

Towards evidence-based practice of allergy and clinical immunology: applying an evidence-based medicine approach to allergen avoidance

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Abbreviation

EBM evidence-based medicine

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In recent years we have witnessed a daunting proliferation of biomedical knowledge. Illimitable research findings unfurl across the pages of scientific journals and lay publications. Studies use a variety of methods that differ in quality, and their findings are often contradictory. Individual projects add to the literature base, but are rarely definitive because of varying contexts and small sample sizes. Traditional means of staying abreast of medical knowledge no longer measure up, and the demands on clinicians and researchers to stay current in any field grow increasingly burdensome [1]. Recent surveys have suggested that in order for a general practitioner to keep up with important developments in medicine, he or she will need to read 19 articles a day, every day, 365 days a year! [2].

The practice of evidence-based medicine (EBM) may hold a solution to the problem. EBM seeks to integrate individual clinical expertise with the best available external clinical evidence from systematic research. Clinical expertise is reflected in the accurate diagnosis and thoughtful recognition of patients' individual circumstances in planning their care. The best available external clinical evidence connotes clinically relevant research, often from the basic sciences of medicine, but above all from clinical investigation, into the accuracy and precision of diagnostic procedures, the power of prognostic markers, and the efficacy and safety of clinical interventions. External clinical evidence validates or refutes previously accepted procedures and treatments and replaces them with new ones thought to be more

effective [2]. The use of evidence generated from systematic reviews and meta-analyses is an integral part of the practice of EBM [3]. EBM should help reduce the time between successful clinical trials of a new treatment and its implementation in the clinic. Once the process is practised and learned well, it will save time by compiling and synthesizing the needed information. It will make staying current with new developments in medicine less demanding [2].

The EBM process involves the questioning, searching, and appraising of publications, and then applying the results and performing a self-evaluation. The five steps to the EBM process are as follows: (1) the formulation of a focused clinical question; (2) the search for and retrieval of scientific evidence; (3) an evaluation of the discovered evidence; (4) the application of evidence-based conclusions; and (5) an evaluation and presentation of the EBM process. The last step allows the practitioner of EBM to undergo self-evaluation. EBM emphasizes the need for clinical and communication skills required to obtain and assess the patient's history, symptoms, and clinical findings, and to recognize and integrate his or her expectations into the therapeutic plan. The entire process relies, in large part, on formulating a focused clinical question that addresses a particular gap in the knowledge. To provide guidance in formulating a clinical question, 'PICO' is applied. 'P', Patient population: on what group do I want information? 'I', Intervention (or exposure): the effect of what medical event do I want to study? 'C', Comparison: compared with what? Better or worse than no intervention at all? Better than another intervention? 'O', Outcomes: what is the effect of the intervention? Combining the four PICO segments should result in a focused clinical question for a given patient or group of patients.

A detailed discussion of the five steps is beyond the scope of this review. However, as an example, we will evaluate the strength of the evidence (step 3) from two recent publications, Rijssenbeek-Nouwens *et al.* [4•] and Koopman *et al.* [5•], that challenge the established tenets of our profession. We urge all readers to examine both papers on their own, but for the moment we will summarize their findings in the conventional non-EBM narrative form.

Prevailing wisdom holds that asthma symptoms and measures of lung function improve in sensitized patients when they avoid aeroallergens [6–9]. However, despite documenting a significant reduction in Der p 1 concentrations in the dust obtained from the bedrooms of patients placed on an active regimen of dust avoidance for a full year, Rijssenbeek-Nouwens and colleagues [4••] did not find a significant decrease in the patients' bronchial hyperresponsiveness. Their results suggest that the regimen currently advocated for dust mite avoidance is ineffective in suppressing the disease activity of patients with moderate to severe asthma. Koopman *et al.* [5••], in a large, randomized, placebo-controlled, birth cohort study, confirmed that a simple house dust mite avoidance regimen reduced a young child's exposure to mite allergens; however, the authors were unable to demonstrate a protective effect of this practice on the prevalence and severity of respiratory symptoms, atopic dermatitis, and atopic sensitization in the first 2 years of life.

Our task is to assess the validity of the evidence presented by the two papers. To accomplish this we may refer to a web page maintained by the Centre for Evidence Based Medicine at the University of Toronto (<http://www.cebm.utoronto.ca>), which provides worksheets for assessment and statistical calculations relating to diagnosis, harm, prognosis, and therapy, as well as guidelines for conducting systematic reviews of therapy.

Question 1: Was the assignment of patients to treatment randomized and was the randomization list concealed?

Randomization helps to ensure that patients in treatment groups are similar at the beginning of the study. It balances the groups for factors (good or bad) that, if unequally distributed among study groups, could increase, decrease or nullify the treatment effect. The randomization list should be concealed from the clinicians who enroll patients into the trial. Both studies were randomized, although neither report provides any details of the randomization process.

Question 2: Was the follow-up of patients sufficiently long and complete?

The duration of follow-up should be sufficiently long for the outcomes of interest to become evident. The investigators should provide details on the number of patients in follow-up and on the outcomes of patients who dropped out of the study. If it is uncertain what effect the dropouts may have had on the study results, a 'sensitivity analysis' for a 'worst case scenario' should be performed. For example, for the group that did better, all the patients who were lost to follow-up should be assumed to have done poorly. For the group that did worse, those lost to follow-up should be assumed to have

done well. If the result still supports the original conclusion, then the follow-up was sufficiently complete. A 20% (or higher) loss to follow-up is a cause for concern.

