LETTER TO THE EDITOR

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It is high time for the scholarly societies to standardize the bronchodilator responsiveness in children

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Dear editor,

I read with curiosity the remarkable article of Mallol et al.¹ aiming at determining the performance of commonly used tests for asthma diagnosis - that is, spirometry, bronchodilator responsiveness (BDR) to salbutamol, methacholine challenge test, and fractional exhaled nitric oxide (F_eNO) to validate the diagnosis of asthma in children. I acknowledge the authors for their captivating idea, and I agree with their conclusion that “spirometry, BDR, and F_eNO have a poor performance to corroborate asthma diagnosis in children.” However, in the methodology section of the aforementioned article,¹ three points related to the bronchodilator test caught my attention.

- (i) Mallol et al.¹ have defined the positive BDR as $\geq 12\%$ increase from baseline in forced expiratory volume in 1 s ($\Delta FEV_{1\%B}$), and they have argued their choice by citing as a reference the 2005 task force published by the American thoracic and the European respiratory societies (ATS/ERS).² The approach of Mallol et al.¹ is practical but “debatable.” In fact, according to the ATS/ERS,² a positive BDR (regardless of the age) is a $\Delta FEV_{1\%B} \geq 12\%$ and a ΔFEV_{1AC} (absolute change) ≥ 200 mL and/or an increase from baseline in forced vital capacity ($\Delta FVC_{\%B}$) $\geq 12\%$, and a $\Delta FVC_{AC} \geq 200$ mL. Consequently, Mallol et al.¹ “omitted” to express the FEV₁ BDR as an increase in Δ_{AC} , and to evaluate an important spirometric datum (i.e., FVC). Notwithstanding its huge use in real-life clinical situation, $\Delta_{\%B}$ presents two key limitations.³ On one hand, $\Delta_{\%B}$ reveals sex- bias and size-bias in evaluating BDR.³ On the other hand, patients with the highest basal FEV₁ displayed the smallest $\Delta FEV_{1\%B}$.³ The approach of Mallol et al.¹ to “omit” ΔFEV_{1AC} is realistic, since ΔFEV_{1AC} exhibits some correlations to age and height, and its changes are greater in tall children than in short ones.³ In children, some scholarly societies^{2,4} still endorse one spirometric standardized and reproducible datum (i.e., FVC) for at least two reasons. First, FVC provides useful information about peripheral airways function and lung hyperinflation/air trapping.^{5,6} Secondly, a decrease in FVC is linked to an increase in air trapping.⁵ Again, the choice of Mallol et al.¹ to “omit” changes in FVC is reasonable since the discrepancy between the flow and the volume impacts on BDR is partially comprehended.⁷

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- (ii) The global initiative for asthma (GINA)⁸ recommends to report FEV_1 change to the predicted value derived from spirometric norms ($\Delta_{\%PV}$). Contrary to the two previous BDR expressions (i.e., $\Delta_{\%B}$, $\Delta_{\%AC}$), $\Delta_{\%PV}$ presents one main merit. It permits the comparison of children irrespective of their height [in the Chilean study,¹ the 95% confidence interval of height was huge, equal to 102–120 cm]. Once more, the approach of Mallol et al.¹ to “omit” $\Delta_{\%PV}$ is convincing since its use is a bit difficult in daily practice (e.g., it cannot be applied in some countries where spirometric norms are missing).
- (iii) The definition adopted by Mallol et al.¹ (i.e., $\Delta FEV_{1\%B} \geq 12\%$) is the one advanced by the British thoracic society (BTS).⁹ This choice is understandable. In fact, several scholarly societies^{2,4,8–11} failed to standardize the expression of BDR in children. Table 1 exposes certain definitions of a “clinically significant” BDR adopted by some scholarly societies. In future studies, the following three questions related to the BDR in children should be treated: (i) which datum/data should be analyzed (FEV_1 , FVC, peak expiratory flow)? (ii) which BDR expression mode should be used (Δ_{AC} , $\Delta_{\%B}$, $\Delta_{\%PV}$)? and (iii) which thresholds should be applied (12%, 20%, and 200 mL)? In adults, the issue related to which BDR definition should be applied was largely addressed.^{12–15} In children with asthma, the question related to which BDR definition should be applied is still under debate.¹⁶

To conclude, the lack of a clear consensus about the BDR in children is a source of confusion for pediatricians, and can hinder asthma diagnosis. Therefore, it is high time for the scholarly societies to standardize the BDR in pediatric populations.

Table 1 Definitions of a “clinically significant” bronchodilator responsiveness adopted by some scholarly societies.

Scholarly society	Reference	Definition
GINA	10	$\Delta FEV_{1\%PV} > 12\%$
BTS	9	$\Delta FEV_{1\%B} \geq 12\%$
GRAPP	8	$\Delta FEV_{1\%B} \geq 12\%$ or $\Delta PEF_{\%B} \geq 20\%$
NAEPP	11	$\Delta FEV_{1\%B} \geq 12\%$ and $\Delta FEV_1 > 200$ mL
ATS-ERS	2	$(\Delta FEV_{1\%B} \geq 12\%$ and $\Delta FEV_1 \geq 200$ mL) and/or $(\Delta FVC_{\%B} \geq 12\%$ and $\Delta FVC \geq 200$ mL)
SATS	4	$(\Delta FEV_{1\%B} \geq 12\%$ or $\Delta FEV_1 > 200$ mL) and/or $(\Delta FVC_{\%B} \geq 12\%$ or $\Delta FVC > 200$ mL)

ATS: American thoracic society. B: basal value. BTS: British thoracic society. ERS: European respiratory society. FEV_1 : forced expiratory volume in 1 s. FVC: forced vital capacity. GINA: global initiative for asthma. GRAPP: research group on advances in pediatric pneumology. NAEPP: national asthma education and prevention program. PEF: peak expiratory flow. PV: predicted value. SATS: South African thoracic society.
 Δ : after bronchodilator value - basal value. $\Delta_{\%PV}$: $100 \times \Delta /$ Predicted value. $\Delta_{\%B}$: $100 \times \Delta /$ basal value.

Competing interest

I report personal fees from Opalia Recordati and Chiesi.

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