Invited Review

aspen LEADING THE SCIENCE AND PRACTICE OF CLINICAL NUTRITION
American Society for Parenteral and Enteral Nutrition

Nutrition in Clinical Practice
Volume 34 Supplement 1
October 2019 S27–S42

DOI: 10.1002/ncp.10388
wileyonlinelibrary.com
WILEY

Management of Exocrine Pancreatic Insufficiency in Children

Senthilkumar Sankararaman, MD[1]; Teresa Schindler, MS, RDN[2]; and Thomas J. Sferra, MD[1]

Abstract

The diagnosis of exocrine pancreatic insufficiency (EPI) can be difficult, as symptoms may be nonspecific. A delayed diagnosis of EPI can negatively impact health through poor weight gain, impaired growth, and malabsorption of nutrients. Because of active growth and development, children are more vulnerable to the consequences of untreated EPI. Pancreatic enzyme replacement therapy is the cornerstone of management and offers both symptomatic relief and improvement in clinical outcomes. Additionally, a high-energy diet with unrestricted fat and supplementation with fat-soluble vitamins is often required to optimize growth and prevent nutrition deficiencies. Cystic fibrosis (CF) is the most common condition in children that causes EPI, and improvement in nutrition management is associated with improved pulmonary function and increased survival. Currently, the management of other conditions leading to EPI in children is not well studied, and inferences from the CF literature are often necessary in caring for these patients. (*Nutr Clin Pract.* 2019;34(suppl 1):S27–S42)

Keywords

child; cystic fibrosis; exocrine pancreatic insufficiency; fat-soluble vitamins; nutrition therapy; pancreatic diseases; pediatrics

Introduction

Exocrine pancreatic insufficiency (EPI) is defined as a decrease in the secretion of pancreatic enzymes, bicarbonate, or both, resulting in the malabsorption of nutrients.[1,2] The pancreas has a large physiological reserve, and a reduction of secretion < 10% of the normal output results in the characteristic symptoms of chronic diarrhea, steatorrhea, and poor weight gain.[3-6] The diagnosis of EPI can be challenging, as symptoms may not be recognized. EPI can negatively impact health and well-being through subclinical maldigestion and malabsorption of both macronutrients and micronutrients, particularly the fat-soluble vitamins.[2,7] The presenting symptoms of EPI are often nonspecific and overlap with other gastrointestinal (GI) conditions, with maldigestion or malabsorption resulting in diagnostic difficulties.[2] Unlike in adulthood, during which the most common cause of EPI is chronic pancreatitis (CP), cystic fibrosis (CF) is the most common etiology of EPI in childhood and adolescence.[8] Children are more vulnerable to the consequences of untreated EPI because of the high energy needs related to their growth and development.[7] A late diagnosis results in growth and developmental delay in addition to poor quality of life from malabsorption-related troublesome symptoms. Pancreatic enzyme replacement therapy (PERT) is the cornerstone of management and offers both symptomatic relief and improvement in nutrient absorption. Additionally, a high-energy diet with unrestricted fat and supplementation with fat-soluble vitamins is often emphasized. As management of CF is well studied, herein we focus the review on the nutrition management of non-CF conditions that cause EPI in children.[9,10] Whenever there is a paucity of available literature for non-CF conditions with EPI, inferences from the CF literature are applied to these conditions.

Basic Physiology of Pancreatic Secretion

The pancreas plays an indispensable role in the digestion of macronutrients. Macronutrient digestion is a prerequisite

From the [1]Division of Pediatric Gastroenterology, Department of Pediatrics, UH Rainbow Babies & Children's Hospital, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA; and the [2]Division of Pediatric Pulmonology, Department of Pediatrics, UH Rainbow Babies & Children's Hospital, Cleveland, Ohio, USA.

Financial disclosure: Financial support for the publication of the supplement in which this article appears was provided by Alcresta Therapeutics, Inc.

Conflicts of interest: Senthilkumar Sankararaman was supported by a sponsored fellowship program in nutrition in 2017 by the Nestlé Nutrition Institute. Teresa Schindler is in the Speaker bureau for Allergan, AbbVie, and Chiesi. Thomas J. Sferra is a member of a scientific advisory committee and local principal investigator for a pharmaceutical trial sponsored by Merck & Co., Inc.

This article originally appeared online on September 19, 2019.

Corresponding Author:
Senthilkumar Sankararaman, MD, Division of Pediatric Gastroenterology, Department of Pediatrics, UH Rainbow Babies & Children's Hospital, Suite 737, MS RBC 6004, 11100 Euclid Avenue, Cleveland, OH 44106, USA.
Email: senthilkumar.sankararaman@UHhospitals.org

for subsequent absorptive processes; in other words, maldigestion leads to malabsorption.[8] The pancreas secretes enzymes to digest macronutrients via hydrolysis. The main enzymes for these processes are amylase for carbohydrate digestion, lipase for fat digestion, and proteases (trypsinogen, chymotrypsinogen) for protein digestion.[4,11,12] Lipase and amylase are secreted in active form, and proteases are secreted as pro-enzymes that are converted to active forms in the proximal small bowel.[11,12] Even though pancreatic enzymes are involved in the digestion of all forms of macronutrients, the major impact of EPI is on fat digestion.[1] Azotorrhoea, excess fecal excretion of nitrogenous substances, can also occur if trypsin secretion falls below 5%–10% of normal.[6] Pancreatic amylase insufficiency usually does not cause significant clinical ramifications, as nonpancreatic sources (eg, salivary and small-bowel glands) are able to partially compensate for the pancreatic deficiencies in most instances.[13] Pancreatic lipase is susceptible to irreversible inactivation by acidic gastric secretion (pH < 4) and also further destroyed by intraluminal proteases.[13-15] Some conditions (such as Zollinger-Ellison syndrome) that are associated with excessive gastric acidity are known to lead to a secondary EPI due to acid-induced inactivation of pancreatic enzymes and denaturation of bile acids, with subsequent impaired absorption exacerbating the maldigestion and malabsorption of fats.[6]

The main secretagogues for pancreatic secretion include the enteral hormones cholecystokinin (CCK) and secretin.[5] CCK is the main secretagogue for the release of pancreatic enzymes and secretin for bicarbonate-rich fluid secretion. The secretion of CCK is stimulated by intraluminal fatty acids and small peptide chains.[5,16] The most prominent stimulus for secretin secretion is acidic gastric contents (pH < 4.5) reaching the duodenal lumen. Secretin stimulation results in secretion of bicarbonate-rich pancreatic fluid via the CF transmembrane conductance regulator. This alkaline fluid (pH 7.5–8.8) neutralizes the acidic gastric chyme and helps preserve the function of pH-sensitive pancreatic enzymes, particularly lipase. In infants, a delay in maturation of amylase and lipase has been noted, but this delay rarely causes symptoms.[3] It is also noteworthy that in breast milk–fed infants, bile salt–stimulated lipase within breast milk also participates in fat digestion.[1,16]

Etiopathogenesis and Epidemiology of EPI in Children

Shwachman-Diamond syndrome (SDS) is the second most common inherited condition (following CF) causing EPI in infants and children.[17] Other genetic syndromes such as Johanson-Blizzard syndrome (JBS), Pearson marrow syndrome, Jeune syndrome, and pancreatic agenesis are rarely seen but are responsible for the most severe forms of EPI[17] (Table 1). In these genetic conditions, EPI is the consequence of lack of functional pancreatic parenchyma leading to reduced pancreatic output. These conditions are described as primary EPI.[3] Other forms of primary EPI in children are CP and, rarely, the developmental anomalies of pancreas (agenesis or hypoplasia) or pancreatic resection, each of which results in reduced amounts of functional parenchyma.