The 1-year duration of the study used by Rijssenbeek-Nouwens *et al.* [4••] is typical for protocols of this type. However, it should be noted that 26% of the placebo mattress cover group, and 16% of the anti-allergic mattress cover group were lost to follow-up. The 2-year study period of Koopman *et al.* [5••] appears to be adequate in length, although additional follow-up is warranted to determine the effects of the intervention later in life. At the end of the 2-year follow-up, data were available for 82% of the active group and 75% of the placebo group.

Question 3: Were all patients analyzed in the groups to which they were randomly assigned?

Anything that occurs after randomization can affect the possibility that a patient has an outcome event. Therefore, the investigators should analyse the patients in the groups to which they were randomly assigned. This 'intention to treat' analysis preserves the value of randomization. An intention to treat analysis was not performed in either study. Koopman *et al.* [5••] arbitrarily divided the patients into groups (independently of randomization) for analysis.

Question 4: Were patients and clinicians kept blind to treatment?

The blinding of clinicians and patients helps to prevent 'additional' treatment. Knowledge on the part of patients or clinicians of the treatment assignment can change the behavior of both patients and clinicians. Clinicians may have the expectation that the treatment is effective and act accordingly. Patients may do the same, undermining the evaluation of effectiveness of the treatment under investigation. Both studies were double-blind; in the study by Rijssenbeek-Nouwens *et al.* [4••] neither patients nor clinicians knew who received the anti-allergic mattress covers; in the study by Koopman *et al.* [5••] neither patients nor clinicians knew who received the mite-impermeable mattress covers.

Question 5: Were groups treated equally, apart from the experimental therapy?

Both reports indicated that this was true.

Question 6: Were the groups similar at the start of the trial?

If the groups are not similar, then a determination should be made as to whether an adjustment was carried out for potentially important confounding factors. Rijssenbeek-

Nouwens *et al.* [4**] made no mention of the similarity of the two groups immediately after randomization ($N=19$, both groups). The authors stated that there were 'no significant differences between the two groups in the provocative concentration of histamine resulting in 20% fall in forced expiratory volume in 1 s (PC_{20}), forced expiratory volume in 1 s, peak expiratory flow, and medication used'. However, the mean age for the remaining patients (after 1-year follow-up) in the placebo group ($N=14$) was 25 years, and in the active group ($N=16$) it was 33 years. There was also an imbalance in the sexes, with 10 men in the placebo group, and seven men in the active group. There is thus a potential that groups may have been different at the start of the trial. For Koopman *et al.* [5**] there was a significant difference at the start of the trial between the intervention and non-intervention groups in the percentage of boys, and in the percentage of patients exposed to pets.

When studies fail to meet any of the criteria discussed above, then it must be determined whether the flaws are significant and threaten the validity of the findings. If this is the case, then other work must be reviewed for evidence that addresses the clinical question at hand. For a question about prognosis, we need proper follow-up studies of patients assembled at a uniform, early point in the clinical course of their disease. The two studies discussed above raise important doubts about the recommendations that we make to our patients. If we are to continue to ask our patients to incorporate environmental controls in their daily lives, then we must find other data or carry out properly designed research with robust clinical outcomes. Interestingly, a meta-analysis of randomized trials of the effects of house dust mite control on asthma has been carried out [10]. The main outcome measures were the number of patients whose allergic symptoms improved, an improvement in asthma symptoms, and an improvement in the peak expiratory flow rate. Twenty-three studies were included: six used chemical methods to reduce exposure to mites; 13 used physical methods; four used a combination. In total, 41 out of 113 patients exposed to treatment interventions improved compared with 38 out of 117 in the control groups (odds ratio 1.20, 95% confidence interval (CI) 0.66–2.18). The standardized mean difference for an improvement in asthma symptoms was 0.06 (95% CI 0.54–0.41). For the peak flow rate measured in the morning the standardized mean difference was 0.03 (0.25–0.19). This difference between the treatment and the control groups corresponds to 3 l/min (95% CI 25–19 l/min). The authors concluded that the current methods for the reduction of exposure to house dust allergens are ineffective as prophylactic treatment for asthma in patients sensitive to mites [10].

We do not wish to suggest that house dust mite avoidance plays no role in the management of patients with asthma,

but rather that current practice appears to be ineffective. If it is to be continued, supporting evidence must be generated. Otherwise, it should be changed or abandoned. EBM provides a framework for the critical appraisal and evaluation of interventions already in use. It may help us reach agreement on methodologies to settle whether a given treatment causes more good than harm or is ineffective. By identifying questions that need to be answered, EBM may help us generate a list of priorities for future research. In the care of asthma, questions concerning outcomes such as the resolution of acute exacerbations and changes in the quality of life are increasingly being answered on the basis of sound and agreed-upon methodology. On the other hand, we have yet to reach consensus regarding such fundamental issues as the measurement of response to therapy, assessment of control or progression of disease, and the role of comorbid conditions. Although we are gaining insight into the consequences of allergen exposure, we have an urgent need for a disciplined, uncompromising examination of the methods to achieve allergen control.

Ill habits gather by unseen degrees, –
As brooks make rivers, rivers run to seas.
John Dryden

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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