

Standard and Specialized Enteral Formulas

Tien-Lan Chang, MD
Ronald E. Kleinman, MD

As research and experience over the past century have advanced our knowledge of the nutrient requirements and digestive functions of infants and children in health and illness, enteral formulas have become more sophisticated and diversified to meet their nutritional and metabolic needs. These liquid meals, together with advances in enteral feeding techniques, have contributed to the increased survival and shorter hospitalizations of pediatric patients with severely compromised intestinal function as well as other children with chronic health conditions. This chapter will provide a brief historical perspective of the development of infant formulas, review the composition of the major groups of available formulas for infants and children, and discuss their use in general. Breast- and formula feeding of infants and the enteral nutrition support of children with specific chronic illnesses are discussed in detail in other chapters. The composition of many formulas available in the United States and other industrialized countries is also listed in detail in Appendix III, grouped by category and by use.

HISTORICAL BACKGROUND

Human milk was the principal source of nutrition for newborns and infants up to the mid-nineteenth century. Wet nurses provided an alternate source of milk when the mother's milk was not adequate or available. Milk from donkeys, horses, and cows was used as a substitute when human milk was not available. The mortality of bottle-fed infants was 4 to 10 times greater than breastfed infants in the early part of twentieth century mainly because of unsanitary methods of preparation and storage of the milks. Innovations toward the end of the nineteenth century and beginning of the twentieth century, such as evaporated cow milk, the rubber nipple, pasteurization, and the introduction of refrigeration into most households in the industrialized world, led to a greater use of formula feeding, and the practice of wet nursing was gradually replaced by cow milk formula.^{1,2} In the 1970s infectious diarrhea and malnutrition, two interrelated causes of morbidity and mortality in infants in the developing nations, were linked to the unsanitary and inappropriate preparation of infant formulas. The marketing techniques employed by the infant formula industry were blamed, among other factors, for the decline of breastfeeding in these nations.

In 1981 the World Health Organization and UNICEF developed the International Code of Marketing of Breast Milk Substitutes, the purpose of which was to promote breastfeeding. The Code set restrictions on direct marketing of the formulas by manufacturers to the general public, display of formulas in the health care facilities, and distribution of formulas by health workers to mothers of infants.³ The United States gave endorsement to the Code only in 1994, when it was presented again at the World Health Assembly. Implementation of the Code by member nations has been incomplete, however, and violations of the Code continue.⁴

The modification of cow milk to make it more similar to the nutrient composition of human milk began in a scientific way with the German pediatrician, Philip Biedert, who added cream, whey, and sugar to cow milk to make it suitable for young infants. Meigs' mixture, formulated by the American physician, John Meigs, was similar in composition to Biedert's mixture.⁵ In addition to changing the quantity of cow milk constituents, the quality of the protein, fat, and carbohydrate in cow milk was also a subject of research and in some cases changed, as with the acid treatment of casein curds to render them smaller and softer.⁶ These early formulas formed the basis for the modern formulas with a defined nutrient composition that are currently fed to human infants.

STANDARD INFANT FORMULAS

In spite of Abraham Jacobi's admonition that "Cow's milk cannot be changed into woman's milk. . . . The efficiency of all alleged improvements in artificial feeding is liable to be overestimated, and not always received with sound criticism,"⁷ modern proprietary formulas intended for infants continue to attempt to simulate human milk. In doing this, however, the nutrient composition has also been adjusted to provide what are currently established as the nutrient requirements of growing infants. The levels of nutrients present in all infant formulas in the United States are subjected to regulations established by the FDA (Table 1).⁸ For many nutrients, minimal and maximal amounts are specified. Modifications in nutrient and nonnutrient content are generally based on recommendations from the scientific and medical

communities. In the United States, the Committee on Nutrition of the American Academy of Pediatrics has had an important role in the development of these recommendations. The Codex Alimentarius Commission, created by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization in 1963 to develop global standards for food items, includes a standard for infant formula composition that was first adopted in 1981. An update on the global

Table 1 Recommended Nutrient Levels for Infant Formulas (per 100 kcal)

Nutrient	Minimum	Maximum
Protein (g)	1.8	4.5
Fat (g)	3.3	6.0
Calories	30.0	54.0
Essential fatty acids		
Linoleic acid (mg)	300.0	—
Calories	2.7	—
Vitamins		
A (IU)	250.0	750.0
D (IU)	40.0	100.0
K (mcg)	4.0	—
E (IU)	0.7	—
C (ascorbic acid) (mg)	8.0	—
B1 (thiamine) (mcg)	40.0	—
B2 (riboflavin) (mcg)	60.0	—
B6 (pyridoxine) (mcg)	35.0	—
B12 (mcg)	0.15	—
Niacin (mcg)*	250.0	—
Folic acid (mcg)	4.0	—
Pantothenic acid (mcg)	300.0	—
Biotin (mcg)†	1.5	—
Choline (mg) †	7.0	—
Inositol (mg)†	4.0	—
Minerals		
Calcium (mg)	50.0	—
Phosphorus (mg)	25.0	—
Magnesium (mg)	6.0	—
Iron (mg)	0.15	3.0
Iodine (mcg)	5.0	75.0
Zinc (mg)	0.5	—
Copper (mcg)	60.0	—
Manganese (mcg)	5.0	—
Sodium (mg)	20.0	60.0
Potassium (mg)	80.0	200.0
Chloride (mg)	55.0	150.0

From Section 412, Food, Drug and Cosmetic Act.⁸

*Includes niacin (nicotinic acid) and niacinamide (nicotinamide).

†Required only for non-milk-based infant formulas.

standard was prepared in 2005 by a group of international nutritional experts coordinated by the European Society of Pediatric Gastroenterology, Hepatology and Nutrition at the request of the Codex Committee on Nutrition and Foods for Special Dietary Uses.⁹

The Infant Formula Act of 1980 and the amendments of 1986 mandate the quality control standards under which all infant formulas are manufactured in the United States. These government regulations on good manufacturing practices came about following reported cases of hypochloremia and alkalosis in infants fed with a chloride-deficient soy formula.¹⁰ However, the potential for error in preparation and contamination of infant formulas pre- and post-marketing continues even in the twenty-first century in different parts of the world. Several infants in Israel, which has similar regulatory safeguards as the United States, developed signs of beriberi, including death in two, as a result of a thiamine-deficient soy formula imported from Germany.¹¹ One infant died of meningitis due to *Enterobacter sakazakii* in Tennessee, USA,¹² and another infant developed botulism due to *Clostridium botulinum* type B toxin in the United Kingdom.¹³ Bacterial contamination of infant formulas remains an active issue in the formula industry because, unlike liquid formulas, powdered formulas cannot be sterilized during the manufacturing process. *Enterobacter sakazaki* is the most common organism isolated, though *Salmonella* species has also been identified in outbreaks.¹⁴ Batches of formulas have also been recalled because of metal pieces found in the formula, or because of an inadequate seal that could lead to oxidation and depletion of vitamin C in the liquid formula.^{15,16} These episodes emphasize the continuing need for constant monitoring of infant formula composition and quality as required by statute, including postmarketing surveillance.

The enteral formulas can be categorized either by their protein composition (cow-milk-, soy-, protein hydrolysate-, and amino acid-based), or by the intended consumer groups (eg, premature infants, healthy infants, children with special metabolic needs).

COW-MILK-BASED FORMULAS

Standard cow-milk-based formulas are marketed in ready-to-use, concentrated liquid and powdered forms. All are based on nonfat cow milk, to which lactose and vegetable oils have been added. These formulas are low in cholesterol because the fat is derived from vegetable sources. In addition, emulsifiers (eg, lecithin) and thickeners (eg, carrageenan) have been added. Their mineral and vitamin content have also been adjusted to suit the needs of human infants.

