REVIEW ARTICLE

Newborn Disorders and Nutritional Guidance

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Newborn disorders vary widely, from premature birth to a myriad of genetic disorders. Although they are commonly encountered in hospital and primary care settings, existing therapies are neither definitive nor distinct, and research is still ongoing. Such disorders of concern include premature birth, gastroesophageal reflux, cystic fibrosis, Down Syndrome, phenylketonuria, maple syrup urine disease, and galactosemia. Nutritional recommendations are critical to these infants who may not survive without specific alterations in their diet to accommodate the stress from their metabolic demand. Nutritional guidance in these patients reduces the incidence of complications and exacerbations of these disorders, which may include failure to thrive, anemia, neurocognitive deficiencies, sepsis, reflux, and diabetes. Breastfeeding has been found to reduce mortality in infants that are premature, reduce complications in gastroesophageal reflux disease, and result in better prognoses in newborns with cystic fibrosis. Supplementation of vitamins, iron, probiotics, and even salt have been beneficial in the management of these newborns. Modified infant formulas and medical foods are the mainstay of treatment for inborn errors of metabolism, as they require specific enzymes and proteins to be supplemented or avoided. Also, knowing which milks, proteins and vegetables to consume may be valuable for physicians and primary caretakers to plan the diet regimens accordingly.

INTRODUCTION

While research in pediatric medicine has historically focused on the medical management of various newborn disorders, research regarding the long-term nutritional aspects of such disorders warrants further discussion. Insufficient nutrition in a developing newborn compounded by a pathologic process may result in a condition known as failure to thrive (FTT), a pattern of inadequate weight gain.[1] Chronic and unmanaged FTT can further progress into neurocognitive deficits and immune deficiencies, which can potentially create significant morbidity throughout the rest of the newborn's life.[2] Preparing a nutritional plan in anticipation of the infant's additional metabolic needs may help in preventing complications exacerbated by a specific newborn disorder. Family Medicine physicians often encounter these issues, and this review focuses on the importance of breastfeeding and additional nutritional components of common newborn disorders in an effort to mitigate potential progression into FTT and its long-term sequelae.

PREMATURITY

Preterm births constitute a substantial portion of childbirths in the United States and are a significant cause of infant mortality and morbidity. In 2016, the incidence of premature births increased for the second straight year to 9.85%.[3] Prematurity is defined as birth before 37 weeks and complications related to prematurity may include anemia, late onset sepsis, necrotizing enterocolitis, or failure to thrive.[1,4–6]

Iron deficiency anemia is a common complication of prematurity due to a lower level of iron stores in the preterm infant.[7] Other causes of anemia can include rapid postnatal growth, losses due to phlebotomy, or delayed enteral feeding during hospitalization.[5] Breastfed preterm infants should be supplemented with 2 mg per kg of iron at discharge and subsequently screened for anemia at 4 and 12 months of age.[8] Comparatively, preterm infants on enriched or standard formula receive an adequate amount of iron through their diet, thereby negating the need for supplementation.[8] Though the primary treatment of anemia in preterm infants is red blood cell (RBC) transfusions, frequent transfusions may be associated with bronchopulmonary dysplasia among other complications.[9] Optimal protein supplementation may reduce the incidence of anemia in preterm infants thus reducing the need for such transfusions.[10]

For premature infants with very low birth weight, early breastfeeding initiation has been shown to reduce mortality.[11] Additionally, the ingestion of breastmilk reduces both the length of time required for full enteral feeding in the hospital and also

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TABLE 1: [31,34,38,39]

Dosages, Goals, and Toxicities of Fat-soluble Vitamin Supplementation for CF Patients

VITAMIN	DAILY DOSE	GOAL	TOXICITY
Vitamin A	1500 IU (Start low)	Normal range of healthy same age individuals	Liver cirrhosis, decreased bone mineral density, increased fracture risk
Vitamin D	400 IU	25(OH)D >20 ng/mL (50 nmol/L)	Vomiting, appetite loss, arrhythmia, confusion
Vitamin E	α-tocopherol: 50 IU	α-tocopherol/cholesterol > 5.4 mg/g	No known adverse effects
Vitamin K	0.3-1 mg	Routine measurement not widely available	No known adverse effects

Abbreviation: 25(OH)D = 25-hydroxyvitamin D

the incidences of retinopathy or sepsis.[11,12] Further, the limited exposure to the maternal microbiota and the use of antibiotics in premature infants that is given to reduce the risk of sepsis, results in the underdevelopment of the gut flora, which can lead to greater infection susceptibility.[13,14] Therefore, probiotics should be implemented to alleviate these effects in the infant and the risk of late onset sepsis.[15]