Secondary EPI is due to nonpancreatic reasons such as small-bowel inflammation and asynchrony in the digestive process[3,8] (Table 1). Inflammatory bowel disease, celiac disease, and other conditions with proximal small-bowel mucosal inflammation can result in EPI due to decreased enteropancreatic stimulation by CCK.[2,4,8,14,16] Postcibal asynchrony is the dissociation between delivery of chyme to the proximal small bowel and discharge of pancreatic secretions mostly due to altered anatomy of the upper GI tract.[2,14] Because of an increase in obesity prevalence, this etiology of EPI is increasingly recognized after bariatric surgeries such as sleeve gastrectomy and gastric bypass surgery.[5,14] In some conditions, EPI could result from a combination of more than one cause.

EPI has been described in children with severe acute malnutrition (SAM), more so in the edematous form (kwashiorkor) of SAM in resource-limited settings.[16,19,20] Severe malnutrition has been associated with both structural (atrophy of pancreatic acini with fibrous tissue replacement, decrease in secretory granules) and functional (decreased lipase and trypsin secretion) changes resulting in EPI.[20] In most instances, these changes in the pancreas are reversible following treatment of SAM.[20] In tropical environments, tropical calcific pancreatitis is a prominent cause of EPI during childhood.[8,17] Unlike what occurs during adulthood, pancreatic malignancies are extremely uncommon in children and account for approximately 0.2% of all pediatric cancers.[21] These rarely encountered malignancies involving the exocrine pancreas include pancreatoblastoma, solid-cystic tumor, ductal adenocarcinoma, and acinar cell carcinoma.[21] Treatment of these conditions frequently requires surgical resection that leads to pancreatic insufficiency.[21] The overall epidemiology of EPI in the pediatric population is unclear and often underdiagnosed and underreported in the early stages in most conditions.[7] The epidemiology of CF, SDS, and other inherited syndromes of EPI are relatively well studied, and details are summarized in Table 2.

Investigators evaluating data from the International Study Group of Pediatric Pancreatitis: In search for a cuRE (INSPPIRE) cohort documented that about a third of the children with CP have EPI.[18] Adult studies quote 30% of EPI in mild CP and up to 85% in severe disease states.[14] Thus, every 6–12 months, children with CP should be screened for EPI using fecal elastase-1 (FE-1) or 72-hour fecal fat collection.[37]

Table 1. Conditions Associated With EPI in Children.[3,5,6,14,18]

Causes	Mechanisms	Associated Conditions
Primary (pancreatic)	Reduced pancreatic output due to decrease in pancreatic parenchyma	Genetic conditions: Cystic fibrosis, Shwachman-Diamond syndrome Johanson–Blizzard syndrome, Pearson marrow syndrome Jeune syndrome
		Chronic pancreatitis: Genetic – *PRSS1, SPINK1, CFTR, CTRC* gene mutations Autoimmune pancreatitis Other causes – pancreatic duct obstruction due to calculi or ductal stenosis, medications, metabolic (hypercalcemia, hypertriglyceridemia), tropical calcific pancreatitis
		Developmental anomalies of the pancreas: Pancreatic agenesis/hypoplasia
		Congenital/fetal infections
		Pancreatic resection
	Deficiency of pancreatic enzyme production	Isolated congenital enzyme deficiencies
Secondary (extra-pancreatic)	Reduced pancreatic output/ impaired pancreatic function despite normal pancreatic parenchyma	Small bowel mucosal diseases (decreased pancreatic stimulation by cholecystokinin due to mucosal inflammation): Celiac disease Inflammatory bowel disease
		Postcibal asynchrony: Upper gastrointestinal surgeries - gastrectomy/other bariatric procedures
		Pancreatic lipase inactivation: Increased gastric acidity - Zollinger-Ellison syndrome

CFTR, cystic fibrosis transmembrane conductance regulator; *CTRC*, chymotrypsin C; EPI, exocrine pancreatic insufficiency; *PRSS1*, serine protease 1; *SPINK1*, serine protease inhibitor Kazal type 1.

Clinical Presentation and Laboratory Investigations

Regardless of the underlying etiology, the clinical manifestations of untreated EPI in children often include loose stools, steatorrhea, abdominal pain, excessive gas, and poor growth.[10,38] Steatorrhea, or the presence of excess fat in the stools, is characterized by loose, bulky, greasy, and particularly foul-smelling stools. Weight gain may be adequate if the infant or child is able to compensate by consuming enough calories, which is generally characterized by a voracious appetite. This mandates that the clinician has a high index of suspicion for this condition and highlights the importance of early laboratory evaluation.[3] Growth failure in EPI is often multifactorial and is attributed to the mismatch between reduced intake, intestinal malabsorption and excessive losses, and increased energy needs.[10,39-41] Most of the inherited syndromes with EPI are multisystem disorders, and the presence of extra-GI manifestations will also help direct the diagnosis (Table 2).

The diagnosis of EPI can be challenging given lack of correlation between subjective symptoms and objective measures of fat malabsorption. Diagnosing EPI in early stages is challenging, as symptoms are minimal and nonspecific. Testing includes indirect tests that estimate the consequences of EPI and direct tests that estimate pancreatic function directly.[1] Direct tests are the gold standard but are invasive and not widely available.[2] The pancreatic function tests are summarized with their advantages and limitations in Table 3. Indirect tests are frequently used in clinical settings, as they are simple, noninvasive, and less expensive. Among the indirect tests, FE-1 is more sensitive and utilized for screening EPI.[42] The European Society for Clinical Nutrition and Metabolism (ESPEN)–European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)–European Society for Cystic Fibrosis (ECFS) guidelines recommend annual testing of FE-1 in pancreatic-sufficient CF patients.[10] The testing should be done earlier in symptomatic patients.[10] An FE-1 value of <200 μg/g of collected stool is conventionally used as a cutoff for EPI; a value of 100–200 μg/g (slightly low) is indicative of mild EPI, and <100 μg/g (low) is indicative of severe EPI.[2,4] Clinicians should be aware of the limitations of FE-1. It is less sensitive in patients with mild EPI.[4] Low FE-1 does not differentiate whether EPI is due to primary or secondary causes.[42] Also, a solid or semisolid stool is

Table 2. Inherited Genetic Conditions Other Than CF Presenting With EPI in Infancy.

