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INVITED REVIEW

Term infant formula macronutrient composition: An update for clinicians

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Abstract

Protein, carbohydrates, and fats comprise the macronutrient components of infant formulas. While all infant formulas in the United States meet specific nutrition standards, the macronutrient composition of formulas is diverse. Each macronutrient in the formula may play a role in treating or managing the disease. In addition, many formulas are marketed as resembling the composition of human milk or improving symptoms such as colic and irritability. For these and other reasons, families are often interested in different formula properties. When choosing a formula for their infant families, they may reach out to clinicians for advice. Therefore, clinicians need to understand the macronutrient composition of the formulas their patients are using. This manuscript discusses the macronutrient composition of term infant formulas and indications of the use of different macronutrient components.

KEYWORDS
carbohydrates, casein, fat, whey

CME module may be found at https://learnonline.naspghan.org/jpgn2

1 | INTRODUCTION

Infant formulas are a critical nutrient source for infants either as a supplement to or substitute for human milk due to medical indications or family preference. In addition to providing the energy and protein needs of infants, the type and composition of macronutrients in formula may be therapeutic (Table 1). There is an abundance of formula options with different macronutrient compositions. Formulas sold in the United States meet strict nutritional standards.[1] Many families may prefer infant formulas with specific characteristics, such as non-cow mammalian milk or low lactose. Providers need to understand the macronutrient makeup of infant formulas and the indications for using different formulas both in the management of disease states and in assisting with enteral nutrition tolerance. This article reviews the macronutrient components of term infant formulas and their use in different clinical scenarios.

What is Known

- Macronutrients are a critical component of infant formulas.
- Protein structure differs between different infant formulas.
- Different forms of carbohydrates besides lactose are added to infant formulas, including sucrose, fructose, sugar alcohols, and corn syrup solids.

What is New

- Specialized formulas with modified macronutrient composition are available for a variety of gastrointestinal pathologies.
- The protein structure of goat milk is similar to cow's milk and has similar allergenic potential.
- Alternative sources of carbohydrates in infant formulas may present unique health-related challenges.

2 | PROTEIN

Protein is an essential macronutrient made up of amino acids. The major proteins in milk are whey (lactalbumin, lactoferrin, immunoglobulins [Ig], albumin, lactoglobulins, and lysozymes) and casein (β, κ, and α).[2–4] Infant formula protein can be derived from human, animal, and plant-based products. The composition of infant formulas is meant to closely mimic the nutritional composition of human milk.[5,6] The characteristics of infant formula proteins can be used to treat different diseases and may impact tolerance.

2.1 | Protein structure

Infant formulas are characterized by the structure of the protein. Categories of formulas include intact protein, partially hydrolyzed protein, extensively hydrolyzed protein, and amino acid-based formulas (Figure 1). Formula in which the protein is kept intact is typically referred to as standard formula. The proteins contained in partially hydrolyzed infant formula and extensively hydrolyzed infant formula undergo hydrolysis techniques that break down the proteins into peptides. The size of the peptides determines the classification of a formula as partially hydrolyzed (oligopeptides with molecular weight of 3–10 kDa) or extensively hydrolyzed (peptides with molecular weight of <3 kDa).[7,8] The protein component in amino acid-based formulas is free amino acids.

2.2 | Partially hydrolyzed formulas

It is believed that partially hydrolyzed infant formulas are more easily digested than formulas with intact proteins.[1,9,10] Partially hydrolyzed formulas are not hypoallergenic. Current guidelines do not recommend using partially hydrolyzed formulas for infants with cow's milk protein allergy or other allergies.[6,7] Many partially hydrolyzed formulas include lower amounts of lactose. Partially hydrolyzed formulas are often recommended for infants with colic, gastroesophageal reflux, and constipation. There is some evidence to suggest that partially hydrolyzed protein promotes faster gastric emptying and the 2018 joint North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition/European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) pediatric gastroesophageal reflux guidelines recommend the use of partially hydrolyzed formulas to treat reflux.[11] However, a recent ESPGHAN position paper on the use of infant formulas for the treatment of functional gastrointestinal (GI) disorders found a lack of evidence that protein hydrolysis is effective in treating gastroesophageal reflux, colic, or constipation.[12]

