

Chapter 6

Potential Allergenic Ingredients in the Formulation of Infant Foods



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Abstract Carbohydrates, fats, proteins, minerals and vitamins are the main ingredients found in infant foods, and may be responsible for the symptoms of allergic reactions such as anaphylaxis, eczema, hives, mucus in stools, skin rash, etc. Cows' milk (CM), soy, partially or fully hydrolyzed protein and amino acid-based formulas are the most common infant foods on the market. Sometimes, the protein present in CM generates intolerance in babies. Some of the supplements in soy formulas may also cause infant enterocolitis or proctocolitis. In soy formulas, whey or casein protein is pre-digested to provide nitrogen in the form of a mixture of amino acids and proteins. However, this hydrolysis process may lead to other unidentified allergic reactions, and therefore, does not make the formula non-allergenic. In this chapter, the nutritional composition of different infant foods and the allergic reactions they can provoke are described and discussed.

Keywords Allergy · Infant formulas · Proteins

6.1 Introduction

A balanced diet is a key to the health of infants. The first years of life are important for the growth of an individual, since during this time many mental, physical and psychological changes occur. Children's food compositions are designed to meet the nutritional requirements of babies and ensure the proper development of the

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body functions. Therefore, infant food manufacturers should work hand in hand with nutritionists to keep themselves informed about the particular nutrients infants require (Prado and Dewey 2014).

Technological advances are continuously finding ways to produce safer and healthier infant foods. Nevertheless, human breast milk is still considered the most desirable food for infant nutrition. The composition of breast milk is very complex and does not cause any serious allergies. However, in some cases, the mother's diet can negatively affect the quality of breast milk. For example, an allergic reaction can be triggered in a breastfed infant due to the consumption of cow's milk (CM) by the mother. In this scenario, the infant may show symptoms such as abdominal discomfort, eczema, severe diarrhea and difficulty with breathing. Some babies may complain or cry after mothers eat spicy or gassy foods. In fact, most foods have the potential to cause a certain degree of allergy, and some may produce acute allergic reactions (Martin et al. 2016).

Globally, the most common food allergens for babies are chicken eggs, CM, nuts, peanuts, soybeans, wheat and seafood such as fish and shellfish. Infants with a family history of immediate allergies are likely to develop allergies, and children with a personal history of immediate allergies, especially those with moderate-to-severe skin disorders, are at a high risk of developing diseases along with other food allergies (Gonzales-González et al. 2018).

The American Academy of Pediatrics (AAP) recommended in 2000 that the introduction of allergy-related crucial foods should be delayed for high-risk people as follows: CM, after babies reach 1 year old; eggs, after 2 years old; and peanuts, nuts and fish after 3 years old. This recommendation was based primarily on research that showed that the late introduction of solid foods can help prevent some allergic diseases, specifically atopic dermatitis (O'Connor and Brennan 2006).

6.2 Different Formula Options for Infants

There is a wide variety of infant formulas available in today's market, however, some of these may produce allergic symptoms due to the proteins contained in them. The different types of formulas are:

Amino-acid based formulas such as EleCare or Neocate. These are also called elemental formulas and provide healthy nutrition to infants.

Extensively hydrolyzed formulas such as Alimentum or Nutramigen that break casein into small pieces and offer a complete nutritional food to infants allergic to CM protein.

Milk-based formulas such as Advance, Enfamil, Lipil or Similac, which are made from CM protein.

Partially hydrolyzed formulas such as Carnation Good Start that break whey and casein protein into large pieces. However, babies still tend to react to these large pieces of milk protein.

Soy-based formulas such as Isomil, Prosobee or Nestle Good Start Soy. These are less allergenic than CM formulas, but 25–60% of infants who consume them

still develop proctocolitis or enterocolitis (inflammation of the gastrointestinal (GI) tract) (Montagne et al. 2009).

6.3 Ingredients Present in Infant Formulations and Their Nutritional Values

Infant formulas are products derived from CM, the milk of other animals or other ingredients, and have compositions specifically designed for infant feeding (Table 6.1). Ready-to-eat infant foods contain not less than 60 kcal or 70 kcal/100 mL of infant formula.

6.4 Differences Between Breast Milk and Infant Formulas

6.4.1 *Breast Milk*

Human breast milk is undoubtedly the best form of nutrition for infants. Human milk contains carbohydrates, fats, proteins, vitamins, minerals, digestive enzymes, hormones, as well as having high levels of immune cells, including macrophages, some stem cells and other bioactive molecules. The composition of breast milk is 87% water, 7% lactose, 3.8% fat and 1% protein (Dewey et al. 1995).

6.4.1.1 Proteins

Casein and whey are the proteins present in human breast milk. When casein reaches the stomach, it turns into curds while whey protein remains in liquid form. It is thus easier for infants to digest the whey. The amino acid profile depends on the particular stage of breastfeeding. However, glutamine is generally the most abundant free amino acid present. Glutamine is important for providing ketoglutaric acid to the citric acid cycle and serves as a neurotransmitter in the brain. The whey proteins (50–80% of the breast milk proteins) include α -lactalbumin, lactoferrin and secretory immunoglobulin A (sIgA). The other breast milk proteins are α_1 -antitrypsin, antichymotrypsin, folate-binding protein, haptocorrin, lipase and amylase, lysozyme and the Bifidus factor (Kilshaw and Cant 1984).

