Specialized infant formula

Clinical Policy ID: CCP.1501

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Policy contains: Eosinophilic gastroenteropathy; feeding intolerance; food protein-induced enterocolitis syndrome; galactosemia; inborn errors of metabolism; lactase deficiency; milk allergy; specialized infant formula; short bowel syndrome.

AmeriHealth Caritas has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas' clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered, on a case by case basis, by AmeriHealth Caritas when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas' clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas' clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas will update its clinical policies as necessary. AmeriHealth Caritas' clinical policies are not guarantees of payment.

Coverage policy

This policy addresses oral specialized infant formula for use in the home setting. This policy does not address enteral tube feedings.

Specialized infant formula for home use is clinically proven and, therefore, may be medically necessary when all of the following criteria are met:

- Breast milk or standard infant formula is insufficient, not tolerated, or contraindicated.
- Formula is deemed medically necessary by a physician/other licensed health care provider who will supervise the use of the oral formula.
- Formula is exempt from the general requirements for standard infant formula for nutritional labeling under the statutory and regulatory guidelines of the U.S. Food and Drug Administration (2023), and labeling contains a description of the medical condition for which the specialized formula is indicated.

- Documentation supports one of the following medical conditions requiring treatment with specialized infant formula:
- Immunoglobulin E-mediated milk protein allergy (O'Connor, 2009; National Institute of Allergy and Infectious Diseases, 2010).
- Galactosemia (O'Connor, 2009).
- Phenylketonuria (MacDonald, 2020).
- Congenital or primary lactase deficiency (O'Connor, 2009).
- Non-immunoglobulin E-mediated food protein allergy (National Institute of Allergy and Infectious Diseases, 2010; Nowak-Węgrzyn, 2017).
- Short bowel syndrome (National Institute of Diabetes and Digestive and Kidney Diseases, undated).
- Inborn errors of metabolism (Genetic Metabolic Dietitians International and the Southeast Regional Newborn Screening and Genetics Collaborative, 2021).
- Homocystinuria (Al-Sadeq, 2020).
- Maple Syrup Urine disease (Hassan, 2022).
- Has gastroesophageal reflux disease and is unresponsive to standard management techniques (Haiden, 2024).
- Other diagnoses mandated by state law.

Requests for specialized infant formula for conditions not listed above are subject to medical review and approval on a case-by-case basis.

Limitations

Continued coverage for specialized infant formulas is subject to medical review of medical necessity at six months of use or as requested.

Alternative covered services

- Enteral tube feedings.
- Parenteral feedings.
- Nutritional counseling.
- Nutritional consultation.

Background

Inborn errors of metabolism are genetic disorders that interfere with the normal metabolism of protein, fat, or carbohydrate and the generation of energy. They are considered present at birth and permanent. Disturbance of these metabolic pathways frequently produces a constellation of nonspecific clinical findings, affecting multiple organ systems with varying severity (Kruszka, 2019).

Newborn screenings have identified multiple inborn errors of metabolism resulting in disorders that remain incurable but treatable with the feeding of medically specialized infant formulas for survival. The inability of the infant's body to breakdown phenylalanine, tyrosine, lysine, tryptophan, and other amino acids can be life threatening and result in poor growth, abnormal motor skill and coordination, slowed development, and learning disabilities. Among those more commonly known and treated are Phenylketonuria, Maple Syrup urine disease, Homocystinuria, Galactosemia (Health Resources and Services Administration, 2023; Nutricia North America, 2023).

Standard infant formula is a manufactured substitute for, or supplement to, human milk for orally feeding term infants younger than 12 months (Martinez, 2011). It is based most commonly on cow's milk fortified with carbohydrates, lipid components, vitamins, minerals, nucleotides, and altered protein content to improve safety

and digestibility. Other animal milk and plant-based milk are alternatives to cow's milk for term infants (Milbrandt, 2017).

Bioactive compounds associated with health benefits found in human milk may be added to upgrade the nutritional quality of infant formulas (Almeida, 2021). Common bioactive additives are α-lactalbumin, lactoferrin, taurine, milk fat globule membrane, folates, polyamines, and long-chain polyunsaturated fatty acids. Prebiotics and probiotics, which attempt to mimic the intestinal flora of breast-fed infants, may be beneficial for preventing necrotizing enterocolitis in preterm infants who are formula-fed (Downard, 2012; Bührer, 2020). While these supplements appear safe and well-tolerated in most instances, there is no consensus on whether they have the same functional effects as human milk or how thermal processing and storage may affect bioactivity (Almeida, 2021).

The U.S. Food and Drug Administration (2023) regulates infant formula as a food supplement. No pre-marketing approval is required, but all formulas marketed in the United States must meet federal nutrient requirements and manufacturers must comply with notification requirements prior to marketing a new formula. These nutrient requirements include minimum amounts for 30 nutrients and maximum amounts for 11 of them (21CFR107.100).

