

Correspondence and Replies

Impact of Spacers on Therapeutic Ratio with Inhaled Corticosteroids



To the Editor:

We read with interest the article of Guilbert et al,¹ which showed, using retrospective observational data, that using a spacer with either extra-fine particle hydrofluoroalkane (HFA) beclomethasone pressurized metered dose inhaler (pMDI) or fine particle fluticasone pMDI did not significantly affect severe exacerbations or risk domain asthma control. Pointedly, this study did not look at the impact of using spacers on systemic adverse effects, and hence the relative therapeutic ratio cannot be deduced.

In vitro studies with extra-fine particle HFA beclomethasone (100 µg ex-valve dose) using an Andersen cascade impactor showed that the overall fine particle dose (particles <4.7 µm) was higher when using an Aerochamber plus than pMDI alone (39.0 µg vs 22.4 µg) along with a lower mass median aerodynamic diameter (0.8 µm vs 1.4 µm).² This drug-device interaction will of course depend on the patient using an optimal inhaler technique with pMDI alone or in conjunction with a spacer.

An important but often overlooked consequence of a higher fine particle dose when using a spacer device will be increased lung deposition and hence enhanced lung bioavailability, in turn resulting in the potential for greater dose-related systemic adverse effects such as adrenal suppression.³ For example, in asthmatic patients, using fine particle HFA fluticasone propionate pMDI where there is almost complete hepatic first pass inactivation for the swallowed dose, the addition of an Aerochamber plus, in conjunction with optimal spacer priming and inhaler technique, has been shown to increase the degree of adrenal suppression by 65%, whereas an Aerochamber max results in a 71% increase,⁴ presumably due to a higher degree of lung bioavailability.⁵ For extra-fine HFA beclomethasone, a reduction in oral bioavailability might be expected to counterbalance increased lung bioavailability when using a spacer, due to the incomplete first pass inactivation for the swallowed dose. Hence in asthmatic patients, chronic dosing with HFA beclomethasone 400 µg/day (ex-valve dose) pMDI with Aerochamber plus produced no significant suppression of overnight urinary cortisol/creatinine compared with inhaled corticosteroid (ICS) naïve baseline values, despite significant improvements in both methacholine hyperresponsiveness and exhaled breath nitric oxide.² Further prospective randomized trials are required to examine both antiasthmatic efficacy and systemic adverse effects to properly define the therapeutic ratio of currently available ICS pMDI formulations used alone and with spacers.

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Sanofi, and Meda; has received lecture fees from Meda, Teva, and Boehringer Ingelheim; has received travel support from Teva and Boehringer Ingelheim. S. Jabbal has received lecture fees from Chiesi Pharmaceuticals, AstraZeneca, Napp, and Pfizer; and has received travel support from Napp, Teva, AstraZeneca, and Chiesi.

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Reply



To the Editor:

We appreciate the recent letter¹ regarding our study comparing asthma outcomes in patients prescribed inhaled corticosteroids with and without spacers.² Lipworth and Jabbal point out some valid limitations of our results, such as the lack of investigation into the systemic adverse effects of spacer use. This is not something that was possible in our database study, and this is one reason why evidence of observational research together with that of randomized controlled trials (RCTs) is so important.³ We relied on routinely collected information from observational databases, which did not include information about side effects. Classical RCTs are required to measure such endpoints, and could be designed to investigate adrenal suppression, for example. Such research questions are highly useful, yet cannot provide the whole picture: RCTs are limited in the generalizability of their results, as they often consist of highly selected samples⁴ and patients are likely to be monitored, which impacts adherence. Patients may also receive specific inhaler training, which is noted by Lipworth and Jabbal as an influential factor. In contrast, observational research seeks to estimate real-life effectiveness, in a heterogeneous sample of patients with varying disease severity, smoking habits, inhaler technique, and so on. Somewhere in between these 2 types of research is the use of pragmatic trials.⁵ These trials widen their inclusion criteria and strive for real-life conditions, whilst investigating a research question that would not be feasible in a strictly observational study.

Our real-life study did not find any evidence of a difference in effectiveness between patients prescribed spacers and those not prescribed spacers. Lipworth and Jabbal refer to several

in vitro studies and RCTs that support the use of particular types of spacer devices. Our own study cites several RCTs that did not find side effects without spacer use. All of this highlights the need for continued research of varying designs as described above.

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Reducing the burden of allergy and asthma in schoolchildren: Air cleaning solutions and microbial diversity—the dark side of the moon?



To the Editor:

The article "School Environmental Intervention to Reduce Particulate Pollutant Exposures for Children with Asthma" by Jhun et al¹ elegantly showed, similarly to other intervention studies in different environments, that high-efficiency particulate arrestance (HEPA) filters in schools are able to significantly reduce the indoor concentrations of particulate matter, which may potentially reduce exacerbations in children with asthma. In this age group, allergic asthma is the prevalent phenotype; therefore, the study's intervention may also impact allergic diseases. This interventional approach has been referred as a highly effective indoor environmental control methodology,² but is "air cleaning the school indoor environment" really the best approach?

Recently, we reported evidence supporting the association between high concentrations of particulate matter and the

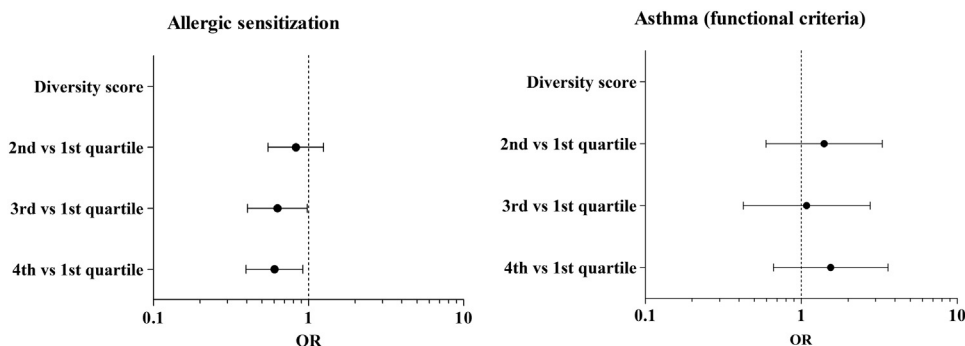


FIGURE 1. The influence of microbial diversity in schools on the development of allergy and asthma in children has been investigated. A microbial diversity score was defined as the sum of all the detected fungi groups/species, categorized into quartiles, with the classrooms with lower diversity score in the first quartile, whereas the fourth quartile included those with higher diversity scores. The graphics represent the logistic regression between fungal diversity scores and the prevalence of allergic sensitization (left) and asthma (right). The results are expressed as odds ratios (ORs) with 95% CI in logarithmic scale. Although a clear tendency for a lower risk of allergic sensitization may be observed as the fungal diversity increases in classrooms, the same was not observed for asthma. Figure adapted from Figure 2 of Cavaleiro Rufo et al.⁷

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