Pediatric Formulas: An Update

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PRACTICE GAP

With the infant formula recall in 2022 and the resulting infant formula shortage, a new demand has evolved for alternative formulas, including infant formulas imported from Europe. There are recent developments in young child formula, including commercially made, food-based blenderized formulas and an increased interest in using plant-based milk during childhood. Pediatricians need to keep up to date with these changes to educate parents on infant and young child feeding.

OBJECTIVES *After completing this article, readers should be able to:*

1. Discuss the recent shortage of infant formulas in the United States and the availability of European formulas.
2. Discuss the older infant–young child formulas and pediatric formulas.
3. Discuss nonformula, plant-based (milk) drinks.

ABSTRACT

The recent shortage of pediatric formulas in the United States, caused by supply chain issues and contamination of formula products in 1 of the major manufacturing plants, led many families to seek an alternate formula for their children. The Food and Drug Administration (FDA) allowed import of infant formulas from selected European and non-European countries. The European infant formulas differ from those produced in the United States regarding the primary source of the formula, age category, mixing instructions, labeling requirements, and formula composition in terms of macronutrients and micronutrients. Although most European infant formulas are nutritionally adequate, pediatricians and families need to be aware of the differences between the European and FDA-regulated formulas for their correct use and preparation for infants and young children. Supplementation with cow milk is recommended for children beyond infancy, and older infant formulas are not recommended for otherwise healthy growing children. However, pediatric formulas have been used to support the nutrition needs of

AUTHOR DISCLOSURE: Drs Imdad, Sherwani, and Wall have disclosed no financial relationships relevant to this article. Even though the authors discuss formula feeding in infants and young children, we fully endorse the position of the American Academy of Pediatrics and the World Health Organization on breastfeeding and agree that human milk is the most optimal nutrition for infants. The names of some of the commercial products have been used in one of the tables. We do not endorse any specific formula for any infant or young child; the names used are for education.

ABBREVIATIONS

AAP	American Academy of Pediatrics
CDC	Centers for Disease Control and Prevention
EFSA	European Food Safety Authority
FDA	Food and Drug Administration
NASPGHAN	North American Society for Gastroenterology, Hepatology and Nutrition
OIYCF	older infant and young child formula

children with feeding difficulties, especially those dependent on tube feeding and with certain medical conditions. The FDA does not regulate the production of pediatric formulas beyond infant formula, and significant variations exist in their composition. The pediatric formulas are available as polymeric (intact), hydrolyzed, elemental, or food-based blenderized formulas. The plant-based nonformula (milk) drinks are being used increasingly for children. These products might not be nutritionally complete and should be avoided in infants and children dependent on liquid nutrition.

INTRODUCTION

The American Academy of Pediatrics (AAP) recommends that infants be breastfed exclusively for approximately the first 6 months of life and that, subsequently, breastfeeding should be supplemented with complementary foods, and continued as long as mutually desired, for at least 2 years and beyond. (1) The 2022 Centers for Disease Control and Prevention (CDC) breastfeeding report showed that for infants born in 2019, approximately 83% were fed initially by breastfeeding, and at 6 months, only approximately 56% were breastfeeding, with approximately 25% breastfeeding exclusively. (2) Globally, approximately 37% of children aged 6 to 24 months do not receive human milk. However, the percentage of children not receiving human milk is approximately 18% in lower-income countries, 34% in lower middle-income countries, and 55% in upper middle-income countries. (3) The Dietary Guidelines for Americans state that nonbreastfed infants should be offered iron-fortified infant formula during the first year of life. (4) In 2017-2019, approximately 216 million kg of powdered infant formula was purchased from major stores in the United States. Approximately 94% of these formula purchases were cow milk–based, and the remaining were soy-based. Of the cow milk–based formulas, approximately 68% had intact protein, and the rest had protein content either partially hydrolyzed (27%) or extensively or completely hydrolyzed (5%). (5) The diversity of breastfeeding practices and formulas used globally and in the United States underscores the importance of understanding the composition of pediatric formulas and the associated safety and health implications. In 2021-2022, the United States experienced a major infant formula shortage due to supply chain issues exacerbated by a large-scale product recall because of possible bacterial contamination of some powdered formula by *Cronobacter sakazakii*.(6)(7) This review discusses the recent formula shortages in the United States and the use of alternate formulas from Europe. We also discuss the young child formulas and the plant-based, nonformula (milk) drinks. The composition of infant formulas has been discussed in another *Pediatrics in Review* article and is not discussed in detail herein. (8) Table 1 gives the definitions of the most frequently used terms concerning formula feeding.

INFANT FORMULA SHORTAGE

The Food and Drug Administration (FDA) and the CDC investigated 4 cases of *C sakazakii*–related illness reported by consumer complaints from September 20, 2021, to February 24, 2022. Four infants were admitted to the hospital, resulting in 2 deaths due to infection with *C sakazakii*.

