

Effectiveness of house dust-mite allergen avoidance through clean room therapy in patients with atopic dermatitis

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We have investigated the effectiveness of house dust-mite (HDM) allergen avoidance through clean room (CR) therapy in patients with atopic dermatitis (AD) having high HDM-specific IgE RAST levels. All patients (N = 30) demonstrated marked improvement in symptom, a long-term remission (mean, 8.4 months), and significant decreases in eosinophil count ($p < 0.01$), basophil count ($p < 0.05$), serum lactate dehydrogenase activity ($p < 0.01$), and HDM-specific IgG levels ($p < 0.05$). By contrast, the patients with AD (N = 11), who scored 0 on HDM allergen-specific IgE RAST score underwent "CR" therapy, and the patients with AD (N = 10) having high HDM-specific IgE RAST levels were hospitalized in a common sickroom (nonclean room). All the patients (N = 21) exhibited slight improvement in symptoms and a significant decrease in serum lactate dehydrogenase activity. The period of recurrence after the therapy was brief. The results of measurement of airborne house-dust particles indicated that our "CR" fell within class 10,000. Therefore, it is very likely that the mechanism at work in the CR therapeutic approach is its ability to eliminate fecal pellets of the HDM. (J ALLERGY CLIN IMMUNOL 1992;89:653-7.)

Key words: Atopic dermatitis, clean room therapy, HEPA filter, house dust-mite allergen, long-term remission, allergen-specific IgG, dust particles

HDM allergen is known to be a main allergen in bronchial atopic disease, that is, allergic rhinitis and bronchial asthma. Patients with AD are presumed to be highly sensitized to HDM allergen on the basis of highly positive IgE RAST, scratch test, and intradermal test. However, the skin pathogenesis of AD is an eczema-dermatitis type reaction that is difficult to explain as merely an immediate allergic reaction. Thus, the causative role of HDM allergen and the histologic reaction to HDM allergen in the patient with AD have been studied in the two research approaches to AD to date, namely, the loading and removal of HDM allergen in the patient with AD.

Abbreviations used

AD:	Atopic dermatitis
HDM:	House dust mite
CR:	Clean room
HEPA:	High-efficiency particulate air
LDH:	Lactate dehydrogenase
Dp:	<i>Dermatophagoides pteronyssinus</i>

Various HDM allergen-load tests have been developed to induce an eczematous reaction by percutaneous loading of this antigen on an unaffected area in the patient with AD.¹⁻⁵ For HDM allergen removal, the removal of house dust in the residence of the patients with AD⁶⁻⁸ or the hospitalization of such HDM allergen-sensitive patients with AD in the ordinary sickroom^{9, 10} has been used to monitor possible improvement in subjective symptoms and objective signs.

We used a special CR, equipped with an air-cleaning system having an HEPA filter, in which the patients with AD were hospitalized for a fixed period.

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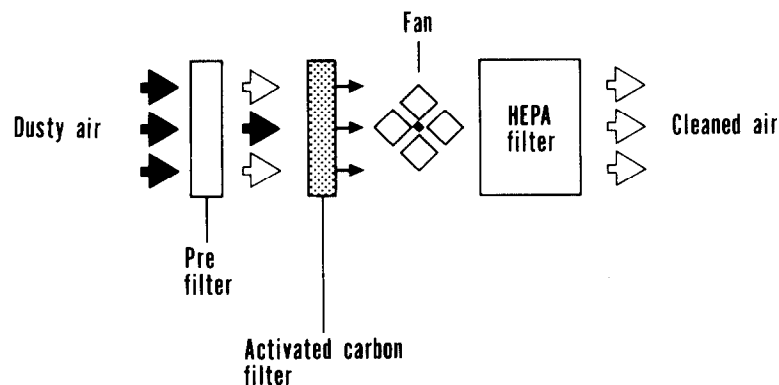


FIG. 1. Air-filter equipment (VIO-600, Keisei Ltd.). Air-cleaning system used in this trial incorporates three filters. Prefilter removes relatively large airborne particles. Carbon filter removes odors. HEPA filter can remove up to 99.97% of dust particles $<0.3 \mu\text{m}$ in size.

TABLE I. Age and sex of subjects

Treatment group	A	B	C
Mean age (yr)	20.1	20.6	25.4
Age range	9-72	8-33	9-75
Sex (M/F)	16:14	7:4	8:2

We called it "CR therapy."⁵ Then, we investigated its effectiveness and the mechanism of action in HDM allergen-sensitive patients with AD.