6.4.1.2 Fats

Fats are the most important component of breast milk, as they help provide energy and also help in the development of the central nervous system (CNS). Triglycerides are the most abundant lipids in breast milk (95% – total lipids). There are several types of fatty acids present in breast milk: (1) saturated fatty acids along with pal-

Table 6.1 Ingredients in infant formulations and their nutritional values

Ingredients	Nutritional values
Proteins	
Hydrolyzed CM proteins	1.8–3 g/100 kcal
Soy protein isolates	2.25–3 g/100 kcal
Milk proteins in CM	1.8–3 g/100 kcal
Lipids	
Alpha-linoleic acid	50 mg/100 kcal
Erucic acid	1% fat
Lauric and myristic acids	20% fat
Linoleic acid	0.3–1.2 g/100 kcal
Total fats	4.4–6 g/100 kcal
Trans fatty acids	3% fat
Carbohydrates	9–14 g/100 kcal
Vitamins	
Biotin	1.5–7.5 µg/100 kcal
Folic acid	10–50 µg/100 kcal
Niacin	300–1500 µg/100 kcal
Pantothenic acid	400–2000 µg/100 kcal
Riboflavin	80–400 µg/100 kcal
Thiamin	60–300 µg/100 kcal
Vitamin A	60–180 µg RE (retinol equivalent)/100 kcal
Vitamin B ₆	35–175 µg/100 kcal
Vitamin B ₁₂	0.1–0.5 µg/100 kcal
Vitamin C	10–30 mg/100 kcal
Vitamin D ₃	1–2.5 µg/100 kcal
Vitamin E	0.5–5 mg α-tocopherol equivalent/100 kcal
Vitamin K	4–25 µg/100 kcal
Minerals and other trace elements	
Calcium	50–140 mg/100 kcal
Chloride	50–160 mg/100 kcal
Copper	35–80 µg/100 kcal
Fluoride	60 µg/100 kcal
Iodine	10–50 µg/100 kcal
Iron (from CM protein or protein hydrolysate)	0.3–1.3 mg/100 kcal
Iron (from soy protein isolate)	0.45–2 mg/100 kcal
Magnesium	5–15 mg/100 kcal
Manganese	1–50 µg/100 kcal
Phosphorous (from CM protein or protein hydrolysate)	25–90 mg/100 kcal
Phosphorous (from soy protein isolate)	30–100 mg/100 kcal
Potassium	60–160 mg/100 kcal

(continued)

Table 6.1 (continued)

Ingredients	Nutritional values
Selenium	1–9 µg/100 kcal
Sodium	20–60 mg/100 kcal
Zinc	0.5–1.5 mg/100 kcal
Other substances	
Choline	7–50 mg/100 kcal
L-carnitine	1.2 mg/100 kcal
Myo-inositol	4–40 mg/100 kcal

Source: Chadare et al. (2017)

mitic acid (23% total fatty acids), (2) monounsaturated fatty acids of which oleic acid is the most dominant (36% of fatty acids), and (3) linoleic acid (15% – total fatty acids) and alpha-linolenic acid (0.35% – total fatty acids). These last are converted to arachidonic acid (AA) and eicosapentaenoic acid (EPA), respectively. In addition, EPA is further metabolized into docosahexaenoic acid (DHA) (Martin et al. 2016).

6.4.1.3 Vitamins, Minerals and Other Bioactive Components

Human breast milk contains most of the vitamins required by infants, except vitamins D and K. Vitamin D deficiency leads to inadequate bone mineralization, which can result in conditions such as rickets. Exposure to sunlight and vitamin D supplementation is thus recommended for breastfed infants. Some children are born with a vitamin K deficiency. Vitamin K plays an important role in blood clotting, and therefore, supplements of this vitamin are recommended for newborns. The minerals found in breast milk are important for a variety of physiological functions and form an essential part of various enzymes, as well as biologically important molecules and structures. Other bioactive components, such as growth factors, hormones and immunological factors, have also been identified in human milk (Bates and Prentice 1994).

6.4.2 Infant Formulas

Infant formulas represent an effective substitute for breast milk. Although the production of formulas identical to breast milk has not been achieved, every effort has been made to mimic, as far as possible, the nutritional profile of human milk. Generally speaking, infant formulas have a higher casein/whey ratio than breast milk, which makes them more difficult for infants to digest. The fatty acids, AA and DHA are added directly to infant formulas in order to reach the amounts required by newborns. The various types of infant formulas are described below:

CM-Based Formulas The most widely available infant formulas are derived from bovine milk. CM contains higher levels of fats, proteins and minerals than human

milk, and therefore, must be diluted and skimmed so that the formulas mimic more exactly the composition of the latter. CM formulas also incorporate added iron, minerals, vegetable oils and vitamins. The high levels of protein in CM formulas compared to breast milk have been associated with weight gain in infants and can also increase the likelihood of becoming obese in adulthood. CM formulas are one of the first foods given to babies and can trigger both immunoglobulin E (IgE) and non-IgE mediated infant allergies. Specifically, the allergies occur due to reactions against one or more of the milk proteins present (usually casein or β -lactoglobulin) and can be of two types: (1) IgE-associated mechanisms: these are responsible for approx. 60% of CM-induced reactions. These types of allergies produce symptoms, either immediately or within 1 or 2 h after ingestion, and affect the skin, GI tract and respiratory system and (2) non-IgE mechanisms: these are associated with late-onset symptoms that start from approx. 2 h to several days after CM consumption. These types of allergies produce clinical symptoms that mainly affect the GI system, such as enterocolitis, enteropathy, eosinophilic esophagitis and proctocolitis (de Boissieu et al. 1997).

Amino-Acid Formulas These types of formulas represent another alternative for infants with a severe cow's milk allergy (CMA) and who are unable to ingest extensively hydrolyzed formulas. Amino-acid formulas provide proteins in the form of free amino acids without the presence of peptides (Grantham 1974).

