

Association between severity of atopic eczema and degree of sensitization to aeroallergens in schoolchildren

Torsten Schäfer, MD, PhD, MPH,^{a,b,c} Joachim Heinrich, PhD,^c Matthias Wjst, MD,^c Heinrich Adam, MD,^c Johannes Ring, MD, PhD,^{a,b} and Heinz-Erich Wichmann, MD, PhD^{c,d}

Munich and Neuherberg, Germany

Background: A subgroup of patients with atopic eczema exhibits aggravation through contact with aeroallergens. Little is known from population-based studies, however, about the association between the severity of eczematous skin disease and the degree of aeroallergen sensitization.

Objective: We sought to investigate the relationship between IgE-mediated allergic sensitization to aeroallergens and severity of atopic eczema in schoolchildren.

Methods: A nested case-control analysis on atopic eczema was performed on the basis of a cross-sectional study of 2201 East German schoolchildren aged 5 to 14 years. Atopic eczema and its severity was identified by dermatologic examination. Total and allergen-specific IgE antibodies to grass and birch pollen, *Cladosporium herbarum*, *Dermatophagoides pteronyssinus*, and cat epithelium in serum were determined, and additional information was obtained by means of standardized questionnaire.

Results: The overall prevalence of actual atopic eczema was 2.5%. Thirty-seven percent of the children were sensitized to at least one allergen. Children with atopic eczema were significantly more often sensitized than those without skin disease (75.0% vs 36.3%; odds ratio, 5.27; 95% confidence interval, 2.54-11.15). This was observed for each single allergen. The prevalence of atopic eczema increased significantly with increasing RAST class (χ^2 trend test for each allergen, $P < .0001$). Also, the prevalence of sensitization increased with the severity of the disease (χ^2 trend test for each allergen, $P < .0001$). This association was pronounced for house dust mite and cat allergen. Multiple linear regression analyses showed significant associations between the severity score of atopic eczema and concentrations of allergen-specific IgE to dust mite ($P = .032$) and cat ($P = .014$) allergens after adjustment for sex, age, location, and parental predisposition.

Conclusions: The degree of sensitization is directly associated with the severity of atopic eczema. We speculate that early epi-

cutaneous sensitization to aeroallergens may be enhanced by damage of the skin barrier function. The specific IgE response seems to contribute to the severity of the disease in a dose-dependent fashion. (*J Allergy Clin Immunol* 1999;1280-4.)

Key words: Aeroallergens, atopic eczema, atopic dermatitis, East Germany, epidemiology, IgE-mediated sensitization, disease severity

Atopic eczema (atopic dermatitis) is the most frequent inflammatory skin disease in childhood.¹ Its manifestation is determined by genetic and environmental factors.²⁻⁴ The role of allergy in the pathogenesis of atopic eczema is still controversial; however, it is known that contact with food or aeroallergens can provoke atopic eczema in a subgroup of patients.⁵⁻⁸ Yet not all patients with atopic eczema are sensitized to common food allergens or aeroallergens. In this context the concept of an IgE-mediated allergic extrinsic and nonallergic intrinsic type of eczema, as is known for asthma, has been proposed.⁹ From epidemiologic studies, however, the proportions of these 2 types of eczema are not clear. For allergic patients with eczema, it seems to be of interest whether the concentration of aeroallergen-specific IgE antibodies is correlated with the severity of the disease. This has, to our knowledge, not been investigated thus far.

Therefore in a health survey of East German schoolchildren,¹⁰ the presence and severity of atopic eczema was assessed by an actual dermatologic examination. The degree of sensitization to 5 aeroallergens was measured by RAST. Here we describe the prevalence of sensitization in children with atopic eczema and the association between degree of sensitization and severity of eczema.

