The effects of a synbiotic in infants with atopic dermatitis
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ABSTRACT

The relationship between infant feeding patterns and the later development of food allergies has been the focus of much debate and research over the last decade. National recommendations have been made by many countries on how to feed infants to reduce the risk of food allergy but due to the lack of firm evidence the recommendations differ widely. This review has been developed as part of EuroPrevall, a European multicentre research project funded by the European Union, to document the differing feeding recommendations made across Europe, to investigate the current evidence base for any allergy prevention feeding recommendations and to identify areas where further research is needed. This review will also provide information which, when combined with the infant feeding data collected as part of EuroPrevall, will give an indication of compliance to national feeding guidelines which can be utilised to assess the effectiveness of current dissemination and implementation strategies.

BACKGROUND

Although there are uncertainties as to the prevalence of food allergy (1), there is some evidence that this prevalence is increasing (2;3). Food allergy is most commonly acquired during the first year of life with a cumulative incidence of 6-8% for the first three years of life (4). The prevalence falls until late childhood where it plateaus at around 2% (5) and remains at this level throughout adulthood (6). A third of children with atopic eczema have associated food allergy (7;8) and food allergy also plays an important role in children with asthma where food may be a causative agent and is associated with severe anaphylactic reactions (9).

Although many young children outgrow their reactions to foods, many develop other allergic disorders including asthma, rhinitis and inhalant allergy, a phenomenon often referred to as the ‘allergic march’ (10). If the link between food allergy and the later development of other allergic diseases is taken to be causative, then prevention of the first stage of the allergic march seems the obvious course of action when trying to reduce the prevalence of allergic diseases. Observations have led to the concept of the “window of vulnerability” in early infancy as the optimal period to which interventions may be targeted, and there have been numerous strategies aimed at reducing the incidence of allergic diseases which have focused on environmental and nutritional factors that exist during pregnancy and the first year of life. Importantly, population implementation of feeding guidelines to prevent food allergy has occurred despite the lack of a significant evidence base to support them. Furthermore, many national guidelines continue to be modified despite any controlled data to demonstrate either evidence for effect or harm of previous guidelines (11).

Historically, the experimental protocols of studies in this area have combined environmental and nutritional interventions (12-14). In such studies it is not possible to separate the influence of infant feeding from the influence of other environmental changes. However, in recent years the relationship between infant feeding and the prevention of allergy has been specifically investigated. Most studies have focused on four main areas of infant feeding: breastfeeding (both duration and exclusivity), the use of cow’s milk hydrolysate infant formulas, the timing of the introduction of solids and, more recently, the use of pro- and/or prebiotic supplements. In addition to these studies, a number of research studies (both observational and interventional) are currently underway examining the relationship between infant feeding and the development of allergic disease.

In this paper, the current knowledge base for the effects of the four main parameters related to infant feeding outlined above will be reviewed and a snapshot of current national feeding guidelines presented. Finally, areas of particular importance for future research will be identified and the implications for future guideline development including issues regarding dissemination and implementation will be considered.

Evidence for infant feeding and food allergy prevention recommendations

The following sections discuss the current evidence for infant feeding guidelines and allergy
Evidence related to the duration of exclusive breastfeeding