Experience accumulated over the past 50 years has shown that casein-predominant milks support normal growth in both premature and full-term infants.¹⁷ Casein has served as a

standard reference protein by which to measure the biologic value of other proteins such as soybean or egg protein. The measure of the biologic value is the grams of weight that reference animal gains for each gram of protein fed. Setting casein as 100%, FDA regulations require protein at a minimum level of 1.8 g/100 kcal of formula. For proteins with a lower biologic value, the formula must contain proportionately more protein. No protein source can be used with a biologic value less than 70% of casein. Cow milk has a relatively greater amount of casein than human milk. Those formulas that are based on casein have an amino acid and mineral composition that more closely resembles that of cow milk than human milk. The osmolality and potential renal solute loads of these standard formulas fall intermediate between human and cow milk, although these values increase, as do those of the other constituent nutrients, if the formulas are prepared to be more concentrated than indicated by the manufacturer.

Renal solute load refers to the sum of solutes filtered by the kidneys. These solutes include amino acids, urea, and electrolytes. The potential renal solute load (PRSL) of an enteral formula refers to the sum total of the solutes present in the preparation, as approximated by the equation¹⁸

$$\text{PRSL (mOsm)} = \text{N}/28 + \text{Na} + \text{Cl} + \text{K} + \text{P},$$

where N is total nitrogen in mg. Assuming that 1 g of protein contains 0.16 g of nitrogen, the equation can also be written as

$$\text{PRSL (mOsm)} = (\text{Protein(g)} \times 5.714) + \text{Na} + \text{Cl} + \text{K} + \text{P}.$$

As the nutrients are digested, absorbed, and metabolized, and waste products are generated, the actual amount of solutes that reach the kidneys may be quite different. Nevertheless, when the solute load is above the handling capacity of the kidneys, dehydration from osmotic diuresis and metabolic derangement, for example, hypernatremia, metabolic acidosis, and an elevated BUN, may occur.

Infants who are fed a casein-predominant formula have a different profile of amino acids in their serum after feeding than breastfed infants, and some have developed metabolic derangements on casein-predominant formulas.¹⁹ For this reason and others, including attempts by manufacturers to simulate human milk, whey-predominant and whey-only formulas have achieved popularity for both premature and full-term infants. By increasing the amount of whey proteins, mainly alpha-lactalbumin and beta-lactoglobulin, the amino acid composition of the formula is altered so that it resembles human milk more than cow milk. This is particularly so for the sulfated amino acids, cystine, taurine, and methionine. Clinical studies have demonstrated the adequate growth of full-term infants taking these formulas. Serum amino acid profiles of infants fed whey-predominant formulas are different from those fed human or cow milk, with a higher percentage of branched-chain amino acids and threonine in circulation.

However, the significance of this finding is unclear.^{20,21}

Iron is added to the standard formulas in order to prevent iron deficiency in newborns in the first year of life. Iron supplementation is particularly important for premature or small-for-gestational-age infants, who have reduced iron stores. The amount of iron present in the formulas range from approximately 4.7 to 14.5 mg/L (equivalent to 0.7 mg to 1.8 mg/100 kcal) in the United States and 4 to 7 mg/L in Europe.²² The proposed global standard is a range of 0.3 mg to 1.3 mg/100 kcal.⁹ The designation "low-iron" on infant formulas now refers to an iron content at the lower end of the range.

Nucleotides are now being added to many of the standard cow-milk-based formulas based on the presence of nucleotides in human milk. The addition of nucleotides is supported by the finding of a decreased incidence of diarrheal disease in a few studies of infants fed formulas supplemented with nucleotides.^{23,24} Furthermore, nucleotides added to infant formula have also increased plasma lipoproteins and enhanced the growth of small-for-gestational-age infants.^{25,26} In a study of term infants, cow-milk-based formula supplemented with nucleotides enhanced antibody responses to Diphtheria and Hemophilus influenzae vaccinations, but antibody responses to polio and tetanus were unaffected.²⁷ In preterm infants on formula supplemented with nucleotides, serum IgM and IgA levels were higher, while IgG and lymphocyte subsets were unaffected.²⁸ The full clinical significance of these observations remains to be demonstrated.

The fatty acid composition of infant formulas remains an area of intense investigation. Oils from a variety of plants such as palm, coconut, corn, safflower, and soybean are used instead of the animal fat in cow-milk-based formulas. Formulas that contain palm olein as part of the oil mixture were designed to imitate the palmitic acid profile of human milk. However, several studies have shown that babies fed with formulas with palm olein had lower calcium and fat absorption and lower bone mineralization compared to those on a formula without palm olein.^{29,30} The position of the palmitic acid in the triglyceride molecule affects its absorption in the gut. Human milk fat has a greater proportion of triglycerides with palmitic acid in the beta position of the glycerol backbone than palm olein. Infants on a formula with a high portion of triglycerides with palmitic acid in the beta position have better fat and calcium absorption than those on a formula with a low percentage of palmitic acid in the beta position.³¹

Human milk contains relatively more mono-unsaturated fatty acids than regular infant formulas and also contains long-chain polyunsaturated fatty acids (LCPUFA) such as arachidonic (AA) and docosahexaenoic acids (DHA). Arachidonic acid and DHA are important structural components of cell membranes in the brain and retina. Studies have shown enhanced cognitive development and visual acuity in premature

infants fed with formulas supplemented with AA and DHA.^{32,33} Another study in preterm infants found increased lean body mass and reduced fat mass by 1 year of age for those fed with AA and DHA supplemented formulas.³⁴ Studies in term infants, however, have shown mixed results.^{35,36} A follow-up study at 39 months of age of these infants who had received AA and DHA supplemented formulas up to 1 year found no difference with respect to their visual and cognitive functions when compared to infants fed either breast milk or unsupplemented formula.³⁷ LCPUFAs also influence the maturation of the immune system. The expression of CD45RO (mature phenotype) on CD4+ cells and IL-10 production were higher in preterm infants fed human milk and those fed with infant formula supplemented with LCPUFAs compared to those in infants fed with unsupplemented infant formula alone, although it is unclear whether this is a clinically important phenomenon.³⁸ The supplemented formulas appear to be safe, as all studies have shown no adverse outcomes and no significant difference in the growth parameters for infants on supplemented formulas with appropriate ratios of AA and DHA.^{39,40}

Cow-milk-based formulas with lactose are contraindicated for infants with galactosemia, cow milk allergy, or lactose intolerance. However, a lactose-free cow-milk-based formula with corn syrup solids as the carbohydrate is an appropriate choice for infants with lactose intolerance. Another cow-milk-based formula with added rice starch was specifically marketed for infants with uncomplicated gastroesophageal reflux. Rice cereal is frequently added to thicken the formula in the management of uncomplicated gastroesophageal reflux. This practice increases the amount of carbohydrate relative to protein in the feeding and potentially may lead to intake of either excessive calories or inadequate protein by the infant. This formula addresses this concern by replacing part of the lactose with rice starch so that the protein:calorie ratio remains at 2.5 g/100 kcal.

A formula containing oligosaccharides as part of the carbohydrates and the synthetic triglyceride with palmitic acid in the beta position is already commercially available in Europe. Besides lactose, oligosaccharides make up approximately 10% of carbohydrates in human breast milk. The oligosaccharides are a mixture of short chain carbohydrates with sialic acid, fucose, and galactose residues. They are poorly digested like soluble fiber and serve as substrates for intestinal bacterial metabolism. They promote growth of Bifidobacteria and Lactobacillus species in the gut.^{41,42} The incidence of moderate to severe diarrheal disease in a group of breastfed infants was found to be inversely related to the concentration of fucosyloligosaccharides in the breast milk.⁴³ Human infants on a formula with added oligosaccharides had softer and more frequent stools and had a lower risk for atopic dermatitis than those without the oligosaccharide supplement.⁴⁴ Future studies will determine whether this type of formula has

other long-term advantages over those without the oligosaccharides.