Hypo-Allergenic Formulas Protein hydrolysate formulas are designed for infants and babies intolerant to CM and soy-based milk formulas. They consist of proteins that have been partially or completely hydrolyzed into smaller pieces than those found in soy or CM-based products. Hydrolyzed formulas are recommended as an alternative for infants who are allergic to proteins (Høst and Halken 2004).

Soy-Based Formulas Formulas produced from soy proteins are effective options for infants suffering from congenital lactase deficiency or galactosemia. Soy products must, however, be avoided in infants under 6 months old, as they may contain phytoestrogens. The use of soy-based formulas is not widespread due to concerns regarding the potential harm that they could cause to infants (Bhatia et al. 2008).

6.5 Pathophysiology of Food Allergens Found in Milk Formulas

Although food allergies are reported to affect almost 12 million Americans (Lee and Sozen 2016), even this could be an underestimate, considering the complexities of the mucosal immune system. Robust immunological mechanisms that include both cell-mediated and humoral responses have evolved to maintain a homeostatic environment among the billions of antigens within the intestine. In order to navigate the allergic cascade, a protein that is ingested must bypass this tolerogenic system. The

sensitization phase begins when certain chemical and physical characteristics increase the allergenicity of dietary proteins. Their capture by inflammatory dendritic cells in the intestine leads to an active immune response that occurs under the influence of the local microenvironment (Gupta et al. 2017). Key signals such as interleukin-4 (IL-4) lead to T-helper-2 (T_H2) differentiation and propagation of the allergic T cell response, as well as isotype switching and IgE production (Gupta et al. 2017). The allergen-specific IgE binds to the surface of mast cells and elicits mediator release within minutes to hours after re-exposure to the allergen (Gupta et al. 2017). The bioactive mediators released by mast cells act on endothelium, epithelium and smooth muscle to produce the symptoms characteristic of allergic reactions (Gupta et al. 2017).

The GI tract, which is the body's largest immune organ, is continuously exposed to a wide variety of exogenous antigens which include ingested proteins and commensal bacteria. A single epithelial layer separates this antigenic load from the antigen-presenting cells (APC), lymphocytes, stromal cells and other immune cells in the lamina propria, which together make up the mucosal-associated lymphoid tissue (MALT) (Brown et al. 2019). Within the MALT, unique populations of dendritic cells (DCs) react with dietary antigens, and therefore, determine the resulting adaptive response, i.e. immunity *versus* tolerance (Brown et al. 2019). The immune tolerance can thus be defined as the antigen-specific suppression of humoral or cellular immune responses (Brown et al. 2019). When initial antigen exposure is mediated along the GI tract, a strong T cell-mediated suppression, known as oral tolerance, begins to develop (Brown et al. 2019). However, in 4–6% of children and 2% of adults with food allergies, this mechanism seems to fail, and the immune response proceeds through two phases: *allergic sensitization* and *elicitation* (Gupta et al. 2017).

Allergic sensitization includes T cell priming followed by DC activation, and the resultant T_H2 response is marked by the production of IL-4, IL-13, and IL-5 from $CD4^+$ T cells. This T_H2 response results in B-cell IgE production and IgE then binds to high-affinity receptor on the surface of mast cells in the intestine, skin, and cardiovascular and respiratory systems, protecting them from reactivity upon re-exposure to the allergen if acted upon later. Within a few minutes of exposure, the IgE-bound mast cells identify the allergen and become activated, thus eliciting classic allergic symptoms (Sicherer and Sampson 2014).

6.6 Physiological Basis of Breastfeeding

6.6.1 Components of Breast Milk

Human breast milk contains all the nutrients, carbohydrates, fat, proteins, vitamins, minerals and water an infant requires in the first 6 months of life. It is also easily digested and efficiently used. Breast milk is also fortified with bioactive ingredients that augment the infant's fragile immune system, provide protection against infections, and assist in the digestion and absorption of essential nutrients (Ballard and Morrow 2013).

6.6.2 Carbohydrates

The sugar, lactose, found specifically in milk is the main carbohydrate. Breast milk contains about 7 g of lactose *per* 100 mL, which is higher than that found in other milk and provides an important source of energy. Other types of carbohydrates in breast milk are oligosaccharides and sugar chains that provide important protection against infection (Newburg and Neubauer [1995](#)).

6.6.3 Fats

Breast milk consists of about 3.5 g of fat *per* 100 mL which constitutes half the energy content of milk. Unlike milk from other sources, the fats in breast milk consist of the long-chain polyunsaturated fatty acids, AA and DHA, essentials for the neurological development of a child. Some varieties of infant formula contain added AA and DHA, however, their beneficial effect is not as potent as that of the AA and DHA found naturally in breast milk (Martin et al. [2016](#)).

6.6.4 Proteins

Breast milk protein contains a balance of amino acids that is particularly appropriate for the fragile constitution of babies. Breast milk contains lower amounts of the protein casein, and the casein found in breast milk has a different molecular structure than other forms of this protein. The casein of breast milk has curds that are much softer and easier to digest than those of the casein found in other milk. As regards the whey, or soluble proteins, human milk contains higher amounts of α -lactalbumin than other milk. On the other hand, β -lactoglobulin, which can cause intolerance in infants, is absent in human milk but is present in CM (Lönnerdal [2013](#)).

6.6.5 Vitamins and Minerals

Breast milk from a healthy mother normally contains all the vitamins necessary to fulfill an infant's requirements. The exception is vitamin D: endogenous vitamin D requires exposure to sunlight for its generation, otherwise a supplement is required. Although minerals such as iron and zinc are present in relatively low concentrations in breast milk, their bioavailability and absorption are high (Gaucheron [2005](#)).