It is widely accepted that breast milk is the food of choice for infants for a great number of reasons such as cost, safety, psychological benefits and the prevention of infant disease such as diarrhea, wheeze, vomiting and cough (15). However, the question considered here is whether breastfeeding is an effective primary prevention measure for allergic diseases. It must therefore be clear that, even if the evidence of such an effect is weak or absent, this will not lead to a change in general recommendations to breastfeed but rather a change in the information and advice physicians give new mothers with regard to allergy prevention. Because of undoubted health benefits of breastfeeding, randomized studies comparing the effects of breastfeeding and alternative infant formulas are scarce (16). Recent reviews of observational studies on the protective effect of breastfeeding have shown conflicting results. Muraro (17) reviewed 15 observational and 14 intervention studies and concluded that breastfeeding high risk infants for at least 4 months was associated with a reduced cumulative risk of cow’s milk allergy until 18 months of age. Friedman and Zeiger (18) also reviewed such studies. They highlighted that 3 studies published in the 1980’s demonstrated that exclusively breastfed infants had lower serum IgE, less eczema and fewer asthmatic episodes but that four studies showed breastfeeding to have no protective effect on the development of food allergy. None of these studies were either randomized or prospective so their results must be interpreted with care (a point emphasised by the authors). In 2001, Gdalovich et al performed two meta-analyses looking at the relationship between breastfeeding and eczema and asthma respectively (19;20) and found a significant protective effect against the development of eczema by breastfeeding. Breastfeeding for at least the first 3 months of life led to a decreased rate of asthma in high risk infants. However, a 2004 systematic review (21) concluded that at least 6 months of exclusive breast feeding did not protect against the development of food allergy by the age of 1 year when compared to infants who where exclusively breastfed for 4-6 months and this work has been supported recently, by Kramer and colleagues (22) who performed a cluster randomized trial comparing infants from centres randomized to an intervention promoting breastfeeding to those not receiving this intervention. At follow-up at age 6.5 years, no differences were seen in the prevalence of asthma, atopic dermatitis, allergic rhinitis, or skin test positivity to common inhalant allergens (22).

Most of the studies that examined the effect of breastfeeding on food allergy were carried out in unselected cohorts with regard to allergy risk (23-29). None were able to demonstrate a protective effect of breastfeeding on food allergy. Relatively few studies have assessed the effect of breastfeeding in high risk infants (27;30;31). One of these (non-randomized) studies reported a prevalence of cow’s milk allergy at age 1.5 years of 3.6% in breast- or hydrolysate fed infants, as opposed to 20% in those not receiving preventive dietary measures (30). Recently, a long term follow-up study of high risk infants examined the role of breastfeeding on a number on allergic outcomes, including food allergy (32). This study showed that while there was a modest protective effect of breastfeeding on food allergy (as well as asthma, atopic dermatitis and allergic rhinitis) up to the age of 7 years, this risk was paradoxically increased after the age of 7. Additionally the German Infant Nutrition Intervention (GINI) study (33) seems to show that any benefit provided by exclusive breastfeeding appears to be conveyed only in high risk infants. In summary, although all authorities agree that breast milk is the food of choice for infants, the evidence that it prevents allergic outcomes is contradictory, with different studies showing, protection, no effect and even increased risk. This may be due to variations in breast milk composition or differences in maternal diet (34), but no studies have shown long term benefits with regard to allergic outcomes. These conclusions also apply to the effect on the prevention of food allergy in particular. Although it would be desirable to have studies that directly assess the effect of breastfeeding on the development of allergy diseases, there are both methodological and ethical problems with conducting such controlled trials which will probably continue to limit the quality of the evidence supporting its role in the prevention of allergic disorders.

Evidence related to infant cow’s milk based formulas

There have been a number of studies examining the merits of cow’s milk hydrolysate as a primary prevention for allergic diseases. Despite the fact that these studies have often been conducted as randomized, controlled trials, they have frequently been characterised by a number of methodological shortcomings, including problems with blinding, inadequate outcome assessments, and inability to distinguish true prevention from delaying symptoms (reviewed in (35)). Also, these studies are nearly always carried out in high risk infants so their findings are only applicable to that sub-population group and not all infants. Intervention studies that have been carried out in high risk infants who are not breast fed have compared both partially and extensively hydrolysed cow’s milk formulas to formulas based on intact cow’s milk. Cow’s milk allergy has been the principle outcome of interest as ascertained by both open and double blind challenge tests. In three studies, a protective effect of hydrolysed infant formulas was found (12,36,37) while in two other studies, no difference was seen (38,39). One study included follow-up to age 7, at which time point no differences were noted (40). The GINI study examined three different hydrolysed infant formulas and standard infant formula, comparing different allergy outcomes between the groups. Both the extensively hydrolysed casein formula and partially hydrolysed whey formula were shown to have a preventative effect on both physician diagnosis of allergic manifestation and atopic dermatitis. Inexplicably, this was not found for the extensively hydrolysed whey formula (41). It is because of these somewhat contradictory findings that many national recommendations may not specify whether an extensively of partially hydrolysed formula should be used but that it should be of “proven reduced allergenicity” (42). It should be noted that the GINI study was designed to compare the allergy preventive effects of hydrolysed formulas as compared to standard infant formula, not breast feeding. A Cochrane review on this topic conducted in 2006 (43) concluded that there is no evidence to support feeding with a hydrolysed formula for the prevention of allergy compared to exclusive...
breastfeeding. In high risk infants who are unable to be exclusively breastfed, there is limited evidence that prolonged feeding with a hydrolysed formula compared to a cow's milk formula reduces infant and childhood allergy and infant cow's milk allergy. In summary, due to inconsistency of findings, there is no clear-cut evidence that the early use of cow's milk hydrolysate exerts a preventive effect on allergic diseases generally or cow's milk allergy in particular. Further carefully designed and correctly powered randomized double-blind placebo-controlled studies are needed before clear recommendations can be made.

