

Allergen avoidance in the treatment of asthma: Problems with the meta-analyses

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Decreasing exposure to indoor allergens has been studied extensively and is a well accepted part of the treatment for allergic disease. The 2007 revision of the evidence-based guidelines recommends allergen avoidance as part of the management of asthma. In contrast, a recent meta-analysis concluded that dust mite avoidance is “of no use” in the treatment of asthma. There are obvious sources of bias that could have influenced the evaluation of published trials either by the guideline panel or by the group conducting the meta-analysis. An important issue is whether meta-analysis is a valid method of evaluating studies such as those on dust mite avoidance that are highly variable. Reading the published series of 4 meta-analyses on this subject from the Cochrane Library suggests that decisions about which trials to include can have a major effect on the outcome. The process of meta-analysis may also have other potential conflicts. The recent meta-analysis on dust mite avoidance appears to be seriously flawed because of the decisions about inclusion and exclusion as well as the way in which studies were evaluated. The conclusion is that the criticisms of the recommendations in the 2007 guidelines were not well founded. (*J Allergy Clin Immunol* 2008;122:694-6.)

Key words: *Dust mites, avoidance, meta-analysis, asthma guidelines*

Decreasing exposure to indoor allergens is a rational and well accepted part of the treatment for chronic allergic disease.^{1,2} In addition, the evidence-based guidelines for asthma management revised for the National Asthma Education and Prevention Program (NAEPP) in 2007 recommend allergen avoidance as part of the management of asthma in patients with known allergen sensitivity.³ It therefore comes as a surprise when Medline Plus and also a Lancet editorial have the headline “Dust Mite Control Measures of No Use” followed on Medline Plus by the remarkable implication that specialists are lying to their patients.^{4,5} The reason for these reports was the publicity created about the recent meta-analysis on allergen avoidance for asthma.^{4,6} Initially this report was published online by the Cochrane Library, which specializes in meta-analyses. Given that the report comes from the Nordic

Abbreviation used

BHR: Bronchial hyperreactivity

NAEPP: National Asthma Education and Prevention Program

Cochrane Center, that report might not be regarded as peer reviewed.⁷ However, the meta-analysis has since been published in *Allergy*.⁸ Clearly it is important to consider why different groups should reach such different conclusions. There seem to be several aspects to this: how were the analyses conducted and written, what is the background of the respective authors, and finally, are there hidden forms of bias in either the guidelines or the meta-analysis?

The NAEPP guidelines were prepared by a panel of physicians and other health care professionals who have extensive experience in both the investigation and the management of asthma.³ Those authors had access to all the reports that were included in the Cochrane analysis and in addition reviewed several thousand other reports on the treatment of asthma. Standard forms of financial or professional conflict were discussed extensively during the process and reported carefully. There are other possible conflicts in that those of us on the panel who care about and have studied the role of allergens in asthma may have been biased in favor of nonpharmacologic approaches to treatment. However, it is equally apparent that many members of the panel have spent years studying pharmacologic approaches, and they may have been biased in favor of those forms of treatment. Overall the guideline panel meetings were very open in discussions of the relative importance of different approaches to treatment.

Dr Gotzsche, the director of the Nordic Cochrane Center, has published widely on the subject of meta-analysis and has been senior author on 4 meta-analyses on dust mite avoidance for asthma in 1998, 2001, 2004, and 2008.^{7,9-11} The first analysis was generally considered to have given too much credence to some of the early studies on avoidance, which used protocols that had never been shown to reduce mite exposure.⁹ Perhaps more important at that time, the Nordic Cochrane Center included studies based on peak flow results and excluded studies in which the outcome was bronchial hyperreactivity (BHR). This restricted the analysis because peak flow results are effort-dependent, and decreased BHR is considered to be an important outcome of allergen avoidance.¹²⁻¹⁵ The exclusion of BHR data came about because of the inclusion of studies that had peak flow as the primary outcome but used avoidance protocols that were not effective in reducing either mites or mite allergen in the homes.⁹ Because of this and for other reasons, it was suggested in 1998 that the conclusions of the meta-analysis were wrong.¹⁶ In 2001 the second meta-analysis corrected some of the problems of the first and reported a significant clinical effect of physical measures for mite avoidance in the treatment of asthma ($P = .02$).¹⁰ Curiously, the authors have

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persisted in referring to that analysis as negative, both in the text at the time, and subsequently.¹⁷ Because of the poor quality of the first analysis and the confusion in the second, we and others have generally chosen not to include references to these meta-analyses. This is important, because clearly it is the prerogative of authors to decide which articles or meta-analyses they choose to quote. An article from the Nordic Center in 2005 analyzing references in the published literature on allergen avoidance showed clearly that most authors did not consider the first 2 meta-analyses useful contributions to the literature.¹⁷ It appears, however, that some authors believe meta-analyses have a special status that puts them above normal academic criticism.