2.3 | Extensively hydrolyzed and amino acid-based formulas

Extensively hydrolyzed formulas contain proteins that have been broken down into small peptides by hydrolysis. These formulas can be used for patients with malabsorption and are the first-line treatment for cow's milk protein allergy and IgE-mediated cow's milk allergy.[13]

Amino acid-based formulas, also referred to as elemental formulas, contain protein in the form of free amino acids. These formulas are reserved for more severe cases of cow's milk allergy (nonresponsive to extensively

TABLE 1 Diseases/conditions and infant formula choice.

Disease state	Recommended formula
Protein	
Cow's milk protein allergy	Extensively hydrolyzed or hydrolyzed rice Amino acid-based formula for refractory cow's milk protein allergy
Allergic GI disease (such as eosinophilic esophagitis or gastroenteritis)	Amino acid-based formula
IgE-mediated food allergies	Extensively hydrolyzed formula Amino acid-based formula
FPIES to milk and or soy	Extensively hydrolyzed formula Amino acid-based formula
Carbohydrate	
Congenital lactase deficiency	Lactose-free formula
Galactosemia	Lactose-free formula
Fat	
Small intestine resection leading to short bowel syndrome (colon remains intact)	High MCT formula
Cholestasis	High MCT formula (extensively hydrolyzed and amino acid options)
Chylous effusions (such as postoperative chylothorax)	High MCT formula Skimmed human milk
Long-chain fatty acid oxidation disorders	High MCT formula

Abbreviations: FPIES, food protein-induced enterocolitis syndrome; GI, gastrointestinal; IgE, immunoglobulin E; MCT, medium-chain triglyceride.

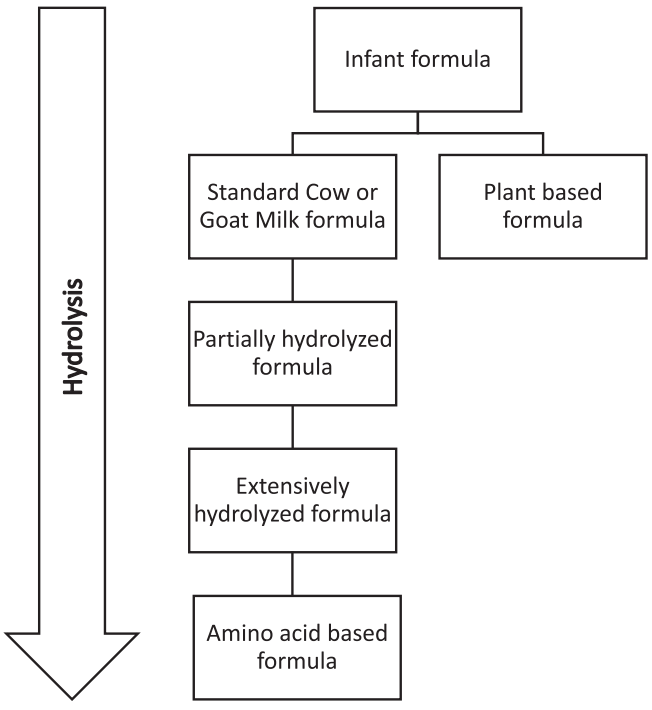

FIGURE 1 Extent of hydrolysis.

hydrolyzed formula), eosinophilic GI disease, multiple food allergies, and impaired nutritional status.[7,10,13]

Extensively hydrolyzed and amino acid-based formulas are considered hypoallergenic, as clinical studies have shown that they do not provoke reactions in >90% of infants or children with confirmed cow's milk allergy with 95% confidence.[4,14] The main disadvantages of extensively hydrolyzed and amino acid-based formulas include increased cost, poor palatability, higher osmolality, and increased renal solute load.