6.6.6 *Anti-Infective Factors*

Breast milk has several factors that help protect infants against infections. These primarily include: (1) immunoglobulin: mainly sIgA which covers the intestinal mucosa and prevents bacteria from entering the cells, (2) white blood cells that kill microorganisms, (3) whey proteins (lactoferrin and lysozyme) that kill bacteria, fungi and viruses and (4) oligosaccharides which prevent bacteria from adhering to mucosal surfaces. In particular, the factor sIgA contains antibodies produced by the mother in the intestine against the bacteria and infections that she has encountered in her life, which protect against the bacteria that are likely to be found in the baby's environment (Welsh and May 1979).

6.6.7 *Other Bioactive Factors*

Bile-salt stimulated lipase helps complete the digestion of fat once the milk has reached the small intestine. The epidermal growth factor activates the maturation of the lining of the infant's intestine so that it can digest and absorb nutrients properly, and cannot be easily infected or sensitized to foreign proteins. Other growth factors present in human milk are targeted towards the development and maturation of nerves and the retina (Hamosh 2001).

6.6.8 *Mature Milk and Colostrum*

Colostrum is a particular kind of milk that is secreted in the first 2–3 days after delivery. It is produced in small quantities, about 40–50 mL the first day, but meets the requirements of an infant. Colostrum contains high amounts of white blood cells and antibodies, especially sIgA, and also has higher percentages of proteins, minerals and fat-soluble vitamins (A, E and K) than breast milk produced later. Colostrum provides essential immune protection to the infant when they are initially exposed to the microorganisms in the environment, and the epidermal growth factor helps prepare the lining of the intestine in order that it can receive the nutrients in the milk (Palmeira and Carneiro-Sampaio 2016).

Higher amounts of breast milk are produced during the first 2–4 days after delivery, making the breasts feel full; the milk is then said to have “come in”. On the third day, an infant usually takes about 300–400 mL every 24 h, and on the fifth day about 500–800 mL every 24 h. From the 7th to the 14th day, the milk produced is called transitional, and after 2 weeks it is known as mature milk (Gibson and Kneebone 1981).

6.6.9 Infant Formulas Prepared Using Animal or Plant-Based Milk

Animal milk is different from breast milk in terms of the amounts of nutrients contained within it and their quality. For infants under 6 months old, animal milk can be modified at home by adding micronutrients, sugar and water, in order to make it usable as a replacement for breast milk for a short period of time is extremely difficult situations. It does not, however, have the same anti-infective properties as breast milk. After 6 months, infants can be fed with boiled full cream animal milk (Roncada et al. 2012).

In general, infant formulas are prepared using CM or soy products as a base. During the production process, specific amounts of nutrients are added in order to achieve formulas equivalent to breast milk. Nevertheless, there are qualitative differences in the fats and proteins between breast milk and infant formulas that cannot be altered, and anti-infective and bio-active factors, e.g. remain absent. In addition, infant formula powder is not a sterile product and may be unsafe if it is not used according to the instructions given. Contamination with pathogenic bacteria, sometimes found in powdered formulas, such as *Enterobacter sakazakii*, can cause life-threatening infections in newborns. Soy formulas contain phytoestrogens which function in a similar way to the hormone estrogen produced in women, and which potentially reduce fertility in boys and bring on early puberty in girls (Roncada et al. 2012).

6.7 Recent Trends, Controversies and Laws Implemented Regarding the Presence of Food Allergens in Infant's Foods

6.7.1 Laws

The food processing industry in India is primarily export-oriented, and the country still needs to establish domestic regulations in some areas, such as food allergies/allergens. Several foods produced for export from India were rejected in 2015 by the U. S. Food and Drug Administration (FDA) citing “the label fails to declare all the major food allergens present in the product, as required by section 403” (FDA 2013). The rejected batches included products from manufacturers such as Haldiram Snacks Pvt. Ltd. and Nestle India Ltd. The FDA can also reject a food product if “the food appears to contain a major food allergen through unsanitary conditions that led to cross-contact” (FDA 2013). More than 160 food materials have been identified as allergens, such as black gram, chickpeas, eggs, fish, milk, mustard, peanuts, rice, wheat, etc. (FDA 2013). Allergic reactions can be mild to severe and can include symptoms such as respiratory problems, hives, vomiting and even life-threatening anaphylaxis. Because of this, many countries have issued food labeling regulations that require the inclusion of precautionary/warning statements regarding the

presence of allergens in order to alert the consumer. North American countries, such as the Canada and United States, South America countries, e.g. Brazil and Chile, Asian countries, such as Japan, Malaysia and Singapore, and the European Union, all have these kinds of labeling regulations. China joined this group in 2012.

6.7.2 Food Allergy & Anaphylaxis Management Act (FAAMA)

FAAMA requires the U. S. Secretary of Health and Human Services to develop and make available to schools a voluntary policy to control the risk of food allergies and anaphylaxis of students. This school-based food allergy management incentive also provides grants to support the implementation of food allergy management guidelines in public schools (Simons [2006](#)).

6.7.3 Food Allergen Labeling and Consumer Protection Act (FALCPA)

FALCPA is a small amendment to the Federal Food, Drug and Cosmetic Act which requires manufacturers to declare the presence of any ingredient from a “major food allergen” on the label. FALCPA recognizes eight foods or food groups as major food allergens: crustacean shellfish (e.g. crab, lobster, shrimp), eggs, fish (e.g. cod, flounder, sea bass), milk, peanuts, soybeans, tree nuts (e.g. almonds, pecans, walnuts) and wheat (Thompson et al. [2006](#)).