**Evidence related to the timing of introduction of complementary foods**

Given the current recommendations in many countries to delay the introduction of all complementary foods until 6 months and for much longer delays for specific allergenic foods, it is surprising that the evidence of the effects of delaying the introduction of allergenic foods into the infant diet is extremely limited. There has been little research looking solely at the relationship between solid food introduction and the later development of allergic disease. Fergusson et al looked at both the timing and rate of introduction of solids into an infant diet with the later development of eczema at two years (44) and found that solid food introduction before 4 months of age and the number of foods introduced was associated with an increased incidence of physician-reported eczema. This association persisted to 10 years of age when a range of confounding factors including family history of atopic disease, other infant diet factors and family socio-economic status were also included in the analysis (45). Also in the 1980 s, Kajosaari compared the introduction of allergenic foods early as compared to after six months of age and showed no differences in the prevalence of food allergy when outcome was assessed by double blind challenge, either in the first year of life (46) or at age five (47). Other studies have looked at the relationship between timing of complementary feeding and allergy development but differences in methodology make it difficult to draw firm conclusions. A recent systematic review looking at complementary feeding before 4 months of age could find little data linking early solid feeding and allergic conditions other than that demonstrated by Fergusson (48).

More recently, infant feeding data collected as part of birth cohort studies have been analysed to investigate the relationship between solid food introduction and the later development of atopy (49-52) No study found any benefit on allergic outcome by delaying the introduction of solids and two found an association between the delayed introduction of milk (51) and egg (50;52) and increased incidence of eczema and atopic sensitisation. More recently it has been suggested that children exposed to cereal grains before 6 months of age (as opposed to after 6 months of age) are protected from the development of wheat-specific IgE (53). However, all studies collected feeding data retrospectively which makes the findings vulnerable to both recall bias and reverse causality. Nevertheless, these studies have raised the possibility that delaying the introduction of foods into an infant's diet (particularly of allergenic foods) is not beneficial and may actually increase the risk of the child developing allergic diseases as suggested recently by a number of authors. (49-54) In summary, further research is needed to establish what effect delaying the introduction of solids in general and allergenic foods in particular into the infant diet has on allergic disease.

**Evidence related to the use of pre- and/or probiotic supplements**

Although the use of pre-, pro- and symbiotics has not yet been incorporated into allergy prevention feeding recommendations, this is a field of tremendous current interest and many infant formulas now include pro- and prebiotics. As these factors are marketed as reducing the risk of development of allergy in formula fed infants the evidence for such claims will be briefly reviewed here.

The intestinal microbiota plays an important role in the development of the mucosal and systemic immune system. It is an important stimulus for the development of the gut associated lymphoid tissue (GALT), the largest mass of lymphoid tissue in the body, and for the development of oral tolerance. Observational studies show differences in gut microbiota composition between atopic and non-atopic infants. Generally, atopic infants have less bifidobacteria and more clostridia than non-atopic infants. These differences precede the development of atopic disease since they already exist in the first few weeks of life, suggesting a causal relationship (55-57).

Manipulating the intestinal microflora of atopic children towards a more “non-atopic flora” with probiotics, prebiotics or a combination of both, (symbiotics), could be a way to prevent allergic diseases. Probiotics are live micro-organisms with various, strain specific immunomodulatory effects. Common probiotic genera are *Lactobacillus* and *Bifidobacterium*. Prebiotics are nondigestible food ingredients that beneficially affect the host by stimulating growth and/or activity of certain bacterial species in the colon (58). A prebiotic mixture of 90% galacto-oligosaccharides (GOS) and 10% fructo-oligosaccharides (FOS), for example, specifically stimulates the growth of bifidobacteria (59;60). Human milk is a rich source of oligosaccharides and this may in part explain the higher populations of bifidobacteria and lactobacilli seen in breast fed infants.