2.4 | Protein source

Infant formulas with alternative sources of protein, including non-cow mammalian products (goat, sheep, camel, horse, and donkey) and plant-based products (soy and hydrolyzed rice), are more readily available and of interest to some families.

2.5 | Casein and whey

Whey protein, which is liquid and readily digestible, provides efficient nutrition and boosts immunity by

supplying key amino acids. A higher ratio of whey to casein may be beneficial during infancy, as it supports fast growth periods by facilitating effective digestion and absorption. Casein protein thickens in the acidic environment of the stomach, forming a curd that slows digestion and delays the release of nutrients. This delayed digestive process helps with continuous food delivery over a longer half-life, which can be beneficial during times of fasting, such as overnight. The standard cow's milk formula casein to whey ratio is around 80:20, while mature human milk has a casein to whey ratio of 40:60.[5] Whey-enhanced cow and goat milk protein-based formulas can achieve a 40:60 casein to whey ratio, similar to human milk.[5,6]

2.6 | Non-cow mammalian milks

Non-cow mammalian milk also derives its protein from casein and whey. The casein haplotypes (α, β, and κ) contribute to the tolerance and allergenicity of formulas (Table 2). For instance, goat's milk has a similar casein and whey ratio as cow's milk, but with a higher proportion of β and κ casein, which may lead to faster gastric emptying.[16,17] Some goat's milk-based formulas add in cow's milk casein to more closely replicate the casein and whey ratio of cow's milk.

The protein structure of goat and sheep milk is more similar to cow's milk than camel, horse, and donkey milk.[6] There is limited data on the use of alternative mammalian milk to prevent and treat cow's milk protein allergy, and the effectiveness of these milks likely depends on the milk source (Table 2). Very few infants with cow's milk protein allergy will tolerate goat's milk, likely due to protein structure similarities.[6,13] Small studies suggest that camel, horse, and donkey milk may be an option for some people with cow's milk protein allergy, although their use is not recommended, and currently, there are no commercially available camel, horse, or donkey milk infant formulas in the United States.[6]

2.7 | Plant-based formulas

Plant-based formulas derive their protein from the plant itself. Vegetable and grain products tend to have a lower amount of essential amino acids compared to mammalian products.[15] Like other formulas, plant-based formulas sold in the United States meet minimal nutrition requirements for infants. Depending on the study, cross-reactivity between cow's milk protein and soy protein is anywhere from 3% to 50%.[6] A meta analysis showed that soy based infant formula did not prevent the development of food allergy.[18] Soy based products may be used for infants older than 6 months of age but not younger per guidelines from the American Academy of Pediatrics.[6] Plant-based formulas are an important alternative option for individuals who may not tolerate or do not wish to use animal milk products.[15,19]

3 | CARBOHYDRATES

Carbohydrates are the main source of energy for infants during the period of rapid growth of development in the first year of life. Lactose is the main carbohydrate in human milk. Other forms of carbohydrates seen in infant formulas include sucrose and fructose, sugar alcohols, and corn syrup solids (CSS). Thickened formulas with added rice, corn, potato, or locust bean starches are commercially available for formula-fed infants who may have persistent regurgitation. These formulas offer the advantage of a balanced composition, controlled viscosity, and calories compared with the addition of thickening agents to a standard formula.[20] While serving to meet specific needs in certain medical conditions, the different carbohydrates may present their own unique health-related challenges.

