

Continuous avoidance measures with or without acaricide in dust mite-allergic asthmatic children

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Background: Improvement in the quality of life in the Western world and increased time spent indoors by children have enhanced the spread of house dust mites and increased the exposure time for sensitive children. Also, exposure to house dust mites in infancy and subsequent development of childhood asthma have been clinically linked. Recently, new acaricides have been developed.

Objective: To test the efficacy of the new acaricide (esdepallethin and piperonyl butoxide—"Acardust") combined with environmental control compared with continuous house dust mite avoidance measures.

Method: Forty-six house dust mite-allergic, asthmatic children were evaluated for 6 months in a prospective, randomized, double-blind, and placebo-controlled study. Patients were randomly allocated to active and placebo acaricide treatment combined with avoidance measures, whereas only continuous avoidance measures were taken in the third group. Symptom score, medication usage, and peak flow measurements were recorded daily. The amount of house dust mite allergen in the dust vacuumed from the bedrooms was also measured.

Results: Morning and evening peak expiratory flow rates and forced expiratory volume in one second remained unchanged throughout the study period. In all groups, the symptom scores improved significantly, whereas the amount of house dust mite allergen decreased significantly at the end of the trial.

Conclusions: Continuous house dust mite avoidance measures have a significant positive effect on the symptomology of children with mild or moderate asthma. "Acardust" combined with continuous house dust mite avoidance measures is not more effective than continuous house dust mite avoidance measures alone in the treatment of house dust mite-allergic, asthmatic children.

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INTRODUCTION

Allergy to *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* is an important causative factor for

asthma in childhood. The microclimate of the modern Western world houses (fitted carpets, soft furnishings, central heating, double glazing, and often poor ventilation) has provided the ideal habitat for the house dust mite.¹ Indeed, the conclusions of the Second International Workshop on dust mite allergens and asthma² emphasized that mite sensitivity is strongly associated with asthma. In some areas, up to 80% of asthmatic children or young adults have strongly positive skin tests to mite extracts.

The improvement in asthma that occurs in hospital or at high altitude sanatoria can be attributed to reduced exposure to mite allergens.³ Reported studies on environmental measures un-

dertaken in patients' houses have been successful^{3,4} or debated.^{5,6} Those studies are important because they demonstrate the need for continuous dust mite avoidance measure procedures to reduce mite exposure. Indeed, clinical improvement can be achieved at home only if continuous dust mite avoidance measure procedures are taken. Simply advising patients to vacuum clean more often reduces neither symptoms nor mite-allergen levels.

Recently, an association between the presence of asthma and $>2 \mu\text{g}$ group I allergen/g of dust in the houses of the asthmatic children has been substantiated in case report studies^{7–9} and in a prospective study.¹⁰ The semi-quantitative assay (Acarex test) requires no expertise and can be completed in about two minutes. Guanine is the major nitrogenous excretory product of Arachnids, and measurement of guanine in house dust should give an indication of the amounts of mite allergen present.^{11,12} There is evidence also that use of the test in conjunction with eradication procedures increases patient compliance.¹³

In the last decade, several products to kill house dust mites have been marketed by various companies. The investigation of a wide variety of chemicals has shown that the killing of house dust mite under laboratory conditions is a relatively simple task. Since there are few long-term, longitudinal, randomized control clinical trials, the following study was designed to test the efficacy of an acaricide-containing aerosol of esdepallethin and piperonyl butoxide in comparison with continuous household avoidance control.

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MATERIAL AND METHODS

Protocol

The 6-month study was prospective, randomized, double-blind, and placebo controlled. The seasons comprised winter and spring. Asthmatic children, aged 6 to 18 years old, were enrolled in the study if the following criteria were met: (1) mild to moderate asthma (American Thoracic Society)¹⁴; (2) duration of asthma longer than 1 year; (3) documented diagnosis of reversible airway disease, ie, variation of forced expiratory volume in one second (FEV₁) or peak expiratory flow (PEF) of >15% (a) before and after inhalation of a β -adrenergic agonist, (b) before and after exercise, (c) diurnal variation; and (4) no cigarette smoking at home during the study period. Children were excluded from the study for the following reasons: (1) respiratory tract infection within the last month, (2) need for regular oral steroids, (3) use of oral or parenteral steroids within the last month, (4) need for regular antihistamines, (5) use of inhaled sodium cromoglycate or inhaled nedocromil sodium within the last month, (6) initiation of immunotherapy within the past 6 months, or (7) hospital admission due to asthma within the past 6 months.

