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Narrative Review

Diet management in congenital diarrheas and enteropathies – general concepts and disease-specific approach, a narrative review

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A B S T R A C T

Congenital diarrheas and enteropathies (CODE) are a group of rare, heterogenous, monogenic disorders that lead to chronic diarrhea in infancy. Definitive treatment is rarely available, and supportive treatment is the mainstay. Nutritional management in the form of either specialized formulas, restrictive diet, or parenteral nutrition support in CODE with poor enteral tolerance is the cornerstone of CODE treatment and long-term growth. The evidence to support the use of specific diet regimens and nutritional approaches in most CODE disorders is limited due to the rarity of these diseases and the scant published clinical experience. The goal of this review was to create a comprehensive guide for nutritional management in CODE, based on the currently available literature, disease mechanism, and the PediCODE group experience. Enteral diet management in CODE can be divided into 3 distinct conceptual frameworks: nutrient elimination, nutrient supplementation, and generalized nutrient restriction. Response to nutrient elimination or supplementation can lead to resolution or significant improvement in the chronic diarrhea of CODE and resumption of normal growth. This pattern can be seen in CODE due to carbohydrate malabsorption, defects in fat absorption, and occasionally in electrolyte transport defects. In contrast, general diet restriction is mainly supportive. However, occasionally it allows parenteral nutrition weaning or reduction over time, mainly in enteroendocrine defects and rarely in epithelial trafficking and polarity defects. Further research is required to better elucidate the role of diet in the treatment of CODE and the appropriate diet management for each disease.

Keywords: neonatal diarrhea, treatment, children, nutrition, formula, food, parenteral nutrition, enteral autonomy, weaning, tube feeding

Introduction

Congenital diarrheas and enteropathies (CODE) is a group of heterogenous, monogenic, and rare disorders presenting in the neonatal period and infancy. They universally present with chronic mild/severe diarrhea and are occasionally associated with extraintestinal manifestations. CODE can be divided into 5 distinct pathophysiologic entities according to the underlying enterocyte or immune system defect. These defects include abnormalities in epithelial electrolyte transport, epithelial enzyme and metabolism, epithelial trafficking and polarity,

Abbreviations: ABL, abetalipoproteinemia; AE, acrodermatitis enteropathica; ApoB, Apolipoprotein B; BAD, bile acid diarrhea; CCD, congenital chloride diarrhea; CMRD, chylomicron retention disease; CODE, congenital diarrheas and enteropathies; CSD, congenital sodium diarrhea; CSID, congenital sucrase-isomaltase deficiency; DGAT1, diacylglycerol *O*-acyltransferase 1; EFA, essential fatty acid; EFAD, essential fatty acids deficiency; FHBL, familial hypobetalipoproteinemia; FSV, fat-soluble vitamin; GGM, glucose-galactose malabsorption; GI, gastrointestinal; IM, intramuscular; IV, intravenous; LCT, lactase-phlorizin hydrolase; MCT, medium-chain triglyceride; MVID, microvillous inclusion disease; PIL, primary intestinal lymphangiectasia; PN, parenteral nutrition; SI, sucrase-isomaltase; TAG, triacylglycerol; TC, total cholesterol; THE, trichohepatoenteric syndrome; TG, triglyceride.

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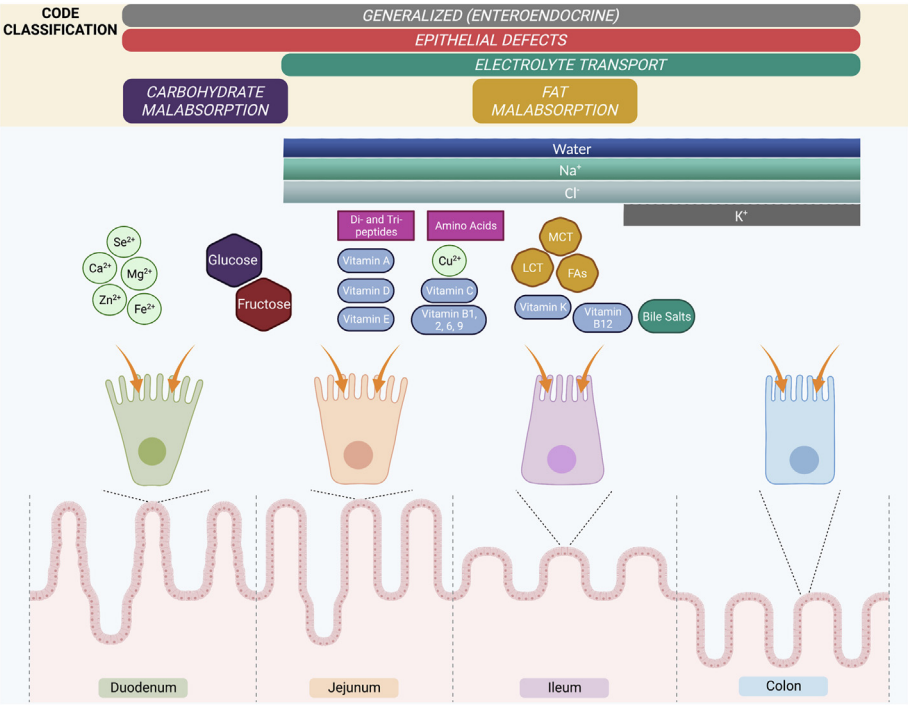

FIGURE 1. Impact of CODE disorders on nutrient and micronutrient absorption. Normal absorption of nutrients, micronutrients, water, and electrolytes according to enterocyte anatomical location is shown. The upper portion of the figure depicts CODE disease groups and the anatomical location affected by each group. Malabsorption of specific nutrients and micronutrients is determined based on the CODE defect and the anatomical location of the affected bowel. CODE, congenital diarrheas and enteropathies; FA, fatty acid; LCT, long-chain triglyceride; MCT, medium-chain triglyceride.

enteroendocrine cells, and immune-mediated defects [1] (Figure 1). CODE poses a clinical challenge for multiple levels of care. They are hard to diagnose, complex to treat, require significant health systems and caregiver resources, and are associated with high morbidity and mortality.

Most CODE disorders do not have a definitive treatment that can correct the cellular defect. To overcome the prolonged and persistent diarrhea and the resultant failure to thrive, supportive nutritional therapy is required, whether through specific formula, solid food diet, or parenteral nutrition (PN) support. In a few of the disorders, specific diet therapy can lead to symptom resolution and the tapering of PN. Despite the importance of diet and nutrition support for CODE, the published data on this aspect are very limited. The aim of this review was to create a clinical guide to the nutritional support for CODE with a focus on the common diseases in the group or those that improve with diet therapy. Where available, medical evidence is provided, and if it is limited or nonexisting, the authors' anecdotal experience is shared.

Clinical Approach and Principles of Diet Management

Nutrition support is the cornerstone of medical management of CODE. Proper nutrition management aims to achieve normal growth and development, normal electrolyte and micronutrient levels, and prevention of dehydration- and nutrition-related pathologies such as renal insufficiency, metabolic bone disease, or vitamin deficiencies. However, beyond these roles of nutrition support, diet management can also contribute to the diagnostic process in certain CODE disorders and lead to improvement or resolution of diarrhea in others.

Principles of diet management

Nutrition support is almost universally required in the first few months of life for children afflicted by CODE. In the early stages, before a definite diagnosis is made, the main goal is to establish the basis of the diarrheal symptoms while avoiding dehydration and electrolyte imbalance and maintaining growth. Therefore, intravenous (IV) fluids are required initially, which may be followed by PN support. High-volume diarrheas require large-volume PN support and frequently, higher than normal amounts of sodium, bicarbonate, magnesium, and occasionally potassium and chloride. Over time, careful monitoring of minerals and vitamins is required to avoid deficiencies. Progression toward enteral autonomy or a reduction in PN dependency through an increase in formula and solid food intake can be achieved in selected cases in which CODE natural history is associated with improved absorption and food tolerance (Table 1). This requires ongoing follow-up and monitoring with repeated attempts to assess bowel function. Tolerance and absorption can be assessed clinically through measurement of stool output, vomiting, abdominal pain, and distention and in a more objective way through stool absorption studies. These include reducing substances for carbohydrates, elastase and 72-h fat collection for lipids, stool α-1 antitrypsin for protein, and stool electrolytes for electrolyte losses.