METHODS

Study design

A cross-sectional study was performed in 3 areas of Saxony-Anhalt (East Germany) between September 1992 and July 1993 to assess various health outcomes, including atopic eczema. Two of these areas (Bitterfeld and Hettstedt) were heavily polluted in the past by emissions from large power plants burning brown coal with a high sulfur content (up to 5%), chemical plants, and smelters. The third area (Zerbst) served as a control area with background pollution. The study design and results regarding health effects and the body burden of pollutants have been published elsewhere in more detail.¹⁰⁻¹³ Because the prevalence of atopic eczema did not differ significantly among these 3 locations, most statistical analyses were performed in the total study population.

From ^athe Department of Dermatology and Allergy, am Biederstein, and ^bthe Division of Environmental Dermatology and Allergology GSF/Technical University of Munich; ^cGSF-Environmental and Health Research Center, Institute of Epidemiology, Neuherberg; and ^dthe Institute of Medical Data Processing, Biometrics, and Epidemiology, Ludwig-Maximilians-University, Munich.

Supported exclusively by a governmental funding source, the Federal Environmental Agency (Umweltbundesamt), Grant No. Z1.5-917420/15.

Received for publication Mar 24, 1999; revised Aug 3, 1999; accepted for publication Aug 4, 1999.

Reprint requests: Torsten Schäfer, MD, PhD, MPH, Department of Dermatology and Allergy, Technical University Munich, Biedersteiner Str. 29, 80802 Munich, Germany.

Copyright © 1999 by Mosby, Inc.

0091-6749/99 \$8.00 + 0 1/1101990

TABLE I. Prevalence of intensity parameters in 55 East German children* with atopic eczema

Parameter (n)	Erythema	Induration	Oozing-crusts	Excoriation	Lichenification	Dryness
Absent	1	0	50	14	32	2
Present	54	55	5	41	23	53
Mild	35	37	4	28	16	29
Moderate	17	16	0	12	6	21
Severe	2	2	1	1	1	3

*Of the entire cohort of 2201 children (5-14 years old).

Abbreviations used

CI: Confidence interval
OR: Odds ratio

Population, recruitment, and response

Children of 3 age groups (5-7, 8-10, and 11-14 years) from all schools in Zerst and Hettstedt were invited to participate. In Bitterfeld schools were chosen to represent each regional district. Parents gave written consent after they had received an informational letter. Of the target population (n = 2772), 89.1% (n = 2470) participated and completed a standardized questionnaire that was distributed with information material. Of these, 2201 (89.0%) or 79.4% of the target population underwent a full skin examination. Forty-nine percent of this group were girls.

Outcome assessment

Dermatologic examination. To identify children with atopic eczema, skin examinations were performed by an experienced senior dermatologist. All examinations were done by the same investigator. For the purpose of the skin examination, the children were wearing their underpants only. The prevalence and severity (0, absent; 1, mild; 2, moderate; and 3, severe) of 6 morphologic characteristics (erythema, induration, oozing-crusts, excoriation, lichenification, and dryness) were recorded according to the SCORAD protocol.¹⁴ On the basis of the single intensity grades, a summation score was calculated and transformed into a categorical variable (0-IV). To achieve almost equal sizes, categories I to IV comprised the following scores: I, 2-3; II, 4; III, 5-7; and IV, 8-17.

Total and specific IgE levels. In serum the concentrations of total (n = 2042) and specific IgE antibodies to 5 aeroallergens were measured by RAST (CAP-FEIA; Pharmacia, Uppsala, Sweden). All analyses were done by Pharmacia (Germany, Freiburg) with the same batches of allergen caps. Valid results for the following allergens are available: *Dermatophagoides pteronyssinus* (n = 2069), grass pollen (n = 2030), birch pollen (n = 1747), *Cladosporium herbarum* (n = 1762), and cat (n = 2027). Differences in the numbers of measurements for the single allergens occurred because of insufficient amount of serum in some cases. Results are given in kilounits per liter and classified into 6 RAST classes. For further analyses, the 6 classes were transformed into 4, merging classes IV to VI into class IV.

Basic demographic information about age, sex, and parental history of atopic eczema was obtained by examination and a standardized questionnaire.

