

# Influence of dietary manipulation on incidence of atopic disease in infants at risk

Maria Bardare\*; Antonia Vaccari†; Elisabetta Allievi‡; L. Brunelli‡; Francesca Coco§; G. C. de Gaspari‡; and U. Flauto§

*Of 5,500 newborn infants whose family histories were screened, 900 were found to have anamnestic risk. Cord-blood IgE was evaluable in 4,677 of these newborns, of which 394 had levels  $\geq 1$  IU/mL; 84 infants had both anamnestic risk and elevated cord-blood IgE levels. Parents of infants with anamnestic risk were informed of their child's risk of atopy. Additionally, for 391 infants at two of the three participating hospitals, a preventive diet was prescribed that recommended breastfeeding for the first 6 months of life, with maternal diet restricted to no more than 200 dL of cow milk per day, no more than one egg per week, and no tomato, fish, shellfish, nuts, or foods allergenic to the mother. Only soy formula was recommended, and introduction of solid foods was also carefully prescribed. Furthermore, doctors recommended against exposure to tobacco smoke, animal allergens, and early entrance into daycare. Evaluable infants whose parents complied with the prescribed diet were found to have a lower incidence of atopy during the first year of life (13.3%,  $n = 158$ ) than infants whose parents had ignored the prescribed diet (54.7%,  $n = 86$ ) or infants whose parents were offered no dietary recommendations (28.9%,  $n = 218$ ). Differences between the compliant group and the two groups with unrestricted diets were significant, indicating that this prescribed diet may protect against or delay onset of food allergies during the first year of life.*

## INTRODUCTION

An estimated 15% of infants may have one or more allergic conditions.<sup>1</sup> Environmental factors, including feeding method, have been implicated in the development or onset of atopy.<sup>1-12</sup> To avoid or delay allergies in infants with first-degree relatives with allergies, infants have been fed by various methods. Prolonged breastfeeding,<sup>2-8</sup> soy formula,<sup>9-11</sup> or other hypoallergenic formulas<sup>1,12</sup> have been offered infants who are at risk for allergy.

Due to improper controls or to varying inclusion criteria, clinical studies assessing the efficacy of such methods have often been controversial. Exclusive breast-feeding did not afford complete protection,<sup>13,14</sup> especially if the mothers did not observe dietary restrictions.<sup>15-17</sup> For-

mulas based on casein or whey protein hydrolysates<sup>1,12,18</sup> or on soy milk<sup>9-11</sup> were studied with no agreement on the preferred diet.<sup>19-21</sup>

This prospective, multicentric controlled trial examined the incidence of atopic disease in newborns with family histories for atopy. Infants were fed either breast milk (with maternal dietary restrictions) or, as necessary, either breast milk and soy formula or soy formula with dietary restrictions through the first year of life.

## METHODS AND MATERIALS

Family histories of 5,500 newborn infants were screened. History of atopy was considered positive if one of an infant's parents or siblings had been clinically diagnosed with an allergy. Respiratory allergies (such as oculorhinitis or asthma) or various symptoms of food allergies (atopic eczema, urticaria, gastrointestinal complaints) qualified a family member as allergic. Contact dermatitis, drug intolerance, or similar nonspecific symptoms were not recorded. Anamnestic scores were graded as follows: one family member with a clinically diagnosed al-

lergy, 1; one family member with a positive specific allergen test, 2; biparental family history, 3 or 4, depending on how the allergies were ascertained.

Cord-blood IgE levels were evaluable in 4,677 of these newborns. Cord-blood IgE levels were considered normal under 1 IU/mL.

Newborns with familial risk of atopy were divided into groups by hospital in order to avoid parental information-sharing. At St. Gerardo Hospital, Monza, 2,514 newborns were screened; 509 were found to be at risk. These infants formed the control group, for whom no diet was prescribed; parents were informed of the child's risk of atopy.