MATERIAL AND METHODS

Eligibility criteria and selection of patient groups

Diagnostic criteria for AD were the same as criteria used by Hanifin and Rajka.¹¹ Patients with AD selected for this study were 4 years of age or older and had 4.5 or higher of grading (severity) of AD¹² within 1 week before entry. In addition, the extent of involvement was at least 18% of the body surface area, which is based on the "rule of nine." All the patients were scored 0 on mold (*Candida*)-specific IgE RAST score, animal dander (cat and dog)-specific IgE RAST score, and pollen (a Japanese cedar and a sun tree)-specific IgE RAST score. The patients were then assigned at entry to one of three groups (Table I): A group: group receiving CR therapy in which HDM allergen-specific IgE RAST score was 3 or higher; B group: patients with AD receiving CR therapy in which HDM allergen-specific IgE RAST score was 0; and C group: group in which HDM allergen-specific IgE RAST score was 3 or higher. These patients were hospitalized in a common sickroom (nonclean room).

Study design

An air-cleaning system incorporating an HEPA filter (VIO-600, Keisei Co., Tokyo, Japan; Fig. 1) was equipped

in the CR, which was an ordinary sickroom for two patients (296 cm by 532 cm by 242 cm). Ventilation exchange of inside for outside air was conducted approximately for 10 min/day. Patients of A and B group were not allowed outside the CR during CR therapy except to go to the washroom or toilet. The ordinary sickroom used for patients of C group had the same number of occupants (two patients) and construction (plain and no carpet) as the CR but did not have an air-cleaning system. Patients of C group during hospitalization were allowed to go freely outside the ordinary sickroom. Time of hospitalization was the same for A, B, and C groups (3 to 4 weeks). No systemic medication (including corticosteroids) were used during the study. The patients had been allowed to use mild intermediate and low potency level topical steroids,¹³ hydrocortisone butyrate, 0.1% (Locoid ointment; Owen/Galderma Laboratories, Fort Worth, Texas), and beclomethasone dipropionate, 0.025% (Propaderm ointment), during the study. The quantity of all the topical steroids that had been used by the patients' groups compared was $<30 \text{ gm/mo}$ per patient. The itchiness was scored by the patients according to intensity score at grading of AD according to the method of Rajka and Langeland.¹²

Laboratory examinations

Laboratory examinations were done for all three groups (A to C) on the first day after admission and immediately after completion of the therapeutic course: serum IgE levels, HDM (*Dp*)-specific IgE and IgG levels, serum LDH activity, and peripheral blood eosinophil and basophil counts (per cubic millimeter). Radioimmunosorbent test was used to obtain serum IgE levels, RAST test for HDM (*Dp*)-specific IgE levels, and ELISA for HDM (*Dp*)-specific IgG levels. Specific IgE antibody (Pharmacia Ltd., Uppsala, Sweden) and specific IgG antibody (Shionogi Ltd., Osaka, Japan) were measured in accordance with the respective manufacturer's instruction manual. HDM (*Dp*)-specific IgE levels were scored on a scale of 0 to 4. Serum LDH activity was measured with pyruvic acid as the substrate at 340 nm ultraviolet absorbance. HDM (*Dp*)-specific IgG level units of measurement were indicated by IgG reference unit per milliliter.

Measurement of house dust particles

A light-scattering, particle counter (KC-01A, Rion Ltd., Tokyo, Japan) was used to determine CR cleanliness. Dust particles per cubic foot of air were counted in terms of three sizes (>5 , 0.5 , and $0.3 \mu\text{m}$). Measurements were performed at 1:30 PM on Sept. 24, 1987 (cloudy weather conditions), on (1) the CR beds, (2) common sickroom beds, (3) the nurse station table, and (4) outside the CR (exterior air).

Statistical analysis

Statistical analyses were made on the logarithmic ($\log_{10}$) transformation of IgE values (units per milliliter) and the other data (eosinophil count [per cubic millimeter], basophil count [per cubic millimeter], LDH activity [units per milliliter], *Dp*-specific IgG [IgG unit per milliliter]) that did not undergo the logarithmic transformation. All data on a blood test were analyzed by Wilcoxon's (matched-pairs) signed-ranks test. Results were reported as statistically significant if the two-tailed p value was ≤ 0.05 .

RESULTS

Clinical symptoms

At 2 to 4 days into the CR treatment, there was decreased itchiness among patients in the A group. By 10 days of CR treatment, an itchiness-free period was reached, with eruption pronouncedly alleviated. Time until subjective symptoms and objective signs recurred after the end of CR treatment averaged 8.4 months (Table II). A slight alleviation of eruption and subjective symptoms was also noted after treatment in B and C groups, but there was no itchiness-free phase. The time from the end of treatment until subjective symptoms and objective signs relapsed averaged 1.7 months in the B group and 1.6 months in the C group.

