LETTER TO THE EDITOR

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_{NO}) 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_{NO} 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 intention.

(i) Mallol et al.¹ have defined the positive BDR as ≥12% increase from baseline in forced expiratory volume in 1 s (ΔFEV_{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 ΔFEV_{1%≥12} and a ΔFEV_{1%AC} (absolute change) ≥200 mL and/or an increase from baseline in forced vital capacity (ΔFVC_{%B} ≥12%, and a ΔFVC_{AC} ≥200 mL. Consequently, Mallol et al.¹ “omitted” to express the FEV, 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, Δ_{AC} presents two key limitations.³ On one hand, Δ_{AC} reveals sex-bias and size-bias in evaluating BDR.³ On the other hand, patients with the highest basal FEV, displayed the smallest ΔFEV_{1%B}.³ The approach of Mallol et al.¹ to “omit” ΔFEV_{1%AC} is realistic, since ΔFEV_{1%AC} exhibits some correlations to age and height, and its changes are greater in tall children than in short ones.¹ In children, some scholarly societies²,⁴ still indorse 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.⁷ 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

KEYWORDS
ATS/ERS; bronchodilator reversibility; FEV₁; FVC; GINA; spirometry

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The global initiative for asthma (GINA)\(^8\) recommends to report FEV\(_1\) change to the predicted value derived from spirometric norms (\(\Delta_{\text{spv}}\)). Contrary to the two previous BDR expressions (i.e., \(\Delta_{\text{sp}}, \Delta_{\text{ac}}\)), \(\Delta_{\text{spv}}\) presents one main merit. It permits the comparison of children irrespective of their height [in the Chilean study,\(^7\) the 95\% confidence interval of height was huge, equal to 102–120 cm]. Once more, the approach of Mallol et al.\(^1\) to “omit” \(\Delta_{\text{spv}}\) 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).

The definition adopted by Mallol et al.\(^1\) (i.e., \(\Delta\text{FEV}_{100} \geq 12\%\)) is the one advanced by the British thoracic society (BTS).\(^9\) This choice is understandable. In fact, several scholarly societies\(^4,6,8,11\) 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 (\(\Delta_{\text{sp}}, \Delta_{\text{ac}}, \Delta_{\text{spv}}\))? 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.

<table>
<thead>
<tr>
<th>Scholarly society</th>
<th>Reference</th>
<th>Definition</th>
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<tbody>
<tr>
<td>GINA</td>
<td>10</td>
<td>(\Delta\text{FEV}_{100} \geq 12%)</td>
</tr>
<tr>
<td>BTS</td>
<td>9</td>
<td>(\Delta\text{FEV}_{100} \geq 12%)</td>
</tr>
<tr>
<td>GRAPP</td>
<td>8</td>
<td>(\Delta\text{FEV}<em>{100} \geq 12%) or (\Delta\text{PEF}</em>{100} \geq 20%)</td>
</tr>
<tr>
<td>NAEPP</td>
<td>11</td>
<td>(\Delta\text{FEV}<em>{100} \geq 12%) and (\Delta\text{FEV} \geq 200\text{ mL}) and/or (\Delta\text{FVC}</em>{100} \geq 12%) and (\Delta\text{FVC} \geq 200\text{ mL})</td>
</tr>
<tr>
<td>ATS-ERS</td>
<td>2</td>
<td>((\Delta\text{FEV}<em>{100} \geq 12%) or (\Delta\text{FEV}</em>{100} \geq 200\text{ mL})) and/or ((\Delta\text{FVC}_{100} \geq 12%) or (\Delta\text{FVC} \geq 200\text{ mL}))</td>
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<tr>
<td>SATS</td>
<td>4</td>
<td>((\Delta\text{FEV}<em>{100} \geq 12%) or (\Delta\text{FEV} \geq 200\text{ mL})) and/or ((\Delta\text{FVC}</em>{100} \geq 12%) or (\Delta\text{FVC} \geq 200\text{ mL}))</td>
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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. \(\Delta\): after bronchodilator value - basal value. \(\Delta_{\text{spv}}\): 100 × \(\Delta/\text{Predicted value}\). \(\Delta_{\text{sp}}\): 100 × \(\Delta/\text{basal value}\).

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### References

13. Saad HB, Préfaut C, Tabka Z, Zbidi A, Hayot M. The forgotten message from gold: FVC is a primary clinical outcome measure