Condition	Epidemiology and Genetics	Clinical Manifestations	Growth and Nutrition
Shwachman-Diamond syndrome (SDS); Shwachman-Bodian-Diamond syndrome (SBDS) (OMIM# 260400)	Second most common cause of congenital EPI after CF Incidence 1:77,000[22] Autosomal recessive 80-90% biallelic mutations in the *SDBS* gene located on chromosome 7q11[23,24] SBDS protein implicated in many cellular pathways; prominently in the ribosome formation and mitotic spindle function[23]	Traditional diagnostic criteria: (i) bone marrow failure (single lineage or multilineage cytopenias), (ii) EPI, (iii) osseous malformations from metaphyseal dysplasia, short stature, and thoracic dystrophy [23-25] Subtle forms increasingly recognized with genetic testing[24,25] Neurodevelopmental abnormalities, hepatic abnormalities, cardiac anomalies, and endocrine deficiencies may be associated[24,25] Predisposition to myelodysplasia (MDS) and leukemia, particularly acute myeloid leukemia[24] Prevalence of EPI over 80%[24]; varied degrees of severity[25] Replacement of pancreatic acini with fatty tissue (termed as pancreatic lipomatosis)[22]	Steatorrhea and failure to thrive during infancy[26] Fat-soluble vitamins levels may be decreased[26,27] Radiological imaging: small pancreatic size or fatty infiltration (pancreatic lipomatosis)[24,25] Spontaneous improvement of pancreatic function in late childhood; by four years of age, half of the SDS patients may have improved function[22,28] Current management of EPI based on consensus recommendations[22,24] Growth potential variable; 50% exhibit diminished growth with parameters below the 3rd percentile[26] If growth does not improve despite administration of adequate balanced nutrition, possibilities such as intrinsic growth failure, endocrine defects should be considered.
Johanson–Blizzard syndrome (JBS) (OMIM# 243800)	Rare syndrome; less than 100 patients have been described[29] Prevalence: 1:250,000 live births[30] Autosomal recessive Mutation of the *UBR1* gene located on chromosome 15q15.2 UBR1 protein, ubiquitin ligase[30] Biologic function is unclear[31]	EPI, nasal wing aplasia/hypoplasia, hypothyroidism, sensorineural hearing loss, ectodermal scalp defects (aplasia cutis congenita), absence of permanent teeth, imperforate anus, urogenital anomalies, poor growth, delayed development[30-32] Near total absence of pancreatic acini and replacement by fat	EPI onset occurs in early infancy Intrinsic growth failure is common

(*continued*)

Table 2. (continued)

Condition	Epidemiology and Genetics	Clinical Manifestations	Growth and Nutrition
Pearson syndrome; Pearson marrow syndrome (OMIM# 557000)	Rare syndrome Prevalence unknown[33] Large deletions or rearrangements in mitochondrial DNA Impaired oxidative phosphorylation	Pancytopenia, EPI, lactic acidosis, and growth failure Refractory sideroblastic anemia is often found in infancy. Normal bone marrow cellularity or ring sideroblasts and vacuoles in bone marrow progenitors. Pancreatic fibrosis or lipomatosis Other: proximal myopathy, neurologic manifestations (seizures, ataxia, abnormal movements), renal tubular acidosis type II, and cutaneous lesions[34]	Many patients die in early infancy or childhood due to sepsis or from severe lactic acidosis Growth failure is common among survivors
Jeune syndrome; Asphyxiating thoracic dystrophy (OMIM# 208500)	Rare syndrome Autosomal recessive	Thoracic dystrophy: small chest and short ribs (bell shaped chest) Severe respiratory compromise Abnormal shaped pelvis and polydactyly	EPI usually occurs early in life; in milder phenotype, EPI recognized later in life[35]
Other rare disorders and their involved genes[1,36] Pancreatic agenesis (OMIM# 260370) – *PDX1* Congenital lipase deficiency (OMIM# 614338) – *PNLIP* Congenital enterokinase deficiency (OMIM# 226200) – *PRSS7* EPI, dyserthyropoietic anemia, calvarial hyperostosis (OMIM# 612714) – *COX412* Pancreatic and cerebellar agenesis (OMIM# 609069) – *PTF1A*			

CF, cystic fibrosis; EPI, exocrine pancreatic insufficiency; JBS, Johanson-Blizzard syndrome; MDS, myelodysplasia; OMIM, Online Mendelian Inheritance in Man; SBDS, Shwachman-Bodian-Diamond syndrome; SDS, Shwachman-Diamond syndrome; UBR1, Ubiquitin Protein Ligase E3 Component N-Recognin 1.

recommended for testing FE-1. If the stool is loose, it should not be used, as the result may falsely indicate EPI because of a dilution of the enzyme concentration.[1] A high normal value probably indicates no significant EPI, and follow-up testing is recommended (repeat FE-1 every year or when needed).[10,42] If the is value <200 μg/g, the testing should be repeated. Two low values of FE-1 (<100 μg/g) is probably consistent with EPI. If a solid or semisolid stool cannot be obtained or if the elastase values continue to be negative despite strong clinical suspicion for EPI, it is probably appropriate to proceed with endoscopic pancreatic function testing using the methodology outlined by Horvath et al.[43] Furthermore, if isolated pancreatic enzyme deficiencies are suspected—for example, congenital lipase deficiency—endoscopic pancreatic function testing should be done, as FE-1 is not helpful here.

Treatment

Prior to the advent of enteric-coated PERT and the importance of nutrition, EPI was primarily managed with fat-restricted diets. This resulted in worsening of the malnutrition and its adverse consequences.[13] Currently, enteric-coated pancreatic enzymes (also referred to as pancrelipase) are the mainstay of EPI management.[50] If adequate PERT is provided, fat absorption is nearly corrected.[13,51] The bulk of evidence regarding the management of EPI in children comes from care of patients with CF, and these general principles are followed in the management of other conditions with EPI.[22,37] Extrapolating from CF management, current treatment for EPI from any etiology emphasizes a high-energy diet with unrestricted fat along with PERT and supplementation with fat-soluble vitamins.[10,52,53] Fat-soluble vitamins follow the same pathway for absorption as dietary fat, and hence, patients with EPI are predisposed to deficiencies of these vitamins. The main goals for EPI treatment include optimization of maldigestion with improvement in nutrient absorption. This enhances the overall nutrition status and concomitantly provides reduction in symptoms and improvement in quality of life and survival.[50,54-56]

Pancreatic Enzyme Replacement Therapy

Apart from amelioration of symptoms, PERT has been objectively noted to improve the coefficient of fat absorption

Table 3. Pancreatic Function Tests—Indirect and Direct Tests.

Test	Description	Advantages	Disadvantages
Indirect tests:			
Stool tests			
Coefficient of fat absorption	Fat content of stool in 72-hour stool collection Difference between fat intake and fat excretion during the collection time[44,45]	Gold standard test for fecal fat malabsorption	Undesirable and challenging for most[1] Low specificity as steatorrhea also occurs in other gastrointestinal (GI) diseases such as mucosal inflammatory diseases, cholestatic diseases, short bowel syndrome, and abnormal intestinal motility[38,46]
Fecal elastase-1 (FE-1)	Pancreatic protease Only secreted by the pancreas Not destroyed during passage through the gut Specific for human elastase-1 Correlates with pancreatic insufficiency.[2]	Easy to perform Pancreatic enzyme replacement therapy (PERT) does not need to be discontinued for testing[47]	False positive if the stool is dilute due to other causes (e.g. infectious diarrhea)[1]
Stool chymotrypsin	Pancreatic protease	Easy to perform Can be used to monitor PERT compliance[1]	PERT interferes with test and needs to be discontinued to test for EPI Less sensitive than FE-1[14]
Blood test			
Serum immunoreactive trypsinogen (IRT)	Elevated in newborns with cystic fibrosis (CF) Reduced in EPI later in life	CF newborn screening – highly sensitive Useful in non-CF EPI conditions (e.g. Shwachman-Diamond syndrome) children younger than 3 years	Low specificity
Breath test			
^{13}C- mixed triglyceride breath (MTG) test	Orally administered 13C-labeled triglycerides Hydrolyzed by lipase $13CO_2$ absorbed from GI tract and excreted in the breath	Noninvasive Easy to perform Normal values in children are available[48] Evaluates EPI or PERT lipase activity[46]	Not widely available[48]
Direct tests			
Secretin or Cholecystokinin (CCK) based pancreatic stimulation tests			
Endoscopic secretin or CCK based pancreatic stimulation test	Based on the originally described Drilling tube technique which is not practical in children[16] Pancreatic secretions are collected from the duodenum during esophagogastroduodenoscopy after intravenous administration of either secretin or CCK Pancreatic enzyme activity is directly measured within the collected fluid[2,7]	Useful in early disease course Identifies isolated enzyme deficiencies	Expensive Invasive requiring sedation Available only in referral centers Lack of standardization[7]