Statistical analyses

Beside descriptive statistics, we used the χ^2 test for linear trend, the Pearson test for bivariate correlation (1-tailed test), the Mann-Whitney *U* test for nonparametric comparison of means, and

Kruskal-Wallis ANOVA. Multiple linear regression analyses were performed with severity score of atopic eczema as the dependent variable. The odds ratios (ORs) and 95% confidence intervals (95% CIs) are given as measures of association and stability. Statistical analyses were done by using the software packages SPSS for Windows 6.0 and EpiInfo 5.0.

RESULTS

Descriptive and bivariate analyses

Of the 2201 examined children, 55 were diagnosed with atopic eczema (2.5%). There was no difference in prevalence between boys (2.6%) and girls (2.5%). Eczema was diagnosed more often in the exposed areas of Bitterfeld (2.7%) and Hettstedt (3.3%) than the control area of Zerst (1.7%) but without statistical significance ($P = .13$).

All children diagnosed with eczema showed some degree of induration, and almost all exhibited dryness and erythema. The frequency and severity distribution of the single morphologic characteristics are given in Table I.

The sample sizes of the categorized intensity score were as follows: 11 category I, 15 category II, 14 category III, and 15 category IV. In contrast to the findings regarding the eczema prevalence, the mean severity score was higher in the control area (8.3) compared with the exposed areas of Bitterfeld (5.4) and Hettstedt (4.4). By using 1-way ANOVA, there was indication for significant heterogeneity of the severity of atopic eczema cases between locations (Kruskal-Wallis, $P = .001$). Therefore location was included in the final regression model.

The median total IgE level in the entire group was 63.8 kU/L and differed significantly between children with (118.5 kU/L) and without atopic eczema (62.3 kU/L, $P < .001$).

Six hundred eighty-six (37.2%) of 1845 children with valid RAST results exhibited at least one positive reaction to the 5 aeroallergens tested. Seventy-five percent of the children with atopic eczema exhibited an IgE-mediated allergic sensitization (extrinsic type) that was significantly higher than that found in children without eczema (36.3%; OR, 5.27; 95% CI, 2.54-1.15). Children with atopic eczema and allergic sensitization also exhibited significantly higher total IgE levels (median, 206.5 kU/L) than those with eczema but without detectable allergen-specific IgE (intrinsic type: median, 63.2 kU/L; $P < .001$).

The prevalence of sensitization to the single allergens in the entire cohort was as follows: *D pteronyssinus*,

TABLE II. Prevalence of specific IgE antibodies* to 5 aeroallergens in children with and without atopic eczema

		Grass pollen	Birch pollen	<i>C herbarum</i>	<i>D pteronyssinus</i>	Cat allergen	<i>D pteronyssinus</i> or cat allergen
Eczema, % (n)	46.0 (23/50)	36.8 (14/38)	25.0 (10/40)	41.2 (21/51)	36.7 (18/49)	51.0 (25/49)	
No eczema, % (n)	22.8 (451/1980)	10.2 (175/1709)	4.3 (84/1762)	14.1 (284/2018)	6.2 (122/1978)	17.1 (339/1988)	
OR (95% CI)	2.89 (1.58-5.26)	5.11 (2.46-10.53)	6.66 (2.94-14.78)	4.27 (2.32-7.83)	8.83 (4.60-16.87)	5.07 (2.76-9.31)	

*As measured by RAST (>0.35 kU/L).