Results of laboratory examinations

$\log_{10}$ IgE, eosinophil count, basophil count, serum LDH activity, and *Dp*-specific IgG on blood tests before and after the therapy at all groups are summarized in Table III.

Laboratory data of after treatment in the A group were significantly lower than data of before treatment as follows: eosinophil count, $p < 0.01$; basophil count, $p < 0.05$; serum LDH activity, $p < 0.01$; and HDM (*Dp*)-specific IgG levels, $p < 0.05$. However, there was no significant reduction in $\log_{10}$ IgE levels.

In the B group, there was significant evidence of a decrease in serum LDH activity ($p < 0.05$), but there was no significant reduction in $\log_{10}$ IgE levels, eosinophil count, basophil count, or HDM (*Dp*)-specific IgG levels.

In group C, there was a significant decrease only in serum LDH activity ($p < 0.01$), but no significant variations in $\log_{10}$ IgE levels, eosinophil count, ba-

TABLE II. Time and period of recurrence after therapy

Treatment group	A	B	C
Mean time (mo)	8.4	1.7	1.6
Period (mo)	2-34	1-4	1-3

sophil count, or HDM (*Dp*)-specific IgG levels. No variations were found between posttreatment and pretreatment levels in HDM (*Dp*)-specific IgE RAST scores in A, B, or C groups.

Measurement of house dust particles

The number of dust particles, $\geq 0.5 \mu\text{m}$ in size per cubic foot of air, were 2600 in our "clean room," 189,000 in the ordinary sickroom, 398,886 in the nurse station, and 236,886 in outside air. According to the Federal Standard 209D, June 15, 1988, for determination of class limits, a CR falls within class 10,000 as compared to an ordinary sickroom, nurse station, or CR exterior (outside air), all of which would even scale out to class 10,000 (Table IV).

DISCUSSION

In the present trial, we attempted to control HDM allergen, which is considered to be one of the key allergens in AD, to determine the effectiveness of HDM allergen avoidance in patients with AD (A group) older than 4 years of age having high HDM allergen-specific IgE RAST levels. It is suggested that the HDM allergen was a major stimulating factor in AD because the CR therapy is effective for A group.

There was also some degree of reduction in the C group in clinical symptoms and signs that corresponds with the findings of Blythe et al.⁹ and Platts-Mills et al.¹⁰; these results demonstrate effective HDM allergen avoidance, even at the clean-space level of an ordinary sickroom. However, the patients in C group failed to enjoy any itchiness-free period during their hospitalization, and the remission phase after their discharge was brief (A group, mean 8.4 months; C group, mean 1.6 months). This presence or absence of itchiness-free period during hospitalization and brevity of postdischarge remission time was a key difference between the treatment results with those cared for in the clean space of an ordinary sickroom and those treated in CR. In the study by August⁶ on the removal of house dust within the residence of a patient with AD, no relationship was found between the clinical response and HDM allergen-specific IgE RAST scores. Thus, two possibilities come to mind, given the foregoing: (1) the therapeutically effective

TABLE III. Log₁₀ IgE, eosinophil count, basophil count, LDH activity, *Dp*-specific IgG in blood test before and after the therapy

	A group		B group		C group	
	Before	After	Before	After	Before	After
Log ₁₀ IgE (U/ml)	3.65 ± 0.68	3.57 ± 0.64	3.41 ± 0.77	3.37 ± 0.72	3.88 ± 0.35	4.00 ± 0.32
Eosinophil count (/mm ³)	527.7 ± 451.9	286 ± 239.3*	502 ± 490.3	266.2 ± 265.7	792.8 ± 532.8	537.0 ± 170.4
Basophil count (/mm ³)	57.9 ± 75.7	25.6 ± 50.4†	68.8 ± 94.2	82.1 ± 78.6	16.2 ± 32.4	44.0 ± 60.7
Serum LDH activity (IU/ml)	526.1 ± 134.8	371 ± 67.7*	561.6 ± 153.8	369.5 ± 19.7†	625.1 ± 221.0	429.0 ± 167.2*
<i>Dp</i> -specific IgG (GRU/ml)	457.4 ± 352.4	359.3 ± 288.0†	81.3 ± 68.0	68.3 ± 75.0	559.6 ± 318.0	430.2 ± 146.9

GRU/ml, IgG reference unit per milliliter.

Values are expressed as mean ± SD.

Significance versus basal (Wilcoxon's [matched-pairs] signed-ranks test):

p* < 0.01.†*p* < 0.05.TABLE IV.** Numbers of house dust particles in terms of size

	Measured particle size (μm)		
	0.3	0.5	5.0
CR	18,371	2,600	29
Common sick room	1,241,686	189,000	343
Nurse station	2,340,886	398,886	686
Outside air	1,526,486	236,886	143

mechanism of treatment in the clean space of an ordinary sickroom is not only through HDM allergen avoidance, but (2) some antibody other than the IgE antibody to HDM allergen serves to trigger the AD onset.