(*continued*)

Table 3. (continued)

Test	Description	Advantages	Disadvantages
Secretin-enhanced magnetic resonance cholangiopancreatography (s-MRCP)	Pancreatic fluid secretion can be quantified after administration of secretin Decreased secretion correlates with EPI	Non-invasive Simultaneous evaluation of pancreatic parenchyma and ductal architecture	Not recommended as a single diagnostic test for EPI due to limited data[7,49] Not widely available Requires sedation for young children

Additionally, gene testing is available for the inherited conditions with EPI (Tables 1 and 2). Imaging modalities such as ultrasound, computed tomography, and MRCP are helpful in the delineation of pancreatic parenchymal changes commonly noted in EPI such as atrophy, fatty replacement, calcifications, and ductal architectural changes.
CCK, cholecystokinin; CF, cystic fibrosis; EPI, exocrine pancreatic insufficiency; FE-1, fecal elastase-1; GI, gastrointestinal; IRT, immunoreactive trypsinogen; MRCP, magnetic resonance cholangiopancreatography; MTG, mixed triglyceride; PERT, pancreatic enzyme replacement therapy; s-MRCP, secretin-enhanced MRCP.

and coefficient of nitrogen absorption and decrease fecal weight with no significant adverse events, compared with placebo.[45,50,51,57,58] All current pancrelipase preparations are porcine in origin and available in various formulations (eg, capsules with enteric-coated beads vs non–enteric-coated tablets). Most preparations are capsules containing enteric-coated microspheres or microtablets that are intended to release the enzymes in a pH milieu of 5.5–6 within the proximal small bowel.[15,39] The capsules must be swallowed without chewing. For infants and younger children who cannot swallow capsules, they can be opened and the enteric-coated beads mixed with a strained food at the start of each feeding or meal.[11] Pancrelipase should be kept at room temperature ranging from 15°C to 30°C. It is inactivated at high temperatures. Patients and families are instructed to pay close attention to the expiration dates, as age of the medication can affect the potency of the enzymes. In the United States, generic brands of pancreatic enzyme preparations do not have US Food and Drug Administration approval and are not available.

Current recommended doses for PERT are based on body weight or the amount of fat present in the food being consumed.[44] Dosing based on body weight is easy to calculate and convenient. However, dosing based on fat content of the meal is more physiologic.[59] PERT should be given with all food, including breast milk, infant formulas, milk, and nutrition supplements. In infants with CF, breastfeeding is recommended over formula in the first year of life.[10,44,60] Doses include 2000–4000 lipase units per 120 mL of infant formula or expressed breast milk in infants <1 year of age based on expert consensus on CF.[60] For breastfed infants, a dose of 1000 lipase units/kg/feeding is recommended. If feeding time is more than half an hour, the entire dose could be split into 2 (eg, half of the dose given at the start and the remaining half in the middle or the end of the feeding).[61] For infants who feed frequently, the lowest effective PERT dose is recommended, as frequently consumed feeds are smaller in volume.[61]

For children >1 year of age, 1000–2500 lipase units/kg/meal with daily maximum dose of 10,000 lipase units/kg is recommended.[44,59,62] Based on the quantity of fat present in food, PERT dosing ranges from 500 to 4000 lipase units/g of fat (average 1800 lipase unit/g fat).[44] Most patients and their parents are provided general guidelines regarding enzyme adjustments based on fat content and size of meals and snacks (ie, "take 1–2 additional enzymes when eating pepperoni pizza"). Snack dosing is generally half the dose used at meals. Enzymes should be taken at the start of meals and snacks. Drinks and foods that are predominantly sugar based (ie, fruit, fruit juice, soft drinks, hard candy) do not require PERT.

In infants, the capsule can be opened and mixed with a small amount of acidic food that does not require chewing, such as applesauce.[11] In breastfed babies, the microspheres can be administered via a baby spoon prior to feeding with a small quantity of applesauce.[10,11] The microspheres should not be crushed, chewed, or dissolved, as these will destroy the enteric coating when administered orally. The presence of enteric coating prevents oral excoriation (from activated protease) and also protects from the gastric acid inactivation of the exposed enzymes. Oral cavity should be checked post feed to ensure microspheres are not left inside, which will cause excoriation. In breastfed babies, these leftover microspheres also may cause maternal nipple excoriation. Cotton swab or a piece of clean cloth dipped with water or a clean finger of the caregiver can be used to wipe the spaces around the gums and under the tongue to remove the leftover microspheres.[61,63]

In patients with persistent symptoms and signs of EPI despite being prescribed an appropriate dosage of PERT, reasons for the nonresponse could include missed doses, improper storage of enzymes, expired enzymes, mistiming of PERT administration (taking PERT after meals), destruction of enteric coating (toddlers may start chewing the enzymes beads), and non–EPI-related conditions (eg, excessive juice intake in toddlers).[2,15,62] Alternatively, there

may be insufficient neutralization of acidic chyme in the proximal small bowel because of diminished or absent bicarbonate secretion from the pancreas.[64] This leads to inadequate dissolution of the enteric coating of the enzyme beads and precipitation of bile salts, exacerbating fat malabsorption.[15] Acid-blockade medication (histamine receptor-2 antagonists or proton pump inhibitors) or a PERT formulation with bicarbonate can be used to increase the pH in the small bowel.[15,65,66] Since the timing of PERT or persistent asynchrony with the gastric emptying could affect the efficacy of PERT, some patients benefit from splitting the enzyme dose and taking throughout the meal.[65] Also, patients with persistent symptoms should be evaluated for other conditions that produce malabsorption similar to EPI such as small-intestinal bacterial overgrowth, lactose intolerance, liver disease, and celiac disease.[62]

PERT is generally well tolerated, and side effects are rare. GI and rare allergic reactions have been reported.[56,67,68] In infants, a diaper rash around the anal region may be noted, as some of the enzymes may pass through in the stools because of fast transit time. This rapid transit usually resolves within 1–2 weeks after starting enzymes. Preventive measures include prompt changing of the diapers immediately following stooling and frequent use of barrier creams such as petrolatum jelly or zinc oxide cream with diaper changes, especially the first week after starting enzymes. When steatorrhea is adequately treated, constipation may occur in some individuals because of the absence of fat as well as underlying conditions that predispose individuals to having constipation. There is no evidence that PERT itself causes constipation. Rather than reducing or stopping PERT therapy in the presence of constipation, there are guidelines for the management of constipation in CF.[69] With very high doses of PERT, a rare but serious complication called fibrosing colonopathy has been reported.[70] Between 1990 and 1994, there were 35 cases of histologically confirmed cases of fibrosing colonopathy.[70] This complication has been reported mostly in individuals with CF.[4] Doses exceeding 6000 lipase units/kg/meal were associated with this disorder. The histopathology of fibrosing colonopathy is characterized by the presence of submucosal fibrosis.[71] In the early stages, fibrosing colonopathy may improve with dose reduction, but advanced stages may require colectomy.[59] Symptoms include abdominal pain, emesis, persistent diarrhea, poor weight gain, or loss of weight.[70,71] To prevent this complication, avoid doses exceeding 2500 lipase units/kg/meal or 10,000 lipase units/kg/d.[59] In SDS patients, dosing guidelines from CF is adopted, but the clinical response to PERT is much better.[22] Here, unlike in CF, for reasons unclear, many patients may recover their pancreatic function, allowing them to wean their doses and ultimately discontinue the PERT as they grow older.[22] This mandates the clinical team to monitor the growth and manifestations of EPI and the need for dose adjustment with PERT during the regular clinical visits.

