Infant Formulas

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Objectives

After completing this article, readers should be able to:

1. Describe the macronutrient content of formulas used as substitutes for human milk for term and preterm infants.
2. Identify appropriate clinical applications of infant formulas that have altered nutrient contents based on the physiologic significance of specific changes in formula composition.
3. Discuss the physiologic role and potential health benefits associated with four components added to infant formulas in the past decade.
4. Delineate current regulatory guidelines that define standards for composition and performance and safety criteria for commercial infant formulas.

Historical Background

Development of infant formulas can be traced to the late 19th century. In 1867, Liebig developed and marketed a product for infant feeding that contained cow milk, wheat flour, malt flour, and potassium bicarbonate. In 1915, Gerstenberger reported a 3-year experience using "synthetic milk, adapted" that contained nonfat cow milk, lactose, oleo oils, and vegetable oils. This product represented early understanding that cow milk required alteration to improve its acceptability for human consumption and is considered the precursor to modern infant formulas. (1)

Government regulation of infant formula composition in the United States began in 1941 and underwent significant expansion with passage of the Infant Formula Act of 1980, a direct and prompt response to an epidemic of a Bartterlike syndrome (hypochloremic, hypokalemic metabolic alkalosis). Most cases were later attributed to consumption of a chloride-deficient soy infant formula. The Infant Formula Act of 1980 and its amendments in 1986 defined minimum concentrations of 29 nutrients and established quality control standards for commercial production of infant formulas. Current standards are summarized in the Electronic Code of Federal Regulations: Title 21:107—Infant Formula. (2) Organic infant formulas must also meet all standards required for United States Department of Agriculture Organic certification.

The addition of nucleotides to infant formulas in 1999 and long-chain polyunsaturated fatty acids (LCPUFAs) in 2002 marked a new era in infant formula development. In 2004, anticipating continued competition among infant formula manufacturers to develop products that mimic the complexities and performance of human milk, a special committee of the Food and Nutrition Board of the Institute of Medicine proposed enhanced regulatory and research procedures to assess the safety of potential new ingredients in infant formulas. (1)

Challenges continue in ensuring the quality and safety of commercial infant formulas. Within the past 5 years, powdered infant formulas have been recognized as potential carriers of food-borne illness after the death of an infant due

Abbreviations

AAP:	American Academy of Pediatrics
ARA:	arachidonic acid
CMPA:	cow milk protein allergy
DHA:	docosahexaenoic acid
EHF:	extensively hydrolyzed formula
GERD:	gastroesophageal reflux disease
Ig:	immunoglobulin
LCPUFA:	long-chain polyunsaturated fatty acid
MCT:	medium-chain triglyceride
NEC:	necrotizing enterocolitis
PHF:	partially hydrolyzed formula
VLBW:	very low birthweight

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to *Enterobacter sakazakii* meningitis in the United States and a case of infantile botulism in the United Kingdom. These incidents led to stricter safety guidelines for home and institutional preparation and handling of commercial infant formulas. (3) The Table offers a comparison of currently available formulas.

Cow Milk–based Formulas for Term Infants

Often referred to as "standard" infant formulas, these products are the most commonly used substitutes for human milk. They are available as ready-to-use liquids (20 kcal/oz or 67 kcal/100 mL) and as powder or liquid concentrates that may be mixed with specific quantities of water to yield caloric densities between 20 and 30 kcal/oz.

Protein

Differences in the serum amino acid profiles of breastfed and formula-fed infants are due to variations in the specific protein content of human and bovine milk. Human milk has a higher whey-to-casein ratio (70:30) than bovine milk (18:82). Unlike casein, which forms large curds on exposure to gastric acid, whey protein is resistant to precipitation and undergoes more rapid gastric emptying. These characteristics are the primary reason for continued modification of the whey:casein ratio of cow milk-based formulas. It is important to note that the whey proteins in human and bovine milk are vastly different from both compositional and functional standpoints. In an effort to match the protein quality of human milk, cow milk-based formulas currently contain almost 50% higher total protein content (2.1 to 2.2 g/100 kcal) than human milk. Most infant formulas also contain supplemental taurine. The physiologic significance of differences in serum amino acid profiles of infants fed cow milk-based formulas versus human milk remains unclear. More importantly, casein-predominant (20:80), whey-predominant (60:40), and 100% whey formulas have all been shown to support normal growth patterns in both term and preterm infants.