3.1 | Lactose

Lactose is a disaccharide made of glucose and galactose. It is the primary carbohydrate source in human milk and standard infant formula. In a reduced-lactose formula, the main source of carbohydrates is brown rice syrup, CSS, or sucrose. Alterations in the lactose composition of infant formulas is associated with other alterations in the formula's nutritional profile including added sugar, protein, and polyunsaturated fatty acids.[21] Term infants express sufficient lactase to digest about one liter of breast milk daily. Physiological lactose malabsorption in infancy confers beneficial prebiotic effects.[22] Lactose intolerance (LI), the inability to digest and absorb dietary lactose due to inadequate lactase, is seen in prematurity, secondary lactase deficiency, such as with acute gastroenteritis, and congenital lactase deficiency. In most cases of transient LI due to gastroenteritis, it is recommended to stay on breast milk or the formula the infant was on before the illness to avoid unnecessary adverse nutritional outcomes.[23] Studies have failed to show a significant impact of reduced-lactose or lactose-free formula on infant behaviors (fussiness, crying), colic, or neonatal abstinence syndrome.[24,25] Lactose-free formula is required for the management of galactosemia, an inborn error of metabolism characterized by the inability to convert galactose to glucose.[26]

3.2 | Sucrose and fructose

Extensively hydrolyzed and amino acid-based formulas often include sources of carbohydrates other than

TABLE 2 Alternative protein sources for treatment and prevention of cow's milk protein allergy.

Source	Prevention of allergy	Treatment of allergy	Casien:Whey	Other considerations	Reference
Goat	No data	Risk of cross-reactivity, not suitable for use	84:16	– May develop separate allergy to this type of milk	5, 6, 12
Sheep	No data	No data, due to protein similarity risk of cross-reactivity, not suitable for use	80:20	– Not commercially available in the United States	6
Camel	Rat model, not effective	Possibly effective	73:27	– Low protein similarity to cow's milk – Not commercially available in the United States – May develop separate allergy to this type of milk	6
Donkey	No data	Possibly effective	58:42	– Low protein similarity to cow's milk – Not commercially available in the United States – May develop separate allergy to this type of milk	6
Horse	No data	Possibly effective	56:44	– Low protein similarity – Not commercially available in the United States – May develop separate allergy to this type of milk	6
Soy	Not effective	Can consider using if >6 months old	N/A	– Only use in infants >6 months of age – Cross-reactivity with cow's milk 3%–50% depending on study – Questionable concern for phytate and phytoestrogens	6, 15
Hydrolyzed rice	Not effective	Second line, if not tolerating extensively hydrolyzed formulas	N/A		6, 12, 15

Abbreviation: N/A, not applicable.

lactose, such as sucrose, maltose, and glucose, to enhance palatability. Consumption of sucrose, a disaccharide of fructose and glucose, may be problematic in children with hereditary fructose intolerance and can lead to severe symptoms, including poor feeding and vomiting. Furthermore, the fermentability of fructose by oral bacteria contributes to dental issues. Multiple studies have revealed that infant formulas with sucrose are acidogenic and more cariogenic than lactose-containing formulas and may play a role in the development of early childhood dental caries.[27–29] Added sugars in infant formula are associated with tendency for preference for sugar sweetened beverages in infants and toddlers.[30,31] Consumption of formula with sucrose as the carbohydrate source has also been linked to higher weight-for-length and abdominal circumference-for-age *z*-scores in infants 0–12 months compared to infants that consume formula without added sucrose. Dietary fructose is associated with metabolic dysfunction-associated steatotic liver disease (MASLD) in older children, but the effects of fructose consumption during infancy on the development of MASLD later in life remains unknown.[32]