A number of double blind randomized placebo-controlled trials have been performed to investigate the ability of probiotics, prebiotics and symbiotics to prevent allergic disease in high risk infants (details of these studies are given in Appendix 1). These studies have mainly focussed on atopic dermatitis (AD) and not on food allergy. The five studies with probiotics show conflicting results. In three studies the incidence of AD was significantly reduced (61-63). However, in two other studies no effect on AD incidence was found (64;65). Also, the *Bifidobacterium* strain used in the trial of Wickens et al, did not reduce the incidence of AD (63). These conflicting results can possibly be explained by differences in study design, the use of different probiotic strains and dosages and/or genetic characteristics of the populations studied. Two studies included prevention of cow’s milk allergy or food allergy as an outcome and found no effect (61). In none of the studies a reduction in the incidence of other allergic diseases, such as asthma or allergic rhinoconjunctivitis, could be demonstrated and one study even showed an increase in the incidence of wheezing bronchitis in the probiotic group (65).

Currently, only one prevention study with prebiotics, has been performed. This study showed a significant decrease in AD incidence (66) and at age two there were significantly less children with recurrent wheeze or allergic urticaria in the prebiotic group (67). Unfortunately, sensitisation was not included as an outcome measure. To date symbiotics have been used in only one prevention study (68) which showed significantly reduced AD incidence in the treated group. However, there was no reduction of the cumulative incidence of allergic diseases or sensitisation.
In summary, although theoretically pro-, pre- and symbiotics are promising candidates to prevent allergic diseases, results of clinical trials are not conclusive. Some trials show favourable results with regard to AD, but there is currently not enough evidence to support the use of pro-, pre- or symbiotics for prevention of allergic disease in clinical practice (69).

Current international recommendations for infant feeding and allergy prevention

For the purposes of this review we have considered the recommendations made for breastfeeding, the use of infant cow’s milk based formulas and the timing of introduction of complementary feeding for the countries involved in the EuroPrevall project and in other countries across the world where they are readily available. We have included recommendations from the USA, as many nations base their advice on the recommendations given by the American Academy of Pediatrics (AAP) as well as those made by the European Society of Pediatric Allergy and Clinical Immunology (ESPACI) and the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN).

Recommendations on the duration of exclusive breastfeeding

ESPACI and ESPGHAN jointly recommended exclusive breastfeeding for 4-6 months for allergy prevention. The WHO recommends exclusive breastfeeding for 6 months (www.who.int). For most countries, there are no specific breastfeeding recommendations for allergy prevention beyond recommending exclusive breastfeeding for 4-6 months (Appendix 2). The exception is Poland. The Polish Experts Committee advises the avoidance of allergenic foods from the mother’s diet.

Recommendations on infant cow’s milk based formulas

ESPACI and ESPGHAN recommend that high risk infants should be fed with a formula of confirmed reduced allergenicity if they are not breast fed (42). Where breast milk is not available for the child, 12 of the 18 countries included in this review follow the recommendations of ESPACI and ESPGHAN and recommend hydrolysed formula, but 6 have no specific recommendations (Appendix 3).

Recommendations on the timing of introduction of complementary foods

The American Academy of Pediatrics (AAP) until recently recommended no solids until 6 months of age, with a further delay in the introduction of cow’s milk until 1 year, no hen’s egg until 2 years and avoidance of peanut, tree nuts & fish until 3 years of age (70). However, AAP has now revised its guidelines based on the lack of evidence of their effectiveness in preventing food allergy and no longer recommend delaying the introduction of allergenic foods beyond 4-6 months (11). In contrast, a joint statement of ESPACI Committee on Hypoallergenic Formulas and the ESPGHAN Committee on Nutrition advised simply that no solids be given before the fifth month (ie 17 weeks) (42). More recently, ESPGHAN has issued a position paper on complementary feeding which states that avoidance or delayed introduction of allergenic foods for allergy prevention is not recommended. It does, however, recommend the avoidance or early (< 4 months of age) and late (> 7 months of age) introduction of gluten to reduce the risk of wheat allergy (71). It should be noted that changes to recommendations by these bodies of experts have been undertaken in the face of rising prevalence of food allergy despite the fact that no controlled population trials have been undertaken to assess whether families were following guidelines or whether they were effective in prevention.