Fat-Soluble Vitamins

The original CF descriptions by Dorothy Andersen in 1939 included vitamin A deficiency.[72] Vitamin A, D, E, and K deficiencies are commonly encountered in untreated EPI patients; monitoring and supplementation are necessary. Fat-soluble vitamin malabsorption occurs in patients with EPI because of shared pathogenesis of fat malabsorption in the absence of pancreatic lipase. Optimal digestion and absorption of fat-soluble vitamins may not be achieved in many patients with EPI with just PERT and without supplementation with fat-soluble vitamins.[12] Some of the reasons for this suboptimal digestive process with PERT (when compared with normal physiological process) could be due to inadequate delivery of active form of lipases at the site of digestion (proximal small bowel) and/or asynchrony between the timing of delivery of active lipase and release of chyme.[12] For this reason, all patients with EPI should be regularly screened for fat-soluble vitamin deficiencies and also should take supplements for fat-soluble vitamins.[10,53] In a study from Australia, fat-soluble vitamin deficiencies were noted in up to one-third of children with CF with pancreatic insufficiency.[73] The CF patients who were pancreatic sufficient rarely developed fat-soluble vitamin deficiencies.[73] Other than vitamin D, ongoing vitamin deficiencies with adequate supplementation are uncommon. Some possible reasons for persistent low vitamin levels, despite supplementation, include missed or insufficient doses of specialty multivitamins or PERT.[22,74] In multisystem disorders like CF, the presence of concomitant liver disease also should be kept in mind as contributing to malabsorption of fat-soluble vitamins. The dosing recommendations for multivitamins in CF patients are mostly based on expert consensus.[44] The content of the multivitamins and detailed product information are available online.[75] CF-specific multivitamins utilized in EPI patients generally have higher amounts of fat-soluble vitamins than the general over-the-counter multivitamins have and are specifically prepared to enhance absorption.

The Cystic Fibrosis Foundation (CFF) recommends screening for fat-soluble vitamin deficiencies near the time of diagnosis and then annually, as well as 3–6 months following any dose change.[10,44] For non-CF causes of EPI in children, the general recommendations from CF experts are often applied in the management of these vitamin deficiencies. Every 6–12 months, children with CP should have fat-soluble–vitamin levels measured.[37] The major physiological functions, deficiency manifestations and toxicity symptoms, laboratory evaluation, and recommended dosage are summarized in Table 4.

Vitamin A. Vitamin A includes the fat-soluble retinoids, namely retinol, retinal, retinoic acid, and retinyl esters.[61]

Table 4. Overview of Role of Fat-Soluble Vitamins in EPI and Dosage Recommendations.[4,44,76-81]

Essential Physiological Actions	Annual Screening Tests[a]	Daily Dosage in CF Patients					
		Recommendations from the CFF[44]				Recommendations from the ESPEN-ESPGHAN-ECFS[10]	
		<1 Year	1–3 Years	4–8 Years	>8 Years	<1 Year	>1 Year
Vitamin A Retinal required for vision and involved in the transduction of light to nerve signals; retinoic acid required for maintenance of epithelial cell integrity, regulation of gene expression, growth, and immunity; β-carotene is a potent antioxidant	Serum retinol	1500 IU[b]	5000 IU[b]	5000–10,000 IU[b]	10,000 IU[b]	Retinol: low dose to be started and follow with serum values to adjust β-carotene (1 mg/kg daily with maximum dose of 50 mg/d for 12 weeks and monitor serum retinol)	
Vitamin D Cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2): Calcium metabolism, bone health, innate immunity	Serum 25-hydroxyvitamin D (preferably checked at the end of winter)[10,79]	400–500 IU[c] (maximum dose of 2000 IU)[79]	800–1000 IU[c] for ages 1–10 years (maximum dose of 4000 IU) and 800–2000 IU for ages >10 years (maximum dose of 10,000 IU)[79]			400 IU[c] (maximum dose of 1000 IU)	800 IU[c] (maximum dose of 2000 IU for ages 1–10 years and 4000 IU for older children)
Vitamin E Antioxidant role in free radical scavenging	Serum α-tocopherol/cholesterol ratio	40–50 IU[d]	80–150 IU[d]	100–200 IU[d]	200–400 IU[d]	50 IU[d]	100–400 IU[d]
Vitamin K Coenzyme for synthesis of biologically active form of many proteins involved in blood coagulation (clotting factors 2, 7, 9, 10) and bone metabolism (osteocalcin)	Prothrombin time, Des-γ-carboxy prothrombin and undercarboxylated osteocalcin		0.3–0.5 mg for all age groups[e]			0.3–1 mg[e]	1–10 mg[e]

CF, cystic fibrosis; CFF, Cystic Fibrosis Foundation; EPI, exocrine pancreatic insufficiency; ESPEN-ESPGHAN-ECFS, European Society for Clinical Nutrition and Metabolism, European Society for Paediatric Gastroenterology, Hepatology and Nutrition, and the European Society for Cystic Fibrosis.

[a]Levels are recommended at the time of diagnosis, 3–6 months after a dosage change and every year.[10]

[b]Vitamin A (retinol).

[c]Vitamin D cholecalciferol (vitamin D3), the preferred form for supplementation in CF. Initial daily dose can be gradually increased based on the serum 25-hydroxyvitamin D to the daily maximum dose. Medication compliance should be ascertained before increasing the dosage.

[d]Vitamin E (α-tocopherol).

[e]Vitamin K1 (phytomenadione).

Retinyl ester is the storage form of vitamin A, and liver is the main site of storage. Serum retinol is used to screen for vitamin A deficiency. It is a better marker of vitamin A deficiency than of an excessive state.[9,81] Serum retinyl ester is used for estimating toxicity.[61] Retinol circulates in the serum as a complex binding with retinol binding protein (RBP), and hence, low serum RBP may reflect low retinol levels. RBP is produced in the liver and is an acute-phase reactant. Thus, low retinol levels are noted in acute pulmonary exacerbations and should not be checked during acute illness.[80] In an older, cross-sectional study with 43 CF patients between 8 and 44 years of age, 8 had delayed adaptation for darkness, and 3 were noted to have xerosis of the conjunctiva.[82] In an Australian study involving 39 CF infants diagnosed by newborn screening, 51% had low vitamin A levels that normalized at 1 year of age with supplementation.[83] Zinc is involved in the production of RBP, and a secondary vitamin A deficiency may result from zinc deficiency because of deficiency of RBP.[82,84,85] Among the fat-soluble vitamins, vitamin A deficiency is easily correctable but also carries a risk of toxicity. In a prospective study on 78 CF patients between 8 and 25 years of age, 42% had levels in the recommended range, and 58% had levels above the US National Health and Nutrition Examination Survey reference range.[86] In another cross-sectional study in 73 preadolescents with CF and EPI, vitamin A from multivitamin supplements exceeded the dosage recommendations in 21% of the participants.[87] Vitamin A toxicity may cause a variety of symptoms and lead to liver- and bone-related complications.[87] It more commonly occurs in the setting of renal insufficiency if vitamin A supplementation is not closely monitored.[88] After lung transplantation in adult patients with CF, elevated vitamin A levels have been noted.[88,89] The etiology of this entity in post-lung transplant CF patients is unknown, and many possibilities such as increased intestinal absorption, altered liver metabolism, impaired renal clearance, and drug-vitamin interactions have been proposed.[88,89] The conversion of β-carotene to vitamin A is physiologically regulated and hence has decreased toxicity risk when compared with vitamin A supplementation.