3.3 | Corn syrup solids

CSS consist of short chains of glucose. They are an alternative carbohydrate source to lactose in some infant formulas. In recent years, lactose-free and reduced lactose formulas containing CSS have become increasingly popular, to improve the palatability for infants with concerns for LI. CSS-based formulas may lead to an altered gut microbiome in infants, including a reduction in *Bifidobacteriacea*, a microbe linked with beneficial properties of human milk, and an increase in *Lachnospiraceae* which is frequently linked to obesity related conditions later in life.[33] One study showed that infants consuming CSS-based formula have altered sugar and insulin metabolism dynamics compared with those who consume traditional lactose-based formula and breast milk.[34] CSS-based formulas may also lead to greater food pickiness and reduced enjoyment of food in the first 2 years of life compared with human milk.[35] Furthermore, a review of the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) shows that children with any CSS-based formula issuance had 10% higher obesity risk than those without, in a dose-dependent manner. This increased risk remains significant throughout the first few years of life.[36] CSS are also implicated in other pediatric conditions, including increased incidence and severity of necrotizing enterocolitis in a preclinical model when compared with lactose-based formula.[37] Taken together, CSS are an added source of sugar in some infant formulas that may have negative implications for growth and development in children.

3.4 | Sugar alcohols

Sugar alcohols are carbohydrates derived from vegetables and fruits or are synthetically produced. Inositol is a sugar alcohol that plays a role in phospholipid formation and cell signaling. It does not significantly contribute to the energy content of infant formula. It is abundant in human milk suggesting its role in early development. Given this, myoinositol is often added to many infant formulas to match the nutritional profile of human milk.[38] A meta-analysis showed mixed results regarding the effectiveness of inositol in preventing severe retinopathy of prematurity. There are no reports, however, of adverse effects of inositol in infant formula.[39]

4 | FAT

Fat is a macronutrient integral for growth and metabolism in infants. Both human milk and infant formula provide varied fats, including essential fatty acids, linoleic and alpha-linolenic, and non-essential acids, oleic and palmitic acid, which comprise most fat in human milk. Linoleic and alpha-linolenic acid are converted to arachidonic acid and eicosapentaenoic acid (EPA), respectively, and then EPA is further converted to docosahexanoic acid. The fat content and concentration of human milk are highly variable and change with the gestational and chronological age of the infant, maternal diet, nutritional status, body composition, time of day, frequency and volume of milk production, and even mode of expression. Infant formulas provide a consistent concentration of fat due to manufacturing limitations, but there is no one fat source, type, or concentration in formula that has proven to be the gold standard. As fats comprise up to half of energy provision in infant formula, this remains an important target of investigation.

4.1 | Medium-chain and long-chain triglycerides (MCTs and LCTs)

MCTs and LCTs are metabolized differently due to their chemical structure. Both have a glycerol backbone which is true of all triglycerides. MCTs have 6–12 carbons and can be absorbed directly from the small intestine into the hepatic portal circulation without requiring emulsification by bile salts or pancreatic enzymes, unlike LCT which are 13–21 carbons in length and require emulsification into chylomicrons.[40] The molecular weight and size of MCTs are lower than LCTs leading to faster and more complete hydrolysis of MCTs compared to LCTs. Essential fatty acids are plentiful in LCTs, while none are present in MCTs. LCTs are required for fat soluble vitamin absorption, and cell membrane function and immune function. LCTs have both anti-inflammatory and inflammatory effects.

4.2 | Clinical indications for high MCT formula

Conditions leading to fat malabsorption are associated with high risk of malnutrition and growth failure. High MCT formula is defined as 30% or more by weight and may be indicated in certain clinical settings (Table 1).[41] Cholestasis is one of the most common indications for higher MCT formula as cholestasis leads to decreased secretion of bile salts and in return malabsorption of fat, in particular LCTs which require bile salts for emulsification, lipolysis, and absorption through the lymphatic system. MCTs are partially water soluble and are passively absorbed and metabolized through the portal system without the need for extensive emulsification or chylomicron formation. No consensus exists on the optimal percentage of MCT recommended in the diet of cholestatic infants. A range of 30%–75% MCT is supported by clinical studies and associated with improved fat absorption, though the effect on growth and clinical outcomes remains unclear. MCT as >80% of triglycerides is not advised due to concern for essential fatty acid deficiency.[42]

