asthma ^a	-		-	
Asthma-like symptoms ^b	1.46 (0.75-2.83)	0.26	1.21 (0.60-2.41)	0.60
>200 mL FEV ₁ decline – pre-BD**				
Asthma ^a	-		-	
Asthma-like symptoms ^b	1.07 (0.62-1.87)	0.80	1.22 (0.67-2.21)	0.52
>200 mL FEV ₁ decline – post-BD**				
Asthma ^a	-		-	
Asthma-like symptoms ^b	1.16 (0.67-2.01)	0.60	1.16 (0.65-2.05)	0.62
Resolution of pre-BD airway obstruction**				
Asthma ^a	-		-	
Asthma-like symptoms ^b	0.65 (0.35-1.22)	0.18	0.52 (0.26-1.07)	0.08
Resolution of post-BD airway obstruction**				
Asthma ^a	-		-	
Asthma-like symptoms ^b	0.44 (0.26-0.76)	<0.01	0.76 (0.60-0.97)	0.04

ACT, Asthma Control Test; BD, bronchodilator; FEV₁, forced expiratory volume in the first second. *Adjusted for age, gender, ACT score at baseline, and asthma maintenance therapy at baseline. **Adjusted for age, gender, equivalent lung-function parameter at baseline and asthma maintenance therapy at baseline. ^aIndividuals with asthma-like symptoms and positive bronchodilator response (BDR) in any of the spirometry tests performed during the study. ^bIndividuals with asthma-like symptoms and persistently negative BDR on spirometry performed during the study.

Table 5. Binary logistic regression to assess whether the trajectory of the immediate response to the bronchodilator (BDR) is associated with the trend in symptoms and lung function in individuals with asthma proven by positive response to bronchodilator (BDR).

	Odds ratio (95 confidence interval)			
	Crude	p	Adjusted	p
Worsening of ACT score*				
Remission of BDR (n=99)	-	0.01	-	0.01
Emergence of BDR (n=85)	2.21 (1.19-4.11)	0.84	2.16 (1.15-4.05)	0.61
Persistently positive BDR (n=59)	0.93 (0.44-1.96)		0.82 (0.38-1.78)	
>200 mL FEV ₁ decline - pre-BD**				
Remission of BDR (n=99)	-	<0.01	-	<0.01
Emergence of BDR (n=85)	13.07 (6.86-24.92)	<0.01	14.79 (7.34-29.82)	<0.01
Persistently positive BDR (n=59)	2.70 (1.33-5.46)		4.48 (2.02-9.96)	
>200 mL FEV ₁ decline – post-BD**				
Remission of BDR (n=99)	-	0.10	-	0.25
Emergence of BDR (n=85)	0.65 (0.37-1.13)	0.95	0.71 (0.39-1.27)	0.48
Persistently positive BDR (n=59)	0.98 (0.56-1.74)		0.80 (0.44-1.47)	
Pre-BD airway obstruction at the last study visit**				
Remission of BDR (n=99)	-	<0.01	-	<0.01
Emergence of BDR (n=85)	6.41 (3.51-11.69)	<0.01	15.49 (5.87-40.86)	<0.01
Persistently positive BDR (n=59)	3.53 (2.10-5.94)		9.69 (4.32-21.71)	
Post-BD airway obstruction at the last study visit**				
Remission of BDR (n=99)	-	<0.01	-	<0.01
Emergence of BDR (n=85)	2.18 (1.25-3.80)	<0.01	2.95 (1.41-6.17)	<0.01
Persistently positive BDR (n=59)	3.14 (1.75-5.62)		3.66 (1.70-7.88)	

ACT, Asthma Control Test; BDR, bronchodilator response; BD, bronchodilator; FEV₁, forced expiratory volume in the first second. Comparison within three groups requires a p-value below 0.017 for statistical significance - Bonferroni correction. *Adjusted for age, gender, ACT score at baseline, and asthma maintenance therapy at baseline. **Adjusted for age, gender, equivalent lung-function parameter at baseline and asthma maintenance therapy at baseline.



investigate whether immediate BDR could be used as additional information to guide the titration of asthma maintenance therapy. The methacholine bronchoprovocation test is a useful tool to guide asthma maintenance therapy in adults and children [21,22], but the lack of availability of the bronchoprovocation test makes its use in clinical practice unfeasible.

It is relevant that individuals with COPD probably did not contaminate the group with airway obstruction and negative BDR because we excluded individuals exposed to risk factors for COPD, and the prevalence of α -1-antitrypsin deficiency is usually very low [23]. Positive aspects of this study were the enrollment of individuals from various primary and secondary outpatient health facilities, the prospective design, and adjusting analyses for confounding variables. Individuals maintained regular follow-up of asthma with their referring physician between the study visits; thus, the management of asthma during the study matches real-life experiences. At the baseline visit, the “asthma” and “asthma-like symptoms” groups differed with regard to some variables such as age, maintenance therapy, and values of some spirometry test parameters. These differences, however, did not bias the conclusions because the binary logistic regressions were adjusted for covariates that could interfere with the interpretation of the results. The researchers carefully quantified maintenance therapy used by study individuals during the 8 weeks preceding each of the two study visits, but they did not monitor maintenance therapy over the 1 year between visits. We do not foresee, however, any reason to suspect that there was a bias in the management of asthma during the follow-up, because the dozens of referring physicians who managed asthma maintenance therapy during the period between study visits were not aware of the study hypothesis. Finally, we adopted the criteria of BDR recommended in the Global Initiative Against Asthma, but some societies have recently proposed new guidelines for BDR [5,24].