Diet as a diagnostic tool

Careful dietary challenges during the early stage of the initial hospitalization are important and can provide useful clues for the likely CODE disorder when testing for food tolerance. Initial assessments focus on classifying either an electrolyte- or dietary-induced form of diarrhea. Approaches for distinguishing between these broad forms

Table 1
CODE classification according to diet approach[1]

Disease	Resolution of diarrhea	Improvement in diarrhea / enteral diet tolerance	No change in diarrhea / enteral diet tolerance
CHO malabsorption			
• Lactose intolerance	Yes		
• CSID	Yes		
• GGM	Yes		
Fat malabsorption			
• Abetalipoproteinemia		Yes, slow response	
• Hypobetalipoproteinemia		Yes, slow response	
• Chylomicron retention disease		Yes, slow response	
• DGAT1		Yes, slow response	
Primary intestinal lymphangiectasia		Yes (not in all cases)	
Acrodermatitis enteropathica	Yes		
Electrolyte transport diarrhea			
• CCD		Yes, very slow response (most patients)	In some patients
• NHE3		Yes, very slow response (some of patients)	In some patients
• SPINT2		Rarely	In most patients
• *GUCY2C*		Yes, in most patients	
Primary bile acid diarrhea		Yes, in response to bile acid sequestrants (most patients)	
General malabsorption			
• NEUROG3		Yes, very slow response	
• PCSK1		Yes, very slow response	
• ARX		Yes, very slow response	
• RFX6		Yes, very slow response	
Epithelial trafficking and polarity defects			Dietary intake can lead to
• MVID	No	No	increased diarrheal intolerance
• Tufting enteropathy			
- EPCAM			
- SPINT2		Yes, very slow response (minority of patients)	In most patients
• THE		Yes, very slow response (minority of patients)	In most patients
- SKIV2			
- TTC37		Yes, very slow response (half of patients)	In about half of patients
		Yes, very slow response (minority of patients)	In most patients
Immune dysregulation associated diarrhea			Yes (will improve after disease directed therapy)

Abbreviations: CCD, congenital chloride diarrhea; CHO, carbohydrate; CODE, congenital diarrheas and enteropathies; CSID, congenital sucrase-isomaltase deficiency; DGAT1, diacylglycerol O-acyltransferase 1; GGM, glucose-galactose malabsorption; MVID, microvillous inclusion disease; THE, trichohepatoenteric syndrome.

[1] Partial improvements in diarrhea and tolerance of enteral nutrition are not necessarily a direct effect of diet management but also relate to the changes in the natural course of the disease. However, these natural course changes allow an increase in enteral diet and weaning of PN.

include careful measurements of stool output (grams per day) and serum/stool electrolytes, with short-term (<2 d) fasting followed by boluses with full caloric (120 kcal/kg/d) challenges with the formula or breast milk that the child consumed prior to admission. Those patients with clear evidence of a diet-induced form of diarrhea can then be tested to discern whether the malabsorption is nutrient-specific or generalized. The use of a carbohydrate-free formula supplemented with various monosaccharides, disaccharides, or maltodextrins is essential to the diagnostic work-up of an abnormality of carbohydrate assimilation (Supplemental Table 1). When such a formula without carbohydrates is used and diarrhea persists, it suggests a generalized malabsorptive disorder in which overall nutrient absorptive capacity is reduced. In this setting, the underlying disorder may result from either congenital short-gut, abnormality of enteroendocrine cell function, abnormalities of the crypt-villus axis (including inflammation), or abnormalities of the brush border (i.e., trafficking and polarity). Other associated abnormalities (e.g., rash, protein-losing enteropathy, etc.) provide useful clues.

In many cases, intestinal biopsies with appropriate staining and next-generation sequencing provide the definitive basis of the clinical phenotype. Conclusive diagnosis allows clinicians and dieticians to provide more directive dietary therapy to enhance long-term growth and development.

Diet therapy

There are 3 conceptual frameworks to dietary manipulation of CODE disorders: elimination, supplementation, and restriction (Figure 2). Dietary elimination refers to removing a specific nutrient from the diet, which in turn leads to the cessation of injury and the improvement in the severity of diarrhea. In diet supplementation, pharmacologic therapy with electrolytes, minerals, or vitamins can either lead to cession or improvement of diarrhea or provide needed supplements to prevent further nutritional deficiencies. In the restrictive approach, diet per se does not improve diarrhea but provides an important tool for promoting enteral autonomy and minimizing PN complications. An overlap between diet approaches may be present in a specific disease, but the dietary effect on the degree of the diarrhea is usually restricted to one approach. Table 1 summarizes CODE according to the effect of diet on diarrhea.

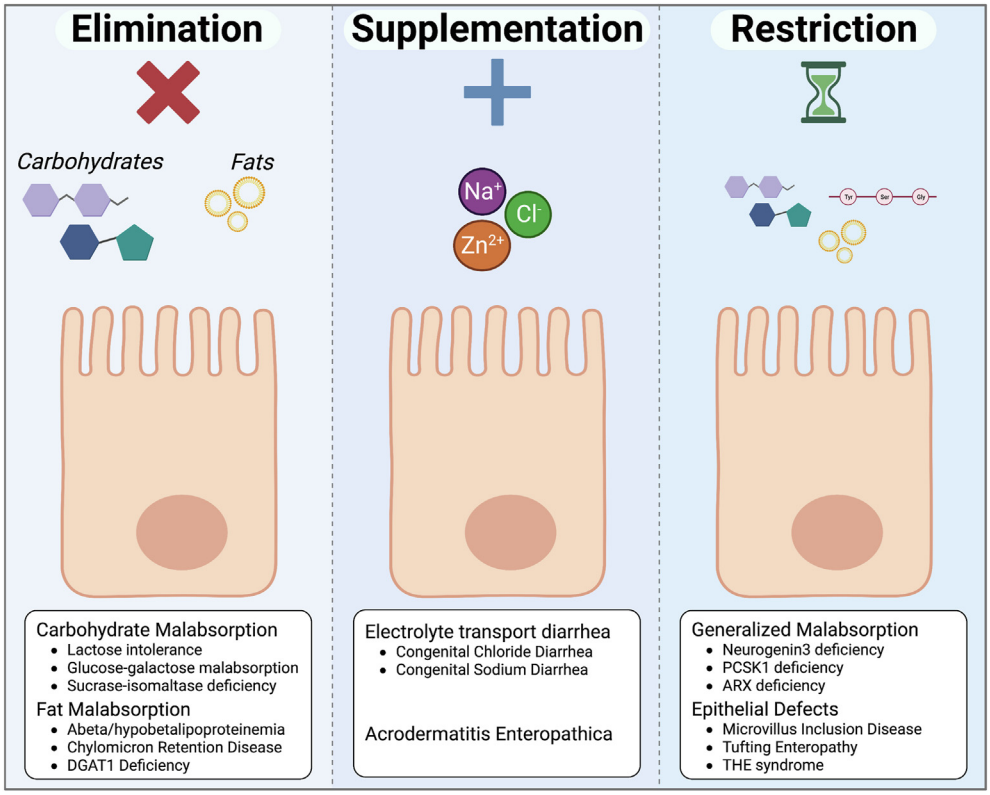

FIGURE 2. Mechanism of dietary therapy in CODE disorders. Three mechanisms of dietary therapy characterize the management approach in CODE—Nutrient elimination: removal of specific nutrients leads to resolution or improvement in diarrhea; Nutrient supplementation: addition of specific electrolytes or micronutrients leads to resolution of diarrhea or improved nutritional balance and food tolerance; Nutrient restriction: general restriction of food type or its amount may improve the degree of diarrhea and allow promotion of food intake and PN weaning. CODE, congenital diarrheas and enteropathies; DGAT1, diacylglycerol *O*-acyltransferase 1; PN, parenteral nutrition; THE, trichohepatoenteric syndrome.

Diet-Induced Diarrheas

Nutrient-specific induced diarrhea

■

Carbohydrate malabsorption

Selective carbohydrate-induced diarrheas result from genetic defects of enzymes involved in digestion of complex carbohydrates and disaccharides or from defects in monosaccharide absorption. Diet-induced diarrhea, gas, and abdominal distention are common clinical features in affected patients. The degree of the clinical symptoms is proportional to the degree to which the offending carbohydrate's dietary load exceeds the intestine's nutrient-specific absorptive capacity. Elimination and stepwise introduction of specific carbohydrates with resolution and then a resumption of diarrhea when challenged is an efficient clinical tool to diagnose this group of disorders. Genetic testing provides a definitive diagnosis. Dietary elimination (or reduction) of the malabsorbed carbohydrate is the definite treatment approach (Table 2).