6.7.4 School Access to Emergency Epinephrine Act

U. S. federal legislation provides financial incentives to states to encourage them to adopt laws mandating schools to maintain stocks of epinephrine auto-injectors for use by any student in case of emergency. All states in the U. S. have legislation that allows students, with the relevant consent, to keep the prescribed epinephrine at school (Gregory [2012](#)).

6.7.5 Review of the Food Code

The Food Code is a summary of the advice prescribed by the FDA ([2013](#)) which aims to provide uniform systems and practices that address the safety of food sold in food-service and retail establishments. The Food Code includes provisions designed to

improve the capacity of restaurants to address the needs of customers with food-related allergies; it also evaluates restaurants and informs retail food service managers about the serious nature of food allergies. According to the Food Code (FDA 2013), catering establishments must have a person in charge during all hours of operation who is able to identify the main food allergens, including the symptoms and treatments for an allergic reaction, as well as the proper cleaning procedures necessary to avoid cross-contact. The person in charge should also provide awareness training on food safety practices and allergy-related precautions (FDA 2013).

6.8 Controversies

There are six key controversies relating to infant nutrition:

- Breastfeeding *versus* bottle feeding. Scientific research has confirmed the main advantages of breastfeeding, namely that it provides immunity and optimal nutrition. Although, in general, breastfeeding is convenient and safe, the need to work outside the home or lack of milk, forces some mothers to move to the bottle-feeding option. The deceptive and aggressive promotional campaigns of infant food manufacturers have been quite effective in persuading mothers of all income levels to choose bottle feeding. However, with better social awareness and a focus on healthy practices, there is a growing understanding of the benefits of breastfeeding, which has changed the trend, i.e. moving from bottle-feeding to breastfeeding, once again (Wen et al. 2009).
- The age to start infants on solids. Breastfed infants do not need solid food before they reach 4–6 months old. However, bottle-fed infants require additional nutrients, the most important of which is iron, which is mainly present in infant cereals. Although there is no proven evidence that the early introduction of solid food helps infants sleep through the night, neither does it cause any adverse health effects. Thus, the current consensus is to feed infants with fat-based cereals at or after 4–6 months, as they contain bioavailable iron (Friel et al. 2018).
- The need for supplemental iron. It is generally recommended that iron supplements are introduced in the form of iron drops or iron-fortified milk formula. A recent study disputes this recommendation for most healthy full-term infants and suggests, instead, that whether they are breastfed or formula-fed, infants who receive infant cereals at 4–6 months do not need iron drops or iron-fortified milk (Kazal 2002).
- Fluorides and vitamins
- There is conclusive evidence that fluoride helps maintain healthy teeth, however, there is no evidence that fluoride supplements are beneficial before the teeth begin growing. Breast milk contains some fluoride, and infants fed with a formula reconstituted with fluoridated water do not need additional fluoride.
- Although human milk contains 400 IU (international units) of vitamin D, additional vitamin D supplementation is preferred for breastfed infants. Nevertheless,

infants fed with commercial formulas usually do not need vitamin D supplements (Khadilkar et al. 2017).

- There is clear evidence that human milk contains adequate amounts of vitamin C. Since commercially available infant formulas also contain vitamin C, formula-fed infants do not need additional supplements of this vitamin (Khadilkar et al. 2017).
- Sterilization of formulas. Good pediatric practices include sterilizing bottles, equipment and the formula itself. The careful washing of the hands, bottles and bottle teats, as well as the refrigeration of the prepared formula, cover most of the necessary precautionary measures (Feldman et al. 1988).
- Food allergies. Many common pediatric problems such as colic, diarrhea, otitis media and rhinitis have been attributed to food allergies. However, the evidence to support this is very flimsy.
- Some authors have suggested that bottle-fed babies are at risk of emotional or medical problems (Metwally et al. 2016). Feeding infants formula in adequate amounts with attention and love will improve their mental and physical health (Feldman et al. 1988).

6.9 Recent Trends

New research studies have helped scientists understand the influence of gut bacteria and genes on allergies in infants and children (Houghteling and Walker 2016). A long-term child study of 166 infants, funded by the Canadian Institute of Health and the Allergy, Genes and Environment Network, led to the discovery that three-month-old babies with fewer varieties of bacteria in their feces and altered levels of specific bacteria were more sensitive (established by the skin test) to eggs, milk and peanuts by year one (Azad et al. 2015). Meanwhile, a U. S. study of 3000 children found that children with peanut allergies showed changes to their DNA (Houghteling and Walker 2016), which according to the author said: “Theoretically, would allow for detecting them at birth”. This researcher is also working on unveiling genetic markers that may identify children as susceptible to allergies other than those caused by peanuts (Houghteling and Walker 2016).

6.9.1 *Aibi*

Aibi is basically an EpiPen redesigned as a portable device with the aim to solve the problem of anaphylactic allergic reactions. Often, triggers of allergy are unexpected, and this together with the complexity of school health services, can hinder a timely medical response. Aibi allows children with allergies to monitor their condition and alerts their caregivers about the start of an allergic reaction. It also offers attractive animal characters for children to play, ensuring that they use Aibi day and night.