Carbohydrate

Lactose is the predominant carbohydrate in most cow milk-based formulas and human milk. The lactase enzyme in the brush border of the small intestine reaches maximum concentrations late in fetal development, but some unsplit lactose usually reaches the distal bowel, where its fermentation permits proliferation of acidophilic bacteria, namely, *Lactobacillus*. Lactose has also been shown to enhance absorption of calcium in term infants between 8 and 12 weeks of age. The significance of this benefit in term infants is unclear because adequate calcium absorption has been demonstrated in infants consuming lactose-free formulas.

Fat

Approximately 50% of the caloric content of human milk is contained in its lipid component, which is rich in palmitic, oleic, linoleic, and linolenic fatty acids. Current formulas contain specific blends of vegetable oils designed to mimic the ratios of saturated, monounsaturated, and polyunsaturated fatty acids in human milk; increase the essential fatty acid content; and reduce gastrointestinal symptoms previously associated with infant feeding of whole cow milk.

Docohexaenoic acid (DHA) and arachidonic acid (ARA) are LCPUFAs present in human milk (mean content of DHA 0.32% and ARA 0.47% of total fatty acids) and have been found to accumulate rapidly in the fetal retina and brain during the last trimester of pregnancy, continuing until 2 years of age. DHA and ARA can be synthesized from precursor essential fatty acids and before 2002 were not added to infant formulas. Studies have shown that breastfed infants have a higher content of DHA in the brain cortex compared with infants consuming nonsupplemented formulas. Furthermore, numerous studies have observed improved visual and neurodevelopmental outcomes in children who had been supplemented with DHA or DHA plus ARA as infants. In 2008, two Cochrane meta-analyses of randomized, controlled trials found that milks supplemented with these LCPUFAs did not improve growth, visual acuity, or neurodevelopment in either preterm or term infants, which called their standard supplementation into question. (4)(5) However, recent studies that have focused on higher doses of DHA (between 0.3% and 0.5% of total fatty acids) and at least equal amounts of ARA have consistently reported significant benefits. Preterm infants may have a higher requirement, based on calculated accretion rates in the last trimester of pregnancy. No negative effects have been observed with DHA and ARA supplementation, and both are presently added to all formulas in a dose range of 0.15% to 0.32% DHA and 0.4% to 0.64% ARA (% total fatty acids). More studies are needed to define better the benefits and the correct dose needed for supplementation. (6)

Vitamins and Minerals

Iron fortification was implemented in 1959 in response to recognition of a high prevalence of iron deficiency anemia among formula-fed infants. Iron from human milk is absorbed at a higher rate (20% to 50%) compared with cow milk (4% to 7%). To compensate for lower bioavailability, all fortified formulas contain 1.8 mg/100 kcal of iron as compared with 0.45 to 0.9 mg/100 kcal in human milk. It is strongly recommended that

Table. **Infant Formula Comparison Chart**[1,2]

	Primary Protein Source					Carbohydrate						Fat		Features				
	Whey: Casein Ratio	Soy Protein Isolate	Partially Hydrolyzed	Casein Hydrolysate	100% Free Amino Acids	Full Lactose	Reduced Lactose (% Carbohydrate)	Lactose-free	Glucose Polymers	Glucose Polymers/ Sucrose Blend	Added Rice Starch (√) or Soy Fiber (x)	LCT/MCT (%)	DHA/ARA (% total fat)	Osmolality	Nucleotides	Prebiotics	Probiotics
Cow Milk-based Formulas (Intact Protein)																	
Enfamil® Premium™	60:40					√						100/0	0.32/0.64	300	√	√	
Similac Advance®	60:40					√						100/0	0.15/0.4	310	√	√	
Parent's Choice® Advantage	60:40						√		√			100/0	0.32/0.64	280	√	√	
Soy Protein-based Formulas (Intact Protein)																	
Enfamil® Prosobee®		√						√	√			100/0	0.32/0.64	180			
Similac Sensitive Isomil Soy™		√						√		√		100/0	0.15/0.4	200		√	
Parent's Choice® Soy Based		√						√	√			100/0	0.32/0.64	164			
Modified Cow- or Soy Milk-based for Term Infants																	
Enfamil AR®	20:80						59%		√		√	100/0	0.32/0.64	230			
Enfamil® Gentlease®	60:40		√				*20%		√			100/0	0.32/0.64	230			
Enfamil® RestFull™	20:80						59%		√		√	100/0	0.32/0.64	230			
Good Start® Gentle Plus™	100:0		√				70%		√			100/0	0.32/0.64	250	√		
Good Start® Protect Plus®	100:0		√				70%		√			100/0	0.32/0.64	250	√		√
Good Start® Soy Plus™		√	√					√		√		100/0	0.32/0.64	180			
Similac Sensitive®	20:80						*trace			√		100/0	0.15/0.40	200	√	√	
Similac Sensitive for Spit-Up™	20:80						*trace			√	√	100/0	0.15/0.4	180	√		
Similac Expert Care™ for Diarrhea (RTU; 20 kcal/oz)		√						√		√	x	100/0		240			
Parent's Choice® Gentle	60:40		√				*25%		√			100/0	0.32/0.64	189			
Parent's Choice® Sensitivity	20:80							√		√		100/0	0.32/0.64	198	√		
Parent's Choice® Added Rice Starch	20:80						√		√		√	100/0	0.32/0.64	206			
Extensively Hydrolyzed Formulas																	
Nutramigen® (liquid concentrate)				√				√	√			100/0	0.32/0.64	260			
Nutramigen® with Enflora™ LGG®				√				√	√			100/0	0.32/0.64	300			√
Pregestimil®				√				√	√			45/55	0.32/0.64	320			
Similac Expert Care™ Alimentum®				√				√		√		66/33	0.15/0.4	370			