Formulas for Premature Infants

Milk feedings formulated specifically for premature and small-for-gestational-age infants are sold in a liquid ready-to-use form for use in hospitals and postdischarge. These formulas differ from the standard formulas by attempting to meet the nutritional requirements of rapidly growing low-birth-weight infants within the limitations of intestinal and renal functions seen in these infants. These formulas have 20, 22, or 24 kcal/oz. When prepared at 20 kcal/oz, these formulas contain more protein than standard formulas. Fat malabsorption is a common occurrence in the low-birth-weight infant. Therefore, a high percentage of the fat in most of these formulas is in the form of medium-chain triglycerides, which have been shown to reduce steatorrhea, enhance calcium absorption, and improve nitrogen retention in low-birth-weight infants.^{45,46} Carbohydrate is provided as a mixture of lactose, maltodextrins, and glucose polymers. Glucose polymers appear to be well tolerated by prematures.⁴⁷ Finally, the concentrations of calcium and phosphorus, in a 2:1 ratio, are increased above levels found in standard formulas. These nutrient concentrations are necessary to support a rate of growth similar to that of a full-term infant in utero. Although the breast milk of mothers delivering premature infants has higher protein and vitamin A concentrations than breast milk of mothers of full-term infants, the amounts of these nutrients are still insufficient to provide the daily requirements. A human milk “fortifier” formula can be added to breast milk to provide additional calories, calcium, phosphorus, other minerals, and vitamins.

Soy-Based Formulas

The soy protein formulas were introduced for use in infants who are cow milk intolerant. Although soy formulas are often fed to cow milk-allergic infants, soy protein is also antigenic and concomitant allergic reactions to soy may occur in cow milk allergic infants. Soybean protein is readily available and is a high-quality protein. Soy protein isolate is supplemented with L-methionine and taurine to balance the amino acid composition relative to animal milks and improve its biologic value.⁴⁸ Soy formulas are also supplemented with carnitine, which is found only in animal proteins. Nucleotides are not added to the soy formulas, as studies of infants fed nucleotide-supplemented soy formula failed to show any obvious immunological advantages, such as an enhanced response to vaccines or enhanced lymphocyte maturation.^{49,50} The carbohydrates in soy formulas consist of sucrose, corn syrup solids, and/or maltodextrin. These formulas are therefore useful in infants with clinically significant lactose intolerance. Infants with acute lactose intolerance fed soy formula may have a shorter duration of diarrhea, although for most infants with acute

infectious diarrhea, lactose intolerance is not clinically significant.^{51,52}

While earlier studies showed that bone mineralization was reduced in infants fed a soy-based formula compared to infants fed a cow-milk-based formula,⁵³ studies from the 1990s of soy formula with improved mineral suspension showed no difference in bone mineralization in term infants fed soy- and cow-milk-based formulas.^{54,55} The bioavailability of phosphorus, zinc, manganese, copper, and iron is reduced by phytic acid and polysaccharides present in the soy protein isolate.⁵⁶ Soy formulas are therefore supplemented with zinc and iron. Iron status appears to be equivalent in infants fed soy and cow milk formulas.⁵⁷

Aluminum has been found in soy formulas at concentrations of 600 to 1,300 ng/mL, compared to concentrations of 4 to 65 ng/mL found in human milk.^{58,59} Aluminum is the most abundant metal in the earth’s crust and is present in many plants. It is present in the formula as a contaminant of calcium salts and the soy protein isolate. Aluminum-induced encephalopathy has been reported in patients with renal disease and those who were taking aluminum salts as an antacid or as phosphate binders. Aluminum also competes with calcium for absorption and may contribute to the osteopenia seen in infants with compromised renal function. No adverse effects of aluminum have been seen in healthy infants consuming soy formulas.

Soy protein isolate also contains isoflavones with estrogenic activity. Plasma concentrations of the isoflavones in infants fed with soy formulas were two orders of magnitude higher than levels found in infants fed with cow milk formulas or human milk.⁶⁰ The high concentrations of isoflavones found in infants fed with soy formulas have raised concern regarding the long-term health effects on infants exposed to soy. While many studies have demonstrated adequate growth for infants fed with soy formulas, up to now only one study has reported on the sexual development of infants fed on soy-based formulas. This retrospective cohort study of young adults who had participated in studies on soy- and cow-milk-based formulas in their infancy found no substantial effects of soy formulas on either growth or sexual maturation of human infants.⁶¹

Other specific indications for use of the soy formulas, in addition to lactose intolerance, include galactosemia and parents who prefer to avoid feeding their infants animal products, that is, vegetarians, or those whose specific religious dietary laws preclude the use of animal-based milks. The majority of infants with cow milk protein intolerance can tolerate soy formula. However, 15–40% of those with cow milk protein intolerance may have concomitant soy intolerance.^{62,63} There is no benefit from the use of soy formulas to treat common problems in infancy such as gastroesophageal reflux, colic, and constipation unless these are symptoms of cow milk intolerance. Weight gain and bone mineralization in preterm infants fed soy formula have been

reported to be lower than those fed cow-milk-based formulas.^{64,65} Because of this and a concern for aluminum toxicity associated with soy formulas, the American Academy of Pediatrics issued a policy statement that “soy protein-based formulas are not designed or recommended for premature infants who weigh < 1800g.”⁶⁶ For the same obvious reason, soy formulas should also be avoided in patients with renal disease, and patients with fructose intolerance should avoid soy formulas that contain sucrose.

Other Non-Cow Milk-Based Infant Formulas

Goat milk has been frequently used to feed cow milk-sensitive infants although studies show that it is as antigenic as cow milk. Like almost all mammalian milks (the California sea lion is an exception), lactose is the carbohydrate in goat milk. Goat’s milk is high in essential fatty acids and has a higher percentage of medium-chain triglycerides than cow milk. It is low in folate, and because of more useful and effective commercial formula alternatives, its popularity has markedly waned in the United States. Goat milk remains a significant source of nutrition for infants after weaning in other countries. Infants fed with home preparations of goat milk are at risk for nutritional deficiencies and infections if the milk is contaminated. A goat milk formula, commercially produced in New Zealand, has been reported to be equivalent to a cow milk formula in terms of its growth-promoting effect and frequency of adverse events in term infants.⁶⁷

Meat-based formula is yet another lactose-free, cow milk protein-free alternative for infant feeding. Its nutritional adequacy for healthy infants has been demonstrated, and it may be used in the management of children with food-induced atopic dermatitis,⁶⁸ but currently there is no commercial preparation of it.

PROTEIN HYDROLYSATE FORMULAS

Protein hydrolysate formulas, sometimes referred to as semielemental formulas (a vague term, implying that the hydrolysis process results in a source of nitrogen close to the free amino acids found in an “elemental” formula), are intended for patients with disorders associated with compromised enteric digestion, such as short bowel syndrome, food protein allergy, autoimmune enteropathy, HIV-associated enteropathy, cystic fibrosis, pancreatic insufficiency, and hepatobiliary disorders such as biliary atresia. The casein or whey in these formulas (Appendix III) is modified by hydrolysis and the addition of free amino acids. The casein hydrolysates are supplemented with L-cystine, L-tyrosine, and L-tryptophan to increase their biologic value to the infant. The major portion of the nitrogen in the formula is in the form of oligopeptides. While the hydrolyzed protein peptides are less likely to induce an antigenic response than whole protein molecules, they are not nonallergenic.⁶⁹⁻⁷¹ One study suggests that peptides consisting of 5, 4, or even

3 amino acids can still activate T cell clones in vitro.⁷² There is evidence to support the considerably faster rate of intestinal amino acid uptake from solutions containing dipeptides, tripeptides, or partially hydrolyzed proteins than from solutions composed solely of free amino acids.⁷³ Formulas with oligopeptides have a lower osmolality than a free amino acid-containing formula, and therefore may have a theoretical advantage over the amino acid-containing formulas for young infants and patients with short bowel syndrome. With immaturity of the intestine or loss of absorptive surface area, either following bowel resection or as a result of inflammation, all of the disaccharidases, but most commonly lactase, may be diminished.⁷⁴ The use of sucrose or glucose polymers (partially hydrolyzed corn starch) would therefore be useful in circumventing the absence of lactase or both lactase and sucrase. Monosaccharides are not used exclusively in any of the prepared formulas because of their high osmolality, which may inhibit gastric emptying^{75,76} and further impair intestinal function.