Newborns at Regina Elena Hospital, Milan and St. Corona Hospital, Garbagnate Milanese together formed the prevention group. Of the 2,986 newborns screened at these two centers, 391 were found to have a risk of atopy. A preventive diet was prescribed for these infants. Mothers were asked to breast-feed infants for 6 months when possible, and the mother's diet during this time was restricted. Mothers could have no more than 200 dL of cow

\* University of Milan, Pediatric Clinic I.

† St. Corona Hospital, Garbagnate Milanese.

‡ Regina Elena Hospital, Milan.

§ St. Gerardo dei Tintori, Monza.

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milk per day and no more than one egg per week. Tomatoes, fish, shellfish, nuts, and foods to which the mother was allergic were completely restricted from the mother's diet.

When supplementation was necessary, a soy formula was used [Isomil, Abbott Italia, Campoverde, (LT), Italy]. Supplementation was delayed until after the sixth month whenever possible, and a selected weaning process was recommended thereafter. Gluten was introduced after the eighth month, and cow milk and other dairy products were introduced after the tenth month. The only meats allowed before the baby's first birthday were lamb, turkey, or rabbit and the only fruits allowed before that time were pear or pineapple. Tomato was avoided until after the baby was 1 year old. Avoidance of tobacco smoke and animal dander was also recommended, as well as delayed entrance into daycare centers.

Newborns with high cord-blood IgE levels but without familial history of atopy were not prescribed any special diet. Parents were simply warned of the child's risk of atopy.

Newborns with anamnestic risk of atopy or with high cord-blood IgE levels were examined at 3, 6, 9, 12, 18, and 24 months. Atopic eczema was diagnosed if clinical examination revealed areas of scaly, erythematous, and itchy rash involving typical regions of atopy (face, scalp, flexural folds, areas behind the ears). Eczema was rated as mild, moderate, or severe according to the Hanifin scale.<sup>22</sup> Possibly allergic asthma was diagnosed if an infant suffered at least three episodes of asthma without fever or other infectious features. Possible allergic rhinitis was diagnosed if an infant had 3 consecutive weeks of rhinorrhea without infectious features and without simultaneous rhinorrhea in household contacts.

## RESULTS

Of 5,500 newborns, 900 (16%) had anamnestic risk. Four thousand six

hundred seventy-seven of these newborns had evaluable cord-blood IgE results, of which 394 (8.4%) tested  $\geq 1$  IU/mL. Table 1 shows a matrix of these two traits. Elevated cord-blood IgE was more prevalent in the group with anamnestic risk by a statistically significant amount ( $P < .001$ ).

The control group and the prevention group had slightly different demographics. As Table 2 shows, the control group had more infants with anamnestic risk, while the prevention group had more infants with high cord-blood IgE. At the first clinical visit, parents of 64 infants in the prevention group and 213 infants in the control group elected not to participate in the trial. The higher level of participation in the prevention group may have been due to the high level of parental involvement or to parental confidence inspired by the more precise diet indications.

Unreliable parental reports or missed clinic visits caused 161 subjects (26%) to be dropped from the

study, most fairly early in the study. These dropouts left 244 evaluable patients in the prevention group and 218 in the control group. Approximately 65% of the infants attended the clinical examinations through 1 year of age. After the 1 year appointments, examinations were attended almost exclusively by symptomatic atopic subjects.

Of the 244 evaluable patients in the prevention group, 86 (35%) did not follow the prescribed diet. These infants were evaluated as a separate group, the noncompliant prevention group, and tracked.

Feeding method appeared to be related to atopic symptoms. Overall, only 13% of the compliant prevention group experienced atopic symptoms, while 55% of the noncompliant prevention group experienced symptoms, and 29% of the control group. Differences were significant between all groups ( $P < .001$ ). The chi-square test gave the following results: 46.954 for the overall matrix; 47.390 when the two prevention groups were compared;

Table 1. Newborns' Anamnestic Risk and Cord Blood IgE, Number of Infants and Percent of Total Infants in that Anamnestic Risk Group

| Family History     | IgE $\geq 1$ IU/mL | IgE $< 1$ IU/mL | Unknown IgE |
|--------------------|--------------------|-----------------|-------------|
| Anamnestic risk    | 84 (9.3)*          | 685 (76.1)      | 131 (14.6)  |
| No anamnestic risk | 310 (6.7)          | 3598 (78.2)     | 692 (15.0)  |

\*  $P < .001$  as compared with the group without anamnestic risk.