Vitamin D. Vitamin D includes 2 forms, ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3). Vitamin D plays a crucial role in bone mineralization, and low levels are associated with osteomalacia and osteoporosis. Low levels in patients with EPI can occur because of multiple reasons such as decreased absorption, reduced sunlight exposure, decreased intake of vitamin D–rich foods, and insufficient supplementation with fat-soluble multivitamins and/or PERT.[79] The CFF recommends a minimum level of 30 ng/mL (75 nmol/L) of 25-hydroxyvitamin D for individuals with CF.[79] Serum 25-hydroxyvitamin D preferably should be checked at the end of winter.[10] Cholecalciferol (vitamin D3) is recommended over ergocalciferol (vitamin D2), based on data that show it is more efficacious at normalizing vitamin D levels.[78] In addition to its role in bone health, vitamin D deficiency has been implicated in the increased risk of respiratory infections, inflammatory states, and colon cancer.[90-92] Some CF patients and families may prefer once-weekly bolus dosing of (equivalent to the sum of daily dosing for a week) vitamin D3 over daily doses. CFF has no specific recommendations for or against the weekly vitamin D3 regimen based on the available evidence.[79] Patients on weekly high doses are at increased risk of both vitamin D toxicity (if the doses are inadvertently taken more frequently) and deficiency (if the weekly dose is missed on a frequent basis).[79]

Vitamin E. Eight similar compounds are classified as having vitamin E activity; among them, α-tocopherol is the most active form.[81] It is present in all cell membranes. It serves an antioxidant role in preventing the deleterious effects of free oxygen radicals on unsaturated fatty acids, (ie, fat peroxidation).[81] Serum vitamin E levels parallel with serum lipid levels.[10] In clinical scenarios with hypolipidemia, low vitamin E may be noted.[93] Similarly, in dyslipidemia with elevated serum lipid levels, elevated vitamin E levels may be encountered.[10] To assess true vitamin E status, the ESPEN-ESPGHAN-ECFS recommend a concurrent lipid panel.[10] The α-tocopherol level is usually measured in conjunction with fats or cholesterol and expressed as a ratio.[94] A plasma α-tocopherol/cholesterol ratio of >5.4 mg/g is preferred in patients with CF.[41] Vitamin E deficiency, once frequent in CF patients without supplementation, is now uncommon.[95] In an Australian study involving CF infants diagnosed by newborn screening, 24% had low vitamin E levels, which normalized at 1 year of age with supplementation.[83] Deficiency of this vitamin can occur as a result of decreased absorption and also increased consumption due to increased oxidative stress from chronic inflammation and recurrent bacterial infections.[81] Deficiency of vitamin E can lead to hemolytic anemia due to erythrocyte cell membrane instability, and neurological manifestations can arise from peripheral neuronal degeneration resulting in ataxia, reduced vibratory sense, diminished deep tendon reflexes, and muscle weakness.[96-98] In young children with CF, vitamin E deficiency has also been associated with poor cognition.[98] With supplementation, there is a risk of toxicity.[99] A recent Polish study involving young children and adults with CF identified vitamin E deficiency in 8% and elevated levels in 11.4%.[95] Similar to vitamin A, elevated vitamin E levels are noted after lung transplantation in CF patients.[88,89] Hypervitaminosis E is associated with bleeding and bruising primarily due to inhibition of carboxylase action of vitamin K, and this entity has not been reported in CF patients.[61]

Vitamin K. Vitamin K is prevalent in green leafy vegetables (phytomenadione or vitamin K1) and also produced by the

gut bacteria (menaquinones or vitamin K2).[81] It plays an important role in γ-carboxylation of glutamate residues in coagulation factors (factors 2, 7, 9, and 10) and also in osteocalcin and hence plays a crucial role in coagulation and also in bone metabolism.[81] Carboxylated osteocalcin has high affinity for calcium and hydroxyapatite and plays a vital role in the extracellular bone matrix formation.[100] Des-γ-carboxy prothrombin, also referred to as protein-induced in vitamin K absence or antagonism-II (PIVKA-II), and undercarboxylated osteocalcin are inactive under γ-carboxylated forms of vitamin K–dependent factors that provide earlier detection and a more accurate measure of vitamin K insufficiency.[101,102] Serum vitamin K levels do not provide accurate assessment of vitamin K status; prothrombin time is often used as a surrogate.[61] However, vitamin K stores are depleted by the time there is notable elevation of these prothrombin time. Early reports in CF documented bleeding episodes from vitamin K deficiency.[103] Routine supplementation ameliorates this issue, and toxicity with vitamin K has not been reported.[81]

Bone Health

Vitamin D deficiency causes reduced bone mass and rickets in children and osteomalacia and osteoporosis in adults.[4,79] Studies from CF patients indicate that the poor bone health in EPI is multifactorial. In CF, the presence of chronic infection/inflammation and a low body mass index (BMI) are the important contributors of poor bone health.[61] The other notable causes include vitamin K deficiency, frequent use of corticosteroids, calcium malabsorption, hypervitaminosis A, and reduced physical activity (particularly weight-bearing exercise).[81] Poor bone health does negatively impact the post-lung transplant status.[4,79] Guidelines from ESPEN, ESPGHAN, and ECFS recommend bone-density assessment using dual-energy X-ray absorptiometry (DEXA) to be performed from 8 to 10 years of life for children with CF and to be repeated every 1–5 years based on past measurements or the presence of risk factors such as steroid therapy.[10,41]

Essential Fatty Acids

Routine screening for or supplementation of essential fatty acids (EFAs) in CF patients is not recommended unless there is unexplained growth failure or other clinical manifestations of EFA deficiency such as dermatitis, alopecia, and low platelets.[44] In EFA-deficient states, Mead acid (5,8,11-eicosatrienoic acid, triene acid) is increased and linoleic and arachidonic acid levels are reduced.[104] Triene-tetraene (T3:T4) ratio evaluates Mead:arachidonic acid ratio. There is no accepted standard ratio, and based on prior studies, a T3:T4 ratio of >0.02 or 0.04 is generally used as a cutoff for the diagnosis of EFA deficiency in CF patients.[104] Serum linolenic acid levels were found to be a better indicator for EFA status in children with CF, and a serum linolenic acid level of $\geq$21 mol% is associated with better growth, and pulmonary function.[104]