(Continued)

Table. **Infant Formula Comparison Chart[1,2]—continued**

	Primary Protein Source					Carbohydrate						Fat		Features			
	Whey: Casein Ratio	Soy Protein Isolate	Partially Hydrolyzed	Casein Hydrolysate	100% Free Amino Acids	Full Lactose	Reduced Lactose (% Carbohydrate)	Lactose-free	Glucose Polymers	Glucose Polymers/ Sucrose Blend	Added Rice Starch (√) or Soy Fiber (x)	LCT/MCT (%)	DHA/ARA (% total fat)	Osmolality	Nucleotides	Prebiotics	Probiotics
Amino Acid-based Formulas																	
Elecare® (unflavored)					√			√	√			67/33	0.15/0.40	350			
Neocate® Infant					√			√	√			67/33	0.2/0.35	375			
Nutramigen® AA™					√			√	√			100/0	0.32/0.64	350			
Milk-based Formulas for Preterm/LBW Infants (RTU 24 kcal/oz liquid)																	
Enfamil® Premature	60:40						40%		√			60/40	0.32/0.64	300	√		
Good Start® Premature 24	100:0		√				50%		√			60/40	0.32/0.64	275	√		
Similac Special Care 24 Advance™	60:40						50%		√			50/50	0.25/0.4	280	√		
Transitional Formulas for Preterm/LBW Infants (RTU 22 kcal/oz liquid)																	
Enfamil® EnfaCare®	60:40						70%		√			80/20	0.32/0.64	250	√		
Similac Expert Care™ NeoSure®	60:40						50%		√			75/25	0.15/0.40	250	√		
Cow Milk-based for Specific Medical Needs																	
Enfaport® (RTU; 30 kcal/oz) (for chylothorax; LCHAD)	0:100							√	√			16/84	0.32/0.64	280			
Similac® PM 60/40 Low Iron (for calcium/ phosphorus disorders)	60:40					√						100/0		280			
Cow Milk-based Follow-Up Formulas (Intact Protein)																	
Enfagrow™ Premium™ Next Step®	20:80						55%		√			100/0	0.32/0.64	270			
Similac Go and Grow™	60:40					√						100/0	0.15/0.4	300	√	√	
Parent's Choice® Older Infants	20:80						71%		√			100/0	0.32/0.64	282			

(Continued)

Table. **Infant Formula Comparison Chart[1,2]—continued**

	Primary Protein Source					Carbohydrate						Fat		Features			
	Whey: Casein Ratio	Soy Protein Isolate	Partially Hydrolyzed	Casein Hydrolysate	100% Free Amino Acids	Full Lactose	Reduced Lactose (% Carbohydrate)	Lactose-free	Glucose Polymers	Glucose Polymers/ Sucrose Blend	Added Rice Starch (√) or Soy Fiber (x)	LCT/MCT (%)	DHA/ARA (% total fat)	Osmolality	Nucleotides	Prebiotics	Probiotics
Soy Milk-based Follow-up Formulas (Intact Protein)																	
Enfagrow™ Soy Next Step®		√						√	√			100/0	0.32/0.64	230			
Similac Go and Grow™ Soy		√						√		√		100/0	0.15/0.40	200			
Cow Milk-based Follow-up Formulas (Modified)																	
Enfagrow™ Gentlease® Next Step®	60:40		√				*50%		√			100/0	0.32/0.64	230			
Good Start® 2 Gentle Plus™	100:0		√				70%		√			100/0	0.32/0.64	265			
Good Start® 2 Protect Plus®	100:0		√				70%		√			100/0	0.32/0.64	265			√
Good Start® 2 Soy Plus™		√	√					√		√		100/0	0.32/0.64	180			