Medium-chain triglycerides form a large percentage of the total fat content of these formulas. Medium-chain triglycerides can be absorbed from the intestine with minimal lipolysis to enter the portal circulation. Because of the enhanced solubility of medium-chain fatty acids in aqueous fluids, absorption of this form of fat can also take place in the absence of bile salts in the intestinal lumen and unstirred layer. None of these formulas contains only medium-chain triglycerides since they would then be devoid of the essential fatty acids. Medium-chain triglycerides increase the osmolality of a formula more so than long-chain fatty acids, and the excessive use of this form of fat may also contribute, in some patients, to excessive losses of stool water.

FREE AMINO ACID FORMULAS

The principal difference between these formulas and the peptide-based formulas is in the amino acid composition. The lipid component is a mixture of safflower, coconut (or MCT), and soy oils to provide essential and nonessential fatty acids. The carbohydrate is from corn syrup solids or maltodextrins, which are both derived from corn starch, differing only in the size of glucose polymers. As free amino acids by themselves are non-immunogenic, these formulas are most useful for infants and children with multiple food allergies that do not tolerate even the peptide-based formulas. Several studies have shown that most infants with cow milk or multiple food allergies are able to grow adequately on amino acid-based formulas.^{77,78} However, depending on the manufacturing and purification process, the soy oil may be contaminated by trace amounts of soy protein and may trigger an allergic response in susceptible individuals.⁷⁹ Children with severe enteropathy or short bowel syndrome unable to tolerate protein hydrolysates can use the amino acid-based formulas as an alternative or as an adjunct to parenteral nutrition.⁸⁰

FOLLOW-UP FORMULAS

Follow-up formulas are defined by the joint FAO/WHO Codex Alimentarium Commission (1988) as: “A food intended for use as a liquid part of the weaning diet for the infant from the 6th month on and for young children.”⁸¹ Currently, several formulas for this use are marketed in the United States. These formulas are either cow milk or soy based, differing from the standard infant formulas only slightly in nutrient concentrations. Even though follow-up formulas are nutritionally adequate, they have no advantage over a combination of solid foods and standard infant formulas and/or human milk and may interfere with the normal weaning process. Ideally, the weaning process should take place over a period of several months, effecting a transition to a solid food diet comprising 30 to 50% of total calories. Solid foods should complement infant formula/breast milk in mineral and vitamin composition.⁸²

FORMULAS FOR CHILDREN 1 TO 10 YEARS OF AGE

Although the use of formulas among healthy children decreases significantly after the first year of life, some children may require continued nutritional support with a liquid formula for a variety of reasons, including inadequate nutrient intake, perhaps as a result of chronic infections or single or multiple organ system dysfunction, compromised digestion or absorption, or inherited disorders of metabolism. These formulas can be cow milk-, soy-, peptide-, or amino acid-based. The carbohydrate is usually corn starch-derived glucose polymers and sucrose, and the fat is a blend of vegetable oils, such as safflower, soy, canola, and coconut oil to provide both medium- and long-chain triglycerides. These formulas are different from the infant formulas with a higher caloric density and protein concentration. The mineral and vitamin concentrations are intended to support the daily requirements for this age group.

Children who are unable to chew and swallow adequately due to neurological impairment, but who have intact intestinal motility, digestion, and absorption, exemplify those with a need for such a liquid enteral formula. For these children, the formulas are often administered via a gastrostomy. Children with critical illnesses or conditions who are unable to eat by mouth due to airway issues may use an enteral formula in the short term via a nasogastric or nasojejunal tube. Until recently, both adult and infant formulas have been used for preschool and school-aged children because of a lack of specific formulations for these age groups. If such formulas are “tailored” and their use is monitored to meet individual patient needs, they can be used successfully in this age group. However, vitamin and mineral deficiencies/excesses, osmotic diarrhea, and an excess renal solute load are a few of the concerns

with the use of adult products in young children. Current products specifically manufactured for this age group have made it easier provide the nutrients required to optimally support their growth. Some of the formulas have added soy fiber. Studies in adult patients have shown fewer problems with diarrhea (and constipation) when fiber is added to the enteral nutrition.^{83,84}

Peptide- and amino acid-based formulas designed for older children are often used for patients with limited digestive and absorptive capacity, such as those with Crohn disease, pancreatitis, and chemotherapy-induced enteropathy, in addition to those disorders mentioned above. In the case of Crohn disease (see also Chapter 48) peptide- and amino acid-based formulas have been used successfully to induce and maintain remission. While a meta-analysis of several randomized, controlled trials indicated that enteral nutrition was less effective than corticosteroids in induction of remission in adults with active Crohn disease,⁸⁵ studies in children suggest the opposite.⁸⁶ Several studies have also demonstrated that enteral nutrition begun early in the course of acute pancreatitis was superior to parenteral nutrition, with fewer septic complications and lower cost.⁸⁷⁻⁸⁹ A recent meta-analysis of enteral nutrition in patients with pancreatitis confirms the safety and efficacy of this route of nutrition.⁹⁰ Children requiring long-term tube feeding support, without any oral supplementation, should be monitored for the development of macro- and micronutrient deficiencies, for example, vitamin B₁₂, zinc and selenium, especially in those with chronic disease processes and severe diarrhea. Children with severe developmental delay and mental retardation are also at risk for obesity and osteopenia because of a low resting energy expenditure and inactivity. Since vitamins and trace elements in these formulas are present in proportion to the calories, provision of supplemental vitamins and minerals may be necessary if the amount of calories provided is substantially less than the usual recommended dietary allowance for age.

MODULAR FORMULAS

Modular formulas may be complete or intended to supplement the diet, and can be used to satisfy a particular nutrient requirement or to augment an already established feeding regimen (eg, caloric supplementation). For example, a carbohydrate-free product containing protein, fat, vitamins, and minerals can be mixed with another carbohydrate source in the treatment of conditions such as fructose intolerance or galactosemia. Carbohydrate-free formulas are also used in a ketogenic diet for infants and young children with intractable seizure disorders. Protein preparations of casein or whey are available separately without lactose and fat. Human milk fortifiers provide a mixture of protein (cow milk), fat (medium-chain triglycerides), carbohydrate (corn syrup solids), vitamins, and minerals to provide

additional nutrients to premature and full-term infants who are fed with breast milk. Problems may arise with their solubility in various commercial formulas, and they may also cause a significant increase in the osmolality of the new mixture.⁹¹ Additionally, when modular formulas are prepared by supplementing a standard liquid diet with extra carbohydrate or fat, changes in the calorie-to-nitrogen ratio occur which may not support optimal growth. In spite of these limitations, when used appropriately, these formulas and additives provide a means of specifically tailoring formulas to meet the nutritional needs of infants and children for whom no standard prepared formula is available. Children with congenital heart disease, renal disease, liver disease, and bronchopulmonary dysplasia are representative of those requiring formulas of increased caloric density because they are often fluid-restricted and have increased calorie requirements.

FORMULAS FOR METABOLIC DISORDERS

Liquid feedings are available to support patients with specific inborn errors of metabolism. These formulas generally use a mixture of amino acids as the protein source, without the specific amino acid(s) that can cause toxicity in patients with that specific metabolic disorder (eg, phenylalanine in phenylketonuria). These formulas are also available for different age groups. Some formulas can be used for more than one metabolic disorder. The formula for patients with Maple Syrup Urine Disease is free of the branched-chain amino acids leucine, isoleucine and valine, and it may also be used for patients with hypervalinemia, methylacetoacetic aciduria, isovaleric acidemia, hyperleucine-isoleucinemia, and leucine-induced hypoglycemia. However, since the omitted amino acid(s) are also essential for growth, a certain minimal amount of additional protein containing the missing amino acid(s) needs to be provided in the diet for these patients. For patients with metabolic disorders of fatty acids, such as long-chain- and very-long-chain acyl CoA dehydrogenase deficiencies, a formula with medium-chain triglycerides as the predominant fat source is used.