TABLE III. Prevalence of atopic eczema in schoolchildren by degrees of sensitization to 5 aeroallergens

		RAST class				
Allergen		0	I	II	III	IV-VI
Grass pollen	% (n)	1.7 (27/1556)	1.9 (2/108)	4.4 (7/158)	6.5 (6/93)	7.0* (8/115)
Birch pollen	% (n)	1.5 (24/1558)	5.0 (2/40)	7.4 (6/81)	4.3 (2/47)	19.0* (4/21)
<i>C herbarum</i>	% (n)	1.8 (30/1678)	4.3 (1/23)	6.3 (2/32)	23.5 (4/17)	25.0* (3/12)
<i>D pteronyssinus</i>	% (n)	1.7 (30/1764)	4.9 (4/81)	3.7 (5/135)	20.9 (9/43)	6.5* (3/46)
Cat epithelium	% (n)	1.6 (31/1887)	7.1 (3/42)	10.0 (6/60)	27.3 (6/22)	18.8* (3/16)

* $P < .0001$, χ^2 trend test.**TABLE IV.** Prevalence of allergic sensitization, total IgE, and severity of atopic eczema in schoolchildren

		Eczema severity (score)				
Allergen		Absent (0)	Mild (1-3)	Moderate (4)	Prominent (5-7)	Severe (>7)
Grass pollen	% (n)	22.7 (449/1981)	54.5 (6/11)	30.8 (4/13)	46.2 (6/13)	69.2* (9/13)
Birch pollen	% (n)	10.1 (173/1710)	50.0 (4/8)	22.2 (2/9)	30.0 (3/10)	63.6* (7/11)
<i>C herbarum</i>	% (n)	4.4 (75/1723)	25.0 (2/8)	20.0 (2/10)	27.3 (3/11)	18.2* (2/11)
<i>D pteronyssinus</i>	% (n)	14.0 (283/2019)	27.3 (3/11)	38.5 (5/13)	46.2 (6/13)	57.1* (8/14)
Cat epithelium	% (n)	6.2 (122/1979)	27.3 (3/11)	33.3 (4/12)	38.5 (5/13)	46.2* (6/13)
Total IgE, median (kU/L)		40.5	45.8	43.4	92.1	316.7†

* $P < .0001$, χ^2 trend test.† $P = .002$, Kruskal-Wallis test.

14.7%; grass pollen, 23.3%; birch pollen, 10.8%; *Cladosporium herbarum*, 4.8%; and cat epithelium, 6.9%. Children with atopic eczema were sensitized to each of the single aeroallergens significantly more often than their healthy peers (χ^2 , all $P < .0001$). The frequencies of sensitization to the single allergens for children with and without atopic eczema are summarized in Table II.

The association between the presence of atopic eczema and the degree of sensitization to the single aeroallergens (RAST classes) exhibited significant linear relationships for all 5 allergens (χ^2 test for trend, all $P < .0001$). A continuous linear trend was present for the allergens *Cladosporium herbarum* and grass pollen (Table III).

We furthermore analyzed the prevalence of sensitization in association with the severity of the disease. For this purpose, the categorized severity score was used. A clear and significant linear association between prevalence of sensitization and severity of atopic eczema was observed for all allergens (χ^2 test for trend, all $P < .0001$). This linear trend was most pronounced for the indoor allergens *D pteronyssinus* and cat epithelium (Table IV). Testing a linear relationship between the severity of atopic eczema (continuous severity score, 2-

17) and degree of sensitization (>0.35 kU/L), a significant result was obtained for *D pteronyssinus* (Pearson, $P = .047$) and cat epithelium (Pearson, $P = .005$).

Multivariate analysis

Two multiple linear regression models were created to test the association between severity of atopic eczema (score 2-17) and concentrations of allergen-specific IgE antibodies to cat epithelium and *D pteronyssinus* (>0.35 kU/L). Sex, age, and location were included as potential confounders. In both models a significant linear relationship between severity of atopic eczema and degree of sensitization was observed. The differences in severity between regions were significant in the model with cat allergen only (Table V).