6.9.2 Allergy Amulet

An Allergy Amulet is a device or “reader” that can be worn as a bracelet, necklace or watch, or used as a key ring. The other part of the kit, the “tester”, is a disposable strip that can be inserted into solid or liquid food and then into the reader. The strip has microscopic cavities that match the molecular shape of the unique proteins in a given allergen. If that allergen is present in a dish, the proteins will bind to the strip. For example, after inserting the strip into the amulet reader, this will signal with a green or red light indicating whether the food contains peanuts or not. This can inform a person if a food product labeled “may contain traces of peanuts” is safe to eat or not.

6.9.3 Ally

Ally is a lollipop-shaped device that can detect whether the food contains lactose or not. It was designed by Imogen Adams, a student in product design engineering at Brunel University, and its name comes from the combination of the words “allergies” and “ally” meaning “friend”. Users crush a small food sample and then add a few drops of water into a small flexible silicone pod. They then dip a test strip into the mixture and insert the strip into a slot in Ally that has a Bluetooth-enabled gadget inside the hard-plastic casing. When the app associated with Ally is opened on a mobile phone and the button is pressed in the middle of the “lollipop”, the application takes 60 s to process the test and the food allergen status appears in the app. Ally can also indicate a positive or negative result with a rapid vibration (Thomas et al. 2012).

6.9.4 Nima

Nima is a portable food sensor. The first Nima product was a gluten sensor that was released in 2016, and the second was a peanut sensor released in 2018. The founders of Nima, Shireen Yates and Scott Sundvor, had struggled with different food allergies, so after a meeting at Massachusetts Institute of Technology (MIT 2013) decided to build a company to bring clarity and security to people when they eat out. The Nima gluten-sensor was named one of Time Magazine’s 25 best inventions of 2015 and its commercialization began in 2016. This portable device can detect from a small food sample whether the food contains gluten or not within 2 min.

6.9.5 *Rescuify*

Rescuify is a mobile app designed to reduce the steps involved in an anaphylaxis action plan during an emergency. In the case of a severe allergic reaction, a touch on a smart-phone home screen activates the Rescuify app which will immediately communicate the user information about the relevant allergy, insurance and medical information and the GPS location to emergency contacts and the nearest first response team. In this way, Rescuify simplifies and greatly accelerates the process of notification to first responders and emergency contacts, and also shares with them important information about the user's allergies and medical information (Matricardi et al. 2019).

6.9.6 *SCiO*

SCiO is the world's first NIR spectrometer that fits in the palm of the hand and is built with a tiny molecular sensor. The Israeli start-up created this multipurpose sensor in order to determine the molecular content of foods, medicines and plants. It uses a system by which the object is illuminated, and the reflection detected by the optical sensors. The device uses a proprietary algorithm and a cloud-based database that is constantly updated to perform the analysis. The information is then made available on a smartphone in milliseconds and consists of the ingredients present in a food product and their molecular composition (Lee et al. 2017).

6.9.7 *Tellspec*

Tellspec is the world's first consumer food sensor that indicates both the presence of allergens and calories. Tellspec is an indispensable tool for diabetics, as it can help them control the disease. It provides predictive information about food by combining near-infrared (NIR) spectroscopy, bioinformatics and learning algorithms in a technology that analyses foods at the molecular level. The company's goal is to create a clean food revolution by informing consumers what is present in food beyond the nutrition label. Tellspec's next goal is to develop a portable food scanner that can inform users about specific ingredients and macronutrients present in a food product (Grifantini 2016).

6.10 Dietary Management of Infants and Children with Food Allergies

The objectives behind the nutritional intervention of patients are to (1) prevent allergic reactions, (2) ensure adequate growth and development, and (3) recognize and treat malnutrition. The following steps should be followed to manage the dietary intake of infants and children with food allergies:

Step 1. Obtain a detailed dietary history to identify the factors contributing to nutritional risk which includes identifying:

- The type of infant feeding (formula or breastfed).
- The age at which solid foods were introduced, the integration schedule and the composition of the solid foods.
- Details of the excluded foods and the reasons for their exclusion.
- The type and amount of water and other drinks are given.
- The consumption of special formulas and daily intake schedule.
- The type and dosage of vitamin and/or mineral supplements given.
- Aversion to certain foods.
- A predilection for certain foods (from those permitted) (Giovannini et al. 2014).

Step 2. Assessment of anthropometric measurements

The most accurate way to perform a nutritional assessment is to use anthropometric measurements since growth is one of the most sensitive indicators of the adequate intake of energy and proteins. During the evaluation, the weight, length and girth of the infant's head should be measured, and for children over 2 years old, the body mass index should also be recorded. The measured values should then be plotted on the appropriate growth curve chart, and any standard deviations noted (Giovannini et al. 2014).

Step 3. Dietary intake and nutritional parameters

Food Frequency Questionnaires (FFQs) are the most common dietary assessment tools used in large epidemiologic studies of diet and health and are designed to estimate the daily intake of nutrients. The self-administered FFQ directs participants to report the approximate frequency of consumption and the portion size of items over a defined period of time. The recording of each item is made simple by listing the foods or beverages of interest. Images and quantities *per* serving are also provided to help users estimate portion size (Venter 2009).

However, FFQs are not an accurate tool, since they only provide qualitative and semi-quantitative information. The three-day food diary, which consists of recording the amount and type of food and beverages consumed by a child during a period of three consecutive days, including two weekdays and one weekend day, represents the most accurate tool for children over 6 months old who undergo a nutritional intervention because it provides quantitative information. The results obtained from the food diary should be compared with the recommended dietary allowance (RDA) (Shim et al. 2014).