Minerals and Trace Elements

Zinc is essential to many enzymes involved in growth, immunity, and pulmonary function.[9] A deficiency state can occur in the setting of chronic diarrhea. Symptoms of deficiency include poor growth, hair loss, diarrhea, decreased appetite, and poor wound healing.[76] Plasma zinc levels do not correlate with zinc deficiency, and a trial of zinc supplementation is recommended in children with unexplained poor growth.[44] Acrodermatitis enteropathica–like symptoms were occasionally a manifestation of zinc deficiency that was noted in newly diagnosed, untreated patients with CF and EPI. It is very rare since the advent of newborn screening for CF and early treatment with PERT.[105]

In the setting of steatorrhea, calcium is poorly absorbed in the bowel. This can negatively impact bone health and also increases the risk of kidney stone formation (calcium oxalate stones).[10,106]

Nutrition Assessment and Growth Monitoring

Children with EPI should be assessed for adequate weight gain and growth on a regular basis. For patients with EPI who are not able to consume adequate nutrients to achieve age-specific anthropometric goals, a thorough evaluation by a multidisciplinary team should be performed.[107] This team consisting of gastroenterologist, various other medical subspecialists based on the underlying condition, registered dietitian, social worker, behavioral psychologist, and nurse specialist will help address issues that could potentially contribute to inadequate oral intake. Behavioral feeding issues such as oral aversion in young children and eating disorders or depression in older children also account for poor feeding. Food insecurity and psychosocial reasons also affect nutrition intake.[9]

Oral caloric supplements may be helpful but lack data to support regular use.[108] Accurate anthropometric measurements (length/height, weight, head circumference) should be documented at every clinic visit, as well as regular dietary and PERT evaluation by a dietitian who has the expertise in managing EPI.[22] The North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition Pancreas Committee and ESPGHAN Cystic Fibrosis/Pancreas Working Group recommended monitoring children with CP for signs of growth impairment and malnutrition every 3–6 months.[37] Children with EPI should be more frequently seen during critical phases that increase the risk of malnutrition such as during infancy, at the time of initial diagnosis, and during pubescent growth spurt. Evidence from CF studies indicates early, aggressive management of nutrition

is associated with improved pulmonary function and overall survival.[10,109] Taking this into consideration, the CFF recommends to follow the anthropometric parameters every month during infancy and every 3 months beyond infancy as part of multidisciplinary CF care.[110] A weight for age > 10th percentile at 4 years of age has been shown to be associated with better adult height, better lung function, fewer CF-related complications, and increased survival.[40] From the epidemiologic study of CF patients collected between 1994 and 2005, weight for age < 50th percentile was noted to be a significant risk factor for mortality before 18 years of age regardless of forced expiratory volume at 1 second (FEV_1) at 6–8 years of age.[111]

Under 2 years of age, calculation of average daily weight gain, length, head circumference, and weight for length (WFL) is recommended for assessment of nutrition status. In children over 2 years of age through adulthood, BMI is utilized.[44,110] Current recommended anthropometric goals for CF patients include maintenance of a WFL (children 0–2 years) ≥ 50th percentile, weight for age (children 2–6 years) > 10th percentile, and BMI (2–18 years) ≥ 50th percentile.[44,112,113] For adults with CF, a BMI ≥ 23 kg/m^2 for men and 22 kg/m^2 for women is recommended.[44,112] These parameters are correlated with higher pulmonary function in both children and adults with CF. In most CF patients, linear growth continues to be stunted even in the setting of adequate weight and is likely due to multifactorial interactions among nutrition, proinflammatory cytokines, and decreased anabolism.[114] In children with SDS, JBS, and Pearson syndrome, reduced growth potential due to intrinsic growth failure also has been reported and should be taken into consideration in cases of refractory growth failure and ruling out all potential treatable causes.

Energy recommendations for CF patients with EPI are 110%–200% of the caloric requirements of healthy children of the same age, with 30%–40% of the calories from fat.[39,61] Energy needs are adjusted based on individual weight-gain patterns. Pubertal growth and parental height should be considered when evaluating an individual's growth. In CP, the effect of disease on the resting energy expenditure (REE) in children is unclear and an area that needs further exploration.[37] High-energy diet is recommended in adults with CP, as the REE may be up 1.5–1.8 times the basal energy expenditure in this population.[37]

The CFF use Centers for Disease Control and Prevention (CDC) charts when evaluating growth/weight-gain goals in relationship to clinical outcomes. In 2010, the American Academy of Pediatrics and the CDC recommended using the 2006 World Health Organization (WHO) growth charts for children younger than 2 years and 2000 CDC growth chart for children older than 2 years.[115] For CF children younger than 2 years, using WHO growth chart instead of CDC growth chart has some clinical implications, and several studies have compared the discrepancies in the utilization between these 2 charts.[57,116,117] Machogu et al utilized the CFF patient registry and studied 1155 patients born between 2001 and 2004.[57] Children with 50th WFL percentile at 2 years on the WHO growth chart had a lower but clinically normal FEV_1 at age 6 years than children at 50th WFL percentile on the CDC chart had.[57] About 43% who were plotted between 10th and 50th percentiles on the CDC chart were ≥50th percentile on the WHO chart.[57]

Using the CFF registry, Zhang et al compared the growth parameters from 1 to 24 months in 2587 children with CF.[116] WFL percentiles were similar between the 2 charts before 12 months of age, but a discrepancy of about 10 percentiles was noted from 12 to 24 months, with higher percentiles noted on the WHO chart than in the CDC chart. At 24 months of age, switching to CDC chart, about 27% of children with normal WFL (>50th) percentile on WHO charts appeared to have lower WFL (<50th) on CDC charts.[116] A 50th BMI percentile in CDC chart was comparable to a 70th percentile in WHO chart.[116] In another study utilizing the same registry, about 3000 CF patients were categorized into 3 groups based on WFL at 2 years of age. The first category included children with WFL < 50th percentile on both charts, the second one with WFL ≥ 50th percentile on WHO chart but not on CDC chart, and the third one with WFL ≥ 50th percentile on both charts.[117] Lung function and lung transplant–free survival were compared at 18 years of age. There was progressive increase in both pulmonary and survival outcome measures noted with an increase in the WFL percentiles.[117]

Apart from the traditional interpretation of WFL or BMI, emphasis on accruing lean body mass has been recently advocated for CF patients. The ESPEN-ESPGHAN-ECFS recommend incorporating analysis of body composition techniques such as DEXA and bioelectrical impedance analysis for CF patients along with the anthropometric measurements.[10] With increasing life span of CF patients, the consequences of obesity, overweight, and metabolic syndrome also have nutrition implications.[115]