DISCUSSION

In this study we report the proportion of sensitization to 5 common aeroallergens in schoolchildren with and without atopic eczema. We found a significant linear association between severity of eczema and degree of sensitization. One major strength of our study is that we assessed the presence and severity of atopic eczema by

examination of the entire skin by an experienced dermatologist. We consider this the gold standard of outcome assessment. Because all examinations were done by the same investigator, interobserver variability cannot occur. Sensitization to common aeroallergens was measured by RAST, which independently of subjective influences provides quantitative results with a higher reproducibility than the skin prick test.^{15,16} In addition, RASTs can be performed in situations in which skin testing is impossible because of skin changes at the testing site or interfering treatment. The degree of sensitization was not known to the investigator at the time of examination, making differential misclassification bias unlikely. Seventy-nine percent of the target population participated in the skin examination, and therefore generalizability should not be affected to a large extent. This is further underscored by the fact that the prevalence of atopic eczema was the same between children who participated in both the skin examination and the blood test (2.4%) and those who only underwent dermatologic examination (2.9%; not significant). Selection bias seems also unlikely because participants were not aware of their sensitization status.

The prevalence of atopic eczema in this study (2.5%) seems to be low compared with earlier investigations in preschool children in East Germany (17.5%).¹⁷⁻²¹ Another German study revealed a prevalence of 4.7% among young adults.²² All but 5 patients with atopic eczema identified in our study also had a positive history of atopic eczema. We therefore believe that these patients are representative, although an overall underestimation cannot be excluded completely, and the rather low number of cases may also have affected statistical power.

Of the children with atopic eczema, 75.0% reacted to at least one allergen in the RAST. Although it is widely accepted that not all patients with atopic eczema are sensitized to allergens, little is known about the proportion of intrinsic atopic eczema on a population basis. Our findings are in accordance with previous hospital-based estimates. A study from Hungary²³ revealed a proportion of extrinsic eczema of 84.5%, whereas a report from France showed that 54.2% of children with eczema exhibited at least one skin prick test reaction.²⁴

From clinical and diagnostic experiences, it is well known that contact with aeroallergens can provoke eczema in a subgroup of patients. This was demonstrated especially for house dust mite allergen,²⁵⁻²⁷ for which intervention studies proved to be effective.^{28,29}

This is the first report of a direct association between the severity of the disease and the degree of sensitization. Indeed, it seems biologically plausible that a higher degree of sensitization is associated with a corresponding pronounced clinical manifestation. This is further supported by the finding that the highest correlations were obtained for the perennial indoor aeroallergens *D pteronyssinus* and cat epithelium. A previous report of 250 children from France showed that allergic sensitization to food allergens and aeroallergens was absent in patients with mild eczema, detectable in 33% of patients with moderate eczema, and detectable in all children

TABLE V. Linear regression models for severity of atopic eczema (continuous score, 2-17) as dependent variable and degree of sensitization (>0.35 kU/L) to indoor aeroallergens (cat epithelium and *D pteronyssinus*), sex, age, location, and parental predisposition as independent variables

Variable	β	P value
Cat		
Sex (female)	-.151	0.465
Parental eczema	-.050	0.811
Age (y)	-.133	0.506
Cat IgE (kU/L)	.570	0.014
Location*	-.590	0.11
<i>D pteronyssinus</i>		
Sex (female)	.192	0.405
Parental eczema	.249	0.203
Age (y)	.328	0.123
<i>D pteronyssinus</i> IgE (kU/L)	.500	0.032
Location*	-.386	0.100

*0, Zerbst; 1, Bitterfeld; and 2, Hettstedt.

with severe eczema.³⁰ Because both these and our results come from cross-sectional studies, one cannot conclude whether atopic eczema preceded the development of allergic sensitization or vice versa. Atopic eczema usually develops very early, whereas concentrations of allergen-specific IgE antibodies increase later in life. In a large German birth cohort study, allergen-specific IgE antibodies were not detectable in cord blood of newborns but rather at 2 years of age.³¹⁻³³ Taieb and Ducombs³⁴ tested children with atopic eczema from 3 age groups (0-12 months, 1-2 years, and 5 years) by using atopy patch tests and skin prick tests.²⁴ Reactions in the atopy patch tests decreased with age (90%, 78.5%, and 28.2%, respectively), whereas allergic sensitization, as measured by prick tests, increased with age (5%, 50%, and 54.2%, respectively). Both allergic sensitization and atopic eczema might be promoted by an underlying genetic predisposition. This may have confounded the association between allergic sensitization and atopic eczema. However, in our analyses the observed associations persisted after controlling for parental history of atopic diseases.