Lactase deficiency

Lactose intolerance is a chronic or transient condition resulting from significantly reduced lactase-phlorizin hydrolase (LCT) activity. The *LCT* gene encodes the β-galactosidase enzyme, located on the apical membrane of enterocytes. Reduced LCT activity impairs lactase breakdown of lactose into glucose and galactose, which results in diarrhea if the consumed lactose load exceeds lactase capacity [2–4].

Chronic lactose intolerance. The most common cause of chronic lactose intolerance is lactase nonpersistence (hypolactasia), an inherited phenotype (MIM #223100) common in children of African, Hispanic, and Asian descent that typically develops in early to mid-childhood. In contrast, the rarest form of chronic lactose intolerance is primary lactase deficiency (MIM# 223000), which presents clinically during the first several days of life and persists indefinitely. Biallelic loss-of-function mutations in *LCT* result in primary lactase deficiency, whereas hypolactasia results from the more moderate, age-dependent monoallelic reduction of LCT expression [2–4].

Dietary management. Management is tailored to the severity of symptoms and consists of dietary lactose restriction, including breast milk, in congenital primary lactase deficiency [2,5–10]. Supplementing patients with lactase enzyme replacement preparations when consuming lactose-containing foods may also be helpful in symptom management in hypolactasia [11,12]. The role of enzyme replacement therapy in congenital primary lactase deficiency is unknown due to lack of reported data. Removing most lactose-containing products from the diet should resolve the diarrhea and associated symptoms. Children who avoid dairy products should be monitored and supplemented to ensure adequate calcium and vitamin D intake [2,5–10].

Products containing lactose include cow milk and related by-products, including milk solids, milk powder, cheese and cheese flavoring, curd, whey, cream, butter, and margarine containing milk solids. Products containing lactic acid, lactalbumin, and lactate do not contain lactose and can be consumed. Some patients with lactase

TABLE 2
Diet interventions for nutritional support and treatment of diarrhea

CODE	Diet	PN	Nutrients at risk of deficiency
Lactase deficiency	• Lactose-free • Low lactose	—	• Protein • Calcium • Phosphorus • Vitamin D
CSID	• Low sucrose • Low isomaltose (starch) • Low maltose (starch)	• In some cases, prediagnosis and postdiagnosis until enteral diet established	Sucrose is naturally found in fruits and vegetables rich in • Vitamin A • Vitamin C • Vitamin E • Folic acid • Magnesium • Phosphorus • Zinc Sucrose is an added food ingredient; sourced mainly from beet and sugar canes. Starches are rich in • B vitamins • Fiber • Iron
GGM	• Low glucose/galactose (starch, isomaltose, maltose, lactose)	• Prediagnosis and postdiagnosis until enteral diet established	Starches are rich in • B vitamins • Fiber • Iron Mother's own milk and dairy are naturally rich in lactose
ABL FHBL CMRD DGAT1	• Minimal-fat diet/low fat diet • Possible enteral supplementation of high-EFA oils (flaxseed, sunflower, corn, walnut, and canola)	• Prediagnosis and postdiagnosis until enteral diet established • In some cases, IM or IV administration of nutrient(s) is recommended if high-dose enteral supplementation fails to correct deficiencies	• Essential fatty acids • Vitamin A • Vitamin D • Vitamin E • Vitamin K • Iron • Calcium • Magnesium • Phosphorus • Selenium • Zinc
PIL	• Minimal-fat diet • Added MCTs • Protein rich diet	• Prediagnosis and in some cases long-term home PN is necessary • In some cases IM or IV administration of nutrient(s) is recommended if high-dose enteral supplementation fails to correct deficiencies	• Essential fatty acids • Vitamin A • Vitamin D • Vitamin E • Vitamin K • Iron • Calcium • Magnesium • Phosphorus • Selenium • Zinc
AE	• Not restricted • High-dose enteral zinc supplementation	• In rare cases, prediagnosis	• Calcium • Copper • Iron
CCD	• Enteral NaCl • Enteral KCl	• Prediagnosis and in some cases, IV Na, K, Cl or PN is maintained or weaned to DAT with Na, K, Cl supplementation	• All
CSD	• Restricted TFI • Small volume enteral oral electrolyte/rehydration solutions • Low concentrated carbohydrate (sugar) diet	• All cases	• All
BAD	• Restricted TFI • Soluble fiber rich diet • Low concentrated carbohydrate (sugar) diet	• Prediagnosis and in some cases, IV Na, K, Cl or PN is maintained or weaned to DAT	• All
NEUROG3	• Low osmolality fluids • Diet to manage blood glucose concentrations • Soluble fiber rich diet	• All cases • PN is maintained or weaned to DAT	• All

(*continued on next page*)

TABLE 2 (*continued*)

CODE	Diet	PN	Nutrients at risk of deficiency
PCSK1	• Low osmolality fluids • Diet to manage blood glucose concentrations • Soluble fiber rich diet • Diet to manage weight velocity and BMI	• All cases • PN is maintained or weaned to DAT	• All
ARX	• Low osmolality fluids • Soluble fiber rich diet	• All cases • PN is maintained or weaned to DAT	• All
MVID	• Minimal/no oral intake • High sodium intake • Additional acetate supplementation may be needed (e.g., baking soda)	• All cases • PN is maintained	• All
Tufting enteropathy	• Restricted oral fluid initially • LCT-rich formula • Low concentrated carbohydrate (sugar) diet • Soluble fiber rich diet	• All cases • PN is maintained or weaned to DAT	• All
THE	• LCT-rich formula • Lactose-free formula • Low concentrated carbohydrate (sugar) diet • High starch intake • Soluble fiber rich diet	• All cases • PN is maintained or weaned to DAT	• All
Food induced allergy	• Elimination of allergenic food (e.g. CMPA)	• Prediagnosis in some cases and postdiagnosis until enteral diet established on medical therapy	• All
Primary immune deficiency AIE VEO-IBD	• Not restricted	—	When established on medical therapy, continue to monitor • B vitamins • Vitamin D • Calcium • Iron • Phosphorus • Zinc • Copper

Abbreviations: ABL, abetalipoproteinemia; AE, acrodermatitis enteropathica; AIE, autoimmune enteropathy; BAD, bile acid diarrhea; BMI, body mass index; CCD, congenital chloride diarrhea; CMPA, cow milk protein allergy; CMRD, chylomicron retention disease; CODE, congenital diarrheas and enteropathies; CSD, congenital sodium diarrhea; CSID, congenital sucrase-isomaltase deficiency; DAT, diet as tolerated; DGAT1, diacylglycerol *O*-acyltransferase 1; EFA, essential fatty acid; FHBL, familial hypobetalipoproteinemia; GGM, glucose-galactose malabsorption; IM, intramuscular; IV, intravenous; LCT, long-chain triglyceride; MCT, medium-chain triglyceride; MVID, microvillous inclusion disease; PIL, primary intestinal lymphangiectasia; PN, parenteral nutrition; TFI, total daily fluid intake; THE, trichohepatoenteric syndrome; VEO-IBD, very early onset inflammatory bowel disease.

deficiency may tolerate fermented products, such as yogurt and kefir because added bacteria assist in the digestion of lactose. Butter and hard cheeses contain trace lactose and are generally well tolerated (Supplemental Tables 2 and 3) [2,5–7,10].

Sucrase-isomaltase deficiency

Congenital sucrase-isomaltase deficiency (CSID; MIM #222900) is a biallelically inherited loss-of-function mutation in the sucrase-isomaltase (*SI*) gene, which encodes a localized enzyme in the enterocyte apical membrane. SI hydrolyzes sucrose, maltose, α1-4 glucose oligomers, branched 1-6 linked dextrins, and starch into glucose. In CSID, sucrase and isomaltase activity is significantly reduced or undetectable [13–16].

Consumption of sucrose or starch in CSID is associated with the typical symptoms observed in carbohydrate malabsorption [15,17]. The severity of symptoms is influenced by enzymatic capacity and the dietary load of sucrose and starch [15,17]. Five clinical phenotypes have been described in CSID—A, B, C, D, and F [18]—with differences based on the degree of enzymatic activity, tolerance of starch and maltodextrin, and resolution of symptoms.