MCT also improves fat absorption in patients who have undergone resection of their small intestine leading to short bowel syndrome, particularly when the colon remains intact. A preserved colon allows improved absorption of medium-chain fatty acids and short-chain fatty acids, which are water-soluble in contrast to lipophilic long-chain fatty acids, which can only be absorbed in the small intestine.[43]

High MCT formulas play a therapeutic role in chylous effusions as they are directly absorbed into the portal circulation and not through the lymphatic system. Chylous effusions may be congenital or iatrogenic, such as postoperative chylothorax. Postoperative chylothorax may be due to traumatic injury to lymphatic vessels during thoracic or abdominal surgery, but may also be seen in systemic venous obstruction, dysfunction of the right ventricle, and lymphangiectasia. Formulas with higher MCT content have a similar effect to skimmed human milk on the resolution of chylous effusion and associated hospital measures, including mechanical ventilation, length of hospital stay, and recurrence.[44] High MCT formulas are low in LCTs and when used patients should be monitored for signs of essential fatty acid and fat-soluble vitamin deficiencies.

5 | OSMOLALITY

Formula osmolality, which is the concentration of osmoles of solute per liter of solution of formula (mOsm/kg), is primarily affected by the concentration of amino acids, hydrolyzed proteins, monosaccharides and disaccharides, medium chain triglycerides, and electrolytes present in the milk. Osmolality increases as proteins are hydrolyzed into peptides. Formula with an osmolality higher than that of normal body fluids (approximately 300 mOsm/kg) produces an osmotic effect that can draw water into the GI tract. Recommendations on formula osmolality are limited to a recommendation made by the American Academy of Pediatrics in 1976 advising that formula should have an osmolality <450 mOsm/kg. However, a recent literature review by Ellis et al found that an osmolality between 300 and 500 mOsm/kg was not associated with adverse GI symptoms in newborn infants.[45,46] Information on the osmolality of formula products is often available from the formula manufacturer.

6 | SUMMARY

Carbohydrates, proteins, and fats are the key building blocks of infant formula. Each of these macronutrients has different forms, and formulas differ in their macronutrient composition. The directed macronutrient composition of the formula may be used in disease and symptom management.

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Akash Pandy is on the speakers bureau for Mead Johanson and Kate Farms and a consultant for Kate Farms. Debora Duro is on the speakers bureau for Abbott and Kate Farms. The remaining authors declare no conflicts of interest.

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REFERENCES

1. Food Safety & Nutrition from FDA. Infant Formula. FDA. Published May 17, 2024. Accessed May 28, 2024. https://www.fda.gov/food/resources-you-food/infant-formula
2. Davoodi SH, Shahbazi R, Esmaeili S, et al. Health-related aspects of milk proteins. *Iran J Pharm Res*. 2016;15:573-591.
3. Donovan SM. Human milk proteins: composition and physiological significance. *Nestle Nutr Inst Workshop Ser*. 2019;90:93-101.
4. Kipfer S, Goldman RD. Formula choices in infants with cow's milk allergy. *Can Fam Physician*. 2021;67:180-182.
5. Prosser CG. Compositional and functional characteristics of goat milk and relevance as a base for infant formula. *J Food Sci*. 2021;86:257-265.
6. Maryniak NZ, Sancho AI, Hansen EB, Bøgh KL. Alternatives to cow's milk-based infant formulas in the prevention and management of cow's milk allergy. *Foods*. 2022;11:926.