Table 2. Demographics of Risk Factors in the Two Clinical Groups Shown as Value and Percentage

| Condition                                             | Prevention Group | Control Group |
|-------------------------------------------------------|------------------|---------------|
| Newborns at risk for atopy in the general population* | 391/2986 (13)    | 509/2514 (20) |
| Anamnestic score 1-2 in "at risk" infants†            | 347/391 (89)     | 469/509 (92)  |
| Anamnestic score 3-4 in "at risk" infants             | 44/391 (11)      | 40/509 (8)    |
| IgE $\geq 1$ IU/mL in "at risk" infants‡              | 49/391 (15)      | 35/450 (8)    |
| Enrolled patients from the "at risk" population§      | 327/391 (84)     | 296/509 (58)  |
| Evaluative patients from the "at risk" population¶    | 244/327 (75)     | 218/296 (74)  |

Statistical analysis: \*  $\chi^2 = 51.015$ ,  $P < .001$ ; †  $\chi^2 = 3.011$ ,  $P > .05$ ; ‡  $\chi^2 = 11.031$ ,  $P < .001$ ; §  $\chi^2 = 11.031$ ,  $P < .001$ ; ¶  $\chi^2 = 0.076$ ,  $P < .05$ .

12.863 when the control group was compared with the compliant prevention group; 17.712 when the control group was compared to the noncompliant prevention group. Table 3 shows how these groups of symptomatic infants related to anamnestic risk.

Table 4 shows how the prevalence of high IgE levels in infants correlates with atopic symptoms. Elevated serum IgE levels were associated with increased incidence of symptomatology regardless of feeding group.

Atopic features were observed earlier both in the noncompliant and the control groups than in the compliant group. In the first 6 months of life, this difference is significant ( $X^2 = 5.17$ ;  $P < .0025$ ) as Figure 1 shows.

Figure 2 shows the incidence of atopic symptoms in the prevention group as it correlates with infant feeding type. No differences in

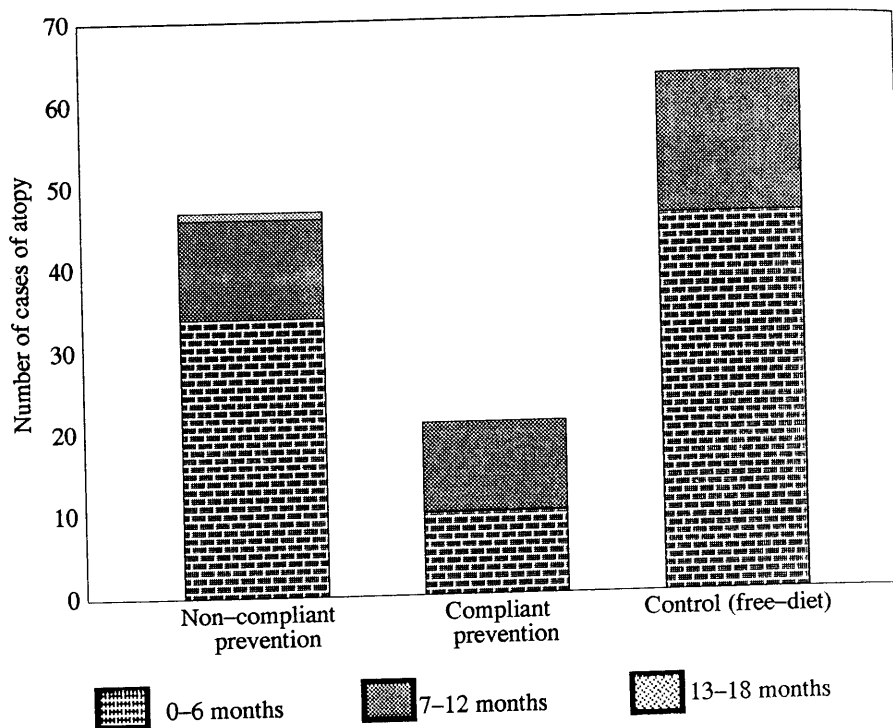


Figure 1. Prevalence of atopic disease in each feeding group during follow-up.