The percutaneous invasion of HDM allergen in patients with AD was earlier demonstrated by proof^{3,4} of HDM allergen localization at the point of eczema-dermatitis-type reaction caused by percutaneous HDM allergen load at a nonaffected site of the patient with AD. The present authors have also demonstrated, from their study¹⁴ with anti-*Dermatophagoides farinae* antibody, the localization of HDM allergen in eruptive tissue of seven of eight patients with AD older than 4 years of age who had demonstrated high HDM allergen-specific IgE RAST score. Furthermore, in this patient group, the post-CR therapeutic results revealed the disappearance of HDM allergen from the formerly eruptive portion in all patients. Thus, the

HDM allergen invading the skin of the patient with AD and causing an allergic reaction before CR therapy began was diminished after the CR therapy. This finding is the reason CR therapy proved clinically effective. However, a fixed quantity of HDM allergen in the skin of patients with AD could not be determined by the method.

In the present trial, we observed an improvement in clinical symptoms that paralleled the significant decrease in serum LDH activity in the A, B, and C groups. Mukai et al.¹⁵ reported a significant relationship between clinical symptoms and serum LDH activity in patients with AD, and they concluded that an elevation of serum LDH activity in patient with AD resulted from the broken epidermal cells of the skin in these patients. In other words, the difference in clinical effectiveness between A group and the other groups can be determined on the basis of a significant decrease in eosinophil count, basophil count, and HDM (*Dp*)-specific IgG levels. Particularly, the fluctuation in the HDM (*Dp*)-specific IgG levels can be an index of HDM allergen avoidance in CR treatment. The blocking-antibody theory¹⁶ and the short-term anaphylactic antibody hypothesis¹⁷ have been proposed as an approach to allergen-specific serum IgG antibody. We would suggest with data of A group that the HDM allergen-specific IgG levels indicate the amount of the HDM allergen exposure in the HDM allergen-sensitive patient.

The HDM (*Dp*)-specific IgE RAST score in any of the groups disclosed no differences between pre- and

posttreatment levels in the hospital. Moreover, even the postdischarge scores of the A group during remission failed to reveal any divergence from the pretreatment scores. Accordingly, the HDM (*Dp*)-specific IgG levels reflect the HDM allergen level in the short term more than the HDM (*Dp*)-specific IgE levels.

The clear difference observed between the effectiveness of CR therapy with that of the hospitalization at the common sickroom would indicate that cleanliness of the room is the key. The cleanliness required for CR air was established by Federal Standard 209D, June 15, 1988. Cleanliness class is the statistically allowable number of airborne particles $\geq 0.5 \mu\text{m}$ in measured particle size per cubic foot of air; that is, the number of particles < 1000 is class 1000, and the number $< 10,000$ is class 10,000 in this size per cubic foot of air. Our present CR falls into class 10,000 according to this criterion, which would be somewhere in between the cleanliness of a sterile operating room or sterile room (either of which is about class 100) and an ordinary sickroom (more than class 100,000). There was no great difference in cleanliness among a nurses' station, the air outside a CR, and an ordinary sickroom. Thus, patients should leave the CR as seldom as possible during treatment. From the fact that the cleanliness of an ordinary sickroom is more than class 100,000, whereas that of a clean room is on the class 10,000 level, there is an obvious difference between the two in the amount of particle size $> 0.5 \mu\text{m}$ in diameter.

Two HDM allergen molecular weights are presently known: that of *Der p* I at approximately 24,000 daltons and that of *Der f* II at about 17,000 daltons. *Der p* I allergen activity is in the house dust particle-diameter range of 6 to 20 μm ,¹⁸ which would belong to the HDM fecal-pellet range and have the physical appearance of mite feces.¹⁹ In addition, the HDM (*D. pteronyssinus* and *D. farinae*) measures approximately 0.3 mm in length. Therefore, it is very likely that the mechanism at work in the CR therapeutic approach is its ability to eliminate fecal pellets of the HDM. Since it is, presently, very difficult to measure accurately HDM allergen in the clean environment, the cleanliness classification would appear to be an effective means to quantitate HDM allergen indirectly.

CR therapy is both castwise and, in terms of effectiveness, a highly effective form of therapy for postinfancy and for patients with AD scoring > 3 on the HDM allergen-specific IgE RAST test. Besides being a form of therapy, the CR approach is also an

effective means to determine the HDM allergen contribution through dust-avoidance procedures.

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