Children from three pediatric health centers (Kfar Saba, Netanya, Petach-Tikva) were recruited. All three centers are located within a radius of 15 km along the seashore, and they all share similar weather conditions with respect to air temperature and humidity. Before enrollment in the study, patients who fulfilled the inclusion criteria were prick tested by a trained nurse under the supervision of a physician, and the same equipment and technique were used each time. Eleven inhalant allergens (Center Laboratories, Port Washington, NY) were applied to each child (mixed grasses, mixed trees, mixed weeds, mixed molds, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, house dust, cat, dog, feathers, and cockroach).

Table 1. Symptom Score Diary

Symptom	Score
Quality of sleep during night:	
Good	0
Awake once	1
Awake over course of time	2
Awake most of the night	3
Dyspnea	
No	0
Yes	1
Wheezing (check twice daily)	
No	0
Few	1
Many	2
Cough	
No	0
Few	1
Many	2
Sputum	
No	0
Little	1
Much	2
Rhinitis	
No	0
Present	1
Sneezing	
No	0
Present	1
Peak flow measurement (specify if bronchodilator preparations were taken 4 hours before measuring)	
Morning	
Evening	
School/kindergarten absence (days):	
Number of inhalations of salbutamol/terbutalin per day:	
Other medication(s) per day:	

Histamine hydrochloride (10 mg/mL) and sodium chloride (9 g/L) were applied as control solutions. The reactions were recorded after 15 minutes. Only children with positive skin reactions (wheal diameter >3 mm) to either or both house dust mite extracts were enrolled in the study.

On the first visit, patients were provided with a peak flow meter (Astech, Center Laboratories) and a daily diary (Table 1). After a run-in period of 2 weeks, children who had not met any of the exclusion criteria, had filled in at least 75% of the daily diary, and had an asthma score >2, were enrolled in the study.

After signing an informed consent, children were randomly divided into

three groups: (1) avoidance group, patients were given written instructions regarding environmental control of house dust mite (Table 2); (2) placebo group, patients were given written instruction regarding environmental control with placebo acaricide; (3) Acardust group, patients were given written instructions with active acaricide, containing aerosol or esdepallethin 0.9% and piperonyl butoxide 7.2% (Acardust, Scat, France).

The placebo group received a canister of acaricide identical to that of the Acardust group supplied by the company. Both placebo and active acaricide were applied twice to the mattress and the floors, according to the manufacturer's instructions (at the beginning of the study and 3 months later). The actual application of the acaricide spray was monitored by ascertaining that the canister was empty, and at each visit, the parents were checked to ensure that all dust avoidance measures were done appropriately.

The study lasted 6 months, during which patients completed a daily symptom score and recorded their morning peak flow and evening peak flow results (Table 1). Upon their monthly visits to their pediatrician, patients were physically examined and new diaries were supplied. House dust specimens were collected and examined for their guanine content at the beginning and at the end of the study.

Patients were asked to vacuum at maximal speed and to use a new empty collecting bag. They were instructed to vacuum the dust for six minutes from the lower side of the mattress, for three minutes from its upper sides, and for five minutes from the bedroom floor. The amount of house dust antigen was semi-quantitatively estimated using the Acarex test (Fison Corp, Bedford, Mass.). Acarex is a dipstick technique with litmus activator with methanol and a diazo compound.

Guanine was extracted from raw dust by potassium hydroxide, and the amount present was estimated by the intensity of color change on the test strip. For the purposes of the test, it was presumed that the guanine thus

Table 2. Instructions to Prevent Dust Accumulation in the Children's Bedrooms

Change bedclothes, ie, mattress, rugs, curtains, upholstered furniture, toys, etc because they are a major source of house dust accumulation. Every object prone to accumulate dust is to be removed. Pillows or blankets made of goose, feather, or wool are forbidden to be used. Use only synthetic blankets and pillows.

Clothing should be stored in closed cupboards and it is advised to decrease the number of garments hanging in the cupboard. Books left in the room should be stored in a closed cabinet.