[1]Nutrient composition based on powdered product prepared at 20 kcal/oz (when applicable) unless otherwise noted.
[2]Differences in nutrient composition and product characteristics may vary among available forms (powder, liquid ready-to-use, liquid concentrate) of a specific product. Manufacturers may alter specific ingredients at any time; refer to product label for the most up-to-date information.
*Formula is marketed for management of "lactose sensitivity."
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ARA=arachidonic acid, DHA=docosahexaenoic acid, LBW=low birthweight, LCHAD=long-chain 3-hydroxyacyl-CoAdehodrogenase, LCT=long-chain triglyceride, MCT=medium-chain triglyceride, RTU=ready to use.

all formula-fed infants receive iron-fortified formulas to prevent anemia. Infant formula content of other micronutrients is based on a combination of data sets, including age-specific dietary reference intakes, human milk composition, inherent differences in the bioavailability of specific nutrients in human milk and formula, and regulatory guidelines.

Nucleotides

These nitrogenous substances have been added to several cow milk-based formulas since the late 1990s due to expanding knowledge of their physiologic role and recognition of their presence in relatively high concentrations in human milk. Nucleotides, which consist of one RNA nucleoside (adenine, guanine, cytosine, or uridine), one 5-carbon sugar moiety, and one or more phosphate groups, have been proposed as conditionally essential during periods of rapid growth because they possess immunomodulating capabilities. In clinical studies, nucleotide supplementation has been shown to enhance growth in small-for-gestational age infants, enhance immunoglobulin A (IgA) and IgM concentrations in preterm infants, decrease the incidence of diarrheal disease, and enhance antibody response to certain vaccines. However, additional research is needed to define the mechanism of action, confirm the clinical response, and monitor long-term effects of nucleotide supplementation of infant formulas.

Prebiotics, Probiotics, and Synbiotics

The intestinal flora of breastfed infants differs from that of formula-fed infants. Breastfed infant flora is predominantly composed of *Bifidobacterium* and *Lactobacillus*, whereas the flora of formula-fed infants is more complex, including also *Bacteroides*, *Enterobacteriaceae, Clostridium,* and *Streptococcus.* This difference is due, in part, to the high concentrations of oligosaccharides present in human milk that selectively stimulate bifidobacteria and lactobacilli. These bacteria are believed to be important for nutrient absorption, protection against pathogen colonization, development of the intestinal and systemic immune systems, and acquisition of mucosal tolerance. In an attempt to reproduce the intestinal flora of human milk-fed infants, prebiotics, probiotics, and synbiotics have been added to formulas with promising results.

Prebiotics are nondigestible short-chain carbohydrates, commonly galacto-oligosaccharides, fructo-oligosaccharides, or lactulose, that stimulate growth and function of specific species of bacteria. When added to formulas, prebiotics have been shown to increase the concentration of bifidobacteria and lactobacilli in the stools of preterm and term infants. The fermentation of prebiotics in the colon can lead to acidic, more frequent, and looser stools, but they are safe at the currently prescribed doses. Probiotics are live microorganisms that survive digestion and colonize the colon, leading to a more beneficial colonic microbiota. Synbiotics are a combination of prebiotics and probiotics. Both prebiotics and probiotics allow for normal growth in infancy.

Prebiotics and probiotics have been used for the prevention and treatment of allergy. The intestinal flora of atopic infants differs from that of nonatopic infants in the first few weeks after birth. These differences were noted before the development of atopy, suggesting a possible causative relationship. A lower number of bifidobacteria and higher numbers of clostridia may lead to an unbalanced, Th2-predominant immune response with increased IgE secretion, which is theorized to be a factor in the development of atopy. Both prebiotics and probiotics have been used in an attempt to achieve a more favorable intestinal flora, thereby preventing the development of atopic diseases. Evidence for the use of prebiotics in the prevention of atopy is inconclusive. This uncertainty could be due to a significant heterogeneity among the studies, including types and doses of prebiotics, types of milk used, and patient selection.