7. D'Auria E, Salvatore S, Acunzo M, et al. Hydrolysed formulas in the management of cow's milk allergy: new insights, pitfalls and tips. *Nutrients*. 2021;13:2762.
8. Nutten S. Proteins, peptides and amino acids: role in infant nutrition. *Nestle Nutr Inst Workshop Ser*. 2016;86:1-10.
9. Billeaud C, Guillet J, Sandler B. Gastric emptying in infants with or without gastro-oesophageal reflux according to the type of milk. *Eur J Clin Nutr*. 1990;44:577-583.
10. Vandenplas Y, Ksiażyk J, Luna MS, et al. Partial hydrolyzed protein as a protein source for infant feeding: do or don't? *Nutrients*. 2022;14:1720.
11. Rosen R, Vandenplas Y, Singendonk M, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr*. 2018;66:516-554.
12. Haiden N, Savino F, Hill S, et al. Infant formulas for the treatment of functional gastrointestinal disorders: a position paper of the ESPGHAN Nutrition Committee. *J Pediatr Gastroenterol Nutr*. 2024;79:168-180.
13. Bognanni A, Fiocchi A, Arasi S, et al. World Allergy Organization (WAO) Diagnosis and Rationale for Action Against Cow's Milk Allergy (DRACMA) guideline update—XII—recommendations on milk formula supplements with and without probiotics for infants and toddlers with CMA. *World Allergy Organ J*. 2024;17:100888.
14. American Academy of Pediatrics. Committee on Nutrition. Hypoallergenic infant formulas. *Pediatrics*. 2000;106:346-349.
15. Liu J, Klebach M, Visser M, et al. Amino acid availability of a dairy and vegetable protein blend compared to single casein, whey, soy, and pea proteins: a double-blind, cross-over trial. *Nutrients*. 2019;11(11):2613.
16. Collard KM, McCormick DP. A nutritional comparison of cow's milk and alternative milk products. *Acad Pediatr*. 2021;21:1067-1069.
17. Muñoz-Salinas F, Andrade-Montemayor HM, De la Torre-Carbot K, Duarte-Vázquez MÁ, Silva-Jarquin JC. Comparative analysis of the protein composition of goat milk from French Alpine, Nubian, and Creole breeds and Holstein Friesian cow milk: implications for early infant nutrition. *Animals*. 2022;12:2236.
18. Osborn DA, Sinn J. Soy formula for prevention of allergy and food intolerance in infants. *Cochrane Database Syst Rev*. 2006;2006:CD003741.
19. Merritt RJ, Fleet SE, Fifi A, et al. NASPGHAN position paper: plant-based milks. *J Pediatr Gastroenterol Nutr*. 2020;71:276-281.
20. Salvatore S, Savino F, Singendonk M, et al. Thickened infant formula: what to know. *Nutrition*. 2018;49:51-56.
21. Mokhtari P, Schmidt KA, Babaei M, Goran MI. Altered nutrient composition of lactose-reduced infant formula. *Nutrients*. 2024;16:276.
22. Heine RG, AlRefaee F, Bachina P, et al. Lactose intolerance and gastrointestinal cow's milk allergy in infants and children—common misconceptions revisited. *World Allergy Organ J*. 2017;10:41.
23. Heyman MB. Lactose intolerance in infants, children, and adolescents. *Pediatrics*. 2006;118:1279-1286.
24. Sherman AL, Anderson J, Rudolph CD, Walker LS. Lactose-free milk or soy-based formulas do not improve caregivers' distress or perceptions of difficult infant behavior. *J Pediatr Gastroenterol Nutr*. 2015;61:119-124.
25. Pandey R, Kanike N, Ibrahim M, et al. Lactose-free infant formula does not change outcomes of neonatal abstinence syndrome (NAS): a randomized clinical trial. *J Perinatol*. 2021;41:598-605.
26. Cerone J, Rios A. Galactosemia. *Pediatr Rev*. 2019;40:24-27.
27. Bowen WH, Pearson SK, Rosalen PL, Miguel JC, Shih AY. Assessing the cariogenic potential of some infant formulas, milk and sugar solutions. *JADA*. 1997;128:865-871.
28. Erickson PR, McClintock KL, Green N, LaFleur J. Estimation of the caries-related risk associated with infant formulas. *Pediatr Dent*. 1998;20:395-403.