Dust mite avoidance measures:

- Daily: 1. Wash the floors and dust furniture with a damp cloth.
2. Shake the bed clothes outside the bedroom while the child is not around. Likewise, bed clothing should be left on the window sill.
- Weekly: 1. Systematically vacuum the mattresses on both sides.
2. It is necessary to thoroughly clean (with a damp cloth) shelves, pictures, furniture, walls, drawers, and cupboards.
3. Change the bed sheets and wash them in a washing machine at 60 °C or hotter.
- Monthly: 1. Wash blankets and pillows at 60 °C.

identified, comes from mite feces and that guanine levels related to the antigenicity of the dust.¹³

The results were rated as: none = 0, very weak = 1, weak = 2, moderate = 3, and strong = 4. On the last visit of the study, the parents were asked to grade the severity of their child's asthma compared with the period before starting the study, according to: same, better or worse.

Statistical Analysis

Comparisons between the treatment groups were made using an unpaired t test and analysis of variance as appropriate. Paired t test was used when comparing the result at the beginning and the end of the treatment period. Power analysis was calculated for the primary efficacy variable—the Acarex test (power calculated on zar 2nd ed). Parents' assessment at the end of the study was evaluated using the Chi Square test.

RESULTS

One hundred twelve asthmatic children from the three pediatric health care centers were asked by their pediatrician to come to the first visit with the study principal investigator (AB), during the fall of 1993. Eighty-five asthmatic children (76%) were positive by prick test to both *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*, or to either. After 2 weeks of

a run-in period, 62 children started the study (the others did not complete a minimum of 75% of the daily diary). During the first 5 weeks of the study, 16 children dropped out (6 from the Acardust group, 4 from the placebo group, and 6 from the avoidance group) for the following reasons: 14, noncompliance; 1, irrelevant disease; and 1, change of residence. The demographic data of the 46 asthmatic children who finished the 6-month study are displayed in Table 3. There were 87% of the children who were exclusively prick test dust mite allergic, while the other 13% were positive to

other allergens and were equally distributed among the three groups.

Monitoring of the Allergenicity of House Dust Mite (Acarex test)

We examined 41 children's bedrooms' dust specimens. In all three study groups, there was a statistically significant improvement (mean score $\pm$ standard deviation) of the Acardust group at the beginning of the study, 3.6 ± 0.7 , and at the end, 3.3 ± 0.9 ; placebo group, 3.3 ± 0.6 to 2.9 ± 0.8 ; and avoidance group, 3.5 ± 0.6 to 2.7 ± 0.8 (Fig 1). The mean score improved in all groups from 3.5 ± 0.6 to 2.9 ± 0.9 ($P < .001$) (Fig 2). There was no statistical difference among the three groups regarding the allergenicity (the Acardust group showed less improvement in the absolute value of the test, but without statistical significance).

Power analysis indicates that there was 90% power to detect a difference as small as 1 unit and there was 80% power to detect a difference as small as 0.75 unit in the Acarex test (power calculated on zar 2nd ed).

Objective Measurements

FEV₁ (Fig 3). Overall, there was an increase in the mean FEV₁ from (73.5 ± 13.2)% at the beginning of the study to (78.2 ± 14.7)% at the end without statistical significance. There

Table 3. Patients' Demographic Data

Variables	Acardust Group N = 13	Placebo Group N = 17	Avoidance Group N = 16
Mean age, yr	9.2 $\pm$ 2.4	10.4 $\pm$ 2.6	11.8 $\pm$ 3.2
Age range, yr	(6.5–13)	(6–15)	(7–16.5)
Mean duration of asthma, yr	7.3 $\pm$ 2.7	6.8 $\pm$ 2.6	9.5 $\pm$ 4.3
<i>Family and atopy history</i>			
Atopy in the family N (%)	7 (54%)	10 (59%)	11 (69%)
Associated allergic rhinitis N (%)	5 (38%)	7 (41%)	7 (44%)
Seasonality of asthmatic attacks N (%)	5 (38%)	6 (35%)	8 (50%)
Carpet in the living room N (%)	5 (38%)	9 (53%)	4 (25%)
Dust as a trigger by history* N (%)	7 (54%)	10 (59%)	11 (69%)
<i>Baseline spirometry</i>			
FEV ₁ % predicted	72%	75%	72%
Morning peak flow (L/min)	222	220	290
Evening peak flow (L/min)	226	232	295

* Eighteen asthmatic children. Almost 40% of the children and their parents did not know at the beginning of the study that there is a relation between house dust mite and the severity of asthma.

was no difference among the three groups (including the spirometry results after 3 months).