We conclude that, in the absence of airway obstruction at baseline, individuals with asthma-like symptoms and persistently negative BDR have a more favorable evolution of lung function compared to individuals with “asthma” proven by positive BDR. In clinical practice, this information may help plan disease management in this understudied population. In individuals with airway obstruction at baseline, the presence of asthma-like symptoms and negative BDR was associated with a lower chance of resolving the airway obstruction. Studies need to investigate whether these individuals have asthma with dominance of airway remodeling and little eosinophilic inflammation. Finally, in individuals with asthma proven by positive BDR, the trend in immediate BDR during follow-up was associated with the evolution of symptoms and lung function.

References

- Ijpma G, Kachmar L, Matusovsky OS, et al. Human tracheal and main bronchi smooth muscle are normoresponsive in asthma. *Am J Respir Crit Care Med* 2015;191:884-93.
- Khan MA. Inflammation signals airway smooth muscle cell proliferation in asthma pathogenesis. *Multidiscip Respir Med* 2013;8:11.
- Regamey N, Ochs M, Hilliard TN, et al. Increased airway smooth muscle mass in children with asthma, cystic fibrosis, and non-cystic fibrosis bronchiectasis. *Am J Respir Crit Care Med* 2008;177:837-43.
- Muniz IS, Ponte EV, Lima VB, Cruz AA. Irreversible airway obstruction in asthma: a risk factor for severe exacerbations in spite of proper treatment. *J Asthma* 2016;53:801-7.
- Reddel HK, Bacharier LB, Bateman ED, et al. Global Initiative for Asthma Strategy 2021: executive summary and rationale for key changes. *Eur Respir J* 2021;59:2102730.
- Janson C, Malinovschi A, Amaral AFS, et al. Bronchodilator reversibility in asthma and COPD: findings from three large population studies. *Eur Respir J* 2019;54:1900561.
- Cavallazzi RS, Polivka BJ, Beatty BL, et al. Current bronchodilator responsiveness criteria underestimate asthma in older adults. *Respir Care* 2020;65:1104-11.
- Currie GP, Fowler SJ, Lipworth BJ. Dose response of inhaled corticosteroids on bronchial hyperresponsiveness: a meta-analysis. *Ann Allergy Asthma Immunol* 2003;90:194-8.
- Puckett JL, Taylor RW, Leu SY, et al. An elevated bronchodilator response predicts large airway inflammation in mild asthma. *Pediatr Pulmonol* 2010;45:174-81.
- Goleva E, Hauk PJ, Boguniewicz J, et al. Airway remodeling and lack of bronchodilator response in steroid-resistant asthma. *J Allergy Clin Immunol* 2007;120:1065-72.
- Roxo JP, Ponte EV, Ramos DC, et al. Portuguese-language version of the asthma control test. *J Bras Pneumol* 2010;36:159-66. [Article in Portuguese].
- Theodoro EE, Rocha DGD, Bertolino JR, et al. Evaluating the effect of antidepressants on the relationship between depression and asthma. *Respir Med* 2023;207:107099.
- Silva JN, Rocha A, de Souza IA, et al. Does peripheral blood eosinophil count predict lung function improvement in adult individuals with asthma? *Ann Allergy Asthma Immunol* 2021;127:388-9.
- Almeida PC, Ponte EV, Souza-Machado A, Cruz AA. Longitudinal trends in clinical characteristics and lung function of patients with severe asthma under treatment in Brazil. *BMC Pulm Med* 2016;16:141.
- Wei J, Ma L, Wang J, et al. Airway reversibility in asthma and phenotypes of Th2-biomarkers, lung function and disease control. *Allergy Asthma Clin Immunol* 2018;14:89.
- Ponte EV, Lima A, Almeida PCA, et al. Age is associated with asthma phenotypes. *Respirology* 2017;22:1558-63.
- Ponte EV, Stelmach R, Franco R, et al. Age is not associated with hospital admission or uncontrolled symptoms of asthma if proper treatment is offered. *Int Arch Allergy Immunol* 2014;165:61-7.
- Bezerra de Menezes M, Ponte EV, Bertagni Mingotti CF, et al. Provision of inhaled corticosteroids is associated with decrease in hospital admissions in Brazil: a longitudinal nationwide study. *Respir Med* 2020;166:105950.
- Ponte EV, Rocha DGD, Guinossi RM, et al. Evaluating the relationship between the type of rescue medication and the adequacy of asthma maintenance therapy. *Respir Med* 2023;217:107364.
- Denlinger LC, Phillips BR, Ramratnam S, et al. Inflammatory and Comorbid Features of Patients with Severe Asthma and Frequent Exacerbations. *Am J Respir Crit Care Med* 2017;195:302-13.
- Nuijsink M, Hop WC, Sterk PJ, et al. Long-term asthma treatment guided by airway hyperresponsiveness in children: a randomised controlled trial. *Eur Respir J* 2007;30:457-66.
- Sont JK, Willems LN, Bel EH, et al. Clinical control and histopathologic outcome of asthma when using airway hyper-



- responsiveness as an additional guide to long-term treatment. The AMPUL Study Group. *Am J Respir Crit Care Med* 1999;159:1043-51.
23. Ashenurst JR, Nhan H, Shelton JF, et al. Prevalence of alpha-1 antitrypsin deficiency, self-reported behavior change, and health care engagement among direct-to-consumer recipients of a personalized genetic risk report. *Chest* 2022;161:373-81.
24. Stanojevic S, Kaminsky DA, Miller MR, et al. ERS/ATS technical standard on interpretive strategies for routine lung function tests. *Eur Respir J* 2022;60:2101499.

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