C sakazakii is a rod-shaped, gram-negative bacteria that can exist in the environment and survive in very dry conditions. (17) *C sakazakii* can cause sepsis/meningitis in very young infants, and infection may present as fever, poor feeding, fussiness, lethargy, and seizures. The diagnosis is confirmed on blood or cerebrospinal fluid culture (no special media is required for growth). The treatment is with broad-spectrum intravenous antibiotics that can be tailored based on sensitivities from the bacterial culture. (17)(18)

All 4 cases of *C sakazakii*–related illness were traced back to formula produced in a manufacturing plant from Abbott Nutrition's Sturgis, Michigan, facility, resulting in a national recall of the products produced in that plant. (6) This recall accounted for approximately 20% of US formula production. Apart from the large-scale recall, other factors that contributed to the infant formula shortage had to do with supply chain issues, including the strict regulation of imports and labor shortages during the COVID-19 pandemic. It is also important to note the significance of the market concentration of the manufacturing capacity for infant formulas: just 4 companies manufacture 99% of the formula in the United States. A multipronged approach might be required to prevent future infant formula shortages with a combined effort from governments and nutrition-related organizations and input from families and providers. (19)(20)

The risk of contamination with *C sakazakii* is only with powdered formula and not with premade, liquid, or concentrate formula. To minimize the risk of contamination, the FDA enforces quality control for the infant formula produced in the United States through regulatory and engineering protocols to minimize the risk of contamination at the production site. However, contamination of powdered formula with *C sakazakii* may occur not only during

Table 1. Terms and Definitions

TERM	DEFINITION (COMMENTS)
Infant formula	"A food which purports to be or is represented for special dietary use solely as a food for infants by reason of its simulation of human milk or its suitability as a complete or partial substitute for human milk." (9)
Older infant–young child formulas	Milk-based drinks or plant protein–based formulas intended to partially satisfy the requirements of children aged 1–3 y. The terms *follow on* or *follow up* or *weaning formulas* or *toddler milk*, *growing-up milk*, or *formula for young children toddler's milk, growing up milk, or formula for young children* are synonyms to older infant and young child formula. (10)(11)
Medical food	Medical foods are specially formulated and processed products that provide partial or sole-source nutrition, may be consumed orally or via feeding tube, and provide nutrition for an individual who, due to a chronic medical condition, has impairments in ability to "ingest, digest, absorb, or metabolize ordinary foodstuffs or certain nutrients, or who has other special medically determined nutrient requirements, the dietary management of which cannot be achieved by the modification of the normal diet alone." (12)
Specialty formula	"Specialty formulas are intended for use by an infant with an inborn error of metabolism, low birth weight, or who otherwise has an unusual medical or dietary problem." The formulas meant for inborn errors of metabolism, renal failure, and cow milk allergy are considered specialized formulas. (9)(13)
Hydrolyzed formula	Hydrolyzed formulas contain hydrolyzed proteins, which may include a mixture of amino acids, peptides, polypeptides, and denatured proteins obtained by chemical, enzymatic, and thermal hydrolysis of proteins.
Partial, extensive, and completely hydrolyzed	Partially hydrolyzed formulas contain ~30% of total protein that is hydrolyzed, extensively hydrolyzed have 90%, and completely hydrolyzed have 100% of the proteins hydrolyzed. The completely hydrolyzed formulas are also called amino acid–based formulas. (13)(14)
Hypoallergenic formula	Extensively hydrolyzed and completely hydrolyzed infant formulas are considered hypoallergenic formulas. (13)(15)
Enteral nutrition	Provision of nutrients to the gastrointestinal tract, bypassing the oral cavity, via a tube, catheter, or stoma. (14)(16)
Blenderized formula	Commercially produced or homemade formulas, administered via feeding tube, composed of foods and liquids blended to a thin consistency. (14)
Dietary reference intakes	Set of nutrient-based reference values used to assess nutrient intake of healthy people. (14)

formula production but also once the formula containers are opened and exposed. Hence, health-care workers must support and educate caregivers about contamination risks with *C sakazakii* and other microorganisms during formula preparation. (21)(22) Table 2 summarizes recommendations from the FDA about the safe preparation of powdered formula.

The European Formulas

European formulas were in use in the United States before the infant formula shortage; however, most of these were imported by families via purchase on the Internet. (15)(23)(24) After the formula shortage, the FDA adopted an enforcement discretion to increase infant formula supplies in the United States. (7) Enforcement discretion by the FDA is issued in selective situations in which the FDA can use its discretion to enforce certain regulations and may choose not to enforce certain regulations if it believes that the risk to public health is low or if it believes that the benefits of the product outweigh the risks. In the case of formula shortages in the United States, exercise of this discretion meant that certain foreign-produced infant formulas could be exempted from particular statutory and regulatory requirements set by the FDA for infant formula production. (25) The FDA regulations for infant formula produced in the United States include multiple requirements to ensure safety

Table 2. Summary of Recommendations from the Food and Drug Administration (FDA) about the Safe Preparation of Pediatric Formula (9)

- Provider should wash hands before preparing the bottles or feeding the baby. The workspace should be cleaned and sanitized.
- Bottles should be cleaned and sanitized.
- If warming the bottle, provider should not use a microwave. Microwaves heat unevenly and risk burning the baby's mouth and throat. To warm the bottle, the bottle should be placed under running warm water.
- If using powdered infant formula, water should be from a safe source.
- Prepared infant formula should not be left at room temperature for more than 2 h.

and suitability of infant formula. The FDA requires that a formula company must present evidence that an infant formula provides adequate nutrition for health and adequate growth for infants. An infant formula regulated by the FDA must meet set, minimum amounts for 30 nutrients (including macronutrients and micronutrients). The FDA oversees the manufacturing practices of infant formula with controls to prevent adulteration and requires an annual audit of the production site. The labeling requirement by the FDA stipulates that the label must include directions for preparation and use, a pictogram showing the major steps for preparing infant formula, and a "use by" date. As part of the enforcement discretion, the FDA sought information from interested foreign companies on the listing of and amount of all nutrients and other ingredients, a copy of the product label and description of packaging, current or anticipated inventory of the formula, microbiological testing results, and facility inspection history. The FDA used this information to consider on a case-by-case basis whether to exercise enforcement discretion and approve formula imports from companies in Europe, Australia, New Zealand, and Mexico. (9)(26)