Morning peak flow (Fig 4A). Overall, there was improvement in this parameter during all 6 months (from mean morning peak flow of 245 ± 85 at the beginning to mean morning peak flow of 282 ± 82 at the end) without statistical significance among the three groups and in the same group during time (Acardust $P = .95$; placebo $P = .7$; avoidance $P = .8$).

Evening peak flow (Fig 4B). Overall, there was a mean nominal increase from 253 ± 85 at the beginning to 291 ± 83 at the end, but without statistical significance. No difference was found among the three groups and within the same group over time.

Subjective Measurement

Symptom score and the use of inhaled β_2 agonists. There was a statistically significant decrease in the mean symptom score at the beginning (2.6 ± 2) relative to the end of the study (1.5 ± 1.5) ($P < .001$). There was no difference among the three study groups (Fig 5). There was also a small reduction in the amount of β_2 -agonists used by the children in all three groups during the study period. There was no significant difference in the use of β_2 -agonists among the three groups.

Other concurrent medication. There was no difference among the three groups regarding use of topical steroids and cromoglycate during the study period.

Parental Assessment

There was no statistical difference among the three groups (chi square test; Table 4).

DISCUSSION

In recent years, there is more conclusive evidence for the role of dust mite exposure in the sensitization to dust mite allergens and the development of asthma.^{15,16} Furthermore, over the last three decades, the amount of time spent indoors has increased, ventilation of houses has diminished, there are more furnishings, particularly carpets, and the mean temperature in the

houses has risen. All these changes are factors that may accelerate house dust mite survival. The conclusions of these impressive data are that house dust mite avoidance measures should be the first step in the preventive management of asthmatic children.¹⁷ It is not surprising that there have been intensive efforts to develop better techniques for reducing mite exposure (including new acaricides). These techniques should help every asthmatic child, especially those with positive prick test to *Dermatophagoides farinae* and/or *Dermatophagoides pteronyssinus* (in the present study, like many other previous studies,^{18,19} this accounts for about 70% to 80% of the asthmatic children).

In this randomized, double-blind, placebo-controlled 6-month study, we found no significant differences in the bedroom allergen content between using pyrethroids as acaricide or continuous dust mite avoidance measures. There were no significant changes in respiratory status as determined by objective criteria (FEV_1 and PEF).

The sensitivity of the study may not have been adequate to detect changes in patients with mild asthma, therefore we found no significant effect of house dust mite avoidance measures on pulmonary function, nevertheless improvement in subjective symptoms usually precedes improved lung function.^{20,21} Indeed in the present study, subjective evaluation for only 6

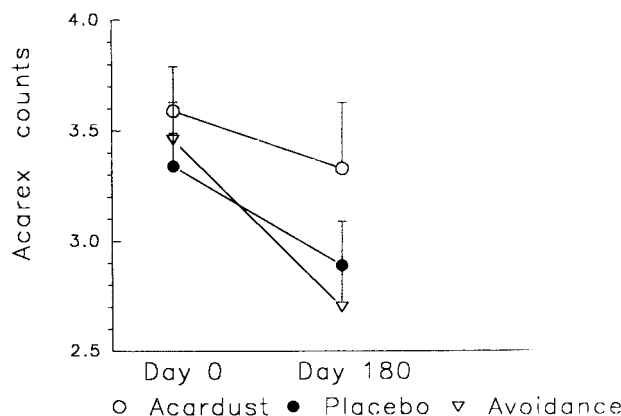


Figure 1. Acarex counts (mean $\pm$ SEM) from day 0 and day 180. While the overall Acarex count decreased significantly between days 0 and 180 ($P < .05$), there was no difference among the three groups.