Dietary management. The management of CSID involves the dietary restriction of sucrose and starch. Initial phases involve limiting sucrose and starch, with stepwise liberalization of type and amount of food based on tolerance and clinical course [16,19]. In some infants with CSID, a formula containing starch (e.g., corn maltodextrin or corn syrup solids) or lactose may not be tolerated, and a carbohydrate-free formula is advised [16,19]. Sucrose can be found in fruits, vegetables, legumes, and in many food products, listed as sucrose or sugar in an ingredient list. It is recommended to choose foods low in sucrose initially, then gradually increase sucrose consumption by increasing the variety of food choices and being mindful of portion size.

Individuals with CSID have varying enzymatic activity affecting starch tolerance [19–21]. The SI enzyme hydrolyzes ~70% of starch in the small intestine, whereas the residual is hydrolyzed by the maltase-glucoamylase enzyme. Sources of starch in the diet include grains such as wheat, corn, rice, and starch-rich foods, such as banana, plantain, carrot, potato, tubers, and pulses (chickpeas, green peas, beans, and lentils). Higher fiber varieties of starches are often better tolerated among individuals with CSID. Starch-restricted diets may be

limited in energy and micronutrients, affecting growth, development, and quality of life. Thus, they must be personalized to the patient with the support of a registered dietitian [19,22] (Supplemental Tables 4–7).

In addition to sucrose and starch eliminations, sacrosidase (Sucraid), a yeast-derived enzyme replacement therapy, is associated with improved symptoms [23–25]. Over-the-counter *Saccharomyces cerevisiae* or *Saccharomyces boulardii* may be an alternative for patients with limited access to Sucraid [13,23,25]. Sucraid can be given to all patients with a confirmed diagnosis and taken with each meal or snack.

Glucose-galactose malabsorption

Glucose-galactose malabsorption (GGM; MIM #606824) is an autosomal-recessive disorder that affects the absorption of the monosaccharides glucose and galactose across the apical border of the intestinal epithelium. Loss-of-function mutations of the sodium-glucose/galactose cotransporter (*SGLT1*/*SLC5A1*) result in GGM [26–28]. Symptoms including diarrhea and dehydration are seen in the first days of life following milk consumption. The lactose in milk is hydrolyzed to glucose and galactose, which are exclusively absorbed across the enterocyte's apical membrane by SLC5A1. If the severity of diarrhea is not detected promptly, prolonged milk consumption can result in early mortality. All subjects with GGM can thrive on a completely fructose-based diet. The monosaccharide fructose is selectively transported across the apical membrane via the facilitated transporter (GLUT5/SLC2A5), and its function is retained in GGM.

Dietary management. Patients with GGM require a lifelong glucose/galactose-depleted diet [29]. This includes all sources of glucose and galactose, complex carbohydrates such as starch (glucose polymers), and disaccharides such as maltose (glucose/glucose), sucrose (glucose/fructose), and lactose (glucose/galactose). The diet is, therefore, high in fat, protein, and fructose [29].

Patients should continue a fructose-based formula through the first year of life. Weaning foods introduced by 4 to 6 mo should be depleted of galactose-glucose, such as vegetables and some fruits. Symptoms appear to marginally improve with age. Close nutrition follow-up should be maintained, and parents should be educated that management of GGM is a lifelong restriction to all sources of glucose and galactose (Supplemental Tables 8–10).

Fat malabsorption

CODE disorders leading to fat malabsorption are characterized by defects in lipid absorption, assembly, or packaging. Clinical symptoms of this group of diseases include steatorrhea, vomiting, failure to thrive, and features of fat-soluble vitamin (A, D, K, and especially E) deficiencies. Laboratory findings show low concentrations of fat-soluble vitamins (FSVs) and an abnormal lipid profile. Diet therapy with a minimal-fat diet can significantly improve diarrhea within days to weeks (Table 2). Some patients can increase their dietary fat over time without recurrence of diarrhea. High doses of FSVs with careful clinical follow-up are required to avoid the evolution of irreversible pathologies. This section focuses on defects in the assembly and packaging of lipids, while diet therapy for exocrine pancreatic insufficiency with lipid malabsorption is beyond the scope of this review.

Abetalipoproteinemia, familial hypobetalipoproteinemia, and chylomicron retention disease are characterized by reduced plasma concentrations of total cholesterol (TC), LDL, and apolipoprotein B (ApoB) [30]. ApoB is the primary apolipoprotein of chylomicrons, VLDL, and LDL particles and is responsible for carrying lipids to all cells and tissues across the body. The clinical severity correlates with the extent of the abnormal production of ApoB (ApoB-100 and/or ApoB-48) [31].

Abetalipoproteinemia

Abetalipoproteinemia (ABL; MIM# 200100) is an autosomal-recessive disorder resulting from abnormal lipoprotein metabolism due to mutations in the *MTTP* gene. MTTP encodes microsomal triglyceride transfer protein, the ApoB chaperone protein. MTTP is required to transfer triglycerides (TGs) and cholesterol in the endoplasmic reticulum to the Golgi apparatus and to package chylomicrons and VLDL in the intestine and liver, respectively [32]. Consequently, the defect leads to chronic fat malabsorption with almost absent plasma TG, significantly decreased TC, nearly absent LDL, VLDL, and ApoB (both ApoB-100 and ApoB-48), and FSV deficiency.

Gastrointestinal (GI) manifestations present in early infancy. The diarrhea may improve later in life through adherence to a fat-restricted diet [30]. Other later symptoms may evolve due to a deficiency of FSVs in unsupplemented individuals, particularly vitamin E [33]. The accumulation of large lipid droplets has been described in hepatocytes, leading to fatty liver disease, and in enterocytes, leading to the characteristic pale mucosa.

Dietary management. A minimal-fat diet is recommended for patients with ABL with $<10\%$ of the total calories from fat [34]. Consumption of long-chain fatty acids is particularly discouraged [35]. Fat restriction increases the risk of growth failure, essential fatty acid (EFA) deficiency, and micronutrient deficiency, including FSVs. In infants, diet enrichment with medium-chain triglycerides (MCTs) can help in nutritional recovery [36,37]. To ensure adequate intake of EFAs, patients may be advised to consume 2 teaspoons olive or soybean oil/d or similar oils rich in PUFAs (Supplemental Tables 11–18, Supplemental Note 1).

FSV replacement is a cornerstone in the dietary management of ABL. The transport of FSVs depends heavily on the integrity of the ApoB lipid transport pathway, almost exclusively for vitamin E and partially for the other FSVs. Thus, high-dose vitamin E supplementation is necessary, but this only results in a partial increase in serum vitamin concentrations to no $>30\%$ of the lower limits of normal [38,39]. Early initiation of vitamin E therapy at <16 mo of age may prevent neurologic and retinal consequences. However, improvement in neurologic dysfunction is seen even in those diagnosed as young adults [37,39,40]. Orally administered, high-dose vitamins are thought to bypass the intestinal chylomicron assembly pathway via the MCT pathway through the portal circulation. High doses of oral vitamin E are typically administered as α-tocopherol supplementation at 50–200 mg/kg/d [41]. Plasma vitamin E concentrations might not accurately reflect the whole-body content of vitamin E. Thus, vitamin replacement and dosing adequacy is difficult to assess from serum concentrations. However, serum vitamin E concentrations, although diminished, can still be used to monitor compliance. Recently, some investigators have suggested that supplementation of vitamin E in the form of tocofersolan (synonym: α-tocopherol glycol succinate; oral load of 100 IU α-tocopherol acetate/kg and then 50 IU/kg daily), a commercially available water-soluble derivative of RRR-α-tocopherol [42], may be a promising enteral supplement in fat malabsorptive conditions [43]. However, if oral supplementation fails, intramuscular (IM) injection of vitamin E once to twice weekly can be used as an alternative to correct serum concentrations and replenish stores [44].

Additionally, general recommendations are for oral vitamin A at 100–400 IU/kg/d with the dose adjusted according to plasma

concentrations. High doses of vitamin A therapy can achieve normal serum concentrations, suggesting that the transport of vitamin A by retinol-binding proteins in serum is intact in ABL.