GASTROESOPHAGEAL REFLUX

Gastroesophageal reflux (GER), common in infants, is due to transient lower esophageal sphincter relaxation.[16] Gastroesophageal reflux disease (GERD) is a severe state of reflux accompanied by troublesome symptoms that may include dysphagia, heartburn, recurrent vomiting, chest or epigastric pain, asthma, wheezing, apnea or cyanosis.[16,17] GERD may also lead to reflux esophagitis, strictures, respiratory complications, failure to thrive, Barrett's esophagus, or esophageal adenocarcinoma.[17] While most reflux cases in the newborn typically resolve during the first year, lifestyle modifications including dietary changes can help decrease the frequency and severity of reflux episodes and such modifications are the recommended first-line of therapy for relieving GERD symptoms.[18]

In order to rule out other disorders aside from GERD, such as a milk allergy, it is recommended that breastfeeding mothers remove cow's milk and eggs from their diet for a 2 to 4 week period.[19] For formula-fed infants with GERD, parents should use a formula consisting of hydrolyzed protein or an amino acid based formula due to beneficial effects on gastrointestinal motility and esophageal acid exposure.[20] Feeding volume should be decreased while frequency of feeding should be increased.[19] Though thickening agents and anti-regurgitant formulas may decrease observable regurgitation, neither has been associated with a decrease in the actual number of reflux episodes and thickening agents containing rice or corn may also contribute to unintended weight gain.[17,19] Moreover, thickening agents have been associated with necrotizing enterocolitis in preterm infants.[21] Overall, the incidence of GERD is lower in breastfed infants versus formula-fed infants.[22]

CYSTIC FIBROSIS

Cystic fibrosis (CF) is an autosomal recessive disorder that leads to impaired chloride transport across cell membranes producing abnormally thick secretions in the lungs, pancreas, gastrointestinal tracts, and hepatobiliary tracts.[23] Common complications include CF-related diabetes, asthma, osteopenia, GERD, and liver disease. Because malnutrition is a serious concern for CF patients, nutrition therapy has become part of the standard of care, in efforts to improve height and weight percentiles.[24] Furthermore, newborn screening has resulted in earlier diagnoses, allowing more effective nutritional intervention.[25,26]

Optimal nutrition is associated with better lung function, fewer CF-related complications, and consequently a longer life span.[27] Achieving optimal nutrition involves adequate energy intake, and regular dietary and growth monitoring.[28,29] Poor nutrition in CF is often a result of the negative energy balance due to increased energy requirements, poor dietary intake, fat malabsorption, and glycosuria.[30] Nutritional goals are assessed via weight and height for age percentiles in infants up until two years of age.

It is recommended that CF infants are breastfed exclusively, at least for the first year of life, as it applies to healthy infants. If unable, regular infant formula can be used, along with nutrition counseling on effective feeding strategies. Standard infant formula may be cow milk-based, which is the most common type, or soy protein-based.[32,33] Hydrolyzed formula is often given to infants with malabsorption issues not related to CF. Solid foods can be introduced at 4-6 months of age.

Because salt loss occurs with CF and can lead to poor growth, breastfed infants should be given 1-2 mmol per kg/day of table salt (NaCl), in small amounts throughout the day, preferably diluted in water or fruit juice. Under special circumstances, such as hot weather or increased fluid loss, up to 4 mmol per kg/day of table salt can be given. The need for supplementation should be evaluated on an individual basis.[23,31]

Daily doses of fat-soluble vitamins (A, D, E, and K) are recommended for infants with suboptimal serum levels, especially

TABLE 2: [31,40]

Dietary Calcium Reference Values for CF Infants

AGE	DIETARY REFERENCES VALUES
0-6 months	200 mg/day
7-11 months	280 mg/day

those suffering from poor fat absorption mediated by pancreatic insufficiency. While symptomatic vitamin A deficiency is rare, low levels are associated with poor clinical status and compromised lung function. Vitamin D and calcium help maintain bone mineral density. Vitamin E deficiency can lead to hemolytic anemia and decreased cognitive function. During pulmonary exacerbations of CF, vitamin E requirements increase with oxidative stress. Vitamin K deficiency can cause poor bone health, and intracranial hemorrhages in infants. While vitamin K is not routinely measured due to cost, levels are generally low in CF infants, prompting empiric supplementation for all infants.[31,34,35] *Table 1 (See page 21)* highlights doses, goals, and toxicities of the fat-soluble vitamins. Regarding calcium levels, the goal is to maintain the same levels as in healthy, same-aged individuals, although it remains unclear as to when calcium supplementation should be initiated.[31,36] *Table 2* shows dietary reference values, starting at 0 months of age, which are derived from the amount of calcium absorbed by healthy breastfed infants. However, other literature recommends that screening for calcium deficiency begin after age 8 if risk factors such as chronic steroid use, low-impact activity, delayed pubertal development, or poor nutrition exist.[29,37] As the infant grows older, recommendations will change according to age range. Generally, for children and adolescents, a high-calorie, fat-unrestricted diet is recommended, in conjunction with antibiotics, pulmonary treatments, and/or pancreatic enzyme replacement therapy (PERT) as needed.[36]