We speculate that sensitization in children with atopic eczema does influence the outcome of skin manifestation. The eczematous skin with a damaged barrier might facilitate sensitization to aeroallergens, which is then followed by an allergen-specific IgE response. This process of sensitization might, in turn, depend on the severity of the disease. The acquired sensitization might then contribute to the severity of the disease in a linear fashion. A prospective study design, however, is needed to further assess the timing of the relationship reported here and the preventive benefit of reducing aeroallergen exposure.

We thank all parents and children for their participation; Mr H. Schneller and Ms K. Honig-Blum for data handling; Dr I. Hörhold, Dr I. Keller, Dr S. Loewe, and Dr D. Bodesheim for collecting the blood and urine specimens; Mr G. Burmester, Mr J. Rudzinski, Ms B. Hollstein, Ms Machander, Ms D. Albrecht, and Ms Boettcher for

gathering regional data and for local assistance; all teachers in Hettstedt, Zerbst, and Bitterfeld, and the local school authorities and health care centers for their support; and Dr O. Dammann, MSc, for carefully revising the manuscript.

REFERENCES

- Williams H. Inflammatory skin diseases I: atopic dermatitis. In: Williams H, Strachan D, editors. The challenge of dermatoeidemiology. Boca Raton: CRC Press; 1997. p. 125-44.
- Ring J, Behrendt H, Schäfer T, Vieluf D, Krämer U. Impact of pollution in allergic diseases. Clinical and epidemiological studies. In: Johansson S, editor. Progress in allergy and clinical immunology 3. Seattle: Hogrefe & Huber; 1995. p. 174-82.
- Ring J. Allergy and modern society: does "Western life style" promote the development of allergies? *Int Arch Allergy Immunol* 1997;113:7-10.
- Ruzicka T, Ring J, Przybilla B. Handbook of atopic eczema. Berlin: Springer; 1991.
- Ring J. Atopy: condition, disease, or syndrome? In: Ruzicka T, Ring J, Przybilla B, editors. Handbook of atopic eczema. Berlin: Springer; 1991.
- Przybilla B, Ring J. Food allergy and atopic eczema. *Semin Dermatol* 1990;3:220-5.
- Darsow U, Vieluf D, Ring J. The atopy patch test. An increased rate of reactivity in patients who have an air-exposed pattern of atopic eczema. *Br J Dermatol* 1996;135:182-6.
- Rajka G. Atopic dermatitis. Correlation of environmental factors with frequency. *Int J Dermatol* 1986;25:301-4.
- Wüthrich B. Atopische Dermatitis. *Ther Umsch* 1989;46:633-40.
- Heinrich J, Hoelscher B, Wjst M, Ritz B, Cyrus J, Wichmann H. Respiratory diseases and allergies in two polluted areas in East Germany. *Environ Health Perspect* 1999;107:53-62.
- Trepka M, Heinrich J, Schulz C, Krause C, Popescu M, Wjst M, et al. Arsenic burden among children in industrial areas of eastern Germany. *Sci Total Environ* 1996;180:95-105.
- Trepka M, Heinrich J, Krause C, Schulz C, Lippold U, Meyer E, et al. The internal burden of lead among children in a smelter town—a small area analysis. *Environ Res* 1997;72:118-30.
- Meyer I, Heinrich J, Lippold U. Factors affecting lead, cadmium, and arsenic levels in house dust in a smelter town in Eastern Germany. *Environ Res* 1999;81:32-44.
- Stalder J, Taieb A, and Task Force on Atopic Dermatitis. Severity scoring of atopic dermatitis. The SCORAD index. *Dermatology* 1993;186:23-31.