The metabolic status of these patients can be easily deranged by an acute viral infection that affects their oral intake. The mainstay of a “sick-day plan” is provision of adequate calories using a glucose polymer to prevent starvation-induced gluconeogenesis and lipolysis and subsequent accumulation of toxic metabolites.⁹² Patients must be monitored closely for clinical and laboratory indices of toxicity and deficiency. These formulas include vitamins and minerals age-adjusted to meet the patients’ needs. However, one study, based on 3-day diet records, indicated that children with maple syrup urine disease were getting only 21 to 66% of recommended daily allowance for selenium.⁹³ Until further studies

have been completed, the long-term efficacy and safety of some of the metabolic formula products remains to be determined.

FORMULAS INTENDED FOR OLDER CHILDREN WITH CHRONIC ILLNESS

Enteral formulas intended for adults can generally be used for children older than 10 years of age with chronic illness. The osmolality of these formulas varies from 280 to over 600 mosm/L. Sucrose is often one of the carbohydrate ingredients, perhaps to make these formulas more palatable. The sources of protein, carbohydrate, and fat are similar to those used for younger children and infants, but differ in their concentrations. Fiber is added in many of the formulas. In addition to standard formulas for the chronically feeding tube-dependent population, a number of disease-specific formulas are available (see Appendix III). Patients with severe pulmonary compromise may benefit from formulas that provide 40 to 55% of calories from fat, which has a lower respiratory quotient—that is, lower CO₂ production—than carbohydrates.⁹⁴ In contrast, formulas with a high-carbohydrate and low-fat content are preferred for patients with burn injury,⁹⁵ and patients with renal failure may benefit from formulas with low protein and salt concentrations. Some enteral formulas have increased concentrations of branched-chain amino acids (BCAA) that may be protein-sparing or reduce ammonia production in patients with chronic liver failure. Recently, single photon emission computed tomography (SPECT) in patients with cirrhosis and healthy controls showed that cirrhotic patients had reduced cerebral perfusion in bilateral, central, parietal, angular, and left pericallosal segments as compared to the healthy controls. The cirrhotic patients had improved cerebral perfusion 70 minutes after taking BCAA compared to those given placebo.⁹⁶ One randomized, controlled trial in adults with cirrhosis found that those given BCAA supplementation for 1 year had a risk for death or clinical deterioration lower than those given lactalbumin but not lower than those given maltodextrins.⁹⁷ A second randomized, controlled trial examined the effect of BCAA supplementation at 12 g/day in comparison to a diet with defined daily protein (1–1.4 g/kg) and caloric (25–35 kcal/kg) intake for 2 years in adults with cirrhosis. The primary end point was a composite of death, liver cancer, rupture of esophageal varices, or progress of hepatic failure, and secondary end points were the serum albumin concentration and quality of life measures. The BCAA group had better outcomes for both primary and secondary endpoints.⁹⁸

FORMULAS FOR CRITICALLY ILL PATIENTS

A number of nutritional substrates may modulate the host response to critical illness including major trauma. Included among these are zinc,

glutamine, arginine, and omega-3 fatty acids. Animal, human, and/or epidemiologic data suggest that one or more of these nutrients may be beneficial in the treatment of diseases such as AIDS,^{99,100} ulcerative colitis,¹⁰¹ lupus,¹⁰² rheumatoid arthritis,¹⁰³ major burns,^{104,105} and coronary heart disease.¹⁰⁶ Possible effects include an improvement in nitrogen balance (arginine), normalization/reduction of platelet aggregation (arginine),¹⁰⁷ substrate availability for energy utilization in rapidly replicating cells such as enterocytes and lymphocytes (glutamine),^{108,109} a decrease in the incidence of bacterial translocation (glutamine),¹¹⁰ and alterations in eicosanoid and cytokine production (omega-3 fatty acids).^{111,112}

Some randomized trials have demonstrated decreased infection rates, improved nitrogen balance, a decrease in hospital stay, and decreased cost of care in adult patients on an enteral formula supplemented with glutamine or with added fish oil, arginine and nucleotides.^{113–116} These findings were corroborated in a systematic review of 22 randomized, controlled trials involving 2,419 surgical and critically ill patients on either an immune-modulating formula or a standard formula.¹¹⁷ However, none of the studies has shown any difference in mortality in patients as a result of these supplements, and few studies have been performed in children.

In addition to the “conditional essential nutrients” mentioned above, there is also research interest in the potential therapeutic role of cytokines and growth factors found in the whey fraction of cow milk. Bovine colostrum is currently available as a diet supplement and has been reported to protect against the nonsteroidal anti-inflammatory drug-induced increase in intestinal permeability.¹¹⁸ Studies *in vitro* have demonstrated that a bovine whey protein concentrate protected against chemotherapy-induced cell injury and suppressed T and B lymphocyte proliferative responses to mitogens.^{119,120} Transforming growth factor beta (TGFβ) is present in bovine whey and especially that of colostrum,¹²¹ but it can account for only some of the effects seen with the use of the bovine whey extract or colostrum. An enteral formula with bovine TGFβ administered to 29 children with Crohn disease was effective in causing clinical remission in 79% after 8 weeks, though it was not a randomized or controlled study.¹²² Further research will determine whether TGFβ or other factors in bovine whey are useful in the management of patients with severe enteropathies.

In all patients with critical illness on a defined diet, the potential for the development of serious metabolic complications, such as azotemia, hypocalcemia, and hypomagnesemia, is high. Thiamine deficiency has been reported in 10 of 80 critically ill children admitted to the intensive care unit for more than 2 weeks and in 4 of 6 patients on chemotherapy.¹²³ Thus, in spite of their label as “complete” enteral feedings, chemically defined diets may lack essential nutrients, especially trace nutrients. A regular system for

monitoring nutritional adequacy, including anthropometric determinations, must be undertaken. Laboratory tests such as complete blood count, total protein, albumin, ferritin, electrolytes, BUN, creatinine, Ca, Mg, and P require only small volumes of blood, while additional tests such as zinc, copper, folate, B₁₂, vitamin A, vitamin E, and so on may also be indicated, depending on the underlying medical condition.

CONCLUSION

Standard infant formulas have evolved significantly since the turn of the century and now provide some but not all of the advantages seen with breastfeeding. There has also been a significant advance in our ability to provide adequate and appropriate nutrition by the enteral route to infants and children who would otherwise have required extended parenteral nutrition support. In spite of the relative ease of enteral feeding, patients must be carefully observed to ensure that they are growing and developing appropriately and that nutritional deficiencies are not developing. Physicians have the responsibility to inform their patients about the risks of enteral formulas. They must also be informed themselves about the evidence for the purported advantages of various formulas, as research efforts continue to define the role of nutrients and nonnutritive substances in the diet that will promote the health and the normal growth and development of infants and children.

