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Environmental interventions for mite-induced asthma: a journey between systematic reviews, contrasting evidence and clinical practice

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SUMMARY

House dust mites (HDM) are one of the most important sources of indoor allergens worldwide. Exposure to high environmental levels of dust mite allergen is associated with an increased risk of sensitization, asthma and deterioration of lung function. On the basis of these data, it would be logical to assume that asthmatic patients with mite allergy could benefit from a reduction of exposure to these allergens. Several environmental prophylactic actions against HDM, either physical or chemical have been tried, alone or in different combinations. However, a recent Cochrane Systematic Review did not detect specific clinical benefits from the use of prophylactic environmental measures in asthmatic patients sensitive to HDM and concluded that such measures can no longer be recommended as they are ineffective. This paper presents the results of a web-based questionnaire, administered to more than 200 Italian paediatricians, and shows that physicians' behaviour in real life is very far from SR conclusions. It also summarizes the indications of the most authoritative guidelines, highlighting some contrasting evidence and some significant weaknesses of the SR, that could make the final conclusions at least uncertain. In the light of these findings, it seems that the recent Cochrane SR cannot be considered the definitive document on the uselessness of environmental prevention of mite-related asthma.

Introduction

House dust mites (*Dermatophagoides* genus, family *Pyroglyphidae*) are one of the most important sources of indoor allergens worldwide (1). HDM allergens are widely distributed in homes, but are particularly present in beds and beddings (2), which represent an ideal environment for their growth due both to the microclimatic conditions of temperature and humidity, and to the presence of abundant food, represented by the desquamation of human skin.

Exposure to high environmental levels of dust mite allergen in early life is associated with an increased risk of sensitization to mites at 3-7 years of age (3). Recent data show that a relevant proportion of high risk children are

already sensitized in preschool years (4) and that sensitization to mites is an important risk factor for developing asthma (5,6). Exposure to high environmental levels of mite allergens in sensitized subjects is associated with an increased prevalence of bronchial hyper-responsiveness, asthma, and deterioration of lung function (7,8). Up to 85% of asthmatics are HDM allergic (9).

On the basis of these data, it would be logical to assume that asthmatic patients with mite allergy would benefit from a reduction of exposure to these allergens. In fact periods spent at high altitude, where the environmental concentration of mites is low, are associated with an improvement in lung function (10). Over the past 30 years, several environmental prophylactic actions against HDM, either physical (air, freezing, heating, washing, barrier

methods, air filters and ionizers, etc.), or chemical (use of acaricide substances), have been tried, alone or in different combinations.

Is there sufficient evidence to suggest that such preventive measures are effective for asthmatic patients? If one looks at the conclusions of the recent Cochrane Systematic Review (11) the answer appears to be no. The authors considered 55 trials (3121 patients). Thirty-seven of these trials studied physical methods, mainly by covering mattresses with waterproof fabrics (26 trials), 10 investigated chemical methods and 8 a combination of the two. In general, the quality of the studies concerned was not considered good, as the authors believed that potential bias might have led to an overestimate of the effects of the intervention (12).

By considering the morning peak flow (the most frequently used outcome measure, $n = 1665$ patients) Gotzsche et al. did not detect specific clinical benefits in asthmatic patients sensitive to house dust mites deriving from the use of prophylactic environmental measures in terms of the number of patients showing improvement (risk ratio 1.01, 95% CI 0.80-1.27), asthma symptom scores (SMD -0.06, 95% CI -0.16 to 0.05) and drugs intake (SMD -0.05, 95% CI -0.17-0.07); in fact, the standardized mean difference (SMD) was 0.01 (95% CI -0.08-0.11). They conclude that such measures can no longer be recommended as they are ineffective.

How is current medical practice?

In order to get a picture of what happens in real life, we invited paediatric allergists subscribing to two popular discussion forums (www.apalweb.it and www.siaip.it) to answer some questions regarding their attitudes regarding environmental prevention measures in cases of asthma and sensitization to mites. Two questionnaires were sent out: one concerning the most common physical methods and the other concerning the use of acaricide substances. The results, unpublished, are visible on the website of the Italian Society of Pediatric Allergology (SIAIP).

