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Dose-related bronchodilator response in obstructive asthmatic children

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Short Report

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Abstract

Purpose

Spirometry with bronchodilator responsiveness (BDR) testing is central to pediatric asthma diagnosis. Despite guideline recommendations of 200–400 µg short-acting beta agonist (SABA), evidence suggests that these doses may lack sensitivity. We evaluated whether a 600-µg dose improves BDR detection in children with baseline airflow limitation compared to the standard 400 µg.

Methods

We retrospectively analyzed spirometry records from the ACCESS database at Armand Trousseau Hospital (Paris, France). Children ≤ 18 years with confirmed asthma and baseline airflow limitation (FEV_1/FVC z-score <-1.64) were included. Positive BDR was defined as a post-SABA increase in FEV_1 and/or FVC > 10% predicted. Multivariable mixed-effects logistic regression accounted for repeated measurements and potential confounders.

Results

A total of 1162 spirometry tests from 682 subjects were analyzed. BDR was detected in 69.2% of tests using 600 µg versus 51.3% with 400 µg ($p < 0.001$). In multivariate analysis, 600 µg (OR 2.73, 95%CI 1.94–3.85) and Afro-Caribbean ancestry (OR 2.96) were the strongest independent predictors of positive BDR. Additional independent predictors included poor asthma control (OR 1.99) and male sex (OR 1.44). Ongoing antiasthmatic treatment (OR 0.56) and increasing age (OR 0.82) were negatively associated with BDR. Results were consistent across spirometry quality grades.

Conclusion

In asthmatic children with airflow limitation, 600 µg SABA dose significantly increases BDR detection compared to 400 µg, suggesting that standard dosing may underestimate reversibility. Prospective studies are warranted.

Introduction

Objective quantification of airflow limitation and bronchodilator responsiveness (BDR) is central to paediatric asthma diagnosis. Current guidelines require compatible respiratory symptoms alongside objective evidence of airflow limitation and positive BDR for a definitive diagnosis in children aged 5–16 years (1). Spirometry before and after short-acting beta-agonists (SABA) administration is standard practice, with positive BDR defined as an > 10% predicted increase in forced expiratory volumes (2).

Despite its widespread use, uncertainty persists regarding optimal SABA dose for maximal bronchodilation. Although guidelines suggest 200–400 µg, evidence indicates that these doses may lack sensitivity, leaving dose selection largely to clinical judgement (2). Recent data further indicate that higher doses may improve BDR detection, potentially reducing underdiagnosis in symptomatic children (3, 4).

Since 2024, our lung function laboratory has increasingly administered 600 µg of SABA to children with baseline airflow limitation, while maintaining the standard 400 µg dose in those without, hypothesizing superior sensitivity of higher dose in this setting. This study aimed to retrospectively assess whether SABA dose influences the diagnostic yield of BDR in asthmatic children with bronchial obstruction.

Methods

This retrospective, single center is based on data extraction in February 2026 from the ACCESS database, established in 2021 at Armand Trousseau Hospital (Paris, France). We included patients aged ≤ 18 years with an asthma diagnosis confirmed by an expert pediatric pulmonologist. Patients with other chronic respiratory conditions were excluded, except for overweight (body mass index (BMI) z-score > 1 and ≤ 2) and obesity (BMI z-score > 2). Spirometry (BodyBox®, MedisoftTM, Sorinnes, Belgium) was performed by six trained technicians and each test was quality-graded from A to F according to ATS/ERS recommendation (5). SABA was withheld at least 6 hours before testing. Salbutamol was standardized through a pressurized metered-dose inhaler with spacer and post-bronchodilator spirometry was performed after a 20-minute interval. The administration technique and timing have remained unchanged since 2021.

Airflow limitation was defined as a baseline forced expiratory volume in 1s over forced vital capacity ratio (FEV_1/FVC) z-score < -1.64 and positive BDR as a 20-min post-SABA (salbutamol) increase in FEV_1 and/or FVC > 10% of predicted values (2). Asthma control was assessed using the four-item GINA symptom-control score (*GINA-2026-Strategy-Report-WMS.pdf pag.41*).