Although non-European companies were allowed to export formula to the United States, because most infant formulas were from Europe we now discuss the difference between regulations by the FDA for infant formulas and regulations by the European Food Safety Authority (EFSA) for European infant formulas. (9)(27) Table 3 summarizes the main differences between EFSA- and FDA-regulated infant formulas. The key differences include the primary source of the formula, age category, mixing instructions, labeling requirements, description of iron-fortified formula, and composition of formula in terms of macronutrients and micronutrients. (9)(27) European formulas include a goat milk–based formula option not available in the United States; age category, with the choice of different formula for the first 6 months called infant formula and a follow-on formula for 6 to 12 months available in Europe but not in the United States. Most European formulas are prepared with a 1:1 ratio (with 1 scoop of formula in 1 oz of water), and most FDA-regulated formulas are prepared with a 1:2 ratio (with 1 scoop of formula in 2 oz of water). This oversight of ratio differences could result in making a diluted or concentrated formula, leading to electrolyte imbalances, seizures, and potential death with long-term use. The FDA sets the degree of iron fortification at 1 mg of iron per 100 cal, and some European formulas may not be fortified to this level. (15) The amounts of macronutrients, vitamins, and minerals are fairly similar, with some differences, such as the mandatory addition of docosahexaenoic acid in European formulas but not in the United States, although many US formulas contain docosahexaenoic acid. (8)(27)(28) Most of the European formulas are safe in terms of risk of infections; however, cases of transmitted infection, including that of *Salmonella,* have been reported. (29) Overall, the European formulas cleared by the FDA can be safely used in the United States with necessary counseling to the families on the issues noted herein.

Approach to Formula Replacement in Case of Shortage

The shortage of infant formula in the United States left multiple families without formula, thereby requiring families to seek substitutes. In the event of a formula shortage, a pediatrician should be prepared to recommend an alternate formula to an affected family should the need arise. We suggest following the steps in the Fig to determine the best alternative for a given formula. The standard cow milk–based formula can be replaced with any other available brand from the United States or from Europe cleared by the FDA. (7) In the case of a specialized formula, additional considerations might be required. The definition of specialized formulas is available in Table 1, and a further description is available in a previous *Pediatrics in Review* article. (8) When using a specialized formula for treating cow milk allergy, an extensively hydrolyzed formula can be replaced with a similar alternative or with a completely hydrolyzed formula or amino acid–based formula. In the case of completely hydrolyzed formula, a similar alternative might be required unless the infant is approximately 1 year of age, when a significant proportion of infants outgrow cow milk allergy. If a soy-based formula is used to treat cow milk allergy, it could be replaced with an alternate soy-based formula or with an extensively hydrolyzed or completely hydrolyzed formula. A formula meant to treat an inborn error of metabolism should be replaced with a similar formula from another brand. The North American Society for Gastroenterology, Hepatology and Nutrition (NASPGHAN) maintains a complete list of alternate formulas that is available online, (30) and the FDA lists the companies that have been allowed to import formulas to the United States. (26)

The FDA and the CDC discourage using homemade formula or diluting existing formula in case of formula shortage, as cases of severe malnutrition (31) and illness have been reported using homemade formula. (31) For infants 6 to 12 months of age who are on a regular cow

Table 3. Differences between Formulas Regulated by the EFSA versus the FDA

DOMAIN	FDA-REGULATED FORMULAS (9)	EFSA-REGULATED FORMULAS (27)
Type of formula	Cow milk, soy-based, partially, and extensively hydrolyzed, amino acid–based formulas.	Cow milk–based, soy-based, partially hydrolyzed, extensively hydrolyzed formulas. Option for goat milk formula.
Age category	The same formula is used for all infants aged 0–12 mo.	Different formula for 0–6 mo, called infant formula, and 6–12 mo, called follow-on formula.
Mixing instructions	Most formulas have mixing instructions in a 1:2 ratio of formula concentrate (scoops) to water, and mixing instructions are given as formula per ounce.[a]	Most formulas have mixing instructions in a 1:1 ratio and mixing instructions are given as formula per milliliter.
Labeling requirements	Instructions must be in English and should include directions for preparation, a pictogram showing the major steps for formula preparation, an expiration date, and whether water should be added to prepare the formula.	Instructions may be in a language other than English as well.
Iron fortification	Iron content minimum 0.15 mg/100 kcal, maximum 3.0 mg/100 kcal. To be labeled as iron-fortified, the formula should have ≥1 mg/100 kcal of formula.	Iron content varies based on formula type, with 0.3 mg/100 cal for infant formula (0–6 mo) and 0.6–1.7 mg/100 kcal for follow-on formula (6–12 mo).
Macronutrient requirement: protein	Minimum 1.8 g/100 kcal, maximum 4.5 g/100 kcal[b]	Cow milk–based: minimum 1.8 g/100 kcal, maximum 2.5 g/100 kcal. Soy-based: minimum 2.25 g/100 kcal, maximum 2.8 g/100 kcal.[c]
Macronutrient requirement: fat	Minimum 3.3 kcal/100 kcal, maximum 6.0 kcal/100 kcal Linoleic acid is required.	Minimum 4.4 kcal/100 kcal, maximum 6.0 kcal/100 kcal Linoleic acid, α-linolenic acid, and docosahexaenoic acid are required.
Macronutrient requirement: carbohydrate	No limit	Minimum: 9 g/100 kcal, maximum 14 g/100 kcal.
Micronutrient requirement: vitamins	FDA regulates minimum levels of vitamins A, C, D, E, and K; thiamine (B_1); riboflavin (B_2); vitamin B_6; vitamin B_{12}; niacin; folic acid; pantothenic acid; and biotin[b]; and maximum values of vitamins A and D.	EFSA regulates minimum and maximum values of vitamins A, C, D, E, and K; thiamine (B_1); riboflavin (B_2); vitamin B_6; vitamin B_{12}; niacin; folate; pantothenic acid; and biotin.
Micronutrient requirement: minerals	FDA regulates minimum values of calcium, phosphorus, magnesium, iron, zinc, manganese, copper, iodine, selenium, sodium, potassium, and chloride and maximum values of iron, iodine, selenium, sodium, potassium, and chloride.	EFSA regulates minimum and maximum values of calcium, phosphorus, magnesium, iron, zinc, manganese, copper, iodine, selenium, sodium, potassium, and chloride and only maximum values of molybdenum and fluoride.