Two-hundred-fourteen allergists responded to the first questionnaire, the sample being represented mainly by family paediatricians and Hospital doctors, most of them involved in clinical allergy. Nearly $\frac{3}{4}$ of the sample routinely recommend the use of physical tissue barriers to asthmatic patients allergic to HDM, and 80% suggest washing the barriers regularly at high temperatures (60 degrees Celsius or more). Sixty per cent of them also rec-

ommend washing bedding weekly, at the same temperatures, together with the use, if possible, of a vacuum cleaner with high efficiency filters (HEPA).

The majority (92%) recommend removing carpets and carpeting from the bedroom, and < 50% advised ventilating the home and controlling the sources of humidity. When this was unfeasible, about one half of the sample advised patients to purchase a dehumidifier, while hardly anyone recommend purchasing an air cleaner.

One-hundred-eleven doctors responded to the second survey (use of acaricides): over 90% did not recommend the use of chemical acaricides on mattresses and pillows, or on carpet and chairs.

What do the guidelines say?

The U.S. guidelines for the diagnosis and management of asthma (EPR3, 2007) suggests for patients with asthma and mite allergy, covering the mattress and pillows with waterproof tissue specific for dust mites, washing sheets and blankets weekly with hot water (> 54 °C) and, possibly, reducing the humidity of the environment, removing carpets and felt animals (13).

The British Thoracic Society guidelines on asthma (14) consider the conclusions of the Cochrane Systemic Review (SR), but underline that the great heterogeneity of the studies included in the review, in terms of action taken and outcomes measured, makes the interpretation of the SR difficult, considering also the fact that some good quality trials using waterproof coatings included in the SR, detected both clinical and functional benefits in asthmatic patients (15, 16). The BTS Guidelines conclude that mite prevention measures cannot be presently considered a cost-effective beneficial intervention, but the fact that many families are strongly motivated to put into practice interventions aiming to reduce the contact with allergens has to be considered. In such cases, a complete system of barrier fabrics for the bed, removing carpets, removing stuffed toys from the bed, high-temperature washing of bed linen, acaricides on sofas and armchairs, and a good ventilation with or without dehumidification should be suggested.

The GINA guidelines (updated to 2011) point out that the HDM allergy is a universal health problem (17) and that, due to the fact that HDM live and breed in homes, it is difficult to reduce their concentration and impossible to eradicate them. Thus a single preventive intervention has little chance of being effective, at least in adults.

There is some evidence of efficacy of a single preventive intervention (waterproof covers) in children (15), but the Guidelines repeatedly underline the concept of an integrated approach between the various methods that have been most able to reduce the concentration of allergen, such as waterproof covers, washing bedding at high temperature (55–60 °C), carpet removal, air purifiers with HEPA filters.

A critical review of the systematic review

The Systemic Review of Gotzsche et al. (11) shows significant “weaknesses” that could make the final conclusions at least uncertain, due to a remarkable heterogeneity of approach and methodological flaws. In fact, only 26 of the 55 studies included used waterproof covers for mattresses, and only in 11 case trials the intervention led to a significant reduction of the concentration of allergen. Small numbers of patients were enrolled in 50% of the studies considered. The majority of studies measured changes in peak flow as the primary events, a parameter that does not appear particularly helpful in asthma self-management programs or directly correlated with the severity of symptoms because of its extreme variability (18).

The choice of including some studies (19) and excluding others (20, 21) seems questionable.

In particular, the negative study by Woodcock et al (19) enrolled a significant number of subjects, thus lending greater weight to the results of the meta-analysis. This study was included despite relevant methodological problems (skin testing not performed before recruitment, covers definitely not waterproof, no educational intervention, no reduction in the concentration of mites in the course of one year).

On the other hand, the controlled trial by Murray et al (20), showing an effect of preventive measures, was excluded because randomisation was not clearly described, a characteristic shared by other studies which instead were included (22, 23).

Likewise the study by Morgan et al (21), reporting a significant clinical benefit, was excluded from the analysis despite the large sample size and excellent methodology, because it included avoidance measures for allergens (cockroach) other than HDM.