Statistical analysis

Continuous variables were expressed as mean (standard deviation (SD)) or median (interquartile range (IQR)), according to distribution (skewness and kurtosis) and categorical variables as frequencies and percentages. Between-group comparison used Chi-square test (categorical variable) and student's t-test (continuous variables), considering all repeated measurements per patient. A multivariable mixed-effects logistic regression modelled BDR as a function of SABA dose, age, sex, BMI, ethnicity, asthma control in the last month, recent exacerbation (last three months), treatment status, and baseline z-score FEV_1 as covariables, with a patient-level random intercept for repeated measurements. Analyses were performed in R (v 4.4.1) and Jamovi (v 2.6.45.0). P-value < 0.05 was considered significant.

The study received approval from the Institutional Review Board of the French learned society for respiratory medicine-Société de Pneumologie de Langue Française-(CEPRO 2026-024) and conducted in accordance with the Declaration of Helsinki.

Results

A total of 9747 pulmonary function test records preformed in asthmatic children were initially identified. Baseline spirometry was available in 6887 cases, with post-SABA assessment in 6231; among these, 1248 showed bronchial obstruction. After excluding ungraded spirometry, those graded F or U and the one with missing clinical information, 1162 tests were retained for analysis. The final study population comprised 682 subjects (416 with only one test, 62.0% male) with a mean age at the time of lung function testing of 12 years old (SD 3.2).

The SABA dose was 400 µg in 782 tests and 600 µg in 380 (33%, 95%CI 30–35). The two dose groups had similar baseline FEV_1/FVC z-score (-2.29 vs -2.31, p = 0.62) (Table 1). Spirometry quality remained stable over the study period, with 71–78% of tests achieving grade A/B in every year. In contrast, the rate of positive BDR increased markedly over the years, coinciding with the introduction of the 600-µg SABA dose.

Table 1
Baseline characteristics of 1162 spirometry showing baseline airflow limitation according to SABA dosing and FEV_1 quality grade

Sex, male - n (%) *	**SABA 400µg N = 782**	**SABA 600µg N = 380**	***P value***	**Pre- and post-SABA A/B curve N = 860**	**Pre- and/or post-SABA C/D/E curve N = 302**	***P value***
	328 (64.1)	**97 (57.1)**	**0.103**	**281 (60.0)**	**144 (67.3)**	**0.070**
Age, year - mean (SD)	12.6 (3.03)	12.6 (3.05)	0.804	12.9 (2.91)	11.7 (3.22)	**< 0.001**
Antiasthmatic treatment – n (%)			**0.031**			0.128
None	272 (34.8)	124 (32.6)		276 (32.1)	120 (39.7)	
ICS alone	41 (5.2)	10 (2.6)		42 (4.9)	9 (3.0)	
ICS + LABA	313 (40.0)	157 (41.3)		353 (41.0)	117 (38.7)	
Anti-leukotrienes	2 (0.3)	1 (0.2)		2 (0.2)	1 (0.3)	
Biotherapy alone	7 (0.9)	1 (0.2)		7 (0.8)	1 (0.3)	
Others	147 (18.8)	87 (22.9)		180 (21.0)	54 (17.9)	
FEV_1 quality grade - n (%)			0.546			
A/B curve	583 (74.6)	277 (72.9)				
C, D or E curve	199 (25.4)	103 (27.1)				
Dose - n (%)						0.546
400µg				583 (67.7)	199 (65.9)	
600µg				277 (32.3)	103 (34.1)	

* Results in 682 children participating in the study.

Abbreviations: FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid, LABA, long-acting beta-2 agonist; SABA, short acting beta-2 agonist; SD, standard deviation.

Sex, male - n (%) *	**SABA 400µg N = 782**	**SABA 600µg N = 380**	***P value***	**Pre- and post-SABA A/B curve N = 860**	**Pre- and/or post-SABA C/D/E curve N = 302**	***P value***
	328 (64.1)	**97 (57.1)**	**0.103**	**281 (60.0)**	**144 (67.3)**	**0.070**
Baseline FEV_1 /FVC z-score - mean (SD)	-2.29 (0.52)	-2.31 (0.53)	0.620	-2.31 (0.52)	-2.26 (0.51)	0.218
Ethnicity -n (%) *			0.826			0.240
Caucasian	311 (60.7)	100 (58.8)		280 (59.8)	131 (61.2)	
African-Caribbean	121 (23.6)	45 (26.5)		121 (25.9)	45 (21.0)	
Others	80 (15.7)	25 (14.7)		67 (14.3)	38 (17.8)	
Overweight - n (%)	189 (24.2)	93 (24.5)	0.909	214 (24.9)	68 (22.5)	0.409
Obesity - n (%)	117 (15.0)	80 (21.1)	**0.009**	148 (17.2)	49 (16.2)	0.695
* Results in 682 children participating in the study.						
Abbreviations: FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid, LABA, long-acting beta-2 agonist; SABA, short acting beta-2 agonist; SD, standard deviation.						