If an infant formula does not meet these nutritional specifications, it is considered an adulterated product. A formula, such as a specialized infant formula, may be considered "exempt" from certain nutrient requirements if it is intended for commercial or charitable distribution and is represented and labeled for use by an infant who has an inborn error of metabolism or low birth weight, or who otherwise has an unusual medical or dietary problem. Recipes for homemade formulas are not regulated (U.S. Food and Drug Administration, 2023).

Preterm formulas have higher caloric density and concentrations of key nutrients (Martinez, 2011). Preterm and enriched formulas are considered the standard of care in the hospital setting, as they may improve short-term growth parameters (O'Connor, 2009). They are usually discontinued at hospital discharge and replaced with transitional formulas for several months. Follow-up formulas are for infants and young toddlers whose solid food intake is not fully adequate to meet age-specific nutritional requirements.

Specialized infant formulas are designed to meet the unique nutritional needs of an infant, when such formulas taken by mouth are the sole source of nutrition, and breast milk or standard infant formula would place the infant at risk for more severe health consequences. These specialized formulas may include added, subtracted, or altered nutrients to ensure adequate nutritional status (Martinez, 2011; Milbrandt, 2017).

Specific health conditions with unique nutritional needs may include genetic deficiencies, inborn errors of metabolism, food intolerance or allergy, and reflux. Specialized formulas for these conditions may contain partially hydrolyzed proteins, lactose-free or lactose-reduced blends, and thickeners. Hypoallergenic formulas contain hydrolyzed proteins that are less likely to stimulate antibody production. Non-allergenic amino acid-based formulas provide simple protein sources that are easier to digest and tolerate. For those wishing to avoid lactose, soy formulas made with corn-based carbohydrate (without lactose) and lactose-free formulas are alternatives. Anti-regurgitation formulas contain thickeners such as cornstarch or an increased amount of casein to reduce the frequency of overt regurgitation and vomiting (Martinez, 2011; Nutricia North America, 2023).

Findings

Standard infant formulas are established alternatives to human milk when breastfeeding is inadequate or not possible to meet infants' nutritional needs (Milbrandt, 2017; O'Connor, 2009). There is consensus among guidelines that the primary therapy for an infant with feeding intolerance involves elimination of the dietary allergen or substance that cannot be adequately absorbed or metabolized and places the infant at risk for serious health consequences (Genetic Metabolic Dietitians International and the Southeast Regional Newborn

Screening and Genetics Collaborative, 2021; National Institute of Allergy and Infectious Diseases, 2010; O'Connor, 2009).

The Genetic Metabolic Dietitians International and the Southeast Regional Newborn Screening and Genetics Collaborative (2021) have developed joint evidence-based nutrition management guidelines for several inherited metabolic disorders, in which diet management is an integral treatment for individuals at all ages. The inherited metabolic diseases addressed in their guidelines are phenylketonuria, maple syrup urine disease, propionic acidemia, very-long-chain acyl-CoA dehydrogenase deficiency, and medium-chain acyl CoA dehydrogenase deficiency. The evidence for medical nutrition therapy for these conditions is based primarily on expert opinion and limited case series, many of which reported outcomes for patients diagnosed prior to newborn screening requirements. For infants diagnosed with inborn errors of metabolism, breast feeding or standard formula feeding may need to be replaced, in part or in whole, with specialized infant formula specific to the diagnosis, severity, and infant tolerability.

A comprehensive review for the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Nutrition Committee, focusing on the effectiveness of specialized infant formulas for treating functional gastrointestinal disorders such as regurgitation, colic, and constipation in infants up to six months old. Study authors reviewed 72 studies in their analysis. For regurgitation, an overview of 13 randomized controlled trials involving (n = 265) infants found that thickened formulas reduced daily regurgitation episodes from an average of 5.4 to 2.5 over 1 to 4 weeks.

However, for colic, the evidence supporting the use of specialized formulas—including those with reduced lactose content, hydrolyzed proteins, or added probiotics—is insufficient, as most studies had small sample sizes and methodological limitations. In the case of constipation, formulas with higher magnesium content or beta-palmitate may improve stool consistency, but the evidence is limited and based on small studies with low certainty. Overall, the study emphasizes that breastfeeding should not be discontinued due to functional gastrointestinal disorders, and that specialized formulas should be used only under medical supervision. The findings are relevant to our policy as they underscore the importance of medical necessity and the limited evidence supporting the routine use of specialized infant formulas for these conditions (Haiden, 2024).

For a minority of infants with feeding intolerance due to milk protein allergy or congenital, primary, or secondary lactase deficiency, specialized formula may be indicated (O'Connor, 2009). Abnormal immunologic reaction to dietary proteins contribute to several different gastrointestinal disorders in infants (National Institute of Allergy and Infectious Diseases, 2010). They are generally classified as immunoglobulin E-mediated, non-immunoglobulin E-mediated, or mixed. Classic food allergies are immunoglobulin E-mediated with a rapid onset of symptoms primarily involve the skin (e.g., itching, hives) that, in severe cases, may lead to anaphylaxis.