REFERENCES

1. Fomon S. Infant feeding in the 20th century: Formula and beikost. *J Nutr* 2001; 131:409S–20S.
2. Fomon SJ. Infant feeding. In: Nichols BL, Ballabriga A, Kretchmer N, editors. *History of Pediatrics, 1850–1950*. Nestle Nutrition Workshop Series, Vol. 22. New York, NY: Raven Press; 1991. p. 77–89.
3. World Health Organization. 1981. International Code of Marketing of Breast Milk Substitutes.
4. Taylor A. Violations of the international code of marketing of breast milk substitutes: Prevalence in 4 countries. *BMJ* 1998;316:1117–22.
5. Wood AL. The history of artificial feeding in infants. *J Am Diet Assoc* 1955;31:474.
6. Brennemann J. Artificial feeding of infants. In: Abt A, editor. *Pediatrics by Various Authors*, Vol. 2. Philadelphia: Saunders; 1923.
7. Jacobi A. The gospel of top milk. In: Robinson WJ, editor. *Colleetana Jacobi*, vol. 3. New York: Critic and Guide; 1909.
8. Rules and Regulations. Nutrient requirements for infant formulas (21 CFR 107.100). *Fed Reg* 1985;50:45106–8.
9. Koletzko B, Baker S, Cleghorn G, et al. Medical Position Paper. Global standard for the composition of infant formula: Recommendations of an ESPGHAN coordinated international expert group. *J Pediatr Gastroenterol Nutr* 2005;41:584–99.
10. Garin EH, Geary D, Richard GA. Soybean formula (NEO-Mull-Soy) metabolic alkalosis in infancy. *J Pediatr* 1979;95:985–7.
11. Vikhanski L. Fatal flaw in baby formula sparks reform in Israeli ministry. *Nat Med* 2004;10:7.
12. Center for Disease Control. Enterobacter sakazakii infections associated with the use of powdered infant formula-Tennessee, 2001. *MMWR Morb Mortal Wkly Rep* 2002;51:297–300.
13. Brett MM, McLaughlin J, Harris A, et al. A case of infant botulism with a possible link to infant formula milk powder: Evidence for the presence of more than one strain of Clostridium botulinum in clinical specimens and food. *J Med Microbiol* 2005;54:769–76.

14. FAO/WHO 2004. Enterobacter sakazakii and other microorganisms in powdered infant formulas: Meeting Report (Microbiological Risk Assessment Series No. 6).
15. FDA News. FDA informs public of nationwide infant formula recall. February 22, 2006. <http://www.fda.gov/bbs/topics/NEWS/2006/NEW01323.html>
16. FDA Recall-Firm Press Release. Abbott voluntarily issues a nationwide recall for one lot of Alimentum, two lots of Similac Advance liquid formula ready-to-feed 32 oz plastic bottles and one lot of hospital discharge kits. September 15, 2006. http://www.fda.gov/oc/po/firmrecalls/abbott09_06.html
17. Fomon SJ. Comparative study of adequacy of protein from human milk and cow's milk in promoting nitrogen retention by normal full term infants. *Pediatrics* 1960;26:51.
18. Fomon SJ, Ziegler EE. Renal solute load and potential renal solute load in infancy. *J Pediatr* 1999;134:11–4.
19. Raiha NCR, Heinonen K, Rassin DK, Gaull GE. Milk protein quantity and quality in low-birth-weight infants. I: Metabolic Responses and Effects on Growth. *Pediatrics* 1976;57:659–84.
20. Janas LM, Picciano MF, Hatch TF. Indices of protein metabolism in term infants fed human milk, whey-predominant formula, or cow's milk formula. *Pediatrics* 1985;75:775–84.
21. Jarvenpaa AL, Rassin DK, Raiha NC, Gaull GE. Milk protein quantity and quality in the term infant. II: Effects on acidic and neutral amino acids. *Pediatrics* 1982;70:221–30.
22. Committee of Nutrition. American Academy of Pediatrics Policy Statement. Iron fortification of infant formulas (RE9865). *Pediatrics* 1999;104:119–23.
23. Brunser O, Espinoza J, Araya M, et al. Effect of dietary nucleotide supplementation on diarrheal disease in infants. *Acta Paediatr* 1994;83:188–91.
24. Lama More RA, Gil-Alberdi Gonzalez B. Effect of nucleotides as dietary supplement on diarrhea in healthy infants. *An Esp Pediatr* 1998;48:371–5.
25. Morillas J, Molto L, Robles R, et al. Lipoprotein changes in small-for-gestational age infants fed nucleotide-supplemented milk formula. *Acta Paediatr* 1994;83:481–5.
26. Cosgrove M, Davies DP, Jenkins HR. Nucleotide supplementation and the growth of term small for gestational age infants. *Arch Dis Child Fetal Neonatal Ed* 1996;74:F122–5.
27. Pickering LK, Granoff DM, Erickson JR, et al. Modulation of the immune system by human milk and infant formula containing nucleotides. *Pediatrics* 1998;101:242–9.
28. Navarro J, Maldonado J, Narbona E, et al. Influence of dietary nucleotides on plasma immunoglobulin levels and lymphocyte subsets of preterm infants. *Biofactors* 1999;10:67–76.
29. Nelson SE, Frantz JA, Ziegler EE. Absorption of fat and calcium by infants fed a milk-based formula containing palm olein. *J Am Coll Nutr* 1988;17:327–32.
30. Koo WW, Hammami M, Margeson DP, et al. Reduced bone mineralization in infants fed palm olein-containing formula: A randomized, double-blinded, prospective trial. *Pediatrics* 2003;111:1017–23.
31. Carnielli VP, Luijendijk IH, Van Goudouever JB, et al. Structural position and amount of palmitic acid in infant formulas: Effects on fat, fatty acid, and mineral balance. *J Pediatr Gastroenterol Nutr* 1996;23:553–60.
32. O'Connor DL, Hall R, Adamkin D, et al. Ross preterm lipid study. Growth and development in preterm infants fed long-chain polyunsaturated fatty acids: A prospective, randomized controlled trial. *Pediatrics* 2001;108:359–71.
33. Carlson SE, Salem N, Jr. Essentiality of omega-3 fatty acids in growth and development of infants. In: Simopoulos AP, Kifer RR, Martin RE, Barlow SM, editors. *Health Effects of Omega-3 Polyunsaturated Fatty Acids in Seafoods*. Basel, Switzerland: Karger; 1991. p. 74.
34. Groh-Wargo S, Jacobs J, Auestad N, et al. Body composition in preterm infants who are fed long-chain polyunsaturated fatty acids: A prospective, randomized, controlled trial. *Pediatr Res* 2005;57:712–8.
35. Auestad N, Halter R, Hall RT, et al. Growth and development in term infants fed long-chain polyunsaturated fatty acids: A double-masked, randomized, parallel, prospective, multivariate study. *Pediatrics* 2001;108:372–81.
36. Hoffman DR, Birch EE, Birch DG, et al. Impact of early dietary intake and blood lipid composition of long-chain polyunsaturated fatty acids on later visual development. *J Pediatr Gastroenterol Nutr* 2000;31:540–53.
37. Auerstad N, Scott DT, Janowsky JS, et al. Visual, cognitive, and language assessments at 39 months: A follow-up study of children fed formulas containing long-chain polyunsaturated fatty acids to 1 year of age. *Pediatrics* 2003;112:e177–83.