- Alonso R, Botey J, Pena J, Eneverri J, Marin A, Ras R. Specific IgE determination using the CAP system: comparative evaluation with RAST. *J Invest Allergol Clin Immunol* 1995;5:156-60.
- Demoly P, Bousquet J, Manderscheid J, Dreborg S, Dhivert H, Michel F. Precision of skin prick and puncture tests with nine methods. *J Allergy Clin Immunol* 1991;88:758-62.
- Schäfer T, Vieluf D, Behrendt H, Krämer U, Ring J. Atopic eczema and other manifestations of atopy: results of a study in East and West Germany. *Allergy* 1996;51:532-9.
- Schäfer T, Ring J. Epidemiologie des atopischen Ekzems. *Allergologie* 1998;6:259-71.
- Behrendt H, Krämer U, Dolgner R, Hinrichs J, Willer H, Hagenbeck H. Elevated levels of total serum IgE in East German children: atopy, parasites or pollutants? *Allerg J* 1993;3:31-40.
- Krämer U, Schäfer T, Behrendt H, Ring J. The influence of cultural and educational factors on the validity of symptom and diagnosis for atopic eczema. *Br J Dermatol* 1998;139:1040-6.
- Mutius von E, Martinez F, Fritzsche C, Nicolai T, Roell G, Thiemann H. Prevalence of asthma and atopy in two areas of West and East Germany. *Am J Respir Crit Care Med* 1994;149:358-64.
- Diepgen T, Fartasch M. Recent epidemiological and genetic studies in atopic dermatitis. *Acta Derm Venereol (Stockh)* 1992;176(Suppl):13-8.
- Somos Z, Schneider I. Serum and secretory immunoglobulins in atopic dermatitis. *Orv Hetil* 1993;134:1359-61.
- Cabon N, Ducombs G, Mortureux P, Perromat M, Taieb A. Contact allergy to aeroallergens in children with atopic dermatitis. Comparison with allergic contact dermatitis. *Contact Dermatitis* 1996;35:27-32.
- Platts-Mills T, Mitchell E, Rowntree S. The role of house dust mite allergens in atopic dermatitis. *Clin Exp Dermatol* 1983;8:233-47.
- Adinoff A, Tellez P, Clark R. Atopic dermatitis and aeroallergen contact sensitivity. *J Allergy Clin Immunol* 1988;81:736-42.
- Mitchell E, Crow J, Chapman M, Jouhal S, Pope F, Platts-Mills T. Basophils in allergen-induced patch test sites in atopic dermatitis. *Lancet* 1982;8264:127-30.
- Tan B, Weald D, Strickland I, Friedmann P. Double-blind controlled trial of effect of housedust-mite allergen avoidance on atopic dermatitis. *Lancet* 1996;347:15-8.
- Sanda T, Yasue T, Ohashi M, yasue A. Effectiveness of house dust-mite allergen avoidance through clean room therapy in patients with atopic dermatitis. *J Allergy Clin Immunol* 1992;89:653-7.
- Guillet G, Guillet M. Natural history of sensitizations in atopic dermatitis. A 3-year follow-up in 250 children: food allergy and high risk of respiratory symptoms. *Arch Dermatol* 1992;128:187-92.
- Bergmann R, Bergmann K, Lau-Schadendorf S, Luck W, Dannemann A, Bauer C, et al. Atopic diseases in infancy. The German multicenter atopy study (MAS-90). *Pediatr Allergy Immunol* 1994;5(Suppl 6):19-25.
- Munir A, Kjellman N, Björkstén B. Exposure to indoor allergens in early infancy and sensitization. *J Allergy Clin Immunol* 1997;100:177-81.
- Sigurs N, Hattevig G, Kjellman B, Kjellman N, Nilsson L, Björkstén B. Appearance of atopic disease in relation to serum IgE antibodies in children followed up from birth for 4 to 15 years. *J Allergy Clin Immunol* 1994;94:757-63.
- Taieb A, Ducombs G. Aeroallergen contact dermatitis. *Clin Rev Allergy Immunol* 1996;14:209-23.