Oral vitamin D at 800 to 1200 IU/d is recommended, although vitamin D deficiency is not always found in ABL. Although there is scant evidence supporting the use of vitamin D analogs to treat vitamin D deficiency in ABL or other fat malabsorption CODE, there may be a persistent deficiency that suggests the need for other vitamin D-based interventions. Other oral preparations include calcifediol (25-hydroxyvitamin D_3) and calcitriol (1,25-hydroxyvitamin D_3; active form of vitamin D; Rocaltrol). Recent reviews of calcifediol suggest it is more effective at treating and maintaining vitamin D status in malabsorption than cholecalciferol (vitamin D_3) and ergocalciferol (vitamin D_2), as it is more polar and thought to be more readily absorbed [45]. Calcitriol can be used to treat metabolic bone disease and has been well studied in children with chronic kidney disease and hyperparathyroidism [46]. IM ergocalciferol may be considered when oral preparations have failed at treating vitamin D deficiency. IM ergocalciferol has been used with success at treating rickets in biliary atresia when 25-hydroxyvitamin D_3 and 1,25-dihydroxyvitamin D_3 have failed [47]. Future studies of fat CODE may consider the applicability and efficacy of doxercalciferol (1-hydroxyvitamin D_2; Hectorol), an injection currently used to treat secondary hyperparathyroidism and metabolic bone disease.

Although bleeding is not often reported, abnormal coagulation parameters are frequently reported. Thus, oral vitamin K supplementation at 15 mg/wk or 5 mg per os daily is recommended, with dosing adjusted according to international normalized ratio levels. Although plasma PIVKA-II (protein induced in vitamin K absence) is a more sensitive marker of vitamin K deficiency, it is not routinely available [48]. Supplementation of other nutrients, such as iron, can also be considered.

Familial hypobetalipoproteinemia

Familial hypobetalipoproteinemia (FHBL; MIM #615558) is an autosomal-recessive disorder usually due to mutations in the *APOB* gene. It is characterized by very low plasma LDL and ApoB concentrations. FHBL is due to truncation mutations leading to loss-of-function mutations in *APOB* or infrequently, in mutations in the *PCSK9* gene. The *PCSK9* gene encodes a protein, mainly expressed in the liver, that regulates the LDL-receptor degradation and the number of receptors available on the cell surface [49]. The clinical phenotype of FHBL is variable, depending on the zygosity of the affected individual, with homozygous patients quite similar to those with ABL, whereas heterozygotes have a mild clinical phenotype [50]. The clinical phenotype severity in homozygotes varies and depends on the mutation and the degree of the truncated ApoB function [51]. Those with PCSK9-related FHBL do not appear to have fatty liver disease [52].

Dietary management. The dietary management will depend on the severity of clinical symptoms, but severe cases would be managed similar to those with ABL as outlined previously.

Chylomicron retention disease

Chylomicron retention disease (CMRD; MIM #246700) is an autosomal-recessive disorder resulting from mutations in the *SARA2* gene, which controls the production of the Sar1b protein, involved in the control of intracellular trafficking of chylomicrons from the endoplasmic reticulum to the Golgi apparatus. This results in the accumulation of prechylomicron transport vesicles in the cytoplasm and formation of lipid droplets within the enterocytes. The gene defect leads to chronic fat malabsorption with normal plasma TG (unlike ABL), and low TC, LDL, and ApoB (ApoB-48 completely absent) to ~25% to 40% of normal concentrations [53].

Digestive symptoms improve significantly within weeks of initiating a minimal-fat diet. The adaptation and improvement of diet fat tolerance over time is variable [53,54]. Hepatomegaly and macrovesicular steatosis are present in <20% of children, starting in infancy or late childhood, but are not associated with cirrhosis [53]. Neurologic, muscular, and retinopathy complications related to FSV deficiencies in CMRD are typically less pronounced than in ABL or homozygous FHBL but may occur during infancy.

Dietary management. A minimal-fat diet enriched with EFAs is required. In infants, milk formulas enriched with MCTs have improved diarrhea within days, although tolerance may be variable. In older children, a diet limited in long-chain fatty acids is usually sufficient to decrease symptoms (Supplemental Tables 11–18, Supplemental Note 1**)**.

As described for ABL, FSV supplementation is a key component of therapy. High doses of vitamin E, albeit lower than that needed in ABL, are reported to improve neurologic and other complications related to vitamin E deficiency [42]. If the disease is diagnosed later in childhood or if clinical complications related to vitamin deficiency are apparent, then monthly IV infusions of vitamin E and A are recommended.

DGAT1 deficiency

Diacylglycerol *O*-acyltransferase 1 (DGAT1) is an enzyme belonging to a family of membrane-bound *O*-acyltransferases involved in lipid metabolism and signaling. It catalyzes the final step in synthesizing triacylglycerol (TAG), specifically adding a third fatty acid chain to diacylglycerol. In enterocytes, TAG or TGs are then incorporated into chylomicrons, which enter the thoracic duct via the lymphatic system and eventually enter the blood for transport to cells. As such, TAG and other nutrients absorbed and transported via chylomicrons, including FSVs, as well as other micronutrients such as calcium and magnesium, are dependent on the enzymatic activity of DGAT1.

In humans, DGAT1 is mostly expressed in the small intestine. Loss of DGAT1 expression is associated with reduced adiposity, increased insulin sensitivity, and reduced body weight [55]. Variants within *DGAT1* can result in loss of enzymatic function and cause a type of CODE characterized by a protein-losing enteropathy, including watery diarrhea with or without steatorrhea, vomiting, normal/elevated serum TGs, elevated transaminases, hypoalbuminemia, low serum IgG concentrations, elevated fecal α-1 antitrypsin, and failure to thrive [56,57].

Dietary management. Individuals diagnosed with DGAT1 deficiency show significant clinical improvement on a lifelong minimal-fat diet, whereas patients with variants in *DGAT1* can tolerate varying amounts of dietary fats. Minimal-fat or occasionally fat-free diet is advised for individuals with DGAT1 deficiency (Supplemental Tables 11–18, Supplemental Note 1). Both diets are limited in energy and micronutrients and should be complemented with formula and/or supplements. Children on fat-restricted diets are at higher risk of suboptimal growth and micronutrient deficiencies requiring close monitoring of nutritional status [58]. In addition, a minimal-fat diet with restricted amounts of DHA and arachidonic acid poses a potential concern for delayed cognitive development, especially among infants [59]. Monitoring of an EFA panel can be helpful in guiding oral or IV supplementation needs and avoiding EFA deficiency.

Depending on DGAT1 phenotype and degree of enteral fat restriction, a subset of children may require PN to provide adequate

energy and micronutrients for proper growth support, especially during infancy.

Supplementation of EFAs is preferred to be enteral, with close monitoring of intolerance with possible looser stools and adjusting dose based on tolerance and laboratory monitoring. Common oils with the highest EFA content are: flaxseed oil, sunflower oil, corn oil, walnut oil, and canola oil (Supplemental Table 17) [60]. It is generally recommended to start by providing 4% of total calories from EFAs. If essential fatty acids deficiency (EFAD) does not resolve, an increase in supplementation by 2%–4% total calories from EFA per month is suggested until it resolves. If oral fats are not readily accepted, a trial of topical oils (using the same high-EFA oils listed above) can be considered, although efficacy is questionable, and application can be cumbersome due to the existence of varying guidelines [60]. Persistent EFAD on enteral and/or topical supplementation can be treated with IV lipid infusions on an intermittent basis.

Protein malabsorption

Intestinal lymphangiectasia

Intestinal lymphangiectasia is a rare form of protein-losing enteropathy characterized by dilatation of intestinal lacteals, resulting in lymph leakage into the small bowel lumen [61]. Significant amounts of protein, fat, and immune cells are lost in the lymph, resulting in severe hypoproteinemia, hypoalbuminemia, lymphopenia, hypogammaglobulinemia, loss of other essential proteins, edema, and diarrhea [62].

Two types of intestinal lymphangiectasia have been described: primary and secondary. Primary intestinal lymphangiectasia (PIL) most commonly occurs in infants and children and is generally diagnosed before the third year of life [63,64]. PIL is caused by congenital abnormalities of the chest and/or intestinal lymphatics. It involves hypoplasia, agenesis, or stenosis in the thoracic duct and mesenteric lymph nodes, leading to increased pressure, expansion, and rupture of intestinal lymphatic vessels [62]. Secondary intestinal lymphangiectasia is caused by various diseases, such as lymphoma, scleroderma, pericarditis, and sarcoidosis, that induce lymphatic obstruction [62,65]. Treatment of the primary disease usually corrects the secondary intestinal lymphangiectasia. Therefore, this section will focus on PIL.

PIL is characterized by bilateral lower limb edema, ascites, pleural and pericardial effusion, lymphedema, abdominal pain, fatigue, anemia, FSV deficiency, diarrhea, hypocalcemia, and metabolic bone disease [63,66]. The primary nutritional deficiencies in this group include FSV deficiency, particularly vitamin D, poor calcium absorption, negative calcium balance, and zinc deficiency.