A significant dose-dependent association between the SABA dose and BDR prevalence was observed ($p < 0.001$); a positive BDR was recorded in 69.2% of tests with 600 µg versus 51.3% with 400 µg. in the multivariable mixed-effect model, 600 µg of SABA (OR 2.73, 95%CI 1.94–3.85, $p < 0.001$) and Afro-Caribbean ancestry (OR 2.96, 95%CI 1.94–4.53,$p < 0.001$) were the strongest independent predictors of positive BDR, followed by poor asthma control (OR 1.99, 95%CI 1.10–3.59, $p = 0.022$) and male sex (OR 1.44, 95%CI 1.01–2.04, $p = 0.043$); ongoing antiasthmatic treatment (OR 0.56, 95%CI 0.40–0.79, $p = 0.001$), older age (OR 0.82/year 95%CI 0.77–0.87, $p < 0.001$) and higher baseline FEV_1 z-score (OR 0.76/per unit increase, 95%CI 0.64–0.90, $p = 0.001$) were inversely associated.

Discussion

In this large real-world cohort of asthmatic children with baseline airflow limitation, 600 µg of SABA was associated with a markedly higher frequency of positive BDR than 400 µg; and remained the strongest modifiable predictor of a positive response after adjustment.

These findings suggest that the currently recommended doses of 200–400 µg may lie on the ascending part of the dose-response curve in children with airflow limitation, so that submaximal bronchodilation is obtained and a positive BDR can be missed. Notably, this 600-µg advantage was consistent whether spirometry was graded A/B or C-E, supporting a true pharmacological rather than measurement-driven effect. Lower-quality grades are relatively common in children who struggle to reproduce their best manoeuvre; including grades C-E therefore reflects the real-world spectrum of paediatric spirometry quality.

Higher baseline FEV_1 z-score was associated with a lower probability of a large bronchodilator response, consistent with paediatric data linking greater reversibility to worse baseline obstruction (6). Poor asthma control was associated with a higher likelihood of positive BDR, as previously shown in preschool wheezers and in children with severe asthma (3, 7). Ongoing antiasthmatic treatment was independently associated with lower BDR prevalence, plausibly reflecting reduced baseline airway inflammation (7). Older age was associated with progressively lower odds of positive BDR, consistent with reported age-related decline in airway reversibility (8, 9). It should be noted, however, that Tommola et al. found no age-BDR correlation in steroid-naïve adult-onset asthma, suggesting that this association may be specific to childhood-onset disease (10).

The main strengths is the large real-world dataset, which provide substantial statistical power to explore the effect of SABA. The consistency of results across spirometry quality grades further supports a true pharmacological effect rather than measurement variability.

The main limitation is the retrospective, monocentre, non-randomised design: confirmation of a true dose-response effect requires a prospective design or a comparison of 400 versus 600 µg in children matched for baseline lung function.

In conclusion, 600 µg of SABA significantly enhances positive BDR detection compared to 400 µg in asthmatic children with baseline airway obstruction, suggesting that standard dosing may underestimate BDR and consequently contribute to underdiagnosis of asthma. We propose that baseline spirometric airflow limitation, beyond clinical judgment alone, be considered as an objective criterion to guide SABA dose decision, with 600 µg recommended at initial asthma evaluation and during follow-up in children with baseline airflow limitation, where maximizing diagnostic sensitivity is paramount.

Declarations

Declaration of interest statement:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Contribution

N.B. conceived and designed the study. A.M., J.T., J.D. collected the data. M.B. performed the statistical analyses. A.M. and N.B. drafted the manuscript. N.B., J.T., and J.D. supervised the study. All authors reviews the manuscript.

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Data Availability

All data supporting the findings of this study are available within the paper.

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