DOWN SYNDROME

As of 2010, Down Syndrome (DS), or trisomy 21, continues to be the most common chromosomal disorder in the United States, with 1 out of 733 infants born with this disorder. DS infants often initially present with a lower birth weight and a reduced metabolic rate eventually becoming progressively overweight and prone to obesity.[41] Additionally, constipation and GER are common complications due to hypotonia and low activity level. Like all other infants, breastmilk is the gold standard for DS infants due to easier digestion and immune supplementation from antibodies since DS infants are more prone to infection. However, unique breastfeeding challenges exist, including excessive sleepiness and hypotonia of facial and lip muscles leading to difficulty in swallowing and sucking.[42,43] Such obstacles may lead to earlier weaning and less frequent feedings, predisposing the DS infant to infections and lower nutritional intake. Furthermore, excessive sleepiness may prevent the infant from receiving hind milk, which comes towards the end of the feeding and is known to have higher caloric and fat content.[42] Physician guidance, along with community resources and outpatient lactation services, should help promote optimal breastfeeding.[43,44]

INBORN ERRORS OF METABOLISM

Out of the 4 to 5 million newborns born each year, newborn screening programs will detect an inborn error of metabolism in 1 out of 800 newborns.[45] It is important to treat these conditions early, as they can lead to moderate to severe neuropsychological dysfunctions, developmental disabilities, and death.[46] A blood sample obtained at 24-48 hours of life is screened for more than 60 conditions and provides results within 24 hours.[46] These conditions include amino acid disorders such as phenylketonuria (PKU) and maple syrup urine disease (MSUD), and multisystem diseases such as cystic fibrosis and galactosemia, a disorder which can lead to failure to thrive, infection, cataracts, liver failure, and death.[46] A majority of these conditions are treated by nutritional management. Metabolic conditions, such as amino acid and fatty acid oxidation disorders, are treated with a protein-restricted diet using specific infant formulas and the avoidance of fasting.[46] Nutritional guidance is critical in these patients as it can mitigate the negative consequences of these disorders, which are often characterized by deficiencies or excesses of amino acids or enzymes that are needed to metabolize nutrients.

PHENYLKETONURIA

Phenylketonuria (PKU), occurring in 1 in 15,000 newborns, is a disorder in which phenylalanine, an essential amino acid found in most dietary intact protein sources, cannot be catabolized into tyrosine and thus creates an excess of phenylalanine in the body.[45] High phenylalanine levels are neurotoxic, and prevent the production of protein and the neurotransmitters dopamine and serotonin, leading to intellectual disabilities, abnormal motor, behavioral, and negative neurocognitive effects, resulting in poor schoolwork and work performance.[47] With treatment, mental retardation can be prevented. Standard treatment of PKU consists of a dietary restriction of phenylalanine and medically-prescribed phenylalanine-free or restricted amino acid-rich medical foods.[48] Medical foods are defined as "products that provide protein and varying amounts of carbohydrate, fat, vitamins, and minerals."[49] In the case of an infant with PKU, a medical food would be a powdered formula that contains all the nutrients required for growth and development, excluding the offending nutrient, phenylalanine.[49] Medical foods are critical for treating individuals with PKU because the extra nutrients included in these foods provide about 85-90% of all the protein that a newborn needs.[49] Supplementation with tyrosine is also an important part of the diet. Although all the medical foods provide tyrosine, if blood concentrations remain persistently low, extra supplemental tyrosine must be included in the diet.[50]

The goal of dietary treatment is to maintain phenylalanine levels of 120-360 μmol/L throughout life.[51] When recommending a medical food plan for a patient, an individualized approach should be used, taking into account the patient's current blood phenylalanine levels, age, growth, and protein needs. The prescribed diet should be frequently monitored to ensure that

there is sufficient phenylalanine, protein, and calories required for growth during childhood, and modified, as needed, if the patient's energy needs are not being met.[52] When a patient is not adhering to a prescribed medical food regimen, an assessment for any vitamin or mineral supplementation should be provided in order to maintain metabolic control and nutritional adequacy.[50] New and alternative protein sources such as glycomacropeptides, elaborated in *Table 3*, may be a replacement option for the medical foods, especially when adherence is difficult.[47]