29. More SG, Sankeshwari R, Patil PA, Jalihal SS, Ankola AV. Infant formula and early childhood caries. *J Dent Res Rev*. 2018;5:7-11.
30. Griebel-Thompson AK, Fazzino TL, Cramer E, Paluch RA, Morris KS, Kong KL. Early exposure to added sugars via infant formula may explain high intakes of added sugars during complementary feeding beyond maternal modeling. *Front Nutr*. 2023;10:1188852.
31. Fazzino TL, Kong KL. A new paradigm for investigating the etiology of obesity in early childhood: exposure to added sugars and hyper-palatable foods in infancy and dysregulation of food reinforcement processes. *Obes Rev*. 2023;24:e13526.
32. Young B. Variation in infant formula macronutrient ingredients is associated with infant anthropometrics. *Nutrients*. 2020;12:3465.
33. Jones RB, Berger PK, Plows JF, et al. Lactose-reduced infant formula with added corn syrup solids is associated with a distinct gut microbiota in Hispanic infants. *Gut Microbes*. 2020;12:1813534.
34. Slupsky CM, He X, Hernell O, et al. Postprandial metabolic response of breast-fed infants and infants fed lactose-free vs regular infant formula: a randomized controlled trial. *Sci Rep*. 2017;7:3640.
35. Hampson HE, Jones RB, Berger PK, et al. Adverse effects of infant formula made with Corn-Syrup solids on the development of eating behaviors in Hispanic children. *Nutrients*. 2022;14:1115.
36. Anderson CE, Whaley SE, Goran MI. Lactose-reduced infant formula with corn syrup solids and obesity risk among participants in the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC). *Am J Clin Nutr*. 2022;116:1002-1009.
37. Call L, Stoll B, Oosterloo B, et al. Metabolomic signatures distinguish the impact of formula carbohydrates on disease outcome in a preterm piglet model of NEC. *Microbiome*. 2018;6:111.
38. Bakshi S, Paswan VK, Yadav SP, et al. A comprehensive review on infant formula: nutritional and functional constituents, recent trends in processing and its impact on infants' gut microbiota. *Front Nutr*. 2023;10:1194679.
39. Howlett A, Ohlsson A, Plakkal N. Inositol in preterm infants at risk for or having respiratory distress syndrome. *Cochrane Database Syst Rev*. 2019;2019:CD000366.
40. Bach A, Babayan V. Medium-chain triglycerides: an update. *Am J Clin Nutr*. 1982;36:950-962.
41. Perretta L, Ouldibbat L, Hagadorn JI, et al. High versus low medium chain triglyceride content of formula for promoting short-term growth of preterm infants. *Cochrane Database Syst Rev*. 2021;2021:CD002777.
42. Mancell S, Manwani K, Dhawan A, Whelan K. Medium-chain triglycerides and the impact on fat absorption, growth, nutritional status and clinical outcomes in children with cholestatic liver disease: a scoping review. *Clin Nutr*. 2023;42:2159-2172.
43. Jeppesen PB, Mortensen PB. The influence of a preserved colon on the absorption of medium chain fat in patients with small bowel resection. *Gut*. 1998;43:478-483.
44. Samanidis G, Kourelis G, Bounta S, Kanakis M. Postoperative chylothorax in neonates and infants after congenital heart

disease surgery—current aspects in diagnosis and treatment. *Nutrients*. 2022;14:1803.
45. Ellis Z-M, Tan HSG, Embleton ND, Sangild PT, van Elburg RM. Milk feed osmolality and adverse events in newborn infants and animals: a systematic review. *Arch Dis Child Fetal Neonatal Ed*. 2019;104:F333-F340.
46. Ng KWP, Dietz AR, Johnson R, Shoykhet M, Zaidman CM. Reliability of bedside ultrasound of limb and diaphragm muscle thickness in critically ill children. *Muscle Nerve*. 2019;59:88-94.

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