The development of food allergy depends on several factors, including genetic factors and early exposure to allergenic proteins in the diet, food protein uptake and handling, and the development of tolerance. Many hypotheses, as regards the possible causal relationships, have been raised during the past few years, including the hygiene theory, the role of bacterial gut flora, and the potential effect of different cytokines in breast milk. Although interesting, these are mainly speculations based on non-interventional and often retrospective/cross-sectional studies including small study populations. These theories remain to be documented in proper, controlled and prospective studies. Breastfeeding and the late introduction of solid foods (>4 months) is associated with a reduced risk of food allergy, atopic dermatitis, and recurrent wheezing and asthma in early childhood. In all infants, breastfeeding should be encouraged for 4–6 months. In high-risk infants a documented extensively hydrolysed formula is recommended if exclusive breastfeeding is not possible for the first 4 months of life. There is no evidence for preventive dietary intervention neither during pregnancy nor lactation. Preventive dietary restrictions after the age of 4–6 months are not scientifically documented. Curr Opin Allergy Clin Immunol 1:229–236. © 2001 Lippincott Williams & Wilkins.

Introduction

The development and phenotypic expression of atopic disease depends on an interaction between genetic factors, environmental exposure to food and inhalant allergens, and non-specific adjuvant factors (e.g. tobacco smoke, air pollution and infections). The expression of allergic diseases may vary with age, and symptoms may disappear and be replaced by other symptoms. In infancy, the main atopic symptoms are atopic dermatitis, gastrointestinal symptoms, and recurrent wheezing, whereas bronchial asthma and allergic rhinoconjunctivitis are the main problems later in childhood. Adverse reactions to foods, mainly cow’s milk protein, are most common in the first years of life, whereas allergy to inhalant allergens mostly occurs later. It is thus very important to take into consideration the natural course of the disease when evaluating the results from interventional studies on the prevention of allergic diseases.

The development of food allergy/food intolerance (FA/FI) depends on several factors, including early exposure to allergenic proteins (time, dose, frequency), food protein uptake and handling, and the development of tolerance. The development and rather high incidence of FA/FI and especially cow’s milk protein allergy/intolerance (CMPA/I) in infancy has been suggested to be caused by an incomplete mucosal barrier, increased gut permeability to large molecules and the immaturity of local and systemic immunological responses. Human colostrum/milk facilitates maturation of the gut and provides a passive protection against bacteria and antigens (allergens) by means of specific secretory IgA and other protecting factors [1].

When evaluating possible risk factors for the development of allergic diseases and the possible effect of preventive measures, it is important to stress some factors. The study design of both non-interventional and interventional studies should be prospective (true), including well-defined diagnostic criteria, a sufficient duration of follow-up, and a proper sample size for adequate statistical evaluation. Besides, interventional studies should include proper randomization, double blinding, and a control for confounders, as well as the proper registration of compliance and follow-up of drop-outs.

As a result of recall bias and selection bias, retrospective studies should not be used for evaluation of predictive/risk factors for the development of allergic diseases. Likewise, cross-sectional studies are not suitable for the
assesssment of cause–effect relationships between exposure to allergens/adjuvant factors and the development of allergic diseases. Generally, it should also be borne in mind that prospective non-interventional studies can be used to generate hypotheses on the relationship between cause and effect in the development of allergic diseases. However, proper confirmation of a possible cause–effect relationship requires a demonstration of the causative mechanism and effect of the elimination/prevention of the suspected causative factor.

Recently, this topic has been reviewed [1,2**,3**], and a position paper from European Society of Pediatric Allergy and Clinical Immunology and European Society of Pediatric Hepatology and Gastroenterology [2**] and an Interim Report on the Primary Prevention on Allergy and Asthma from a WHO/International Association of Allergy and Clinical Immunology Meeting [3**] have been published. During the past year only a few prospective studies addressing the prevention of allergic diseases have been published. The aim of this review is to discuss recently published data on the influence of dietary factors on the development and prevention of atopic diseases especially FA/FI.

Non-interventional studies
Atopic heredity
From prospective studies many possible predictive factors of the development of allergic diseases have been identified. Although it is well documented that atopic heredity is associated with an increased risk of the development of allergic diseases [4–7], it has also been demonstrated that most children who develop atopic symptoms during the first years of life come from families without an atopic heredity. The majority of children with recurrent wheezing/asthma thus do not belong to high-risk groups for the development of atopic disease [4], whereas a higher proportion of children with allergic disease, including other manifestations than asthma, will have atopic heredity [7].