Details of each country’s recommendations for breast and formula feeding and introduction of complementary foods are detailed in Appendix 2-4. As many countries have adopted the WHO recommendations to some extent, these have also been included in the tables. Table 1 summarises the most commonly recommended feeding guidelines and highlights which countries follow these recommendations. One country (Russia) does not specify which type of hydrolysed formula should be used (extensively or partially) so are not included in that aspect of the table. A search of the national websites for infant feeding recommendations made in some developing countries (China, India and some African countries) showed their recommendations are only concerned with breastfeeding duration and the provision of safe nutritious solids into the infants’ diet. Allergy prevention measures are not considered. This may be because the allergy burden in rural areas of developing countries remains low (72) and is therefore not a major public health concern. Nine countries follow the original recommendation made by the American Academy of Pediatrics (70). Appendix 4 shows the country recommendations in detail.

<table>
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<th>Table 1. Summary of international infant feeding practices</th>
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<tr>
<td>Exclusive breastfeeding to 6 months (all infants)</td>
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<td>Use of partially hydrolysed formula (high-risk infants)</td>
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<td>Use of extensively hydrolysed formula (high-risk infants)</td>
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<td>Introduction of solids after 6 months (all infants)</td>
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<td>Introduction of solids 4-6 months (all infants)</td>
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<td>Delayed introduction of allergenic foods (high-risk infants**)</td>
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<tr>
<td>Detailed guidance regarding order of food introduction (all infants)</td>
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* these countries do not specify which type of hydrolysed formula
** for some countries recommendation is for all infant see appendix 4 for details
*** recently revised and now delayed introduction of allergenic foods no longer recommended for high risk infants by peak body.

Areas of discrepancy

More detailed examination of national recommendations show that the main discrepancies between country recommendations and the evidence base are related to the use of hydrolysed infant formulas (partial, extensively or ‘proven reduced hypoallergenicity’), what age to introduce solids and whether to delay the introduction of allergenic foods into the infants diet. Further
examination of the recommendations show that of the 17 countries considered in this paper, 7 countries recommendations are given by different professional bodies and in all these cases the advice differs depending on which body has issued the recommendations. In addition it has been reported that for at least 3 countries with national recommendations the advice being given by healthcare practitioners can differ greatly and does not always follow national guidelines (personal communication K. Grimshaw) and in Australia where Health Departments are state government funded there are 6 separate state-based guidelines that are not necessarily consistent with the National Government recommendations (NHMRC) nor with the peak body (ASCIA).

Dissemination and implementation
It is important to consider dissemination of recommendations to the consumer as this is likely to significantly impact on population compliance to guideline recommendations. General infant feeding guidelines are usually provided by National Health Departments through pamphlets to all parents of infants in the first few weeks of life, with more specialist advice being provided by medical specialists and their professional associations at clinic visits or through web-based portals. Patient support groups such as national breastfeeding support groups including La Leche also have a significant impact on which recommendations are disseminated to the general public. Health information is easily accessible from the internet, books and magazines so that many women question the role of health professionals in advising how mothers should feed their infants. It appears that mothers in the UK are resistant to directives on infant feeding unless there is a clear indication as to why the advice is being given. Instead they would rather refer to books and other mothers for advice on how to feed their child (either face to face or via ‘blogs’ on the internet), adapting recommendations as they feel appropriate (Boulay et al, unmanuscripted data). However, in other European countries, mothers appear more willing to follow the paediatrician’s instructions (73). Bearing this in mind it is obvious that dissemination of any feeding recommendations has to be given consideration to prevent it being by-passed by mothers for more socially acceptable sources of advice as this may have a significant impact on the ultimate effect of these recommendations. In fact, in most countries, recommendations have not been implemented in a formal way, resulting in an increased risk of non-compliance. Feeding guidelines should be communicated clearly to the consumer as this may have a significant impact on the ultimate effect of these recommendations. In addition it has been reported that for at least 3 countries with national recommendations the advice being given by healthcare practitioners can differ greatly and does not always follow national guidelines (personal communication K. Grimshaw) and in Australia where Health Departments are state government funded there are 6 separate state-based guidelines that are not necessarily consistent with the National Government recommendations (NHMRC) nor with the peak body (ASCIA).