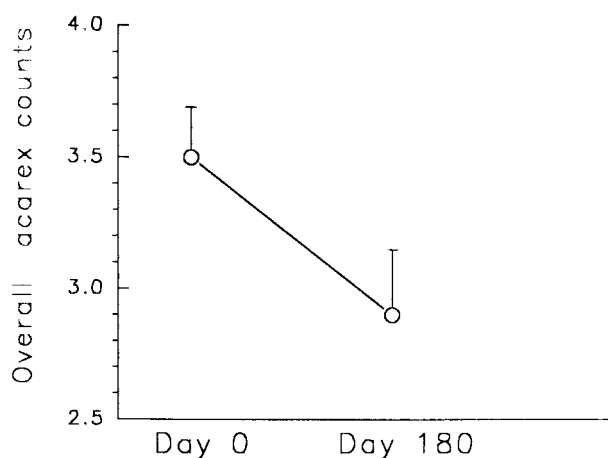


Figure 2. Overall Acarex counts (mean $\pm$ SEM) in the three groups decreased significantly between days 0 and 180 ($P < .001$).

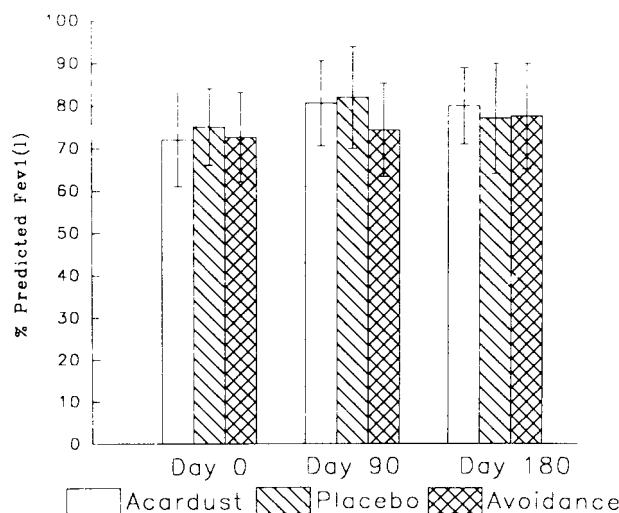


Figure 3. There was no statistical difference in FEV₁% predicted (mean $\pm$ SEM) between the groups.

months using a daily diary shows alleviation of disease symptoms due to environmental control in the children's bedrooms. Power calculation has demonstrated that there is enough power to compare the placebo and avoidance group to the Acardust group on the major variable, the Acarex test. By definition, the primary expected effect of the treatment (use of the acaricide) should be to lower the Acarex test count, and all the other secondary efficacy variables depend on this result. It is not surprising that our study showed no overall difference.

Regarding the ineffectiveness of the Acardust, incorrect application techniques of the acaricide product or microclimates within the houses may have had a decisive effect on several possible biases that must be taken into consideration for the *Dermatophagoides* population²² (indeed, in our study we did not check these parameters, including the relative humidity in the houses), and the Acarex test may not reflect changes in allergen exposure as accurately as more direct measurements. Certainly, there is no agreement about the accuracy of the Acarex test to assess precisely the actual mite antigen level. Nevertheless, there is good correlation between the Acarex test and the monoclonal antibody test for dust mite antigen.²³ We therefore

believe that the Acarex test is accurate for detecting changes in mite antigen

levels that are high enough to be of clinical importance.

Over the last few years, a number of products have been commercially marketed for reducing exposure to allergens of mites. Investigation of a wide variety of chemicals has shown that killing house dust mites under laboratory conditions is a relatively simple task, but the high degree of mite mortality achieved in laboratory experiments cannot be reproduced easily in the home.² Great variability is evident between homes regarding reductions in allergen concentration. Most probably, the method of delivery of the acaricides is an important determinant of efficacy. Furthermore, the penetration rate of currently available acaricidal spray, solutions, foams, or powder into mattresses or carpets cannot be evaluated fully.