A Cochrane review showed that probiotic supplementation to high-risk infants decreased the incidence of clinical eczema but not of other atopic diseases. However, caution was raised about the heterogeneity of studies, the low follow-up numbers, and the fact that this effect did not hold for eczema with proven sensitization. (7) Probiotics have been studied for the treatment of allergies. One study showed that infants suspected of having cow milk protein allergy (CMPA) had faster recoveries when *Lactobacillus GG* was added to an extensively hydrolyzed formula, with faster resolution of blood per rectum and increased reduction of fecal calprotectin concentrations. (8)

Perhaps the most promising effect of probiotics is in the prevention of necrotizing enterocolitis (NEC). NEC is believed to have a multifactorial cause, with contributory factors including prematurity, aggressive initiation of feedings, pathogenic bacteria, and ischemia, all of which ultimately lead to immunologic injury to the gut. The intestinal flora of preterm infants contains less beneficial bacteria, which may be due to delayed feedings, broad-spectrum antibiotic courses, and acquisition of pathogenic environmental bacteria. Probiotics are believed to reduce the intestinal inflammatory response and may prevent NEC. In a recently updated meta-analysis, probiotics led to a reduction in cases of NEC (at least a 30% reduced incidence) and all-cause mortality in very low-birthweight (VLBW) infants (1,000 to 1,500 g).

Probiotics did not reduce the risk of sepsis or mortality due to NEC. (9) There are rare reports of probiotic-associated sepsis in neonates, but this complication was not seen in the studies reviewed for the meta-analysis. Other potential concerns about the safety of probiotics have been raised, including risks for transmission of antibiotic resistance and negative effect on neurodevelopment. In conclusion, probiotics appear to be effective in reducing the risk of NEC, but more studies are needed to determine the most beneficial type, dose, and duration of probiotic therapy. The safety and efficacy need to be established for each product. Currently, data in extremely low-birthweight (<1,000 g) infants are insufficient to reach any conclusions. The evidence for use of prebiotics in the prevention of NEC is very limited.

Studies have shown that formulas supplemented with prebiotics led to prevention of respiratory and intestinal infections. In one study, this beneficial effect persisted at 2 years of age. (10)

Preterm Infant Formulas

Preterm formulas were developed to meet the unique nutritional needs of rapidly growing preterm or low-birthweight infants. These products have a higher caloric density than standard formulas (24 kcal/oz or 80 kcal/100 mL). They contain supplemental taurine and 3 to 3.3 g/100 kcal of whey-predominant protein, which has been demonstrated to support growth and body composition changes comparable to intrauterine standards. The fat and carbohydrate compositions of these formulas are designed to overcome nutrient losses from low concentrations of lipase, bile salts, and intestinal lactase. In currently available products, medium-chain triglyceride (MCT) oil provides between 40% and 50% of total fat, with the remainder derived from a vegetable oil blend and supplemental DHA and ARA. MCT is absorbed directly into the portal vascular system and does not depend on the availability of bile acids for micellar solubilization.

Although lactase concentrations do not reach maximal values until term, carbohydrate is provided as a 60:40 or 50:50 mixture of glucose polymers and lactose due to the beneficial effects of lactose for calcium absorption and as a prebiotic. Preterm formulas contain higher amounts of numerous minerals and vitamins (particularly calcium, phosphorus, and vitamins A and D). It is important to note that intakes of some nutrients may be excessive if preterm formulas are consumed in quantities that exceed 12 oz/day (360 mL), and this risk increases as the infant's weight approaches 2,000 g. Preterm formulas should always be discontinued before hospital discharge.

Preterm Transitional Formulas

"Transitional" or "enriched" formulas that have intermediate nutrient concentrations have been available for several years and are marketed to bridge the gap between preterm and term formulas. Preterm infants are usually transitioned from preterm formulas to enriched formulas (22 kcal/oz or 73 kcal/100 mL) at 1,800 to 2,000 g or 34 weeks gestational age and continued on these formulas until 6 to 9 months of age. These formulas can achieve vitamin and mineral goal requirements without additional supplementation. However, the data on growth and neurodevelopment have been disappointing. In fact, a 2007 Cochrane meta-analysis found no evidence that feeding enriched formulas (versus standard infant formulas) to preterm infants after hospital discharge leads to improvements in growth or neurodevelopment by 18 months of age. (11)

Human Milk Fortifiers

Human milk alone is inadequate to meet the nutritional needs of preterm infants, particularly VLBW infants (<1,500 g). Thus, fortification of human milk (ie, the addition of multinutrient supplements) is recommended. Currently available commercial human milk fortifiers contain protein, carbohydrate, fat, and up to 23 vitamins and minerals. When mixed according to manufacturer's directions, fortified human milk matches growth and metabolic effects of preterm infant formulas. As with preterm formulas, ongoing use of commercial human milk fortifiers eventually may lead to excessive intake of certain nutrients that have known potential for toxicity. Therefore, it has become common clinical practice to use specific quantities of standard infant formula powder or liquid concentrate to fortify human milk in preterm infants who have progressed beyond specific age, weight, and intake volumes.