MAPLE SYRUP URINE DISEASE

Maple syrup urine disease (MSUD), occurring in 1 out of 185,000 newborns, is caused by a deficiency in branched-chain α-ketoacid dehydrogenase (BCKD), leading to the accumulation of the branched chain amino acids (BCAA): leucine, isoleucine, and valine and their corresponding α-ketoacids.[45,53] Exogenous, or dietary, BCAA are major precursors for protein synthesis and a major energy source when there is enough BCAA from endogenous

breakdown of muscle.[53] Excess amounts of BCAA in classic MSUD, which is less than 3% residual enzyme activity, causes cerumen and urine that may smell of maple syrup, which presents as early as 12-24 hours and 48-72 hours after birth, respectively.[53] Aside from the maple syrup urine, newborns may appear normal, although symptoms such as vomiting, lethargy, poor suckling, and irritability may develop within the first week of life.[54] MSUD may also cause convulsions and coma, if left untreated.[45]

Treatment of MSUD includes rapidly reducing and restricting dietary BCAA, while maintaining sufficient amounts for anabolism and turnover. It is also important to initiate treatment within 7-10 days after birth before irreversible neurologic damage can occur.[54] Dietary recommendations are noted in *Table 3*.[53] Nutritional status must be monitored to ensure normal growth, development, and health maintenance.[53]

GALACTOSEMIA

Galactosemia, occurring in 1 out of 100,000 newborns, is an autosomal recessive disorder in which there is a profound defect

TABLE 3: [47,53,56]
Allowed and Restricted Diets for PKU, MSUD, and Galactosemia.

DISORDER	ALLOWED DIET	RESTRICTED DIET
PKU	Phenylalanine-free or restricted amino acid-rich medical food (powdered formula) Calculated amounts of breastmilk or standard infant formula Foods modified to be low in protein Glycomacropeptide, a protein derived from cheese whey that is rich in specific essential amino acids but is naturally free of tyrosine, tryptophan, and phenylalanine	Dietary Phenylalanine High protein/calorie (non-modified) foods
MSUD	BCAA-free medical food Intact protein (breastmilk or infant formula with known leucine content)	Dietary BCAA
Galactosemia	Soy-based infant formulas containing soy protein isolate, amino acid-based elemental infant formulas All fruits, vegetables and their juices, pickled fruits and vegetables All legumes (e.g. navy beans, kidney beans, garbanzo beans, soybeans) Sodium and calcium caseinate, a precipitated form of casein, which is a protein in cow's milk. Caseinates are extensively washed and do not contain whey	-Breastmilk, all milk-based infant formulas All milk-based foods and beverages except for caseinates and aged cheeses All milk-based ingredients including buttermilk solids, casein, dry milk protein, dry milk solids, hydrolyzed whey protein, hydrolyzed casein protein, lactose, lactalbumin, whey Organ meats, meat-by-products Soy products that are fermented Fermented soy sauce

in the enzyme galactose-1-phosphate uridylyltransferase.[55] Early diagnosis, followed by immediate dietary restriction of galactose, can prevent or reverse sequelae of classic galactosemia which, without intervention, could potentially be fatal.[55] Treatment consists of restricting galactose and dairy intake by switching infants to either an alternative formula that is soy-based or a prescribed elemental formula which in some cases has even lower levels of galactose.[55] Dietary recommendations for galactosemia are noted in *Table 3 (See page 23).*[56] All forms of soy formula are acceptable, but premature infants with galactosemia will need elemental infant formulas instead.[56]

Treating galactosemia through a strict diet is crucial and necessary, but this alone is not enough to eliminate the long-term effects of the disorder. Most patients still report complications including cognitive disabilities, speech problems, and neurological and/or movement disorders.[55] More research on statistically powerful comparative studies is needed to understand the benefits and harms of differing approaches.[55] Some studies suggest the need for evidence-based best practice guidelines regarding optimal strictness and duration of dietary galactose restriction.[57]

CONCLUSION

Different strategies are needed to manage the unique nutritional needs of infants suffering from prematurity, GER, CF, Down syndrome, and IEM disorders. Since infants develop quickly and are especially vulnerable, providing immediate optimal nutritional care, along with medical therapy when needed, will improve the chances of survival and reduce the likelihood of negative outcomes including FTT and further neurological or immunological sequelae. With the exception of infants suffering from galactosemia, breastmilk has been shown to be beneficial for those infants diagnosed with the conditions discussed. Furthermore, premature infants should be given probiotics, and CF infants should have salt and fat-soluble vitamin supplementation, as needed. Infants with GERD and DS necessitate optimal breastmilk or formula feeding strategies. Lastly, management of PKU, MUSD, and galactosemia involve carefully monitoring a restricted diet of phenylalanine, BCAA, and galactose, respectively. It is important to employ an individualized approach, based on an infant's laboratory values, age, and weight and height percentiles. For specific conditions such as CF and IEM disorders, multi-disciplinary specialty teams exist to treat and support the infants and their families. However, within the primary care setting, the practitioner should have a basic understanding of nutritional management, so as to be prepared when the appropriate situation arises. While certain recommendations have been well established for many years, new research and studies will continue to improve our understanding about the nutritional needs of newborns, including those with special disorders.

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No relevant financial affiliations

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