EFSA=European Food Safety Authority, FDA=Food and Drug Administration.
[a]1 oz=30 mL.
[b]Certain other amino acids, such as choline and inositol, might be required for nonmilk US-based recipes; also, if the biological quality of the protein is less than that of casein, the minimum amount of protein shall be increased proportionately to compensate for its lower biological quality. For example, an infant formula containing protein with a biological quality of 75% of casein shall contain at least 2.4 g of protein (1.8/0.75), as is the case for soy-based formulas produced in the United States.
[c]Additional amino acids might be required for specific formulas, such as goat-based formulas; also, the amount of protein might differ for hydrolyzed formula. Each of the indispensable and conditionally indispensable amino acids must be available in amounts at least equal to that contained in the dietary reference.

milk–based formula, if the family is unable to obtain an alternate formula as an urgent replacement, regular whole cow milk can be used on a short-term basis (1 week). (32)(33) However, the long-term use of cow milk during infancy should be avoided because the use of cow milk in infancy is associated with a risk of gastrointestinal blood loss and iron deficiency anemia. (34) In case of formula shortage for infants with cow milk allergy who are on a hypoallergenic formula, we suggest using an electrolyte rehydration solution for emergency situations when an alternate hypoallergenic formula is unavailable, but for no more than 24 to 48 hours with the aim of finding another alternate for the hypoallergenic formula.

OLDER INFANT AND YOUNG CHILD FORMULAS

At 1 year of age, human milk and infant formulas are no longer complete sources of nutrition for children, (1)(4) and the AAP and Dietary Guidelines for Americans recommends

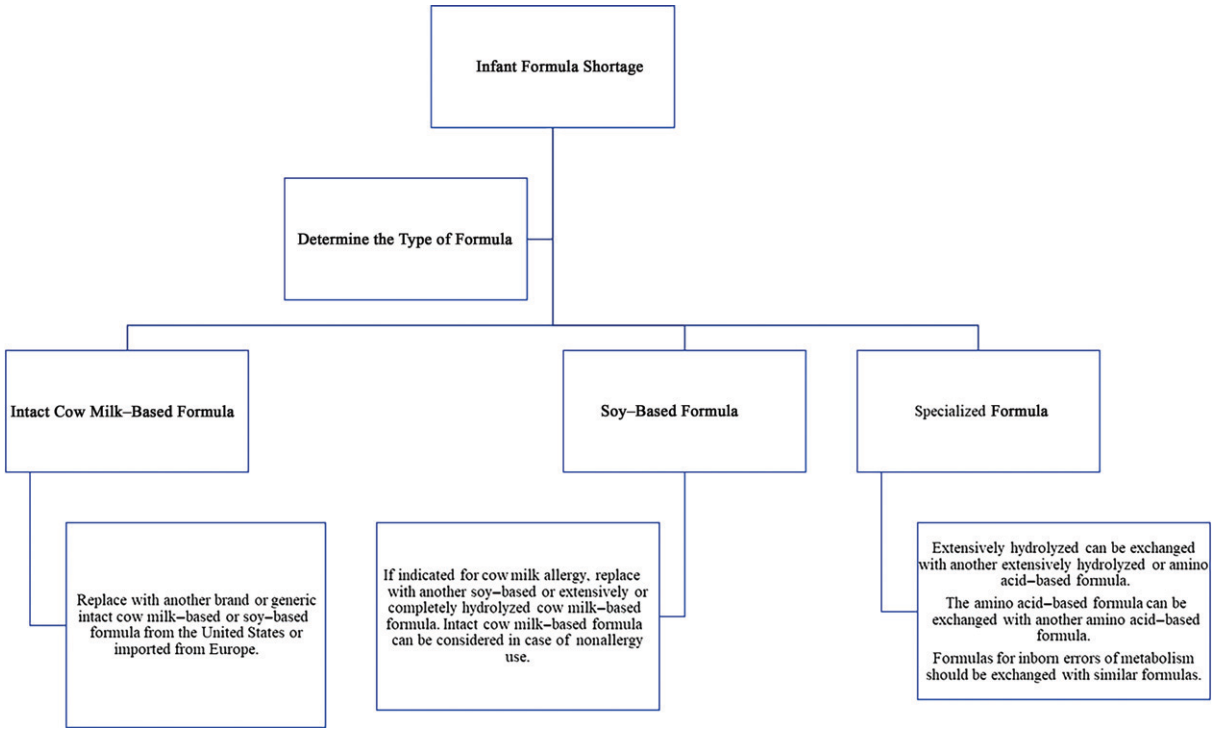

Figure. Approach to alternate infant formula in case of shortage. This guidance is based on expert opinion and is meant for infant formula. Specialized formulas herein are formulas with extensively hydrolyzed proteins or amino acid formulas or those used for treating inborn errors of metabolism.