If this was an admission criterion, the meta-analysis might have included only studies in which all patients were monosensitized to mites, which is not the case.

A previous SR by Gotzsche et al (24), reaching negative conclusions about the benefits of environmental measures for asthmatic HDM sensitized patients, was questioned on the BMJ.

In summary, the main critical points of the SR are: the effectiveness of prophylactic measures may also depend on the duration of disease, being reduced in patients whose asthma began a long time before (25); studies that were not able to obtain a decrease in the concentration of mites should not be included in the SR; it is clear that in these cases the clinical improvement could not be achieved (26);

almost all trials had low statistical power, due to the small number of patients enrolled, which makes the results unreliable (27);

the SR included mainly studies in which the primary outcome was a modification in PEF values and excluded those considering bronchial hyper-responsiveness (BHR) as a more reliable marker of the efficacy of preventive measures (20, 28–30).

Platts-Mills (31) points out that a further meta-analysis published by the same authors in 2001 (32), reported a significant benefit from physical measures in asthmatic mite-allergic patients ($p = 0.02$), thus amending some problems of the meta-analysis published the previous year, but despite this, the authors curiously continued to report negative findings.

Conclusions

In the light of these findings, it seems that the recent Cochrane SR cannot be considered the definitive document on the uselessness of environmental prevention of mite-related asthma. We believe, however, that interventions aimed at reducing the level of environmental allergens can be insufficient singularly but show a greater chance of success in combined form (21). As pointed out by the GINA guidelines, mites are present throughout the home and it is virtually impossible to eradicate them if, as evidenced by a study conducted in Denmark on the life cycle and the developmental stages of mites, there is the possibility of contamination from the outside environment (33).

In conclusion, in keeping with the main guidelines and with the usual behaviour of the vast majority of specialists, the best strategy is to reduce the level of exposure of asthmatic patients sensitized to mites by implementing all the preventive measures (tissue barrier, periodic cleaning

of mattress covers at high temperatures and weekly cleaning of bedding, frequent ventilation of environments, removal of carpets and stuffed animals, reducing sources of moisture and possible use of HEPA vacuum-cleaners.