Table 3. Infants Expressing Atopic Symptoms (numbers and percentages) and their Prevalence by Anamnestic Score and Clinical Group

| Clinical Group          | Symptomatic Infants with Anamnestic Scores of 1-2* | Symptomatic Infants with Anamnestic Scores of 3-4† |
|-------------------------|----------------------------------------------------|----------------------------------------------------|
| Compliant prevention    | 20/145 (14)                                        | 1/13 (8)                                           |
| Noncompliant prevention | 40/75 (53)                                         | 7/11 (64)                                          |
| Control                 | 52/196 (27)                                        | 11/22 (50)                                         |

\*  $\chi^2 = 39.310$  for  $2 \times 3$  test ( $P < .001$ );  $\chi^2 = 38.964$  for compliant versus noncompliant ( $P < .001$ );  $\chi^2 = 8.118$  for compliant versus control ( $P < .01$ );  $\chi^2 = 17.378$  for noncompliant versus control ( $P < .001$ ).

†  $\chi^2 = 0.550$  for noncompliant versus control ( $P > .05$ );  $\chi^2 = 8.445$  for compliant versus noncompliant + control ( $P < .01$ ).

Table 4. Prevalence of High IgE (numbers and percentages) in the Presence or Absence of Atopic Symptoms in the Various Clinical Groups

|                         | IgE > 1 IU/mL in Asymptomatic Infants* | IgE > 1 IU/mL in Symptomatic Infants |
|-------------------------|----------------------------------------|--------------------------------------|
| Compliant prevention    | 48/137 (35)                            | 17/21 (81)                           |
| Noncompliant prevention | 15/39 (38)                             | 42/47 (89)                           |
| Control                 | 55/155 (35)                            | 43/63 (68)                           |

\* Comparing asymptomatic infants with symptomatic infants in each clinical group showed the following significance: all cases,  $\chi^2 = 67.050$ ,  $P < .001$ ; compliant group,  $\chi^2 = 15.854$ ,  $P < .001$ ; noncompliant group,  $\chi^2 = 24.707$ ,  $P < .001$ ; and control group,  $\chi^2 = 19.439$ ,  $P < .001$ .

atopic symptoms were noted between any of the three compliant prevention groups, regardless of feeding method. When diet restrictions were violated by nursing mothers, however, a higher incidence of atopy was observed in infants less than 6 months old. When the recommendations against early introduction of cow milk or solid foods were violated, higher incidence of atopy was also observed—37% in infants age 0 to 6 months and 20.4% in 6- to 12-month-old infants.

This correlation between feeding method and atopic symptoms is substantiated by a pair of monozygotic twins entered in the study. One twin followed the prescribed diet, while the other twin was noncompliant due to a dislike for soy formula. The twin on the cow milk-based formula presented with atopic eczema due to cow milk sensitization.