Soy Formulas

Currently available soy formulas contain a higher concentration of protein (2.45 to 2.8 g/100 kcal) and supplemental amino acids (L-methionine, taurine, and L-carnitine) to improve their biologic value. Glucose polymers from corn syrup solids or maltodextrin are the primary source of carbohydrate in soy formulas. Some products also contain sucrose, and all soy formulas are lactose-free. Fiber oligosaccharides, naturally occurring soy carbohydrates, are also present in soy formulas. These compounds and soy phytates have a high affinity for calcium, phosphorus, zinc, and iron and have been shown to interfere with their absorption. Therefore, soy formulas contain 20% higher concentrations of calcium and phosphorus and additional zinc and iron to compen-

sate for their diminished bioavailability. The fat content of soy formulas is similar to cow milk-based formulas, containing a blend of vegetable oils and supplemental ARA and DHA in all currently marketed products.

According to the 2000 United States Census, 18% of infants were fed soy formula in their first postnatal year. However, evidence-based indications for their use are limited. Soy protein-based formulas have been shown to be safe in term infants, with evidence for adequate growth rates and bone mineralization compared with infants fed cow milk-based formulas. However, for preterm infants, soy formulas cannot meet the increased requirements for calcium and phosphorus to match intrauterine accretion values, and this inadequacy can lead to osteopenia. Soy formulas contain increased concentrations of aluminum, which may compete with calcium for absorption, further affecting bone mineralization. For these reasons, soy formulas are not recommended for preterm infants. Concerns have been raised about the high concentrations of phytoestrogens/isoflavones in soy. These compounds bind to estrogen receptors and have been reported to have various negative effects on estrogen-related functions in animal studies, although results are conflicting and may be species-specific. In fact, a recent retrospective follow-up study showed no reproductive or estrogen-related adverse effects in adults who had been fed soy formula exclusively as infants. (12)

Soy formulas have not been shown to be of benefit in the management of infantile colic or cow milk intolerance, and there is no indication for their use in the prevention of atopic diseases. Infants who have nonIgE allergic enteropathy or enterocolitis due to CMPA have a 30% to 64% rate of cross-reaction to soy protein. Therefore, soy formulas are not indicated in the management of nonIgE allergies to cow milk protein. However, only 8% to 14% of infants who have IgE-mediated allergic reactions to cow milk proteins are sensitized to soy.

A statement by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition recommends that use of soy formulas be limited to infants older than 6 months of age who have signs consistent with IgE-mediated allergy after successful clinical challenge. (13) Soy formulas are free of all lactose and are indicated when strict lactose avoidance is required, as in the rare case of congenital lactase deficiency or in the management of galactosemia. It is important to note that cow milk protein formulas said to be free of lactose, in which other sugars are the predominant source of carbohydrates, still can contain small amounts of lactose and are not appropriate for infants who have galactosemia. Any formula said to be lactose-free may be used for transient lactase deficiency, such as a postviral enteropathy, although such affected infants generally tolerate continuation of a standard lactose-containing formula. Because soy formulas in this setting were only shown to decrease the duration of the diarrhea from 6 to 4 days without a significant change in weight at 14 days, their use for this purpose is discouraged. (14) Finally, strict vegetarian families may prefer soy formula for their infants.

Hydrolyzed and Amino Acid–based Formulas

More than 50 years ago, infant formulas containing extensively hydrolyzed protein were developed for feeding infants who were unable to digest or tolerate formulas containing intact cow milk protein. Casein, which is heat-treated and enzymatically hydrolyzed, is the protein source for all currently marketed formulas of this type in the United States. Hydrolysis results in a combination of short-chain peptides and free amino acids. Specific free amino acids are supplemented to improve the biologic value of the resulting nitrogenous content. It has been shown that peptides containing as few as three amino acids can induce T-cell activity in vitro. Thus, to be labeled as hypoallergenic, the American Academy of Pediatrics (AAP) guidelines state that "formulas must demonstrate that they do not provoke reactions in 90% of infants or children with confirmed cow milk allergy with 95% confidence when given in prospective randomized, double-blind, placebo-controlled trials." Currently, only extensively hydrolyzed and free amino acid-based formulas are considered to be hypoallergenic by these criteria.

Glucose polymers from various combinations of ingredients are the primary carbohydrate source in extensively hydrolyzed formulas (EHFs). One currently available formula (Similac Expert Care Alimentum®, Abbott Nutrition, Columbus, OH) contains a combination of glucose polymers and sucrose. All formulas are lactose-free.