38. Field CJ, Thomson CA, Van Aerde JE, et al. Lower proportion of CD45RO cells and deficient interleukin-10 production by formula-fed infants, compared with human-fed, is corrected with supplementation of long-chain polyunsaturated fatty acids. *J Pediatr Gastroenterol Nutr* 2000;31:291–9.
39. Tantibhedyangkul P, Hashim SA. Medium-chain triglyceride feeding in premature infants: Effects on calcium and magnesium absorption. *Pediatrics* 1978;61:537–45.
40. Tantibhedyangkul P, Hashim SA. Medium-chain triglyceride feeding in premature infants: Effects on fat and nitrogen absorption. *Pediatrics* 1975;55:359–70.
41. Euler AR, Mitchell DK, Kline R, Pickering LK. Prebiotic effect of fructo-oligosaccharide supplemented term infant formula at two concentrations compared with unsupplemented formula and human milk. *J Pediatr Gastroenterol Nutr* 2005;40:157–64.
42. Knol J, Scholtens P, Kafka C, et al. Colon microflora in infants fed formula with galacto- and fructo-oligosaccharides: More like breast-fed infants. *J Pediatr Gastroenterol Nutr* 2005;40:36–42.
43. Morrow AL, Ruiz-Palacios GM, Altaye M, et al. Human milk oligosaccharides are associated with protection against diarrhea in breast-fed infants. *J Pediatr* 2004;145:297–303.
44. Moro G, Arslanoglu S, Stahl B, et al. A mixture of prebiotic oligosaccharides reduces incidence of atopic dermatitis in the first 6 months of life. *Arch Dis Child* 2006;91:814–9.
45. Tantibhedyangkul P, Hashim SA. Medium-chain triglyceride feeding in premature infants: Effects on calcium and magnesium absorption. *Pediatrics* 1978;61:537–45.
46. Tantibhedyangkul P, Hashim SA. Medium-chain triglyceride feeding in premature infants: Effects on fat and nitrogen absorption. *Pediatrics* 1975;55:359–70.
47. Cicco R, Holzman LR, Brown DR, Becker DJ. Glucose polymer tolerance in premature infants. *Pediatrics* 1981;67:498–501.
48. Fomon SJ, Ziegler EE, Filer LJ, Jr, et al. Methionine fortification of a soy protein formula fed to infants. *Am J Clin Nutr* 1979;32:2460.
49. Ostrom KM, Cordle CT, Schaller JP, et al. Immune status of infants fed soy-based formulas with or without added nucleotides for 1 year. Part 1: Vaccine responses, and morbidity. *J Pediatr Gastroenterol Nutr* 2002;34:137–44.
50. Cordle CT, Winship TR, Schaller JP, et al. Immune status of infants fed soy-based formulas with or without added nucleotides for 1 year. Part 2: Immune cell populations. *J Pediatr Gastroenterol Nutr* 2002;34:145–53.
51. Allen UD, McLeod K, Wang EL. Cow's milk versus soy-based formula in mild and moderate diarrhea: A randomized, controlled trial. *Acta Paediatr* 1994;83:183–7.
52. Santosham M, Goepf J, Burns B, et al. Role of a soy-based lactose-free formula in the outpatient management of diarrhea. *Pediatrics* 1991;87:619–22.
53. Steichen JJ, Tsang RC. Bone mineralization and growth in term infants fed soy-based or cow milk-based formula. *J Pediatr* 1987;110:687–92.
54. Mimouni F, Campaigne B, Neylan M, Tsang RC. Bone mineralization in the first year of life in infants fed human milk, cow milk formula or soy-based formula. *J Pediatr* 1993;122:348–54.
55. Venkataraman PS, Luhar H, Neylan MJ. Bone mineral metabolism in full term infants fed human milk, cow milk-based and soy-based formulas. *Am J Dis Child* 1992;146:1302–5.
56. Lonnerdal B. Trace element absorption in infants as a foundation to setting upper limits for trace elements in infant formulas. *J Nutr* 1989;119:1839–44.
57. Hertrepmpf E, Cayazzo M, Pizarro F, Stekel A. Bioavailability of iron in soy-based formula and its effect on iron nutriture in infancy. *Pediatrics* 1986;78:640–5.
58. Koo WWK, Kaplan LA, Krug-Wispel SK. Aluminum contamination of infant formulas. *JPEN J Parenter Enteral Nutr* 1988;12:170–3.
59. Litov R, Sickle VS, Chan GM, et al. Plasma aluminum measurement in term infants fed human milk or a soy-based infant formula. *Pediatrics* 1989;84:1105–7.
60. Setchell KD, Zimmer-Nechemias L, Cai J, Heubi JE. Exposure of infants to phyto-oestrogens from soy-based infant formula. *Lancet* 1997;350:23–7.
61. Strom BL, Schinrar R, Ziegler EE, et al. Exposure to soy-based formula in infancy and endocrinological and reproductive outcomes in young adulthood. *JAMA* 2001;286:807–14.
62. Zeiger RS, Sampson HA, Bock A, et al. Soy allergy in infants and children with IgE-associated cow's milk allergy. *J Pediatr* 1999;134:614–22.
63. Klemola T, Vanto T, Juntunen-Backman K, et al. Allergy to soy formula and to extensively hydrolyzed whey formula in infants with cow's milk allergy: A prospective, randomized study with a follow-up to the age of 2 years. *J Pediatr* 2002;140:219–24.
64. Naude SP, Prisoloo JG, Haupt CE. Comparison between a humanized cow's milk and a soy product for premature infants. *S Afr Med J* 1979;55:982–6.
65. Callenbach JC, Sheehan MB, Abramson SJ, Hall RT. Etiologic factors in rickets of very-low-birth-weight infants. *J Pediatr* 1981;98:800–5.
66. Committee on Nutrition. American Academy of Pediatrics. Soy protein-based formulas: Recommendations for use in infant feeding (RE9806). *Pediatrics* 1998;101:148–53.
67. Grant C, Rotherham B, Sharpe S, et al. Randomized, double-blind comparison of growth in infants receiving goat milk formula versus cow milk infant formula. *J Paediatr Child Health* 2005;41:564–8.
68. Martino F, Bruno G, Aprigliano D, et al. Effectiveness of a home-made meat based formula (the Rezza-Cardi diet) as a diagnostic tool in children with food-induced atopic dermatitis. *Pediatr Allergy Immunol* 1998;9:192–6.
69. Hill DJ, Cameron DJS, Francis DEM, et al. Challenge confirmation of late-onset reactions to extensively hydrolyzed formulas in infants with multiple food protein intolerance. *J Allergy Clin Immunol* 1995;96:386–94.
70. Saylor JD, Bahn SL. Anaphylaxis to casein hydrolysate formula. *J Pediatr* 1991;118:71–4.
71. Niggemann B, Nies H, Renz H, et al. Sensitizing capacity and residual allergenicity of hydrolyzed cow's milk formulae: Results from a murine model. *Int Arch Allergy Immunol* 2001;125:316–21.
72. Hemmer B, Kondo T, Gran B, et al. Minimal peptide length requirements for CD4(+) T cell clones—implications for molecular mimicry and T cell survival. *Int Immunol* 2000;12:375–83.
73. Mathews DM, Adibi SA. Peptide absorption. *Gastroenterology* 1976;71:151–61.
74. Phillips AD, Smith MW, Walker-Smith JA. Selective alteration of brush-border hydrolases in intestinal diseases in childhood. *Clin Sci* 1988;74:193–200.
75. Meeroff JC, Go VL, Phillips SF. Control of gastric emptying by osmolality of duodenal contents in man. *Gastroenterology* 1975;68:1144–51.
76. Graham GG, Klein GL, Cordano A. Nutritive value of an elemental formula with reduced osmolality. *Am J Dis Child* 1979;133:795.
77. Sicherer SH, Noone SA, Koerner CB, et al. Hypoallergenicity and efficacy of an amino acid-based formula in children with cow's milk and multiple food hypersensitivities. *J Pediatr* 2001;138:688–93.
78. Niggemann B, Binder C, Dupont C, et al. Prospective, controlled, multi-center study on the effect of an amino-acid-based formula in infants with cow's milk allergy/intolerance and atopic dermatitis. *Pediatr Allergy Immunol* 2001;12:78–82.
79. Awazuhara H, Kawai H, Baba M, Komiyama A. Antigenicity of the proteins in soy lecithin and soy oil in soybean allergy. *Clin Exp Allergy* 1988;28:1559–64.