Dietary factors
Breastfeeding
Previous prospective non-interventional studies in unselected infants have shown an association between early infant feeding of cow’s milk formula and the development of atopic eczema and CMPA/I (Table 1) [8–10,11**]. One cohort study [8] demonstrated an association between early cow’s milk formula feeding and the development of cow’s milk protein allergy. A previous non-interventional study [9] indicated a preventive effect of breastfeeding as regards eczema and food allergy at 1 and 3 years and asthma up to 17 years of age, but no adjustment for confounders were performed. A recent prospective Australian study [10] including 2979 children showed a substantial reduction in the risk of childhood asthma assessed at 6 years of age, if exclusive breastfeeding was continued for at least 4 months of life. In that study, logistic regression analysis including important confounders was used. However, it is important to bear in mind that several studies have shown that mothers who choose to breastfeed their infants behave in another way compared with mothers who choose formula feeding. Exclusively breastfed infants also belong to a higher social class, are less exposed to tobacco smoke and pets, and have solid foods introduced at a later age, which are factors shown to affect the risk of the development of atopic disease, especially respiratory symptoms [12**].

A possible protective effect of breastfeeding on the development of atopic diseases may be caused either by: (i) a protective effect of human milk (the constituents) or (ii) the avoidance of a ‘high dose’ of cow’s milk proteins.

Low concentrations of food allergens especially cow’s milk proteins are shown to be present in human milk when consecutive testing is done. According to the low incidence of CMPA/I in exclusively breastfed infants at 0.5% in unselected infants [8], and 1.3% in high-risk infants [12**] in prospective birth cohort studies, this low-degree exposure seems to induce tolerance rather than disease.

Recent studies indicated that variations in the composition of human milk, e.g. low levels of alpha-linolenic acid and a disturbed relationship between the n-3 and the n-6 fatty acids [13] or varying concentrations of cytokines [14*,15*], may partly explain some of the controversies regarding the protective effect of breastfeeding against allergy. These observations are based on the analyses of samples of breast milk from mothers on a restrictive diet because of diagnosed CMPA/I in their children compared with a small number of samples from mothers on an unrestricted diet and children without CMPA/I. No consecutive testing of breast milk was performed. No association between nucleotide and polyamine levels in human milk and atopy development during the first year of life has been found [16]. These observations are interesting, but not conclusive, and prospective long-term follow-up studies with a proper sample size are desirable for confirmation of these possible relationships.

Solid foods
As for the introduction of cow’s milk proteins before 4 months of age, the introduction of complementary foods (solid foods) before 4 months of age has been associated with a higher risk of atopic dermatitis up to the age of 10 years [17].
It has been hypothesized that the intestinal microbial flora may influence the development of sensitization [18,19*,20*]. Two of the studies [18,19*] are cross-sectional, including a small number of children at the ages of 2 years and 13 months with and without atopic symptoms. In one prospective study of 76 atopic predisposed infants [20*], a significant difference in the bacterial cellular fatty acid profile of stool samples was found by 3 weeks, but not at 3 months of age in atopic infants compared with non-atopic infants. Atopic infants (n = 18) were defined as having at least one positive skin-prick test to any of 16 allergens at the age of 12 months. The authors concluded that differences in the neonatal gut microflora precede the development of atopy, suggesting a crucial role for the balance of indigenous intestinal bacteria for the maturation of human immunity to a non-atopic mode. Meanwhile, the study did not provide firm evidence for such a conclusion. Convincing evidence for this theory, as well as the hypothesis (speculation) that an unclean lifestyle with lots of infections during early childhood may prevent the development of atopic disease, needs confirmation by prospective studies.

### Intestinal microbial flora

It has been hypothesized that the intestinal microbial flora may influence the development of sensitization [18,19*,20*]. Two of the studies [18,19*] are cross-sectional, including a small number of children at the ages of 2 years and 13 months with and without atopic symptoms. In one prospective study of 76 atopic predisposed infants [20*], a significant difference in the bacterial cellular fatty acid profile of stool samples was found by 3 weeks, but not at 3 months of age in atopic infants compared with non-atopic infants. Atopic infants (n = 18) were defined as having at least one positive skin-prick test to any of 16 allergens at the age of 12 months. The authors concluded that differences in the neonatal gut microflora precede the development of atopy, suggesting a crucial role for the balance of indigenous intestinal bacteria for the maturation of human immunity to a non-atopic mode. Meanwhile, the study did not provide firm evidence for such a conclusion. Convincing evidence for this theory, as well as the hypothesis (speculation) that an unclean lifestyle with lots of infections during early childhood may prevent the development of atopic disease, needs confirmation by prospective studies.