Nutritional management. The goal of nutrition management in PIL is to reduce the formation and minimize the loss of lymph and its constituents into the intestinal lumen (Table 2). This can be achieved through a diet high in protein and low in long-chain fats with adequate amounts of EFAs to prevent EFAD. A total of ~3% of total energy should come from linoleic acid and ~0.5% from α-linolenic acid to prevent EFAD [67,68]. The principles of a minimal-fat diet are similar to those in fat malabsorption (Supplemental Tables 11–18, Supplemental Note 1). The amount of fat required should be calculated based on total energy needs (calculated using the Schofield equation or through indirect calorimetry) to prevent EFAD. MCT oil should comprise the highest proportion of fats in the diet. FSV supplements should be in water-soluble form. In addition, calcium, zinc, and iron supplements are needed while monitoring patients' blood concentrations. These diet modifications are lifelong, as liberalization of diet or noncompliance leads to relapse of clinical symptoms [69,70]. In extensive disease, some patients do not respond to a high protein, minimal-fat diet therapy, and PN is required. PN is often used for in-hospital management during the initial diagnosis, after which some patients are discharged and maintained on home PN for 3–5 nights per week as a complementary therapy to the minimal-fat diet [64,71].

Other micronutrient malabsorption

Acrodermatitis enteropathica

Acrodermatitis enteropathica (AE; MIM #201100) affects zinc uptake and can be inherited (congenital) or acquired [72]. AE is associated with zinc deficiency. Clinical symptoms vary, reflect the consequences of zinc deficiency, and range in severity from mild to severe [72,73]. Common signs and symptoms of AE include diarrhea, dermatitis, poor growth, anorexia, dysgeusia, mood changes, neurologic and cerebral disturbances, alopecia, nail deformity, recurrent infections, and rarely, ophthalmic and hepatic abnormalities [72,74]. If left untreated, AE can be fatal; however, symptoms can reverse with enteral zinc supplementation [72,73].

The congenital form of AE results from *SLC39A4*/*ZIP4* mutations and impairs the active transport of zinc across the duodenal mucosa [72,73,75]. A mutation in *SLC30A2*, a gene encoding the zinc transporter ZnT2, can lead to a decreased zinc secretion in breast milk and transient AE, such as in breastfed neonates [76]. Acquired forms of AE are variable and include zinc-deficient breast milk [77] or concurrent conditions such as malabsorptive disorders (e.g., cystic fibrosis, celiac disease, cholestatic liver disease) or in cases in which the duodenal surface area is bypassed (e.g. surgery, postpyloric/jejunal nutrition support) [73,74].

Nutritional management. Treatment of AE is 1 to 3 mg zinc/kg/d [73], divided twice or thrice daily. Zinc supplements exist in different forms, including zinc sulfate, gluconate, or acetate. Each form contains a different percentage of elemental zinc that needs to be considered when calculating treatment doses. To date, there is very little evidence assessing the bioavailability, absorption, and tolerability of the different forms of zinc in AE or other conditions. In addition, there are known zinc-drug and zinc-nutrient interactions to consider as part of monitoring response to zinc therapy for AE [74,78]. Antibiotics (e.g. quinolone and tetracycline), penicillamine, and diuretics can interact with zinc [74]. Zinc can also interfere with the absorption of iron, copper, and calcium [74]. As such, zinc supplements should be taken apart from certain medications and iron, copper, or calcium supplements. Zinc toxicity, which has only been documented to occur from supplementation, is also a risk, thus zinc concentrations need to be monitored in patients treated for AE [74,78]. Beyond supplementation, there is no special diet to follow for congenital or inherited AE.

Electrolyte transport diarrhea

Forms of CODE associated with impaired electrolyte transport include defects to chloride or sodium transporters with high fecal losses of either chloride or sodium in the stool. Patients present with watery diarrhea, dehydration, and severe changes to electrolytes and acid-base balance, if left untreated. PN, IV fluids, and electrolyte supplementation are required in the first months of life. Over time, oral supplementation of electrolytes, fluids, and specialized formulas can support increasing enteral tolerance up to enteral autonomy (Table 2).

Congenital chloride diarrhea

Congenital chloride diarrhea (CCD; MIM #214700) is a disorder of the intestinal Cl^-/HCO_3^- exchange transporter, resulting in high fecal Cl^- loses, hypochloremia, hypokalemia, and metabolic alkalosis [79,80]. It is an autosomal-recessive disorder caused by mutations in the *SLC26A3* gene [81–83].

Most children are born prematurely with hydramnios and absence of meconium, suggesting an intrauterine onset of diarrhea [79,84,85]. Similar to congenital sodium diarrheas, the condition can go undiagnosed in the early neonatal period due to high-volume stool output resembling urine. During the first days of life, patients usually have a large, distended abdomen, and the neonatal weight loss is unusually high [79]. Dehydration is common and can lead to death, particularly during the early neonatal period [86].

Clinical symptoms include failure to thrive and high output of very watery stool containing high chloride, >90 mmol/L. However, stool chloride may be low in patients with chronically depleted serum chloride. Urine chloride is dependent on serum chloride, and in cases in which the serum chloride is <95 mmol/L, urine testing is associated with an absence of chloriduria [79].

Nutrition management. During the early neonatal period, patients are treated with IV fluids aiming to replace stool losses of fluids, NaCl, and KCl. Oral salt substitution therapy is an effective diet therapy as the child ages, with a gradual introduction of oral feeding with the addition of oral electrolyte solutions containing 0.7%–0.9% NaCl (120–154 mmol/L) and 0.3%–0.2% KCl (15–20 mmol/L) solutions. Doses are adjusted to maintain normal serum electrolytes, as well as some urine chloride [79], aiming for urine concentrations of 10–50 mmol/L [87]. In the neonatal period, chloride and potassium needs are 6–10 and 3–4 mmol/kg/d, respectively, and as the child grows, the needed amount slightly drops or may remain the same [79]. Oral salt substitution therapy administered 3–4 times/d [86,87] should meet these targets. Older patients are prescribed 1.8% NaCl (300 mmol/L) and 1.9%–2.2% KCl (130–150 mmol/L) 3–4 times daily with meals [79]. Beyond the maintenance therapy, acute exacerbations should be treated with aggressive IV rehydration to correct the electrolyte abnormalities that tend to worsen during such episodes. The treatment of CCD is lifelong as the high chloride and voluminous stools persist, although a decrease in stools has been reported with age [87]. Over time, most patients can be maintained on oral supplements and will not require PN or IV support [85].

Congenital sodium diarrheas

Congenital sodium diarrheas (CSD) are a group of diseases with a similar diarrheal phenotype caused by impaired intestinal Na^+ absorption and characterized by high-fecal sodium loss, serum hyponatremia, and metabolic acidosis [88,89]. CSD is a heterogeneous group of disorders, and this heterogenicity is observed genetically and clinically. Biallelic mutations in *NHE3*/*SLC9A3* (MIM #616868), a sodium hydrogen antiporter, and gain of function autosomal dominant mutation in *GUCY2C* (MIM #601330), an apical receptor activating cGMP, cause nonsyndromic CSD, whereas syndromic CSD results from *SPINT2* mutations (MIM #270420) [89,90].

Patients with CSD have watery electrolyte transport diarrhea, abdominal distension, and dilated fluid-filled bowel loops [90]. The condition can go undiagnosed initially because the stools are voluminous and resemble urine. The large stool volume is responsible for progressive weight loss and dehydration [88,90]. Stool sodium is very high, and the acid-base aberration in CSD is metabolic acidosis as opposed to the metabolic alkalosis in CCD [89]. Chloride fecal loss, in addition to sodium losses, can be found in patients with *GUCY2C* mutation due to the downstream effect of the mutated protein on NHE3 and CFTR [91,92]. Urine sodium will be low when body fluid status is uncorrected. Fractional sodium excretion is a more accurate marker of sodium status because it is independent of urine flow [93–95]. Progressive weight loss and dehydration are common at disease onset, and acute renal failure may develop in patients with delayed diagnosis [96]. Inflammatory bowel disease has been sporadically reported in patients with *GUCY2C* and *NHE3* mutations [89].