Step 4. Nutritional intervention and nutrient requirements

Energy and proteins: Children with food allergies, particularly if they are multiple, are at risk of a very low intake of proteins and calories. Protein and calorie intake depending on the number of diagnosed allergies. In general, the number of food items consumed, the number of meals during the day, the caloric density of the food and the size of the portions influence the caloric intake. Infants have a natural ability to self-regulate caloric intake (e.g. they consume larger portions than average

if the frequency of meals is reduced) (Martin et al. 2016). However, taste can influence eating behavior more than hunger.

Children with allergies require an adequate caloric intake, as otherwise free amino acids will be oxidized to produce energy, and therefore, will not be available for protein synthesis. The protein sources of highest biological value include primary allergens such as eggs, fish, milk, nuts and soy. Therefore, planned diets should ensure the adequate intake of essential amino acids along with complementary and alternative protein sources, such as legumes and other high-protein content vegetables. Children who remove two or more sources of animal protein from their diet and/or consume proteins exclusively of plant origin need additional care (Giovannini et al. 2014).

Lipids: Putting a child on an exclusion diet may result in an inadequate lipid intake both qualitatively and quantitatively. This situation needs specific consideration not only because of the resulting decrease in the caloric intake but also due to a probable deficiency in essential fatty acids.

The plasma fatty acid profile observed in children with allergies on an exclusion diet shows that not only is there a reduced intake of fatty acids, but that long-chain ω -3 polyunsaturated fatty acids can also be consumed, thus causing the allergic inflammation. Monounsaturated fatty acids, polyunsaturated fats and essential fatty acids in adequate amounts can be provided using olive oils or other vegetable oils for individuals with food allergies. The amount of the oils required in the diet is unique for each patient and is based on the number of foods allowed and the daily amounts consumed (Giovannini et al. 2014).

Carbohydrates: For children with allergies on exclusion diets, 90–95% of the total energy consumed, as measured by the glycemic index, comes from the carbohydrate component of the diet. The recommended intake of carbohydrates (cereals, fruits, and vegetables are good sources) is between 40–60% of the total daily calories. The intake of carbohydrates is important for children with or without allergies, not only because of their nutritional contribution but also for the fiber they provide. Even though cooked fruits and vegetables may contain lower amounts of nutrients compared to the raw forms, they still provide the same amount of fiber (Giovannini et al. 2014).

Micronutrients: Micronutrients include vitamins, minerals and trace elements (Table 6.2). A varied diet should mean that all nutrients, both macro- and micronutrients, are ingested in adequate amounts (Giovannini et al. 2014).

The administration of pharmacological supplements should be considered if dietary modifications due to allergies mean that mineral, trace element and vitamin requirements are not met.

Allergy to the Proteins Found in CM CMA is quite prevalent in childhood and requires specific dietary interventions. A low intake of minerals and vitamins such as calcium, phosphorus, vitamin B₂ (riboflavin), B₅ (pantothenic acid), B₁₂ (cobalamin), D, proteins and lipids can result from a CM-free diet, given that CM is rich in

Table 6.2 The vitamin and mineral content of key foods

Foods	Vitamins and minerals
Eggs	Biotin, pantothenic acid, riboflavin, selenium and vitamin B ₁₂
Fish	Iron-heme and zinc
Grains	Folate, iron, niacin, riboflavin and thiamine
Milk	Calcium, pantothenic acid, phosphorus, riboflavin and vitamins A, B ₁₂ and D
Peanuts	Magnesium, manganese, niacin and vitamin E
Soy	Calcium, folate, iron, magnesium, phosphorus, pyridoxine, riboflavin, thiamine and zinc

these nutrients. While breastfeeding is recommended for infants with any type of food allergy, if an infant is allergic to CM, it may be useful to discard this from the mother's diet. If the infant is fed with formula, the formula should be given based on the age and clinical conditions of the infant, the nutritional value of the formula and the residual allergenicity. Parents will also consider the palatability of the formula, and in some social strata, the cost. Other alternative milk beverages, such as almond milk, are not adequate for the nutritional requirements of children, and therefore, should not be given as CM substitutes (Giovannini et al. 2014).

An alternative to mammalian milk that can be given to infants during their first year is donkey's milk. Donkey's milk has a proteomic profile similar to human milk and has been shown to be well tolerated in clinical studies performed on CM allergic children aged 1 year or more. However, since donkey's milk has a low energy value related to its low-fat content, therefore, its use for infants on an exclusive milk diet is not recommended. Nevertheless, it may be considered for infants on a solid food diet or after the first year of life on a case-by-case basis (D'Auria et al. 2011).

Goat's milk is not suitable for infants and children with CMA, due to its high protein content, excessive osmolarity and low amounts of vitamin B₁₂ and folic acid, together with the fact that there is a high risk of cross-reactivity (up to 90%) for CM allergic infants. Substitute formulas should thus be continued until the child develops tolerance, or if this does not occur until the child reaches at least 2 years old and maybe even older to ensure an adequate intake of nutrients and proteins (Giovannini et al. 2014).

Allergies to Other Foods: Wheat Allergy and Multiple Food Allergies Wheat is abundant in low glycemic index carbohydrates, vitamin B₁ (thiamine), B₂, B₃, niacin and iron (Tekin et al. 2018). However, individuals allergic to gluten protein (celiac) should avoid all the foods containing wheat, including many processed and manufactured products, such as bread, cakes, cereals, cookies, crackers and pasta (Ross et al. 1987; Gutiérrez 2018).

Many alternative grains such as amaranth, barley, buckwheat, millet, oats, quinoa and rye, are available to patients with a wheat allergy. However, 20% of individuals with a single-grain allergy are at risk of being clinically reactive to another grain. Therefore, the use of alternative products should be tailored to the needs of

each individual and based on their tolerance as advised by an allergy specialist (Gutiérrez 2018).