The fat content of EHFs varies considerably. All contain a blend of vegetable oils similar to that in standard formulas and a total fat content of 48%. In two of three currently marketed products (Pregestimil®, Mead Johnson Nutritionals, Evansville, IN, and Similac Expert Care Alimentum®, Abbott Nutrition, Columbus, OH), a portion of this oil blend is replaced with MCT oil, which is helpful in certain malabsorptive conditions. Because essential fatty acids are long-chain triglycerides, no formula contains 100% MCT as a fat source.

Carbohydrate and fat composition are important criteria for specific EHF selection because clinical application of these formulas has expanded over time to include various conditions characterized by malabsorption of nutrients. Examples include short bowel syndrome,

hepatobiliary disease, pancreatic insufficiency, autoimmune diseases, and immunodeficiency syndromes. These formulas may be poorly accepted unless introduced early in infancy, and their high cost necessitates judicious use.

In recent years, formulas containing partially hydrolyzed whey protein have been marketed in the United States. They contain fat blends similar to those in standard formulas as well as reduced lactose content (lactose partially or fully replaced by glucose polymers).

Three amino acid-based formulas have been approved by the United States Food and Drug Administration: Neocate® (Nutricia North America, Gaithersburg, MD), Elecare® (Abbott Nutrition, Columbus, OH), and Nutramigen AA® (Mead Johnson Nutritionals, Evansville, IN). Unlike EHFs, the protein content of amino-acid based products is composed of individual free amino acids.

Glucose polymers from various dietary sources are the primary source of carbohydrate. With regard to fat content, one product (Nutramigen AA®) contains an oil blend similar to that in standard formulas. The other two products (Neocate® and Elecare®) contain a combination of oils resulting in a long-chain triglyceride-to-MCT ratio (67:33) that can be beneficial for certain malabsorptive disorders.

The increasing incidence of atopic diseases in recent decades has prompted interest in the use of hydrolyzed formulas for the prevention of atopy, particularly eczema, asthma, and food allergies. Hydrolyzed protein formulas appear to be superior to standard cow milk formulas, but not to human milk, in the prevention of allergy. The German Infant Nutritional Intervention Program, a longitudinal prospective study, showed that infants who had a high risk for developing atopic diseases (first-degree relative who had allergy) had a 33% lower incidence of atopic dermatitis when human milk was supplemented with hydrolyzed protein formula compared with supplementation with regular cow milk formula in the first 4 postnatal months. (15) This beneficial effect persisted at 6 years of age. Extensively hydrolyzed casein was more effective than partially hydrolyzed whey; extensively hydrolyzed whey showed no benefit.

In 2008, updated AAP recommendations stated that for infants at high risk of developing atopic disease who are not breastfed exclusively for 4 to 6 months or are formula-fed, there is evidence that atopic dermatitis may be delayed or prevented by the use of EHF or partially hydrolyzed formula (PHF) compared with cow milk-based formula. (16)

A more recent meta-analysis of 18 studies of high-risk infants who were fed a partially hydrolyzed whey formula found a 45% reduced risk for atopic dermatitis at 1 year of age and 36% reduction at 3 years of age. (17) Considering the high prevalence of allergic diseases in the population, one third of all infants would be candidates for a hydrolyzed formula, but their higher cost must be taken into consideration. Amino acid-based formulas have not been studied in the prevention of allergy.

Today, CMPA or hypersensitivity is reported in 2% to 3% of all infants. PHFs are not indicated for the management of CMPA due to the high percentage of reactions to these formulas. Therefore, infants who have proven CMPA and are not breastfeeding should be fed EHFs. A subgroup of patients who have CMPA, those who have nonIgE-mediated enterocolitis and failure to thrive, severe eczema, or symptoms during exclusive breastfeeding, may respond better to amino acid-based formulas than hydrolyzed formulas. (18) However, amino acid-based formulas should be reserved for those who do not respond to EHFs.

A percentage of infants who experience colic do respond to hydrolyzed formulas. Thus, a 1- to 2-week trial of a hydrolyzed formula can be recommended.

Modified Cow Milk– and Soy–based Formulas for Term Infants

In the past several years, the infant formula market has expanded to include several formulas marketed as solutions to specific conditions such as acid reflux, diarrhea, and excessive gas or fussiness often associated with colic. These formulas vary considerably in their macronutrient profile and typically contain one or more of the following modifications: partially hydrolyzed whey and soy proteins; reduced lactose or lactose-free carbohydrate blends; and other added ingredients such as thickeners, soy fiber, and prebiotics. With the exception of thickened formula, evidence for and against these modifications has been addressed in previous sections of this review.