that infants should be transitioned to pasteurized whole milk at 1 year of age in addition to appropriate solid foods for this age. (1)(4)(10) Whole milk is an essential staple in a toddler's nutrition as it provides a consistent protein source, hydration, calcium, and vitamin D for bone growth, and fat for growth and brain development. (35) The term *older infant and young child formula (OIYCF)* is used interchangeably with *follow on* or *follow up* or *weaning formulas* or *toddler milk, growing-up milk,* or *formula for young children*. (10)(14) The use of OIYCFs is discouraged in otherwise healthy infants or children younger than 3 years. (10)(11) The regulation of young child formulas is less strict compared with FDA regulation for infant formulas because the FDA considers noninfant, young child formulas as medical foods (definitions in Table 1). Because of the lack of uniform regulations of OIYCFs, there is significant variation in the composition of these formulas from both the United States and Europe. (11)(14)(36) It is, therefore, important for health-care professionals to interpret with caution the package labeling and claims made by formula manufacturers of OIYCFs because nutritional deficiencies have been described in children on enteral nutrition. (14)(11)(37)(38) A clinical report from the Committee on Nutrition of the AAP discourages the marketing of OIYCFs with names similar to infant formulas and recommends OIYCFs be clearly distinguishable from infant formulas in terms of promotional material, logos, product names, and packaging and should not be kept on store shelves next to infant formulas. The labeling should not be similar to that of infant formulas, and the name of the product should be something such as *follow on drink* or *follow on beverage* rather than *follow on formula* or *toddler formula*. (10)

PEDIATRIC FORMULAS

Although formula feeding is not recommended beyond 1 year of age, certain groups of older children might require support from formula feeding, such as those with feeding difficulties, especially those dependent on tube feeding; children with certain medical conditions such as eosinophilic gastrointestinal disorders, inflammatory bowel disease, short-bowel syndrome, and oropharyngeal dysphagia; and those with multiple severe food allergies. (4)(13)(14) The medical or therapeutic use of enteral formula in these circumstances is justified; however, these formulas should be differentiated from OIYCFs, which are mainly used for transition from infancy to early childhood (Table 4). The formulas used for a medical indication are nutritionally complete and could be used as the sole source of nutrition for children. (14) We will use the term *pediatric formulas* for these formulas. The nomenclature around the pediatric formulas varies. Due to the multiple products available in the

Table 4. Differences among Infant Formula, OIYCFs, and Pediatric Formulas

NAME	INFANT FORMULA (8)	OIYCFs (10)	PEDIATRIC FORMULAS (14)
Regulation	The FDA regulates infant formula production in the United States and the EFSA in Europe.	This category is treated as a medical food by the FDA, and regulation is applied just like any other food item considered medical food.	It is treated as a medical food by the FDA
Age	Infant formulas are used for infants aged <12 mo.	Most used as a transitional milk for children aged 9–36 mo.	Most used for children aged 1–13 y.
Indication	Infant formula is recommended when a baby is not receiving human milk in the first year after birth	There is no medical indication for use of OIYCF for an otherwise healthy infant and young child.	There is no medical indication for a pediatric formula for an otherwise healthy child; however, it can be used for a medical or therapeutic indication.
Composition	Infant formulas could be cow milk–based or soy-based. The macronutrient content varies for different types of infant formulas, with options available with reduced lactulose, high MCT content, or hydrolyzed protein. Infant formula could be used as a sole source of nutrition in the first 6 mo of age, could be continued along with introduction of solid food.	The composition varies significantly, with no standard set by the FDA or the EFSA. Most of these formulas are not nutritionally complete and cannot be used as the sole source of nutrition for a medical indication.	Pediatric formulas could be cow milk–based, soy-based, and commercially produced plant-based blenderized formulas. Most pediatric formulas are nutritionally complete and could be used as the sole source of nutrition. The composition varies based on type of formula, as given in Table 5.

EFSA=European Food and Safety Authority, FDA=Food and Drug Administration, MCT=medium-chain triglyceride, OIYCF=older infant and young child formula.

market and the fact they are constantly changing, it is not feasible to cover each formula product. We, however, provide a general nomenclature described by the American Society for Parenteral and Enteral Nutrition. (39) The pediatric formulas can be classified into intact or polymeric, extensively hydrolyzed or peptide, completely hydrolyzed or elemental, and blenderized food-based (Table 5). It is important to note that these categories are not inclusive of all the products available and that some of the formulas could include more than 1 category, for example, some of the blenderized formulas could be extensively or completely hydrolyzed.