### Interventional studies

#### Dietary measures

**Unselected/non-high-risk infants**

Only a few prospective intervention studies have been performed in infants without a hereditary atopic predisposition (Table 2). In premature unselected infants, Lucas et al. [21] found no difference as regards the development of atopic symptoms or CMPA/I whether the infants were fed human bank milk or cow’s milk-based formula. Other studies [22–24] concluded that cow’s milk-based formula given during the first few days of life did not increase the cumulative risk of atopic disease at the age of 2 [24], 4–6 [22] and 14 years [23]. However, those studies only included intervention diet for the first few days of life, one [22] only included low birthweight infants, one [23] was not randomized, and the outcome was based on data from medical files and questionnaires obtained at 7, 11 and 14 years. In one study [24] the diagnostic criteria were unspecific, and outcome measures were mainly based on questionnaires. In a recent randomized study including a large number (n = 6209) of full-term, unselected newborns [25,26*], the infants with a need for supplementary formula received either adapted liquid cow’s milk formula, pasteurized human milk or extensively hydrolysed formulas (eHF). The results indicated that the feeding of cow’s milk-based formula at the maternity hospital increased the risk of CMPA when compared with feeding an eHF, but exclusively breastfeeding for 8 weeks did not eliminate the risk of CMPA. Besides, the results indicated that significant risk factors for the presence of IgE antibodies to cow’s milk in allergic infants were a long duration of breastfeeding, exposure to cow’s milk at the maternity hospital, and breastfeeding during the first 2 months at home either exclusively or combined with infrequent exposure to small amounts of cow’s milk [26*]. However, the dietary intervention only included the first 4 days of life, after which period the mothers chose the diet themselves, and it is hard to exclude the possibility that this ‘self-selection’ influenced the results.
control cohort [28*]. In the intervention cohort significantly more infants were exclusively breastfed from the age of 3–6 months, and weaning foods were introduced at a significantly later age, which the authors concluded was as a result of the dietary recommendations in the study [27*]. However, the two study cohorts represented two different regions and were significantly different as regards parent education, household pets, the number of older siblings, exposure to tobacco smoke and urban residence. The study allows no conclusions as regards allergy prevention. It is astonishing that such an intervention study including an allergen-reduced diet did not include specific allergic disease as an outcome measure.

High-risk infants

An effect of dietary allergy prevention has only been demonstrated in high-risk infants, i.e. infants with double parental atopy or at least one first-degree relative (parent or sibling) with documented atopic disease (doctor diagnosed), the latter possibly combined with elevated cord blood IgE in the case of single atopic predisposition. It is difficult to compare the effect of these different prevention programmes because of the great variations in study design and diagnostic criteria [1,29].

Breastfeeding

In high-risk infants, exclusively breastfeeding for 4 months in combination with the avoidance of solid foods has resulted in a significant reduction of the cumulative incidence of CMPA/I and atopic dermatitis during the first 4 years of life [21,30–35] (Table 3). Infants cannot ethically be randomly assigned to breast or formula feeding to enable a definitive study. Confounding factors may thus greatly influence the results of comparisons. In one study by Lucas et al. [21], preterm infants were randomly assigned to human bank milk or cow’s milk-based formula, and a significant reduction in the incidence of atopy and CMPA/I was found in high-risk infants fed human bank milk. Although some doctors advise pregnant women to avoid some ‘allergenic foods’ such as peanuts, there is no evidence of a protective effect of a maternal exclusion diet during pregnancy [36–39] (Table 4). A few studies indicated that the preventive effect of breastfeeding on the development of atopic dermatitis may be enhanced by maternal avoidance of potential food allergens (milk, egg, and fish), whereas other studies did not confirm this finding [39–44] (Table 4).

Formulas

Results from prospective studies including formula feeding are summarized in Table 5. Some prospective studies have shown that soy formulas are as allergenic as conventional cow’s milk-based formulas, and on this basis they should not be recommended for the prevention of food allergy [29,33], but different views exist [45–47]. There is no evidence that formulas based on whole proteins other than cow’s milk protein are less allergenic.

Several prospective studies [12**,33,35,43,44,48–54] demonstrated a preventive effect of eHF in combination with the avoidance of cow’s milk proteins and solid foods during at least 4 months in high-risk infants on the cumulative incidence of atopic dermatitis and food allergy, especially CMPA/I until the age of 4–7 years. A real preventive effect, and not only a postponement of the onset of the disease, was thus documented.