Distribution of the atopic signs and symptoms in the 131 sympto-

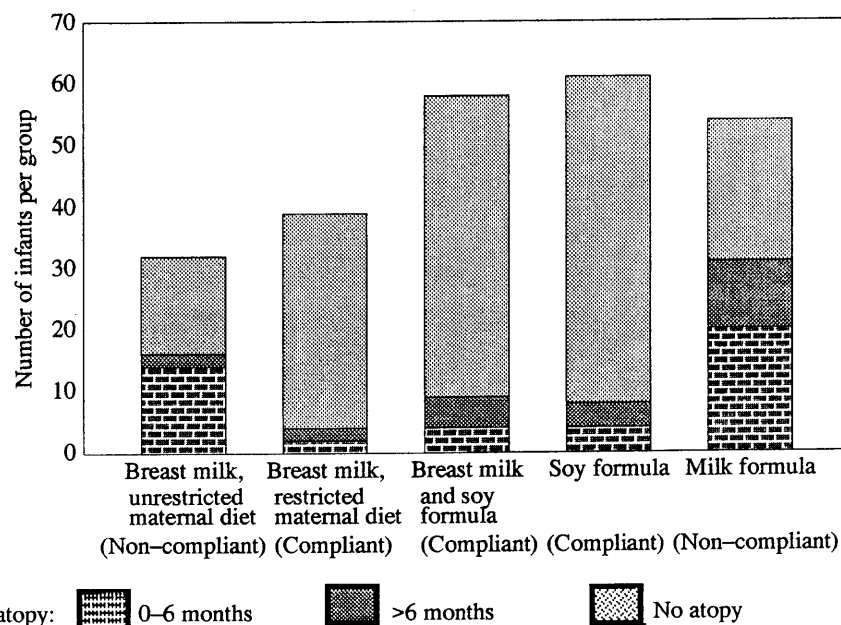


Figure 2. Type of feeding and prevalence of atopic symptoms in the prevention group.

matic patients is shown in Figure 3. The most common symptom was eczema which, as Table 5 shows, was likely to be more severe in patients who did not follow the prevention regimen.

Mild respiratory symptoms were detected in 25 subjects (19%). One was sensitive to molds, another to *Dermatophagoides*. The remaining subjects were sensitized to foods. Sensitization was determined by skin-prick testing.

Rare gastroenteric symptoms (6%) disappeared after the diet was corrected. Both cases of shock occurred when breast-fed infants were first fed formula: one infant reacted to cow-milk-based formula, the other to soy formula.

★ Table 6 shows the food allergens responsible for atopy. Sensitization to soy was verified by provocation-diet test, by skin-prick test, and by RAST (positive early in three infants, late in two).

Of 310 infants with no anamnestic history but with high IgE levels in cord blood, 92 could be tracked. Forty-one (44%) of these infants had normal IgE levels at 3 months; eight infants in this group had atopic symptoms. Symptoms were statistically more likely to be present in the group with persistent elevation of IgE levels ( $P < .01$  for two-tailed Fisher test).

## DISCUSSION

The increasing incidence of atopic diseases, with their burden of suffering and social cost, has prompted preventive measures, among them dietary manipulation, in the early months of life.

Obviously, prevention requires identifying infants at risk for atopic diseases. In this study, elevated cord-blood IgE returned to normal in 44% of infants by 3 months of age, and atopic symptoms were present in only 16% of those infants whose IgE was still elevated at 3 months. More prolonged tracking might have yielded higher incidence of atopy in this group, as other investigators have reported.<sup>23-25</sup>

Our study found among the con-

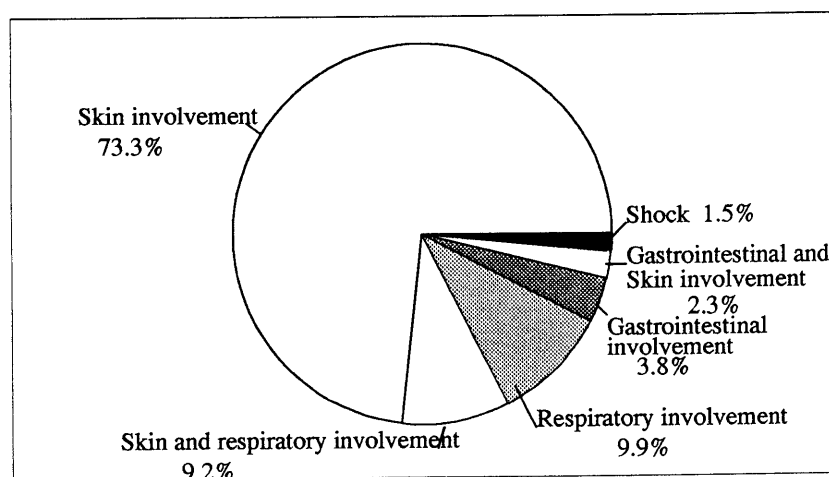


Figure 3. Systems displaying atopic symptoms.