Nutritional management. Oral supplementation of $NaHCO_3$ and potassium citrate has been reported to lead to clinical recovery in some cases [97]. In addition, loperamide has also been described as a successful treatment for increasing intestinal sodium absorption in patients with CSD [98]. However, the evidence for these approaches is limited, and they do not significantly affect diarrhea or electrolyte balance in most cases. Total home PN has been the mainstay of treatment in patients with CSD, mainly in patients carrying *NHE3* and *SPINT2* mutations, whereas the minority of patients with *GUCY2C* mutation require PN. Patients require up to 22 and 10 mmol/kg/d of sodium and acetate, respectively, with a total IV fluid intake of 160–180 mL/kg/d. The variation in the effectiveness of the different treatments likely lies in the heterogeneous nature of the disease. Most patients with *NHE3* and *GUCY2C* mutations and the minority with *SPINT2* [99] mutation may be able to reduce their PN requirements over time and tolerate enteral feeding.

Our collective experience in these rare diseases suggests a focus on PN in early infancy with restrictions on all oral fluids except for oral rehydration solution. During the weaning years, low-sugar solid foods are introduced and maintained as textures progress. The volume of oral rehydration solution is slowly increased, and stools with fluid and electrolyte balance are frequently and carefully monitored to assess tolerance. If tolerance improves, PN volume and hours of infusion are weaned. Weaning is progressed until it is determined that growth, electrolyte balance, or hydration status are compromised. Specifically for patients with *GUCY2C* mutation, with the improvement in diarrhea after infancy, most patients will tolerate full oral diet with a need to avoid simple sugars, fruits, and dairy products [100].

Primary bile acid diarrhea

Bile acid diarrhea (BAD) is a common but underdiagnosed cause of chronic diarrhea [101–103]. BAD is the result of impaired enterohepatic cycling of bile acids and can be subcategorized into the following 3 types: *1*) ileal mucosal dysfunction; *2*) excessive hepatic synthesis of bile acids; and *3*) an idiopathic or primary etiology involving genetic variants [104,105]. Diarrhea associated with BAD is thought to be multifactorial. Mechanisms for the role of bile acids in BAD include stimulation of the colon to secrete fluid, sodium, or mucus; increased gastric motility and/or defecation; and a damaging effect on the intestinal mucosa [101–103]. In addition, diet will further exacerbate the diarrhea and worsen GI symptoms. Several genetic defects have been identified in bile acid metabolism and provide insights into the pathophysiology of BAD. These include variants in *SLC10A2* (MIM #601295), which codes for an apical sodium-dependent bile acid transporter thought to be important in the enterohepatic circulation of bile acids, and in *SLC51B*, which is thought to be involved in bile acid recycling [106]. Compared to adults, pediatric cases of BAD are rare, assumed to be primary in nature, and generally present with more severe symptoms and malnutrition [107].

BAD in infancy is associated with chronic diarrhea, steatorrhea, reduced plasma cholesterol concentrations, and growth faltering [101, 104,105].

Nutritional management. The mainstay of nutritional management of pediatric BAD parallels other forms of CODE and includes IV fluid resuscitation, correction of metabolic acidosis, correction of electrolyte abnormalities, and provision of nutrition via PN support and/or enteral nutrition support if tolerated. Hydrolyzed, extensively hydrolyzed, or amino acid formula will not ameliorate symptoms of BAD. Bile acid sequestering with anion exchange resins such as cholestyramine is integral to differentiating pediatric BAD from other CODE disorders, with improvement in the diarrhea following its introduction in many cases. Although there is no specific diet management, nutrition principles that may minimize loose, frequent bowel movements may have some therapeutic benefits in pediatric BAD. These include adding soluble fiber and limiting the consumption of simple sugars (anecdotal author experience).

Generalized malabsorption

Enteroendocrine defects

At least 5 monogenic disorders result in enteric endocrinopathies, including loss-of-function mutations of the *NEUROG3*, *PCSK1*, *PERCC1*, *ARX1*, and *RFX6* genes. These disorders have identical consequences associated with their enteric endocrinopathies; however, all are associated with distinct systemic endocrinopathies that distinguish the disorders from one another and may influence their long-term nutritional management. The following 3 characteristics set this group of patients apart from those with other forms of CODE: *1*) normal-appearing small bowel mucosa; *2*) inability to tolerate all forms of enteral nutrients; and *3*) the requirement of PN during the first several years of life.

Patients with endocrinopathies develop dehydration, metabolic acidosis, and diarrhea during the first several weeks of life. Diarrhea is of the general malabsorptive type and worsens with the selective dietary challenges of any form of carbohydrates, amino acids, or fats, and resolves entirely during fasting.

Dietary management. The initial dietary options for most enteric endocrinopathies rely primarily on PN, slow advancements of low osmolality enteral feeds, and loperamide. The requirement for PN is generally limited to the first several years of life, although the diarrheal symptoms never abate. Therefore, parenteral and enteral nutrition should be balanced to target the ideal body weight, but the parenteral component can be tapered over time. Anecdotally, the diarrheal symptoms improve when liquid formulas are minimized, and semisolid feeds are advanced (Table 2).

Nutritional considerations by specific endocrinopathies

NEUROG3

Enteric anendocrinosis is an autosomal-recessive disorder caused by mutations of the *NEUROG3* gene (MIM# 610370) [108]. NEUROG3 is required for endocrine cell development in the pancreas, intestine, and portions of the hypothalamus. Unlike the other CODE endocrinopathies, this disorder results in a paucity of enteroendocrine cells. A component of the diarrheal symptoms may be related to pancreatic insufficiency in some patients. Diabetes mellitus is a common occurrence in most of these children, but the age of onset is rarely in early infancy. Severe forms of FSV deficiency have also been seen in some patients.

Measuring fecal elastase-1, chymotrypsin, and 72-h fat collection should be considered as pancreatic insufficiency can present early on. If there is evidence of pancreatic insufficiency, enzyme replacement therapy is indicated. Anticipatory guidance and management including diet for diabetes mellitus resulting from systemic endocrinopathy is indicated.

PCSK1

Proprotein convertase 1/3 deficiency is an autosomal-recessive disorder caused by mutations in the proprotein convertase subtilisin/kexin type 1 (*PCSK1*) gene (MIM# 600955) [109]. Prohormone convertase 1/3 is a calcium-dependent serine endoprotease essential for the conversion of a variety of prohormones into their bioactive forms; it is highly expressed in endocrine cells, in the gut, in the arcuate and paraventricular nuclei of the hypothalamus, and in β cells of the pancreas, where it has a well-defined role in processing proinsulin. A uniformly common clinical feature in PCSK1 deficient infants is significant hypoglycemia that persists in the fed and fasted states, which may be related to elevated proinsulin level resulting from improper conversion to insulin. Adrenal insufficiency is common in early infancy, and diabetes insipidus generally results subsequently and needs careful anticipatory monitoring and modulations of fluids and nutrients.

As *PCSK1* deficiency is associated with profound hyperphagia and moderate obesity as the infant ages, weight and total caloric intake monitoring should be continuously reviewed and modified as needed. PN support is usually limited and needed in the first few years of life.

ARX (MIM #308350/300215) and RFX6 (MIM #615710)

The usual dietary options recommended for the other enteric endocrinopathies apply to these patients as well. Similar to NEUROG3, evidence of exocrine pancreatic insufficiency should be sought, and a trial of enzyme replacement therapy should be implemented if indicated [110].

Epithelial trafficking and polarity defects

Diseases of epithelial trafficking and polarity defects are characterized by abnormalities in the structure and, thus, the function of enterocytes. These defects disrupt the normal function of the cellular membrane, intracellular organelles, transporters, and electrolyte channels. They lead to severely impaired absorption of nutrients, electrolytes, and micronutrients. Patients present with an early onset severe high output diarrhea and almost universally require PN support. PN management is the cornerstone of nutritional therapy in these diseases, with a specific emphasis on complex and frequently challenging fluid and electrolyte management. Lifelong PN is needed in most patients; however, over time, in some cases, enteral nutrition can be introduced with the use of specialized formulas (Table 2). Partial PN dependency or enteral autonomy has been reported in some patients [99]. The cause and mechanism of the improvements over time is not clear and requires further research.

Microvillous inclusion disease

Microvillous inclusion disease (MVID) is an autosomal recessive enteropathy [111] characterized by profuse neonatal diarrhea resulting in malabsorption, dehydration, and electrolyte derangements. The most common cause of MVID results from biallelic mutations in *MYO5B*

gene (MIM #251850) [112]. However, *UNC45A* and *STX3* gene mutations have also been reported to cause cellular phenotype similar to MVID (MIM #619377 and #619445, respectively) [113]. Mutations in these genes lead to abnormal cytoskeletal motor proteins that in turn affect intestinal cell structure and primarily cause a loss of sodium fluid absorption, also known as electrolyte transport induced diarrhea [1].