There are of course many ways in which a meta-analysis could reach an incorrect conclusion. Some are well recognized such as poor screening of the literature, inappropriate statistical analysis, and poor quality of the studies being analyzed.¹⁸ The Cochrane Library has developed an excellent reputation for its screening techniques and statistical analysis, but also has generated controversy at times.¹⁹

Successful protocols for allergen avoidance are multifaceted.² Not surprisingly, there is a high degree of variability between studies on avoidance, and the interventions are not easy to maintain without extensive education. Many of the patients are allergic to more than 1 allergen, and it is very difficult if not impossible to provide education about appropriate avoidance measures while maintaining the structure of a controlled trial. The problems with attempting to carry out avoidance as a controlled trial are illustrated very well by a recent avoidance study on allergic rhinitis.²⁰ In that study, the allergen-proof covers were evaluated as “part of a program that included washing and cleaning bedding weekly in water that is 60°C as well as cleaning, heating and ventilating the house according to international guidelines.” The result was inevitably that both groups (ie, those with active or placebo covers) experienced highly significant improvement.²⁰ Some authors have suggested that patients should not be skin-tested before the study because the demonstration of a positive skin test result will inevitably lead to a change in behavior. Similarly we have argued that a home visit can have an effect on behavior of the family.²¹ For these and other reasons, there are bound to be differences of opinion about which avoidance studies provide useful information.

Given the variability of published studies on allergen avoidance, it is reasonable to ask whether meta-analysis can be used. The variability applies to the evaluation of patients, the intervention used, and the assessment of outcome. Meta-analysis is only valid when the studies are comparable, and this may not be true for the successful studies on allergen avoidance. The most recent meta-analysis may turn out to be important for a reason not envisaged by the authors. This analysis illustrates the ways in which decisions about either the inclusion or the evaluation of different studies within the meta-analysis can warp the result.⁷ The new analysis is clothed in elegant language about the search techniques used and the statistical analysis. It is not until the details are examined that the questions arise. I would like to draw attention to the analysis of 3 studies. The article by Woodcock et al²² was designed to answer whether a single intervention—that is, covers on the mattress and pillows—would be successful. The study did not perform skin tests before enrollment, involved almost no education, only visited a minority of the homes, and did not achieve a significant decrease in mite exposure at 1 year. Despite these problems, this negative study was included

in the meta-analysis. By contrast, the study of Morgan et al,²³ which reported a significant clinical benefit, was excluded because those authors had included avoidance measures for allergens other than mites. For this to be a rational argument for exclusion, the meta-analysis should include only studies in which all the patients were monospecifically sensitized to mites. The analysis of another study is equally troubling. In the 1998 meta-analysis, the study by Ehnert et al¹⁴ from Berlin was excluded because the primary analysis of that study was BHR.⁹ In the 2001 meta-analysis, the same study was reported as positive.¹⁰ In 2008, in a convoluted analysis, the meta-analysis halved the number of controls analyzed for each of the intervention groups and managed to reach a negative conclusion.⁷ The Berlin study had a control group and 2 intervention groups. One of the intervention groups used a chemical foam that had no effect on mites in their study or in other studies that used the same treatment.¹⁴ By contrast, the protocol that included education and physical barriers produced a greater than 90% reduction in mite concentrations in the dust and a highly significant decrease in BHR.¹⁴ Thus, for these 3 studies (ie, Woodcock et al,²² Morgan et al,²³ and Ehnert et al¹⁴), there is no consistency in the way the meta-analysis included, excluded, or analyzed the reports.^{14,22,23}

That the meta-analysis on mite avoidance can be criticized is not surprising. Equally it is not surprising that the authors, who have spent considerable effort analyzing the literature, would feel disappointed that their work is not widely quoted.^{4,6,17} However, more troubling is the question of whether the Nordic Cochrane Center would use the reputation of meta-analysis to pursue an agenda with the intent of creating controversy.

In conclusion, it seems clear that the recent meta-analysis is not a useful contribution to our field. There is a whole series of studies on allergen avoidance that have reported prolonged decrease in allergen exposure and positive clinical results. Each of these studies have problems of some kind, but that is almost inevitable because of the nature of the interventions recommended.^{12-14,21,23-25} I believe that the conclusions of the NAEPP guidelines are correct and that a comprehensive program designed to reduce exposure to relevant indoor allergens should be recommended as part of the management of asthma.

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