Table 5. Prevalence and Severity of Atopic Eczema in Each Study Group

| Study Group                   | Mild Eczema | Moderate Eczema | Severe Eczema |
|-------------------------------|-------------|-----------------|---------------|
| Compliant prevention group    | 8           | 8               | 1             |
| Noncompliant prevention group | 13          | 18              | 10            |
| Control (free-diet) group     | 35          | 13              | 5             |

Table 6. Food Allergens Responsible for Atopy and Prevalence of Each

| Allergen               | Prevalence |
|------------------------|------------|
| Milk and milk products | 28         |
| Egg                    | 25         |
| Cereal                 | 8          |
| Tomato                 | 8          |
| Fruit                  | 5          |
| Soy                    | 5          |
| Seeds                  | 4          |
| Fish                   | 4          |
| Meat                   | 3          |
| Potato                 | 1          |

control group of infants an incidence of atopic symptoms of 27% for those with a single relative with atopy and 50% for infants with a biparental history of atopy. These percentages were higher than the incidence observed in the general population, and would indicate that anamnestic history does identify infants at risk, as other authors have suggested.<sup>1-12</sup>

Breast feeding effectively reduced the incidence of atopic symptoms, when the mothers observed prescribed dietetic restrictions. (Only 13% of the compliant prevention group experienced atopy; 55% of the noncompliant prevention group developed atopy, as did 29% of the control group.) When mothers did not observe dietary restrictions, atopic symptoms were actually more likely to occur, as observed with the noncompliant prevention group. This finding underscores the importance of a prescribed maternal diet for nursing mothers.

Soy formula—alone or as a breast-milk supplement—also prevented atopy, since the number of soy-fed infants with atopic symptoms either 0 to 6 or 6 to 12 months of age was less than that for infants on unrestricted diets. Allergic reactions to soy occurred in only five

subjects, probably due to the limited prevalence of soy in the diets of Italians. Either soy or cow milk, however, can cause severe systemic reactions.

Regarding anamnestic scores, the control group had a significantly higher incidence of symptoms among infants with anamnestic scores of 3 or 4 than among infants with scores of 1 or 2 (50% vs 27%). Symptomatology for infants with biparental risk was similar among free-diet infants and noncompliant infants. Symptomatology was considerably lower for infants given the prescribed diet. This may indicate that biparental risk makes dietary restrictions especially important.

Atopic dermatitis was by far the most common allergic feature in this study. This was expected because younger subjects frequently exhibit this symptom and because food allergies are often associated with eczema.<sup>26,27</sup>

Respiratory symptoms are more commonly associated with environmental factors such as tobacco smoke, animal dander, or early entrance into daycare centers. We believe a more extensive follow-up would have shown these symptoms to be unrelated to diet, but they were included in this analysis.

Our study comparing infants given a prescribed diet with infants given a free diet indicates that our prescribed diet decreases the incidence of atopic symptoms during an infant's first year of life. A more prolonged follow-up is required to determine whether this diet will also prevent atopy later in life.

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*Request for reprints should be addressed to:*  
*Maria Bardare, Associate Professor of*  
*Pediatrics*  
*10 Pediatric Clinic of University of Milan*  
*Via Commenda 9*  
*20122 Milan*  
*Italy*

## NEARLY 50 YEARS AGO

### IMMUNOTHERAPY BENEFICIAL THROUGH MULTIPLE MECHANISMS

The authors agreed with perceptions that the beneficial effects of immunotherapy usually were due to neutralization of antigen by circulating antibody but ascribed a more prolonged effect to "de-allergization." De-allergization included all mechanisms that counteracted actions of allergic antibodies, including suppression of their production and tolerance following anaphylaxis.

Subsequent extensive research has confirmed that immunotherapy can elicit not only blocking antibodies but also suppression of IgE synthesis, which may be due to induction of suppressor T-cells or production of  $\gamma$  interferon by helper T-cells. Reduction in skin test reactivity and lymphocyte responsiveness to allergen in vitro suggests a downregulation of effector cells may also occur.

—RMS

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