References

- Hart BJ, Whitehead L: Ecology of house dust mites in Oxfordshire. *Clin Exp Allergy* 1990; 20: 203–209
- Dharmage S, Bailey M, Raven J, et al: Residential characteristics influence Der p 1 levels in homes in Melbourne, Australia. *Clin Exp Allergy* 1999; 29: 461–469.
- Wahn U, Lau S, Bergmann R, et al: Indoor allergen exposure is a risk factor for sensitization during the first three years of life. *J Allergy Clin Immunol* 1997;99(6 Pt 1):763–9.
- Lodge CJ, Lowe AJ, Gurrin LC, et al: House dust mite sensitization in toddlers predicts current wheeze at age 12 years. *J Allergy Clin Immunol*. 2011;128(4):782–788.e9
- Corver K, Kerkhof M, Brussee JE, et al: House dust mite allergen reduction and allergy at 4 yr: follow up of the PIAMA-study. *Pediatr Allergy Immunol* 2006;17(5):329–36
- Illi S, von Mutius E, Lau S, et al: Multicentre Allergy Study (MAS) group. Perennial allergen sensitisation early in life and chronic asthma in children: a birth cohort study. *Lancet*. 2006 Aug 26;368(9537):763–70
- Sporik R, Holgate ST, Platts-Mills TA, et al: Exposure to house-dust mite allergen (Der p 1) and the development of asthma in childhood. *N Engl J Med* 1990;323:502–7.
- Platts-Mills TA, Thomas WR, Aalberse RC, et al: Dust mite allergens and asthma: report of a second international workshop. *J Allergy Clin Immunol* 1992;89(5):1046–60.
- Gregory LG, Lloyd CM: Orchestrating house dust mite-associated allergy in the lung. *Trends Immunol*. 2011 Sep;32(9):402–11
- Peroni DG, Boner AL, Vallone G, et al: Effective allergen avoidance at high altitude reduces allergen-induced bronchial hyperresponsiveness. *Am J Respir Crit Care Med* 1994;149(6):1442–6.
- Gøtzsche PC, Johansen HK: House dust mite control measures for asthma. *Cochrane Database of Systematic Reviews* 2008, Issue 2. Art. No.: CD001187
- Jadad A. From individual trials to groups of trials: reviews, meta-analysis and guidelines. In *Randomised Controlled Trials* BMJ Books 1998.
- <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf>, pag.129
- <http://www.brit-thoracic.org.uk/guidelines/asthma-guidelines.aspx>
- Halken S, Host A, Niklassen U, et al: Effect of mattress and pillow encasings on children with asthma and house dust mite allergy. *J Allergy Clin Immunol*. 2003;111(1):169–76.
- Van Den Bemt L, Van Knapen L, De Vries MP, et al: Clinical effectiveness of a mite allergen-impermeable bed-covering system in asthmatic mite-sensitive patients. *J Allergy Clin Immunol*. 2004;114(4):858–62
- Platts-Mills TA, Thomas WR, Aalberse RC, et al: Dust mite allergens and asthma: report of a second international workshop. *J Allergy Clin Immunol*. 1992 May;89(5):1046–60
- Powell H, Gibson PG: Options for self-management education for adults with asthma. *Cochrane Database Syst Rev* 2003; (1):CD004107.Wensley D, Silverman M. Peak flow monitoring for guided self-management in childhood asthma: a randomized controlled trial. *Am J Respir Crit Care Med* 2004;170:606–12
- Woodcock A, Forster L, Matthews E, et al: Medical Research Council General Practice Research Framework. Control of exposure to mite allergen and allergen-impermeable bed covers for adults with asthma. *N Engl J Med*. 2003 Jul 17;349(3):225–36
- Murray AB, Ferguson AC: Dust-free bedrooms in the treatment of asthmatic children with house dust or house dust mite allergy: a controlled trial. *Pediatrics*. 1983 Mar;71(3):418–22,
- Morgan WJ, Crain EF, Gruchalla RS, et al: Inner-City Asthma Study Group. Results of a home-based environmental intervention among urban children with asthma. *N Engl J Med*. 2004 Sep 9;351(11):1068–80
- Frederick JM, Warner JO, Jessop WJ, et al: Effect of a bed covering system in children with asthma and house dust mite hypersensitivity. *Eur Respir J*. 1997 Feb;10(2):361–6
- Carswell F, Birmingham K, Oliver J, et al: The respiratory effects of reduction of mite allergen in the bedrooms of asthmatic children—a double-blind controlled trial. *Clin Exp Allergy*. 1996 Apr;26(4):386–96.
- Gøtzsche PC, Hammarquist C, Burr M: House dust mite control measures in the management of asthma: meta-analysis. *BMJ* 1998;317:1105–1110
- Cloosterman SGM, van Schayck OCP: Effectiveness of measures depends on stage of asthma. *BMJ* 1999;318:870. (letter)
- Platts-Mills TAE, Chapman MD, Wheatley LM: Conclusions of meta-analysis are wrong. *BMJ* 1999;318:870. (letter)
- Muncer SJ: Power dressing is important in meta-analysis. *BMJ* 1999;318:870. (letter)
- Walshaw MJ, Evans CC: Allergen avoidance in house dust mite sensitive adult asthma. *Q J Med* 1986;58:199–215.
- Ehnert B, Lau-chadendorf S, Weber A, et al: Reducing domestic exposure to dust mite allergen reduces bronchial hyperactivity in sensitive children with asthma. *J Allergy Clin Immunol* 1992;90:135–8.
- Platts-Mills TA, Tovey ER, Mitchell EB, et al: Reduction of bronchial hyperactivity during prolonged allergen avoidance. *Lancet* 1982;2:675–8.)
- Platts-Mills TA: Allergen avoidance in the treatment of asthma: problems with the meta-analyses. *J Allergy Clin Immunol*. 2008 Oct;122(4):694–6
- Gøtzsche PC, Johansen HK, Burr ML, et al: House dust mite control measures for asthma. *Cochrane Database Syst Rev* 2001;3:CD001187
- Hallas TE: House-dust mites in our homes are a contamination from outdoor sources. *Medical Hypotheses* 2010;74:777–779