The most widely used and least expensive pediatric formula is the standard polymeric (intact) formula, primarily available in sterile, ready-to-use form. (14)(40) The polymeric formulas are available in standard (1 kcal/mL), low (~0.6 kcal/mL), or high (1.2–1.5 kcal/mL) calorie density formulations. Most of the polymeric formulas could be used as sole sources of nutrition and meet the dietary reference intakes for essential vitamins and minerals if adequate volumes are administered, typically between 750 and 1,500 mL, depending on the specific formula and the age of the child. (14) The polymeric formulas could be delivered via tube feeds. Polymeric formulas can be an attractive option for oral supplementation as multiple options with different flavors, including vanilla, chocolate, strawberry, and banana, are available. (16)(41) The carbohydrate content typically provides 44% to 53% of the required daily total calories. Although the carbohydrate source may vary, the polymeric formulas typically include carbohydrates from a combination of corn maltodextrin, rice syrup solids, sugar, and cornstarch. (14)(16)(41) Most of the polymeric formulas are considered lactose-free and could be used in children with lactose intolerance; however, these formulas are not suitable for patients with galactosemia because a small amount of lactose (<4 g/L) is present in the cow milk–based pediatric formulas. (14) The protein source in polymeric formulas could include cow milk, soy, and pea, and the proteins typically contribute approximately 12% to 15% of the required daily total calories. Some of the cow milk–based formulas could have soy in them, so parents of formula-fed children should check the labels for sources of protein if their child needs to avoid soy. (14) The polymeric formulas are not appropriate for patients with a cow milk, soy, or corn allergy. Most of the polymeric and pediatric formulas are gluten-free. Polymeric formulas contain fat derived from plant oils, contributing 35% to 45% of the required daily total calories in a standardized polymeric formula. (14)(16)(41) Some of the pediatric formulas contain only protein and carbohydrates and some micronutrients but no fat (also called clear formulas), and these formulas are not a complete source of nutrition. They should be avoided in patients who are completely dependent on formula feeding. (14)

The hydrolyzed protein formulas contain proteins hydrolyzed by adding enzymes that break down peptide bonds. The hydrolyzed formulas may contain hydrolyzed

Table 5. Description of Commonly Used Pediatric Formulas

CHARACTERISTIC	POLYMERIC/ STANDARD/INTACT PROTEIN FORMULAS	HYDROLYZED	ELEMENTAL	BLENDERIZED
Caloric density, kcal/mL; kcal/oz	0.6–1.5; 18–45	1–1.5; 30–45	0.8–1; 24–30	1–1.3; 30–39
Carbohydrate, % kcal	44–55	48–54	40–63	32–43
Sources of carbohydrate	Corn maltodextrin, rice syrup solids, sugar, cornstarch	Corn maltodextrin, sugar, cornstarch	Solid corn syrup, tapioca starch, potato starch	Fruits, vegetables, rice
Protein, % kcal	12–20	12–14	12–15	11–20
Sources of protein	Milk, soy, pea (Pea protein formulas lack dairy, soy, and corn)	Milk, pea	Amino acids	Milk, peas, beef, poultry, quinoa, fish, brown rice, hemp, oats, molasses, etc
Fat, % kcal	25–45	35–60	25–45	34–57
Sources of fat	LCTs (canola oil, soybean oil, safflower oil, sunflower oil, flaxseed oil, coconut oil) MCTs	LCTs (canola oil, soybean oil, safflower oil, sunflower oil, flaxseed oil, coconut oil, fish oil) MCTs	LCTs (safflower oil, soybean oil, coconut oil, palm kernel oil, sunflower oil) MCTs	LCTs (canola oil, olive oil, flaxseed oil, fish oil, almond butter, grapeseed oil, beef, poultry, sesame seeds, sunflower seeds, fish, egg, hemp powder, etc) MCTs
Volume to meet DRIs, mL				
Ages 2–8 y	750–1,300	750–1,000	1,000–1,500	900–1,000
Ages 9–13 y	1,500–1,680	1,500	1,500–1,900	1,200–1,500
Osmolality, mOsm/kg (mmol/kg)	300–600 (300–600)	250–450 (250–450)	390–675 (390–675)	500–780 (500–780)
Potential indications	Children with normally functioning gastrointestinal tracts who cannot meet their nutritional needs with an age-typical diet.	Children with intolerance to polymeric formulas or with altered gastrointestinal tract function.	Children with allergies.	Might be better tolerated in patients with gastrointestinal symptoms. Fulfills any caregiver preference for plant-based food.
Market examples	Boost® Kid Essentials™, PediaSure®, Kate Farms®, Compleat® Pediatric	Peptamen Junior®, PediaSure® Peptide, Kate Farms® Pediatric Peptide	EleCare®, Alfamino®, Neocate®	Compleat® Pediatric Organic Blends, Nourish, PediaSure® Harvest, Real Food Blends®
Retail price, $				
Per ounce	0.26–0.48	0.78–0.86	0.67–0.72	0.57–0.82
Per 1,000 kcal	7.80–13.60	25.87–28.70	22.45–24.00	15.80–18.00
Special considerations	Lactose-free but contains <4 g of lactose per liter, so contraindicated in galactosemia	Poor palatability	Poor palatability	Poor palatability, if undiluted, requires 12 or 14 Fr or large-diameter enteral access device

DRI=dietary reference intake, Fr=French gauge, LCT=long-chain triglyceride, MCT=medium-chain triglyceride.
Modified with permission from Klepper et al. (14)

protein consisting of a short chain of amino acids and free amino acids, and the elemental formulas contain completely hydrolyzed proteins in the form of free amino acids. (14)(42) Some formulas may use porcine enzymes to hydrolyze the proteins, and, therefore, these formulas are not considered halal or kosher. (43) Information on the mode and extent of hydrolysis might be available on the label of the product, and if so, could be used to help families who prefer to use a formula that is halal or kosher. The calorie density for hydrolyzed formulas ranges from standard 1 kcal/mL to high 1.5 kcal/mL. Elemental formulas could be available in either low 0.8 kcal/mL or standard 1 kcal/mL calorie form. The carbohydrate content makes 48% to 54% of the hydrolyzed formula and approximately 40% to 60% of the elemental formulas. (14) The carbohydrate sources are similar to polymeric formulas except that some hydrolyzed formulas may contain tapioca starch and potato starch. The protein source in hydrolyzed formula is from milk and peas. The hydrolyzed and elemental formulas have a higher proportion of medium-chain triglycerides and a small proportion of long-