DISCUSSION
The contents of this paper reflect a wide international sample of infant feeding recommendations. However it is limited to those members of the EuroPrevall consortium and its external partners. Over half (52%) of member states of the European Union have been captured as well as Australasia, South Africa and Russia. Our justification for selecting the European nations is to provide a baseline of infant feeding recommendations from those countries for which prevalence data will become available from the EuroPrevall project. These results will enable comparisons to be made between countries as allergy prevalence data comes to light. Our survey highlights the significant diversity of recommendations for infant feeding across Europe and around the world. Despite this diversity, common themes were found including widespread support for exclusive breast feeding until 6 months of age, use of hypoallergenic formulas and advice as to when to introduce complementary foods (although these recommendations varied from introduction at 3 months to no solid introduction until after 6 months of age). In addition to the timing of solid food introduction, there was significant national variation in the type of first foods recommended to be introduced into the weaning diet with some countries giving advice on the order in which to introduce specific foods. As has been pointed out, there is, from an allergy prevention point of view, little definitive evidence supporting any of the infant feeding recommendations made. Hence, the observed inter-country diversity is probably unsurprising.

In addition to the diversity of recommendations, feeding guidelines for infants at risk of atopy were usually recommended by medical specialist societies and were often at significant variance to national government recommendations for infant feeding in the general population. This trend appears to be increasing as some professional and advisory bodies are changing their recommendations based on recent studies but national recommendations are not being altered as readily. At the time of submission of this paper, the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment, had recently revised their recommendations surrounding consumption of peanut during infancy and by women during pregnancy and breastfeeding, following a full consideration of the scientific evidence (76). The UK Department of Health is now actively considering the new recommendations but as yet their advice on peanut avoidance for high risk infants has not been revised. Several other countries such as Australia and Germany are dismantling recommendations due to the lack of evidence that delaying the introduction of allergenic foods into the diet has any impact on allergy prevention. However, concern has been expressed by other authorities that there is insufficient data to show that a delayed introduction of allergenic foods has not had some effect on preventing the rise in food allergy. The reasons for this are that it is not clear whether the rate of food allergy may have been even higher if such measures had not been recommended, and as many simply did not follow recommended guidelines (75) it is difficult to establish their effect. The opposite view held by some authors is that early introduction of foods (77;78) should be promulgated based on evidence from animal studies that this was effective at preventing food allergy. According to these authors, the age of 4-6 months could be a critical window of ‘tolerance induction’. There are clinical studies underway examining this key issue.

A limitation of this review is that although this paper outlines country-specific recommendations, it does not provide information regarding population-based compliance with such guidelines. The EuroPrevall birth cohort study will provide such information so that the effectiveness of guidelines
can be more formally assessed. Our study with its associated quality of life surveys may help provide evidence on how best to implement future guidelines and ensure appropriate community acceptance.

In conclusion, there is little evidence supporting current recommendations on infant feeding with the objective of reducing the prevalence of allergic disease. Breastfeeding is widely regarded as the ideal food for infants, although its effect in the prevention of allergic diseases has not been conclusively demonstrated. Given the ethical and methodological limitations of studies on breastfeeding, it is unlikely that current evidence will be improved significantly or that current recommendations on breastfeeding will change. The use of milk based hydrolysates is also widely recommended although the evidence supporting this is weak. There is a clear need for better studies examining this issue. The evidence supporting the delay of introduction of allergenic foods is contradictory. The evolution in our understanding of the development of oral mucosal tolerance in the first 12 months of life raises the possibility that early complementary food introduction may hasten and/or maintain tolerance rather than increase the risk of food allergy. This issue must be explored further with carefully controlled interventional trials. Some studies of this kind are currently underway and their results are eagerly awaited. In the meantime it is perhaps premature to be making new recommendations without the evidence base to support them.

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Reference List
Chapter 7

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