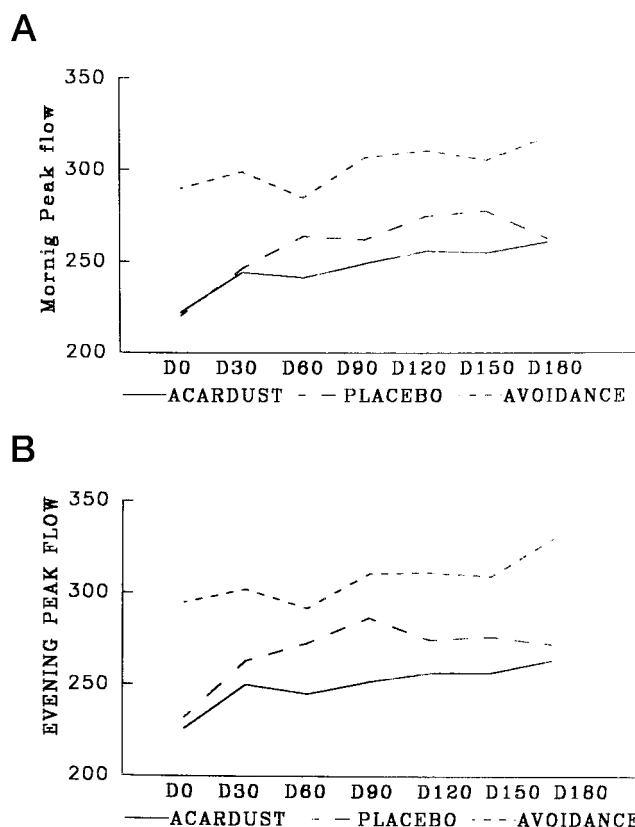


Figure 4. No statistical difference found in morning peak flow rates (A) and evening peak flow rates (B) during the 6-month study period among the three groups.

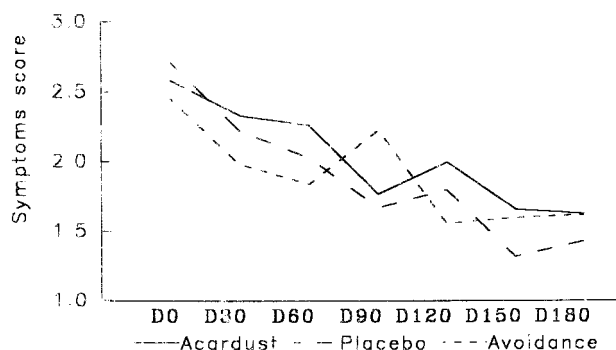


Figure 5. While the overall symptom score decreased significantly during the 6-month study period, no difference was found among the three groups.

Table 4. Parental Assessment of Quality of Change

	Acardust Group N = 13	Placebo Group N = 17	Avoidance Group N = 16
Same	6	8	9
Better	7	9	6
Worse	0	0	1

Recently, several new acaricides failed to prove effective when tested. The clinical effect of the acaricide depends, most probably, also on local climatic conditions, and not only on the quality of the specific product. Manjra et al²⁴ in the Cape Peninsula demonstrated that at present it is not possible to reduce Der p I antigen levels with the available acaricides (benzyl benzoate). Ridout et al²⁵ using the same acaricide on the Isle of Wight, concluded that a chemical acaricide may help reduce house dust mite antigen levels, but is not by itself sufficient to reduce levels below those considered critical for sensitization. Kalra et al²⁶ emphasized that neither benzyl benzoate nor liquid nitrogen reduces the concentration of Der p I for as long as 6 months after application. Tovey et al²⁷ showed that tannic acid was only temporarily effective when applied at the manufacturer's recommended level, and additional approaches were required to control the bulk of allergens in houses. Rieser et al²⁸ evaluating natamycin, showed not only no change in clinical symptoms, but also no change in allergen concentration. Marks et al²⁹ tested the effectiveness of house dust mite allergen avoidance

strategy. He concluded that in a high house dust mite allergen environment, simple chemical treatment, and encasement of bedding is not sufficient to cause a sustained, beneficial reduction in allergen levels. Effective allergen avoidance requires an active strategy to remove allergen reservoirs and control accumulating allergen within the house.

In our study, we did not use mattress and pillow covers, which can be viewed as a study limitation. If these covers were so crucial to the study results, we would not have found improvement in the symptom scores for our three groups due to allergen overload. In fact, we did find a decrease in the severity of the disease as well as a reduction in the dust load.

The study was conducted primarily in the winter months, during which dust is the dominant allergen. Furthermore, 87% of the children were exclusively prick test positive to house dust mites. The other 13% who were equally distributed among the three groups did not clinically deteriorate (measured by symptom score and lung function tests) during the weed season (late fall) when the study began or

during the blossoming season of the spring when the study ended.

In conclusion, appropriate environmental measures, such as continuous house dust mite avoidance measures in the bedrooms of dust mite allergic asthmatic children, is likely to be an important component in the management of those children. The result of this study confirms the finding of previous studies about using acaricides. The role of acaricides needs to be better defined and further work is necessary concerning methods of application and clinical effectiveness of these products.

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