

Reply

To the Editor:

In response to the comments by Dr Salo et al¹ on my editorial² discussing the paper by Salo et al³ in the October issue of the Journal, I would like to make some comments.

It is essential to use major allergen concentrations, not total antigen content, when reporting on the concentrations of allergens in indoor dust. The total antigen content gives no idea about the clinical importance of the findings. The major allergens constitute a minor part of the protein extracted from a mold culture. Thus, determination of antigen can never be compared to major allergen.

All available data on allergens in dust documenting concentrations needed for sensitization or induction of acute asthma⁴ are based on the major allergen content per gram of dust.

Thus, the clinical importance of the findings by Salo et al³ can never be understood.

For 2 decades, knowledge has been accumulated on major allergen concentrations indoors: in schools,⁵ day-care centers,⁶ and other public places.⁷ We have also learned about the transportation of allergens in clothes⁸ and hair,⁹ and data have been accumulated on allergen concentrations causing sensitization⁴ and those increasing the risk of acute asthma.⁴

One important point mentioned in the editorial was the fact that allergens isolated from natural source materials sometimes contain several different isoallergens. Not all isoallergens have exactly the same epitopes. mAbs are directed against only 1 of these epitopes, whereas polyclonal antibodies, raised against isolated naturally occurring major allergens, at best, contain antibodies directed against all possible variants. In major allergen assays, most often, the combination of mAbs and a recombinant allergen as standard is used. Such systems do not always give information on the total amount of major allergen in dust or air. As long as the same system is used, the data may be comparable between trials and also between regions of the world. However, for some allergens, it may be that the best solution would be to use a mix of several mAbs and a mix of recombinant allergens to be able to get data reflecting the true concentration of allergen.

The drawback with the polyclonal rabbit antibodies used by the authors and marketed by Greer Laboratories can never be copied. If new blood is drawn from the same rabbits, they have most probably changed their antibody repertoire, and if new rabbits are immunized, they will not produce antibodies resembling the antibody mixture used by the authors.

Thus, and this is scientifically important, the results of Salo et al³ can never be copied.

The comments on the International Union of Immunological Societies (IUIS) reference standard stands for the authors. The IUIS standards should not be copied but are valuable as references for comparison. If Greer Laboratories does it better, that would be great.

Avoidance of tobacco smoking indoors is one of the major conclusions of the paper by Salo et al³ and defended

in their reply to my editorial,² because *Alternaria* spores are often present in tobacco leaves (as on most plants), *Alternaria* spores have been detected in cigarettes, and *Alternaria* antigens have been detected in cigarette ash. However, as stated in the reply by Salo et al,¹ "...further research is warranted to evaluate this relationship"—that is, between smoking and exposure to *Alternaria* antigen (better, allergen).

For obvious reasons, tobacco smoking should be banned everywhere, but not because of the probably negligible content of *Alternaria* spores in cigarettes and *Alternaria* antigen tobacco ash.

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Bronchial obstruction: A limited, out-of-fashion approach to measure treatment efficacy in childhood asthma?

To the Editor:

In the Characterizing the Response to a Leukotriene Receptor Antagonist and an Inhaled Corticosteroid study analyzing 144 children with mild to moderate persistent asthma at the clinical centers of the Childhood Asthma Research and Education (CARE) Network, Szeftler et al¹ found that 55% of the children did not respond to either medication, although "response to treatment" was fixed at a "relatively low" improvement of FEV₁ values,

7.5% or greater. In the editorial with this article, Stempel and Fuhlbrigge² discussed the opportunity to consider prebronchodilator or postbronchodilator FEV₁ values as measure of treatment efficacy. After a revision and discussion of other similar studies,³⁻⁵ they conclude on the importance of establishing a consensus on specific parameters, including measures of disease activity, that should be included in the definition of *responder*.

Indeed, in the CARE study, there seems to be a major inconsistency: one of the inclusion criteria was the demonstration of an increase in FEV₁ values greater than 12% after bronchodilator testing. This improvement, however, could be achieved after 6 to 8 inhalations of albuterol⁶—that is, with doses 3 to 4 times greater than those usually used to calculate bronchodilator reversibility. This suggests that reversible bronchial obstruction was not one of the major components of disease, at least in some of the children evaluated, and probably, because FEV₁ (mean $\pm$ SD) was 95.0% $\pm$ 12.9% predicted, not the primary outcome measure to be considered to define “response to treatment.” Low degree of bronchodilator reversibility at baseline, before entering the studies,^{4,7} and small if any effect on FEV₁ values, often within the range of the reproducibility for spirometry,²⁻⁵ have been frequently reported in studies performed in children with asthma, at least in those with mild to moderate disease.

A second issue is that not all the participants in the CARE study had signs of active eosinophilic inflammation, at least as detected by exhaled nitric oxide levels and peripheral blood eosinophilia.⁶ Because, as also underlined by Stempel and Fuhlbrigge,² a greater improvement in lung function with anti-inflammatory drugs should be expected when asthma is associated with “active disease,”^{2,5} this may explain the observed poor response to inhaled corticosteroids and leukotriene receptor antagonists.

There is no question that in childhood asthma, various clinical aspects related to the subjects and to the phenotype of their disease should be considered in designing clinical studies and interpreting their results. Need and response to therapy should probably also be evaluated on the basis of a variety of indicators that must include a combination of symptoms, medication use, morbidity, physiologic measures, and, possibly, inflammation indexes.

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Reply

To the Editor:

We agree with Silvestri et al¹ regarding the points made on the limitations of pulmonary function measures as an indicator of response, especially in children. There is no doubt that need and response to therapy should be based on a number of indicators; however, it has become apparent that many of these indicators are not correlated with each other, as clearly described by Zhang et al.² Therefore, we chose to evaluate one of these indicators very carefully, namely, improvement in FEV₁, our primary outcome variable.³

Silvestri et al¹ correctly note that we had a high percentage of nonresponders to the 2 medications, an inhaled corticosteroid or a leukotriene antagonist. This may be a result of the high FEV₁% predicted at baseline, 95% $\pm$ 12.9%. Although they are correct in saying that bronchodilator response greater than 12% was one of the inclusion criteria for the study, it was not a requirement. Either a bronchodilator response or a methacholine PC₂₀ of less than or equal to 12.5 mg/mL qualified children for this study. It is now recognized that children with moderate to severe asthma can have normal FEV₁% predicted; however, their FEV₁/forced vital capacity ratio shows evidence of obstruction.⁴ Although a proportion of the nonresponders may be related to true mechanisms of steroid resistance,⁵ another group may be near their plateau response. Of further interest is our observation that approximately 1/3 of the population with FEV₁ greater than 95% predicted had greater than 7.5% increase to one or both medications. Therefore, a proportion of children with a normal FEV₁% predicted by current standards (derived primarily from experience with adults) still have room for improvement. Biomarkers or clinical characteristics identified in our study should be useful predictors for children with asthma who will be responsive to these medications. It should be pointed out that bronchodilator response was not a predictor of response to inhaled corticosteroid as previously noted in adult patients.⁶ We are currently testing these proposed predictors in a separate Childhood Asthma Research and Education Network protocol.

Silvestri et al¹ also point out that not all participants had signs of active eosinophilic inflammation, at least as