Table 6. Nutritional Comparison of Cow Milk and Plant-Based Nonformula Milk (Drinks)

PER 1 CUP (240 mL)	COW MILK	ALMOND	CASHEW	COCONUT	FLAXSEED	HEMP	OAT	PEA	RICE	SOY
Calories	150	30–100	25–80	45–90	55	70–170	130	115	110	90
Protein, g	8	1–5	0–1	0–1	0	2–4	4	8	1	6
Fat, g	8	3	2–3.5	5	2.5	5–6	2.5	5	2.5	3.5
Carbohydrates, g	13	9–22	1–20	8–13	9	1–35	24	11	20	15
Sugar, g	12	7–20	0–18	0–9	9	0–23	19	10	13	9
Calcium, mg	300	300	100–450	100–450	300	400	350	450	300	400
Vitamin D, IU	120	110	125	125	100	150	120	150	120	120

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chain fatty acids. This is important to know because fat absorption can be facilitated via medium-chain triglycerides in cases of malabsorption such as seen with severe cholestasis and pancreatic insufficiency (patient may still need enzyme replacement therapy for pancreatic insufficiency). (14)(42) Elemental formulas are considered anallergenic because they do not contain intact proteins. Consequently, such formulas could be used with patients who are allergic to cow milk. Elemental formulas could also be used with patients who have certain eosinophilic gastrointestinal disorders, for example, as exclusive enteral nutrition in individuals with eosinophilic esophagitis. (14) The hydrolyzed formula can also be used in children with intolerance to standard intact formulas. Both the hydrolyzed and elemental formulas are available in powder form but are less palatable for oral use compared with polymeric formulas, although flavored versions of the hydrolyzed and elemental types have become available recently. The osmolality of elemental formulas is high (390–675 mOsm/kg [390–675 mmol/kg]) and can lead to loose stools. The cost of hydrolyzed or elemental formulas is higher than intact formulas, and the insurance coverage varies based on the amount needed, route administered, and type of insurance. (16)(42)(44)

Although administration of home-based blenderized foods is a common practice that was accepted by the medical community, commercially produced blenderized feeds have recently become available. (45)(46) Blenderized feeds are made of whole foods, and the contents may include vegetables, fruits, meat, legumes, whole grains, and dairy/dairy alternatives that have been blended or liquified for enteral feeding. (14)(47) The commercially blenderized formulas are also available in hydrolyzed form and in combination with intact cow milk–based formulas, called *hybrid formulas*. The available evidence on the use of blenderized feeds suggests better tolerability, lower need for medications, improvement in chronic respiratory symptoms, decreased emergency department visits, and adequate growth. (42)(48)(49) However, generally speaking, randomized controlled trials comparing different formula types are lacking, although we did identify a few ongoing trials comparing thickened formulas/feeds to improve outcomes in children with aerodigestive problems. (50)(51)(52) The plant-based formulas also give families the option of whole food–based formulas. However, plant-based blenderized formulas have limited palatability, and due to their increased viscosity, there might be challenges to administering the formula, especially with smaller-diameter tubes. (14)(41) Families interested in making blenderized feeds at home should consult a dietitian to help with recipes to ensure the adequacy of nutrients in the blenderized feeds while still under the supervision of a medical provider. (53)(54)

PLANT-BASED NONFORMULA MILK (DRINKS)

Plant-based, nonformula milk is increasingly used by parents and caregivers of infants and young children as an alternative to cow milk. (55) The term *milk* is technically reserved for the fluid secreted from the mammary glands of mammals, (28)(56) and the term *plant-based drink* might be more appropriate for plant-based fluids meant for nutritional support. (57) The FDA considers the plant-based, nonformula drinks to be medical food, and the macronutrient and micronutrient components of these products vary significantly compared with infant formula regulated by the FDA. (56)(57) Families might be interested in using plant-based drinks in the setting of cow milk allergy during infancy, concerns for lactose intolerance, and concerns related to the presence of unsaturated fat in cow milk or because of a preference for plant-based products as part of a lacto-ovo-vegetarian diet or the social preference(s) in certain cultures. (57)