Children with MVID commonly experience high stool volume losses between 150 and 400 mL/kg/d associated with severe dehydration, metabolic acidosis, impaired renal function, and mild/severe hyponatremia [111,114,115]. Low urine sodium with low fractional Na excretion, high urine osmolality, and hyperaldosteronism with high urine potassium are common findings. Stool output and electrolyte derangements are exacerbated by enteral intake secondary to minimal absorptive capability and lack of intestinal transporters [1]. Exacerbation of stool output with enteral intake leads to limitations to oral intake and primary dependence on parenteral support with some variation in tolerance, as in the case of *STX3* gene mutation [116]. Cholestatic liver disease can be expressed among this cohort as part of the phenotype as well as secondary to intestinal failure-associated liver disease due to long-term dependence on PN [117].

There is no medical treatment capable of overcoming the intestinal failure, with the mainstay of treatment centered around parenteral support and decreasing the risk of associated comorbid conditions. Surgically, intestinal transplantation has shown promise [115,118–120], and subtotal enterectomy as a means to better control bowel losses or as a bridge to transplantation has been recently described [121].

Nutrition management. Patients with MVID are managed exclusively with PN and IV fluids. Nutritional management aims to provide adequate nutrients, promote growth, and replace fluid and electrolyte losses, with patients often requiring greater than twice the estimated maintenance fluid daily provision. Ongoing assessment of fluid balance is critical for prevention of electrolyte dysregulation and kidney injury, while cycling of PN is dependent on clinical and laboratory signs of hydration. Given intestinal loss of bicarbonate and sodium, patients often require substantial PN provision of sodium and acetate. Usually, sodium provision in PN can range between 9 and 17 mEq/kg/d, with acetate often maximized in PN and ranging between 6 and 16mEq/kg/d with additional enteral supplementation in the form of sodium bicarbonate (i.e., baking soda) to prevent acidosis (authors' personal experience).

The lifelong dependence on PN requires close monitoring for possible multiple comorbid conditions (Supplemental Note 2). Micronutrient deficiencies can include copper and zinc due to high stool output [122], requiring periodic monitoring. Iron deficiency anemia can often be appreciated in the setting of minimal nutritional intake, varied absorption, and impaired epithelial function, often requiring IV iron supplementation [123]. Long-term PN support without enteral or dietary supplementation can lead to iodine deficiency when trace minerals do not include iodine; thus, routine screening may be prudent in identifying potential deficiencies [124]. Possible metabolic bone disease can be appreciated among patients who are on PN support secondary to compounding limitations of calcium, phosphate, and vitamin D (in multivitamin formulation) with need for additional enteral vitamin D, vitamin K, and calcium supplementation [125]. A balanced lipid emulsion with a low proinflammatory profile and cycling is recommended to reduce the risk of intestinal failure-associated liver disease. Reliance on long-term PN utilization can be associated with risk for aluminum toxicity given PN composition and requires monitoring [126]. Given patients' predominant dependence on PN with symptoms exacerbated by enteral intake, oral aversion may be seen early in life.

Tufting enteropathy

Tufting enteropathy is characterized by neonatal diarrhea with nutrient malabsorption and failure to thrive. It is an epithelial mediated disorder with disruption in cell adhesion regulation caused by mutation in the *EPCAM* gene (MIM #613217) leading to disorganization of villi [1] appearing with intestinal villous atrophy and "villi tufts." Patients can present with a varied degree of malabsorption and dependence on PN, and some can be weaned off total PN over time. In one cohort in Malta and the United Kingdom, those who achieved enteral autonomy were more likely to be older, requiring less caloric support, with up to 75% of patients being fully enterally dependent by age 25 [127].

Nutrition management. The dietary goal is to minimize PN dependence by advancing enteral nutrition as tolerated [127,128]. There is no consensus on an optimal dietary regimen that leads to improvement in enteral advancement, particularly as enteral tolerance and absorption differ among patients. There are conflicting reports on the benefit of elemental formula use, with some showing good tolerance whereas others show no benefit [127]. The authors' clinical experience has noted improvement of enteral advancement with the use of blenderized formulas, including home blends that are mainly composed of complex carbohydrates (such as rice, vegetables) mixed with other food purees based on nutritional need, in addition to commercial formulas. Utilizing rice as a base ingredient has led to enteral advancement over time, likely secondary to its binding effect with bulking of stool and longer time for digestion. Enteral access (gastrostomy tube) has been beneficial among this population as this allows slow titration of nutrients over time. In general, tolerance of dairy products can be variable and likely secondary to the degree of villous atrophy. Foods and ingredients that may cause diet-induced diarrhea are generally avoided. To optimize enteral tolerance, we recommend slowly integrating protein and vegetables, one food group at a time.

From a micronutrient standpoint, patients with tufting enteropathy maintained on PN often require supplemental enteral calcium and vitamin D due to PN-compounding limitations. Close monitoring of iron stores and zinc concentrations should be routinely monitored. Patients with large-volume diarrhea may have high fluid needs and varied need for acid-base support (Supplemental Table 19, Note 3).

Trichohepatoenteric syndrome

Trichohepatoenteric syndrome (THE) is an autosomal-recessive disorder caused by mutations in *TTC37* (MIM #222470) in 60% of cases and *SKIV2L* (MIM #614602) with diarrheal symptoms beginning in the first few months of life [129–134]. In some cases, diarrhea improves with age, allowing for a partial or complete wean from PN to elemental feeds [135,136]. A recent systematic review showed the achievement of enteral autonomy in 50% of patients with *SKIV2L* mutation and 22% with *TTC37* mutation [99]. Clinically common and constant symptoms include intractable diarrhea, facial dysmorphism, and hair abnormalities, and in ~90% of the reported cases, immunodeficiency, growth failure, short stature, and intrauterine growth retardation. Other symptoms with varying penetrance are frequent liver disease, skin abnormalities, platelet anomaly, or congenital cardiac

defects [129,131–133,137–144]. Nutritional deficiencies are common in patients with THE and include FSV deficiencies, particularly vitamin D, and deficiencies in zinc, selenium, and iron.

Nutritional management. The main goal of treatment is to minimize PN use and advance enteral nutrition [135,145]. Patients who have been weaned off PN support often relied on a combination of an oral diet (with no reported restrictions) and formula supplementation either by mouth or via gastrostomy tube [136,146]. Most case studies report utilizing amino acid-based formulas, although there is no evidence that polymeric or semielemental formulas are not well tolerated [146,147]. Lactose-free, low MCT formulas are generally better tolerated. Oral diet recommendations include a standard high calorie, high protein diet to support adequate growth. When attempting PN weaning and use of solid foods, the authors' practice is an initial introduction of foods low in simple sugars. Starches, meats, and low-sugar vegetables are introduced first. Fruits are added after a wide selection of vegetables are tolerated. Fruits are introduced from the lowest sugar content and progress based on tolerance. Egg, soy, and cow milk protein allergies have been described; thus, slow introduction of these feeds is recommended [136]. Patients weaned off PN may require calcium, vitamin D, zinc, and selenium supplementation, and concentrations should be closely monitored at least twice per year (Supplemental Note 4; Supplemental Tables 20–21 for THE and other CODE disorders).

In summary, diet and nutritional management remain at this stage the most effective supportive therapy for children with CODE and in specific defects it can lead to symptom resolution. Appropriate enteral or parenteral treatment allows normal growth and development and avoids electrolyte and micronutrient deficiencies. Stratification of enteral diet management to the 3 approaches—elimination, supplementation, and general restriction—provides a practical framework to the nutritional management of the various CODE groups. Additional clinical studies and observations focusing on diet and nutrition support will provide stronger evidence to current anecdotal clinical experiences and will improve the outcome of patients with CODE.

Author contributions

The authors' responsibilities were as follows – YA, LJ, IM, SA, AM, JRT, MGM: designed the concepts and structure of the review; all authors: wrote sections of the review; YA, MGM: had primary responsibility for the final content; and all authors: read and approved the final manuscript.

Conflict of interest

YA, SA, AM, MGM, and JRT report financial support was provided by National Institute of Diabetes and Digestive and Kidney Diseases. GC-M reports consulting or advisory relationships with Mead Johnson Nutrition Company and Reckitt Benckiser LLC. IM reports a consulting or advisory relationship with Mirum Pharmaceuticals Inc. All other authors report no conflicts of interest.

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Appendix A. Supplementary data

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