In randomized prospective studies [32,34,53–57] in high-risk infants an allergy preventive effect of partly hydrolysed formulas (pHF) has been reported. Because of great variations in study design and diagnostic criteria, the relative efficacy of the different interventions tested in the various studies cannot be compared directly with each other, and only a few studies comparing the effect of eHF and pHF have been published. A recent Swedish study [58] reported a lower cumulative incidence of atopic symptoms up to the age of 18 months with both an eHF and a pHF diet, compared with a cow’s milk protein-based formula; a greater effect was reported with eHF. These data are supported by a Danish prospective randomized, double-blind study.

Table 2. Dietary allergy prevention: interventional studies in unselected infants

| Study                  | N   | Follow-up | Diet                     | Effect of diet          |
|-----------------------|-----|-----------|--------------------------|-------------------------|
| Lucas et al. 1990 [21]*| 777 | 18 months | Human bank milk vs CMF   | → Atopic disease        |
| Lindfors et al. 1992 [22]* | 183 | 4–6 years | HM ± CMF                  | → Atopic symptoms       |
| Gustafsson et al. 1992 [23] | 736 | 14 years  | HM vs CMF                 | No effect               |
| de Jong et al. 1999 [24] | 1533| 2 years   | CMF vs no CMF             | → Atopic symptoms       |
| Saarinen et al. 1999 [25] | 5385| 18–34 months | CMF vs eHF/HM            | ↑ CMPA                  |
| Saarinen and Savilahti 2000 [26*] |     |           |                          |                         |

Effect of infants’ diet indicated by arrows: ↑ indicates increase, ↓ indicates decrease or → no change in the incidence of disease/symptoms in infants having the diet mentioned.

aPremature infants; bLow birthweight infants; cIncluded diet only for the first few days.

CMPA, Cow’s milk allergy; CMF, cow’s milk-based formula; eHF, extensively hydrolysed formula; HM, human milk; RAST, radioallergosorbent test.
from birth to 18 months of age comparing the allergy preventive effects of two eHF and one pHF, published last year [12**]. The study included a 1-year birth cohort of high-risk infants (n = 478) randomly assigned at birth to one of the three hydrolysed formulas if breastfeeding was not possible or sufficient. Only a few infants were never breastfed, most of the infants were breastfed exclusively (n = 232) or had varying amounts of supplement with formula (n = 246) until the age of 4 months. The introduction of complementary foods was not recommended until the age of 4 months. After the age of 4 months no dietary restrictions were recommended, and all mothers had an unrestricted diet during pregnancy and lactation. In the study the overall incidence of confirmed CMPA/I was low (1.3%) and significantly lower in infants fed eHF (0.6%) compared with pHF (4.7%). The study thus showed a better allergen-specific preventive effect of eHF, but did not exclude an effect of a pHF also.

The duration and the dietary restrictions vary in different studies. All studies showing a preventive effect

Table 3. Dietary intervention in ‘high-risk’ infants. Prospective studies including control group: infant diet breastfeeding for at least 4 months

| Study                      | N   | Follow-up (months) | Diet           | Effect of diet          |
|----------------------------|-----|-------------------|----------------|-------------------------|
| Chandra et al. 1985 [30]   | 121 | 24                | BF            | ↓ AD, wheeze           |
| Miskelly et al. 1988 [31]  | 487 | 12                | BF            | ↓ Atopy                |
| Chandra and Hamed 1991 [34]| 263 | 18                | CMF=soy       | → Atopy                |
| Chandra et al. 1989 [33]   | 221 | 18                | BF            | ↓ AD, atopy            |
| Vandenplas et al. 1988 [32]| 45  | 4                 | BF            | → AD                   |
| Lucas et al. 1990 [21]     | 160 | 18                | BF            | ↓ Atopy                |
| (777 preterms)             |     |                   |                | ↓ CMPA                 |
| Halken et al. 1993 [35]    | 141 | 18                | BF            | ↓ CMPA                 |

Effect of infants’ diet indicated by arrows: ↑ indicates increase, ↓ indicates decrease or → no change in the incidence of disease/symptoms in infants having the diet mentioned.

AD, Atopic dermatitis; BF, breastfeeding compared with formula feeding; CMF, cow’s milk-based formula; CMPA, cow’s milk protein allergy.