Thickened infant formulas are commonly used to help manage gastroesophageal reflux disease (GERD). A recent meta-analysis reviewed 14 randomized, controlled trials that used different thickeners, including carob-bean gum, cornstarch, rice starch, cereal, and soy fiber. (19) Thickened milk was associated with an increased percentage of infants who had no regurgitation and reduced number of episodes of vomiting, regurgitation, and signs of GERD such as irritability and crying. However, the clinical significance of this reduction is unclear because vomiting was reduced by only 0.9 episodes/day. pH probe indices were not significantly improved, with the exception of a shorter duration of the longest episode of pH lower than 4. Thickened feedings may reduce nonacidic episodes of reflux, which may explain the disparity between clinical observations and standard pH probe measurements. Prethickened formulas are not supe-

Summary

- Based on strong research evidence, formulas supplemented with DHA (between 0.3% and 0.5% of total fatty acids) and at least equal amounts of ARA are beneficial for visual and neurological development.
- Based on strong research evidence, formulas supplemented with probiotics reduce the incidence of clinical eczema in high-risk infants (parent or sibling who has atopy).
- Based on strong research evidence, formulas supplemented with probiotics reduce the incidence of NEC and all-cause mortality in VLBW infants.
- Based on some research evidence, formulas supplemented with prebiotics or probiotics decrease the risk of infections during infancy.
- Based on strong research evidence, partially or extensively hydrolyzed formulas are effective in preventing or delaying development of atopic dermatitis in high-risk infants.
- Based on strong research evidence, thickened formulas reduce the number of episodes of vomiting, regurgitation, and signs of GERD such as irritability and crying.

rior to formulas thickened later with corn starch or rice cereal. Concerns have been raised about the safety of thickened milks, including malabsorption of macro- and micronutrients. The only adverse effects reported in the meta-analysis were increased coughing and diarrhea. Larger studies are needed to address these safety concerns better.

Follow-up Formulas

Follow-up formulas were developed to meet the nutritional needs of infants and young toddlers whose solid food intake is not fully adequate to meet age-specific nutritional requirements. As compared with standard formulas, follow-up formulas are slightly higher in the content of protein and selected minerals. They are available as modifications of both cow and soy milk-based products. According to the AAP, follow-up formulas are considered nutritionally adequate when used in combination with solid foods but offer no clear advantage over infant formulas designed to meet 100% of nutritional needs throughout the first postnatal year. These products may offer a small cost advantage over standard infant formulas.

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PIR Quiz

Quiz also available online at: http://pedsinreview.aappublications.org.

1. Which of the following statements about infant nutrition is true?

   A. Human milk contains more casein than infant formulas.
   B. Infants who receive increased whey protein have been shown to grow better than those who receive primarily casein.
   C. Iron is absorbed better from cow milk formulas than from human milk.
   D. Lactose-free formulas result in decreased absorption of calcium.
   E. There are no apparent negative effects from the addition of DHA and ARA to formulas.

2. Which of the following statements regarding prebiotics and probiotics is true?

   A. Both have been proven to decrease the incidence of atopy.
   B. Prebiotics are live microorganisms.
   C. Probiotics are carbohydrates that stimulate bacterial growth.
   D. The use of probiotics has been shown to reduce the incidence of necrotizing enterocolitis.
   E. They should be routinely prescribed to exclusively breastfed infants.

3. The characteristic that is more typical of casein than of whey is that it:

   A. Forms large curds on exposure to gastric acid.
   B. Is only found in trace amounts in cow milk.
   C. Is resistant to precipitation.
   D. Is the predominant protein in human milk.
   E. Undergoes more rapid gastric emptying.

4. Which infant feeding is *best* for the prevention of atopic disease?

   A. Cow milk-based formula.
   B. Extremely hydrolyzed formula.
   C. Human milk.
   D. Partially hydrolyzed formula.
   E. Soy formula.

5. Which of the following supplements has been added to formulas for the longest period of time?

   A. Arachidonic acid.
   B. Docosahexaenoic acid.
   C. Iron.
   D. Nucleotides.
   E. Prebiotics.

6. A young mother has brought her newborn to your clinic for his first visit. She has heard that soy formulas are better than milk-based formulas. For which of the following conditions is soy formula indicated?

   A. Allergic enteropathy.
   B. Colic.
   C. Galactosemia.
   D. Gastroesophageal reflux.
   E. Prematurity.

Infant Formulas

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