Follow Up Regular follow-up visits to specialists (pediatricians) are needed for children with allergies and on an exclusion diet. Children's diet changes as they age, as do their nutritional requirements. The periodic re-evaluation of a child is thus necessary to assess any modifications required to the dietary regime. It is imperative that parents understand the importance of regular visits to ensure that the prescribed diet meets the changing nutritional requirements of the child. Follow-up visits should be scheduled based on the child's age and their growth pattern, in accordance with the following plan:

- The weight, and height of the child together with their adherence to the diet should be monitored at one, 2 and 4 months old in the first 6 months, and then on a quarterly basis (6, 9 and 12 months).
- The growth rate should continue to be monitored every 6–12 months after the first year.
- The nutritional intake should be assessed at least once a year for children with a normal growth pattern, and two or more times *per* year if there is any change to this pattern.
- Nutritional and anthropometrical follow-up visits can best be provided through a continuous relationship between the family pediatrician (primary care level) and the relevant specialists (secondary and tertiary care levels) (Giovannini et al. 2014).

Finally, a summary of the main allergic reactions associated with infant foods is given in Table 6.3.

6.11 Conclusions and Remarks

Food allergies represent a significant health burden for babies and children. Infant foods that may cause allergies should be introduced with caution and under the supervision of a pediatrician. Care must be taken to ensure the adequate intake of nutrients, particularly with respect to cow's milk allergies, when selecting an appropriate hypoallergenic formula. There is emerging evidence of the roles of fats, pre- and probiotics, commercial foods, healthy eating and micronutrients in food allergies. A better understanding of how nutrients and other aspects of food, food patterns and food preparation can affect the immune system and allergy outcomes is required in order to best advise both individuals with current food allergies and those at risk of developing them.

Table 6.3 Summary of allergic reactions of infants in different age groups

Topics	0–3 months	3–6 months	6–9 months	9–12 months
Type of food fed	Breast milk and formula milk	Cooked potatoes, mashed banana and avocado, milk formulas with peanut oil, and wheat and related cereals	Any cereal including baby cereals, bread and rolls, rice and pasta crackers/pretzels/rice cakes Any fatty/sugary foods-sweet drinks, french fries, candy/cookies/cakes/pastries/pies, ice cream, carbonated sodas, salty snacks Any fruit (e.g. apples, bananas, berries, citrus fruits, melons) Any vegetables (e.g. baby food carrot, baby food sweet potato, squash, green beans, peas/mixed vegetables) Breast milk or CM-based infant formula CM and other CM-derived products Meat, chicken, any meat/protein substitute, fish/shellfish, peanuts/peanut butter/nuts and seeds, eggs, soy, dried beans and peas, yogurt Sugar and water	Barley, cereals, cucumbers, curd rice, fruits (e.g. apples, bananas), milk, porridge, pulses, soup with mashed vegetables and vegetables (e.g. carrots, potatoes, squash)
Possible Allergenic foods and compounds	Allergens in formula milk: Extensively hydrolyzed protein formulas Breast milk is the best option to provide optimal nutrition for children. However, if the mother consumes CM, she exposes her child to small amounts of bovine milk proteins that can act as booster doses that cause allergic reactions	Allergens present in avocados and bananas Proteins present in peanut oil. The proteins, glycoproteins and alkaloids present in potatoes are heat sensitive, thus cooked potatoes are potential allergens Wheat ω -5 gliadin (Tri-a 19) is an important allergen in wheat	Almonds, apples, avocados, bananas, beef, cashews, cherries, chestnuts, CM, cucumbers, eggs, fish, garlic, kiwis, meat, milk (casein and whey), onions, peaches, peanuts, potatoes, pumpkins, rice, shellfish, soybeans, tomatoes, tree nuts, walnuts, watermelons and wheat	CM, eggs, fish, nuts, soy and wheat

Possible Allergies caused	CMA: Mild allergic reactions (diarrhea, hives, stomach aches, swelling of lips and vomiting) Hypersensitive reactions (anaphylactic shock, bloody diarrhea)	Eczematous lesions, rashes, atopic dermatitis No reactions in the gastrointestinal tract only produce skin allergies: Atopic dermatitis and eczema Wheat allergies: Ingestion (induced anaphylaxis) and inhalation (asthma and rhinitis) wheat	Diarrhea, frequent spitting up of blood and vomiting Blood in stools, coughing and wheezing, hives, scaly skin rash, stuffy nose, swelling and watery eyes Signs of abdominal pain, or colic-like symptoms, such as excessive crying and irritability (especially after feedings)	Belly pain, coughing, diarrhea, eczema, fainting, hives, nausea, runny nose and wheezing
Reasons and mechanism for allergic symptoms	Bovine milk proteins in human milk react with the allergens in CM and accelerate allergic reactions mediated by IgE antibodies Allergic reactions are IgE mediated	Allergic reactions caused by potato specific IgE immunoblasts leads to IgE-mediated allergic skin reactions Peanut hypersensitivity reactions caused by peanut-specific IgE antibodies Wheat allergens trigger allergic reactions mediated by IgE antibodies	Whenever the immune system mistakenly identifies a specific food or substance in a food, as harmful, the immune system responds by triggering cells to release antibodies known as IgE to neutralize the harmful substance The next time even the smallest amount of that food is ingested, the IgE antibodies will detect it and send a signal to the immune system to release histamine and other chemicals into the bloodstream. These chemicals produce allergic symptoms	A food allergy occurs when the body reacts against harmless proteins found in foods The reaction usually occurs shortly after eating. Allergic reactions to food can vary from mild to severe

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