Table 4. Dietary intervention in ‘high-risk’ infants. Prospective studies including control group

| Study                      | N   | Follow-up (months) | Diet           | Effect of diet          |
|----------------------------|-----|-------------------|----------------|-------------------------|
| Maternal diet during pregnancy |    |                   |                |                         |
| Fälth-Magnusson et al. 1987 [36] | 180 | 0                 |                | → Spec. IgE             |
| Fälth-Magnusson and Kjellman 1992 [37] | 180 | 60               |                | → Atopy                 |
| Lilja et al. 1989 [39]      | 163 | 18                |                | → Atopy                 |
| Maternal diet during pregnancy and lactation |    |                   |                |                         |
| Chandra et al. 1986 [38]    | 109 | 12                |                | → AD                   |
| Zeiger et al. 1989 [43]     | 225 | 48                |                | ↑ CMF AD               |
| Zeiger et al. 1992 [44]     |     |                   |                | ↑ FA                   |
| Lilja et al. 1989 [39]      | 107 | 18                |                | → Atopy                |
| Study                      | N   | Follow-up (years) | Diet           | Effect of diet          |
| Maternal diet during lactation |    |                   |                |                         |
| Businco et al. 1983 [40]    | 101 | 2                 | BF, soy        | ↓ Atopy                |
| Chandra et al. 1989 [33]    | 225 | 1½                | CMF            | ↑ Atopy                |
| Lilja et al. 1989 [39]      | 107 | 1½                | BF + D         | ↓ AD                   |
| Sigurs et al. 1992 [41]     | 115 | 4                 | BF + D         | → Atopy                |
| Hattvig et al. 1999 [42]    | 105 |                   | BF + D         | ↓ AD                   |
|                           |     |                   |                | → SPT, RAST             |

Effect of infants’ diet indicated by arrows: ↑ indicates increase, ↓ indicates decrease or → no change in the incidence of disease/symptoms in infants having the diet mentioned.

AD, Atopic dermatitis; BF, breastfeeding compared with formula feeding; CMF, cow’s milk-based formula; D, maternal diet; FA, food allergy; RAST, radioallergosorbent test; SPT, skin prick test.
have included solely breastfeeding or eHF and the avoidance of cow’s milk and solid foods for 4–6 months or longer. Studies including restrictive diets for a long period of more than 12–24 months and studies with dietary restrictions for only 4–6 months have shown comparable results. In the last published Danish study [12**, the infants had dietary restrictions for the first 4 months of life only, and this regimen resulted in a very low incidence of CMPA/I and other food allergies until the age of 18 months. In one recent study [59], no significant effect of supplement with eHF compared with cow’s milk-based formula after the age of 6 months in breastfed high-risk infants was found. Controlled studies concerning the possible preventive effect of the avoidance of other potential food allergens, e.g. egg, fish, etc., after the age of 4–6 months of life have not been published. There is thus no evidence of an allergy preventing effect of restrictive diets after 6 months of age.

**Conclusion**

As summarized in Table 6, recent prospective intervention- and non-interventional studies have demonstrated a preventive effect of simple dietary measures during the first 4–6 months of life as regards the development of food allergy, especially cow’s milk allergy and atopic eczema.

**Table 6. Primary prevention: present evidence-based recommendations**

| Study | N  | Follow-up (months) | Diet    | Effect of diet |
|-------|----|--------------------|---------|---------------|
| Vandenplas et al. 1988 [32] | 45 | 4                  | pHF     | CMPA, atopy   |
| Chandra and Hamed 1991 [34] | 263| 18                 | pHF     | AD, atopy     |
| Vandenplas et al. 1992 [54] | 67 | 12                 | pHF     | CMPA 15.6%    |
| Chandra et al. 1989 [33]    | 221| 18                 | eHF     | AD            |
| Zeiger et al. 1989 [43]     | 225| 48                 | eHF     | FA            |
| Zeiger et al. 1992 [44]     |    |                    |         |               |
| Halken et al. 1993 [35]     | 141| 18                 | eHF     | CMPA (3.6%)   |
| Oldaas 1997                 | 50 | 18                 | eHF     | Atopic symptoms 51% |
|                             | 45 | 18                 | pHF     | Atopic symptoms 64% |
|                             | 46 | 18                 | CMF     | Atopic symptoms 84% |

Effect of infants’ diet indicated by arrows: ↑ indicates increase, ↓ indicates decrease or → no change in the incidence of disease/symptoms in infants having the diet mentioned.

AD, Atopic dermatitis; BF, breastfeeding compared with formula feeding; CMPA, cow’s milk allergy; CMF, cow’s milk-based formula; CMPA, cow’s milk protein allergy; eHF, extensively hydrolysed formula; FA, food allergy; pHF, partly hydrolysed formula.

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