80. Andorsky D, Lund D, Lillehei C, et al. Nutritional and other postoperative management of neonates with short-bowel syndrome correlates with clinical outcome. *J Pediatr* 2001;139:27–33.
81. Fomon SJ. *Nutrition of Normal Infants*. St. Louis: Mosby-Year Book; 1993.
82. Committee on Nutrition, American Academy of Pediatrics. Follow-up on weaning formulas. *Pediatrics* 1989;83:1067.
83. Nakao M, Ogura Y, Satake S, et al. Usefulness of soluble dietary fiber for the treatment of diarrhea during enteral nutrition in elderly patients. *Nutrition* 2002;18:35–9.
84. Homann HH, Kemen M, Fuessenich C, et al. Reduction of diarrhea incidence by soluble fiber in patients receiving total or supplemental enteral nutrition. *JPEN J Parenter Enteral Nutr* 1994;18:486–90.
85. Griffiths AM, Ohlsson A, Sherman PM, Sutherland LR. Meta-analysis of enteral nutrition as a primary treatment of active Crohn disease. *Gastroenterology* 1995;108:1056–67.
86. Papadopoulou A, Rawashdeh MO, Brown GA, et al. Remission following an elemental diet or prednisolone in Crohn disease. *Acta Paediatr* 1995;84:79–83.
87. Olah A, Pardavi G, Belagyi T, et al. Early nasojejunal feeding in acute pancreatitis is associated with a lower complication rate. *Nutrition* 2002;18:259–62.
88. Windsor AC, Kanwar S, Li AG, et al. Compared with parenteral nutrition, enteral feeding attenuates the acute phase response and improves disease severity in acute pancreatitis. *Gut* 1998;42:431–5.
89. Kalfarentzos F, Kehagias J, Mead N, et al. Enteral nutrition is superior to parenteral nutrition in severe acute pancreatitis: Results of a randomized prospective trial. *Br J Surg* 1997;84:1665–9.
90. McClave SA, Chang WK, Dhaliwal R, Heyland DK. Nutritional support in acute pancreatitis: A systematic review. *JPEN J Parenter Enteral Nutr* 2006;30:143–56.
91. Shike M. Enteral feeding. In: Shils M, et al, editors. *Modern Nutrition in Health and Disease*, 8th edition. Philadelphia: Lea & Febiger; 1994. p. 1417–29.
92. Dixon MA, Leonard JV. Intercurrent illness in inborn errors of intermediary metabolism. *Arch Dis Child* 1992;67:1387–91.
93. Gropper SS, Naglak MC, Nardella M, et al. Nutrient intakes of adolescents with phenylketonuria and infants and children with maple syrup urine disease on semisynthetic diets. *J Am Coll Nutr* 1993;12:108–14.
94. Ferreira I, Brooks D, Lacasse Y, Goldstein R. Nutritional intervention in COPD: A systemic overview. *Chest* 2001;119:353–63.
95. Garrel DR, Razi M, Lariviere F, et al. Improved clinical status and length of care with low-fat nutrition support in burn patients. *JPEN J Parenter Enteral Nutr* 1995;19:482–91.
96. Yamamoto M, Iwasa M, Matsumura K, et al. Improvement of regional cerebral blood flow after oral intake of branched-chain amino acids in patients with cirrhosis. *World J Gastroenterol* 2005;11:6792–9.
97. Marchesini G, Bianchi G, Merli M, et al (Italian BCAA Study Group). Nutritional supplementation with branched-chain amino acids in advanced cirrhosis: A double blind, randomized trial. *Gastroenterology* 2003;124:1980–2.
98. Muto Y, Sato S, Watanabe A, et al. Long-Term Survival Study Group. *Clin Gastroenterol Hepatol* 2005;3(7):705–13.
99. Bell SJ, Apour CS, Burke PA, Forse RA. Enteral formula: An update. In: Torosian M, editor. *Nutrition for the Hospitalized Patient: Basic Science and Principles of Practice*. New York: Marcel-Dekker; 1995. p. 293–306.
100. Bell SJ, Mascioli EA, Forse RA, Bistrain BR. Nutrition support and the HIV virus. *Parasitology* 1993;107:S53–67.
101. Hawthorne AB, Daneshmend TK, Hawkey CJ, et al. Treatment of ulcerative colitis with fish oil supplementation: A prospective 12 month randomized controlled trial. *Gut* 1992;33:922–8.
102. Drevon CA. Marine oils and their effects. *Nutr Rev* 1992;50:38–45.
103. Kremer JM, Jubiz W, Michalek A, et al. Fish-oil fatty acid supplementation in active rheumatoid arthritis. *Ann Intern Med* 1987;106:497–503.
104. Trocki O, Heyd TJ, Waymack JP, et al. Effects of fish oil on postburn metabolism and immunity. *JPEN J Parenter Enteral Nutr* 1987;11:521–8.
105. De-Souza DA, Greene LJ. Pharmacological nutrition after burn injury. *J Nutr* 1998;128:797–803.
106. Burr ML, Fehily AM, Gilbert JF, et al. Effect of changes in fat, fish, and fibre intakes on death and myocardial infarction: Diet and reinfarction trial (DART). *Lancet* 1989;2:757–61.
107. Wolf A, Zalpour C, Theilmeier G, et al. Dietary L-arginine supplementation normalizes platelet aggregation in hypercholesterolemic humans. *J Am Coll Cardiol* 1997;29:479–85.
108. Windmueller HG, Spaeth AE. Respiratory fuels and nitrogen metabolism in vivo in small intestine of fed rats. *J Biol Chem* 1980;255:107–12.
109. Calder PC. Glutamine and the immune system. *Clin Nutr* 1994;13:2–8.
110. Gianotti L, Alexander JW, Gennari R, et al. Oral glutamine decreases bacterial translocation and improves survival in experimental gut-origin sepsis. *JPEN J Parenter Enteral Nutr* 1995;19:69–74.
111. Hwang D. Essential fatty acids and immune responses. *FASEB J* 1989;3:2052–61.
112. Endres S, Grobani R, Kelley VE, et al. The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. *New Engl J Med* 1989;320:265–71.
113. Gottschlich MM, Jenkins M, Warden GD, et al. Differential effects of three enteral dietary regimens on selected outcome variables in burn patients. *JPEN J Parenter Enteral Nutr* 1990;14:225–36.
114. Daly JM, Lieberman MD, Goldfine J, et al. Enteral nutrition with supplemental arginine, RNA, and omega-3 fatty acids in patients after operation: Immunologic, metabolic, and clinical outcome. *Surgery* 1992;112:56–67.
115. Bower RH, Cerra FB, Bershady B, et al. Early enteral administration of a formula (Impact) supplemented with arginine, nucleotides, and fish oil in intensive care unit patients: Results of a multicenter, prospective, randomized, clinical trial. *Crit Care Med* 1995;23:436–49.
116. Jones C, Palmer TE, Griffiths RD. Randomized clinical outcome study of critically ill patients given glutamine-supplemented enteral nutrition. *Nutrition* 1999;15:108–15.
117. Heyland DK, Novak F, Drover JW, et al. Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. *JAMA* 2001;286:944.

118. Playford RJ, MacDonald CE, Calnan DP, et al. Co-administration of the health food supplement, bovine colostrum, reduces the acute non-steroidal anti-inflammatory drug-induced increase in intestinal permeability. *Clin Sci (Lond)* 2001;100:627–33.
119. Cross ML, Gill HS. Modulation of immune function by a modified bovine whey protein concentrate. *Immunol Cell Biol* 1999;77:345–50.
120. Taylor VL, Goddard C, Read LC. A milk growth factor extract reduces chemotherapeutic drug toxicity in epithelial cells in vitro. *In vitro Cell Dev Biol Anim* 2001;37:310–8.
121. Pakkanen R. Determination of transforming growth factor-beta (TGF-beta 2) in bovine colostrum samples. *J Immunol* 1998;19:23–37.
122. Fell JM, Paintin M, Arnaud-Battandier F, et al. Mucosal healing and a fall in mucosal pro-inflammatory cytokine mRNA induced by a specific oral polymeric diet in paediatric Crohn disease. *Aliment Pharmacol Ther* 2000;14:281–9.
123. Seear M, Lockitch G, Jacobson B, et al. Thiamine, riboflavin, and pyridoxine deficiencies in a population of critically ill children. *J Pediatr* 1992;121:533–8.