Table 6 gives an overview of available plant-based drinks and their comparison with cow milk. The number of calories per 240 mL (1 cup) varies among the plant-based products; most do not have equivalent calories as the same volume of cow milk. The amount of protein also varies, with some products having very little protein, such as flaxseed- and rice-based drinks, and other products, such as soy-based drinks, might have an equivalent amount of protein compared with cow milk. In addition to the variation in

the available protein in a given volume, the protein quality in terms of the protein efficiency ratio also varies among different plant-based beverages. (58) For example, compared with the most abundant protein in cow milk, casein, the protein efficiency ratio value is 80% for soy, 72% for oat, 66% for coconut, 60% for rice, 57% for pea, and only 16% for almond protein. (56) This means that the bioavailability of the protein from plant-based drinks could be lower compared with the same amount of protein from cow milk. The amount of fat and carbohydrates also varies, and different products might have sugar as a flavor additive. Finally, the level and diversity of fortification also varies. Although these products may have adequate amounts of calcium and vitamin D, other micronutrients might not meet the dietary reference intake. (57) Although adding some of the plant-based drinks such as soy (nonformula), pea, and oat-based drinks to a child's diverse and nutritionally adequate diet might be reasonable, the plant-based beverages are not nutritionally complete. Plant-based beverages should be avoided during infancy and for children on enteral nutrition who are dependent on liquid food. Plant-based, nonformula drinks should also be avoided as a replacement for cow milk for toddlers and young children, and if there is a need for replacement of cow milk, a pediatric formula might be a more appropriate replacement. Future studies must assess whether plant-based drinks are adequate to promote growth and bone mineralization in young children. (56)(57)

CONCLUSIONS

Significant advances have been made in the available formula products for infants and children, with a substantial increase in demand and supply leading to a multibillion-dollar industry. Although there are clear guidelines for infant formula production from the FDA and the EFSA, there is a lack of universal regulation for formula products beyond infancy. The lack of universal regulations for producing OIYCFs and pediatric formula has led to significant variation in these products with concerns for excess and deficiency of certain micronutrients. (11)(38) With an increasing number of products available in the market, it is highly challenging for pediatricians to have complete knowledge of each product. There is a need for a registry that should encompass basic information for each product that should be publicly available to medical providers and families. There is a need for universal regulation of pediatric formula with clear guidance on the indications for their use, composition, labeling requirements, and safety. Finally, the terminology around OIYCFs and plant-based drinks should be regulated, and the terms *formula* and *milk* should be prohibited for these products to avoid confusion with FDA-approved infant formula and mammalian-source milk, respectively.

Summary

- The European pediatric formulas imported under Food and Drug Administration (FDA) guidance differ from those produced in the United States in certain aspects (15); however, they are comparable with formulas produced in the United States in their nutritional value. (9)(27) (Based on some research evidence)
- Older infant and young child formulas or pediatric formulas are not recommended for otherwise healthy children. (10)(14) (Based on some research evidence as well as consensus among experts)
- Thickened plant-based blenderized pediatric formulas may help with aerodigestive problems in children dependent on tube feeding. (42)(48)(49) (Based on some research evidence)
- The plant-based nonformula (milk) drinks are not nutritionally complete and should be avoided in infants and children dependent on liquid nutrition. (56) (Based on some research evidence and consensus among experts)

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Take the quiz! Scan this QR code to take the quiz, access the references and teaching slides, and view and save images and tables (available on July 1, 2024).

PIR QUIZ

1. A 2-month-old girl is brought to the clinic by her mother for a health maintenance visit. The mother expresses a desire to stop exclusively breastfeeding her infant daughter. The mother consumes a regular, unrestricted diet. The infant's growth parameters are within the expected range, and the infant's physical examination findings are normal. You recommend that human milk meals be replaced with which one of the following in this patient?

   A. Blenderized whole foods.
   B. Elemental infant formula.
   C. Goat milk.
   D. Iron-fortified infant formula.
   E. Whole cow milk.

2. In the midst of a commercial formula shortage in the United States, the family of a 4-month-old child purchased a European Food Safety Authority–approved cow milk–based formula because they are readily able to obtain it via an Internet merchant. The family received a supply of sealed, unexpired powder formula and mixed it as they did the child's previous American-made formula. After 3 weeks of use, the parents noted their child to be more irritable and somnolent. They present to the emergency department after a tonic-clonic seizure at home that self-resolved. On physical examination the child is noted to be edematous and hypothermic. Serum sodium level is 116 mEq/L (116 mmol/L). Which one of the following is the most likely cause of the infant's abnormal sodium level?

   A. Bacterial contamination of the formula powder.
   B. Food protein–induced enterocolitis syndrome.
   C. Improper mixing of formula powder and water.
   D. Milk protein allergy.
   E. Unrecognized inborn error of protein metabolism.

3. A 5-month-old infant consumes soy-based formula due to anaphylaxis to cow milk–based formula. The family calls your office seeking advice because they have been unable to locate any soy-based formulas locally. Until the family can obtain a soy-based formula, you advise them to use which one of the following alternatives?

   A. Cow milk–based infant formula.
   B. Donor human milk.
   C. Extensively hydrolyzed infant formula.
   D. Goat milk.
   E. Whole cow milk.

4. You are seeing an underweight 4-year-old boy and recommend a polymeric formula to provide supplemental oral calories. The family is hesitant to use any product made from cow milk because the child has lactose intolerance, which typically manifests by gassiness, bloating, belly pain, and loose stools after the consumption of ice cream or cottage cheese. The most appropriate approach is to provide the family with which one of the following statements at this time?

   A. Children outgrow lactose intolerance.
   B. Newborn screening typically tests for lactose intolerance.
   C. Polymeric formulas can be used in individuals with lactose intolerance.
   D. Screening for celiac disease should be performed.
   E. The child needs a lactose hydrogen breath test.

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5. After an encounter with a child with multiple food allergies who is on an elemental formula, you review child nutrition with the medical student who is rotating in your practice. In the discussion about types of formulas, which one of the following is the most appropriate statement about standard elemental formulas?

   A. Are calorically inadequate for sole-source nutrition.
   B. Are widely available and of low cost.
   C. Contain free amino acids.
   D. Contain intact soy protein.
   E. Have an incomplete profile of vitamins.