A non-immunoglobulin E-mediated reaction to foods is characterized by profuse vomiting and diarrhea; and, with continued ingestion, poor growth (National Institute of Allergy and Infectious Diseases, 2010). Atopy or a strong family allergy history may also exist. An example is food protein-induced enterocolitis syndrome.

Hypoallergenic formula with hydrolyzed protein is indicated for infants with true immunoglobulin E-mediated milk protein allergy (O'Connor, 2009). Hydrolyzed formula appears to be safe and well-tolerated among infants with cow's milk protein allergy (Stróżyk, 2020). It may have protective effects against atopic disease and a short trial may be beneficial in cases of refractory colic, but systematic reviews cited low-quality evidence supporting these indications (Gordon, 2018; Ng, 2019; Osborn, 2018; Vandenplas, 2019).

In rare cases, nonallergenic amino acid-based elemental formula may be indicated if the infant is unable to digest or tolerate whole proteins found in other formulas due to food protein allergies or malabsorptive gastrointestinal conditions, such as food protein-induced enterocolitis syndrome, eosinophilic gastroenteropathies, and short bowel syndrome (National Institute of Diabetes and Digestive and Kidney Diseases, undated; Nowak-Węgrzyn, 2017; O'Connor, 2009).

There is insufficient evidence to support a clear preventive or protective health benefit of prebiotics and probiotics for managing cow's milk protein allergy. One systematic review (Sorensen, 2021) of four randomized controlled trials (n = 410 infants) found that infants with confirmed immunoglobulin E-mediated and nonimmunoglobulin E-mediated cow's milk protein allergy who were fed an amino acid formula with a "synbiotic" supplement (i.e., a mix of prebiotic and probiotic supplements) had significantly fewer infections (odds ratio 0.35, 95% confidence interval 0.19 to 0.67; *P* = .001), lower antimicrobial medication use, and fewer hospital admissions (*P* = .036; 56% reduction), than infants receiving unsupplemented amino acid formula. The supplement improved gut microbiota profile. All studies used a special formula blend of bifidobacterium breve M16-V and prebiotics including chicory-derived oligofructose and long-chain inulin. The study results are not generalizable to other synbiotic supplements, and the relationship of supplement to gut microbiota profile requires further study.

Soy formula is indicated for term infants with galactosemia or congenital lactase deficiency or for vegan families who wish to avoid animal protein (O'Connor, 2009). Soy formula is not indicated for preterm infants. There is insufficient proven benefit of soy formula for preventing or treating other conditions including animal milk protein allergy, generalized colic, and acute gastroenteritis (O'Connor, 2009; Gordon, 2018). In the treatment of infant colic, parental counseling is more effective than changing formula (O'Connor, 2009).

Lactose-free formulas are indicated for galactosemia and congenital lactase deficiency, as well as primary lactase deficiency (O'Connor, 2009). Some infants younger than three months or those who are malnourished may benefit from a trial of lactose-free formula following acute gastroenteritis.

While most episodes of infant reflux will resolve on their own, anti-regurgitation formula is safe and may be trialed for severe or persistent cases (O'Connor, 2009; Kwok, 2017). There is no consensus on which anti-regurgitation formulas are most effective. Commercial thickening agents should not be used because of their association with necrotizing enterocolitis (O'Connor, 2009).

In 2023, we identified no newly published, relevant literature to add to the policy. No policy changes are warranted.

In 2024, we identified a new systematic review (Bognanni, 2024).. We also found a new guideline that focused on the use of formula for children with significant regurgitation. Policy was revised based on guideline (Haiden, 2024). The systematic review by the World Allergy Organization focused on infants and toddlers with cow's milk allergy who cannot be breastfed. The review analyzed 14 randomized controlled trials and seven observational studies, involving a total of n = 2,430 participants (n = 1,132 from trials and n = 1,298 from observational studies).

The study evaluated the efficacy and safety of various specialized formulas—including extensively hydrolyzed cow's milk-based formulas, amino acid formulas, hydrolyzed rice formulas, and soy formulas—with or without added probiotics. Findings indicated that extensively hydrolyzed cow's milk-based formulas might increase the likelihood of infants outgrowing cow's milk allergy compared to amino acid formulas (risk ratio 2.32; risk difference 25 more per 100) and might reduce the risk of severe vomiting and development of food protein-induced enterocolitis syndrome. However, the evidence was of very low certainty due to limitations in study quality and sample sizes (Bognanni, 2024).

References

On October 5, 2024, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were "Metabolism, Inborn Errors/diet therapy" (MAJR), "eosinophilic enteropathy," "galactosemia," "lactase deficiency," "food intolerance", "milk hypersensitivity" (MeSH), "phenylketonuria" (MeSH), "homocystinuria" (MeSH), and "maple syrup urine disease". We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-

analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

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11/2022: Policy references updated.

11/2023: Policy references updated.
11/2024: Policy reference updated.