Role of Enteral Tube Feeding

Despite a thorough evaluation and intervention by the multidisciplinary team, if individuals with EPI are not able to consume adequate nutrients orally to promote sufficient weight gain and growth, enteral tube feedings should be considered.[18,107] Enteral tube feedings include both short-term administration (usually <3 months) using nasogastric or nasojejunal tubes and long-term administration with gastrostomies, gastrojejunal tubes, or jejunal tubes.[18] Current recommendations for tube feeding in CF patients include administration of 30%–65% of their total estimated calorie needs as a nocturnal infusion.[107] This practice allows patients to receive supplemental calories in addition to their daytime oral diet. About 10%–12% of CF

patients need supplemental tube feedings.[118,119] Polymeric formulas are usually used, and semi-elemental formulas are used if the patient is intolerant to polymeric formulas.[107] Beyond infancy, high-energy formulas with 1.5–2 kcal/mL are usually preferred.[10] Evidence-based guidelines for administration of PERT for enteral tube feeding have not been established.[18,39] Current consensus on PERT management includes oral administration of PERT prior to the bolus feeds; however, at the time the guidelines were written, there were no recommended methods for enzyme administration with nocturnal tube feedings.[107,120] CF patients receiving nocturnal feeds are encouraged to take enzymes orally at the beginning of nocturnal feed and at the end of the feeding; also, if possible, PERT is provided in the middle of the feed.[120] For patients who are not able to take PERT orally, the microspheres can be administered via the feeding tube.[121] The practice of mixing enzymes with the enteral feeds can potentially lead to tube occlusion and inconsistent enzyme delivery.[121] A digestive lipase cartridge (RELiZORB, Alcresta Therapeutics, Inc., Newton, MA, USA) was introduced in 2015 and is approved for use in children (>5 years of age) and adults.[39] This cartridge has also been used in younger children. When formula transverses through the cartridge, triglycerides are hydrolyzed to free fatty acids and monoglycerides by the impregnated microbial lipase.[39,118] With the available evidence, the use of RELiZORB appears to be safe, convenient, and effective in CF patients requiring enteral feeds.[119,122] In a prospective study with participants' ages ranging 5–33 years, RELiZORB use was well tolerated and resulted in fat absorption with favorable increase in plasma and red blood cell levels of long-chain polyunsaturated fatty acids.[118]

Conclusions

Children with EPI should undergo frequent nutrition assessments and management by a multidisciplinary team. Causes of growth failure could be multifactorial. PERT is the mainstay of EPI management along with high-energy diet and fat-soluble vitamin supplementation. Aggressive management of nutrition in CF patients is associated with better survival. The literature on children regarding the impact of nutrition on EPI conditions other than CF is limited. Use of oral nutritional supplements should be considered early in the management of EPI. Enteral tube feeding should be offered to children with EPI who cannot meet the intake goals orally. Currently, the nutrition management of non-CF EPI in children is not well studied, and inferences from the CF literature are often necessary in caring for these patients.

Statement of Authorship

S. Sankararaman, T. Schindler, and T. J. Sferra contributed to the conception/design of the manuscript; S. Sankararaman, T. Schindler, and T. J. Sferra contributed to the acquisition, analysis, and interpretation of the data; S. Sankararaman drafted the manuscript; S. Sankararaman, T. Schindler, and T. J. Sferra critically revised the manuscript; S. Sankararaman, T. Schindler, and T. J. Sferra agree to be fully accountable for ensuring the integrity and accuracy of the work and read and approved the final manuscript.

References

1. Taylor CJ, Chen K, Horvath K, et al. ESPGHAN and NASPGHAN report on the assessment of exocrine pancreatic function and pancreatitis in children. *J Pediatr Gastroenterol Nutr*. 2015;61(1):144-153.
2. Shandro BM, Nagarajah R, Poullis A, Shandro BM, Nagarajah R, Poullis A. Challenges in the management of pancreatic exocrine insufficiency. *World J Gastrointest Pharmacol Ther*. 2018;9(5):39-46.
3. Durie P, Baillargeon J-D, Bouchard S, Donnellan F, Zepeda-Gomez S, Teshima C. Diagnosis and management of pancreatic exocrine insufficiency (PEI) in primary care: consensus guidance of a Canadian expert panel. *Curr Med Res Opin*. 2018;34(1):25-33.
4. Singh VK, Haupt ME, Geller DE, Hall JA, Diez PMQ. Less common etiologies of exocrine pancreatic insufficiency. *World J Gastroenterol 2017*. 2017;23(39):7059-7076.
5. Vujasinovic M, Valente R, Thorell A, et al. Pancreatic exocrine insufficiency after bariatric surgery. *Nutrients*. 2017;9(11):1241.
6. Keller J, Aghdassi AA, Lerch MM, Mayerle JV, Layer P. Tests of pancreatic exocrine function – clinical significance in pancreatic and non-pancreatic disorders. *Best Pr Res Clin Gastroenterol*. 2009;23(3):425-439.
7. Trout AT, Wallihan DB, Serai S, Abu-El-Haija M. Secretin-enhanced magnetic resonance cholangiopancreatography for assessing pancreatic secretory function in children. *J Pediatr*. 2017;188:186-191.
8. Keller J, Layer P. Human pancreatic exocrine response to nutrients in health and disease. *Gut*. 2005;54(suppl 6):vi1-vi28.
9. Lusman S, Sullivan J. Nutrition and growth in cystic fibrosis. *Pediatr Clin North Am*. 2016;63(4):661-678.
10. Turck D, Braegger CP, Colombo C, et al. ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children, and adults with cystic fibrosis. *Clin Nutr*. 2016;35(3):557-577.
11. Berry AJ. Pancreatic enzyme replacement therapy during pancreatic insufficiency. *Nutr Clin Pract*. 2014;29(3):312-321.
12. Fieker A, Philpott J, Armand M. Enzyme replacement therapy for pancreatic insufficiency: present and future. *Clin Exp Gastroenterol*. 2011;4:55-73.
13. Pongprasobchai S. Maldigestion from pancreatic exocrine insufficiency. *J Gastroenterol Hepatol*. 2013;28(suppl 4):99-102.
14. Othman MO, Harb D, Barkin JA. Introduction and practical approach to exocrine pancreatic insufficiency for the practicing clinician. *Int J Clin Pr*. 2018;72(2):e13066.
15. Domínguez-muñoz JE. Pancreatic exocrine insufficiency: Diagnosis and treatment. *J Gastroenterol Hepatol*. 2011;26(suppl 2):12-16.
16. Horvath K, Mehta DI, Hill ID. Endoscopic pancreatic function test (ePFT) and its indications. *J Pediatr Gastroenterol Nutr*. 2019. https://doi.org/10.1097/MPG.0000000000002230.
17. Durie PR. Pancreatic aspects of cystic fibrosis and other inherited causes of pancreatic dysfunction. *Med Clin North Am*. 2000;84(3):609-620, ix.
18. Schwarzenberg SJ, Bellin M, Husain SZ, et al. Pediatric chronic pancreatitis is associated with genetic risk factors and substantial disease. *J Pediatr*. 2016;166(4):890-896.
19. Bartels RH, Bourdon C, Potani I, et al. Pancreatic enzyme replacement therapy in children with severe acute malnutrition: a randomized controlled trial. *J Pediatr*. 2017;190:85-92.e2.

20. Pitchumoni CS. Pancreas in primary malnutrition disorders. *Am J Clin Nutr*. 1973;26(3):374-379.
21. Perez EA, Gutierrez JC, Koniaris LG, Neville HL, Thompson WR, Sola JE. Malignant pancreatic tumors: incidence and outcome in 58 pediatric patients. *J Pediatr Surg*. 2009;44(1):197-203.
22. Dror Y, Donadieu J, Koglmeier J, et al. Draft consensus guidelines for diagnosis and treatment of Shwachman-Diamond syndrome. *Ann N Y Acad Sci.* 2011;1242:40-55.
23. Dhanraj S, Matveev A, Li H, et al. Letter to blood to the editor: biallelic mutations in DNAJC21 cause Shwachman-Diamond syndrome. *Blood*. 2017;129(11):1557-1563.
24. Myers KC, Bolyard AA, Otto B, et al. Variable clinical presentation of Shwachman-Diamond syndrome: update from the North-American Shwachman- Diamond Syndrome Registry. *J Pediatr*. 2014;164(4):866-870.
25. Andolina JR, Morrison CB, Thompson AA, et al. Shwachman-Diamond syndrome: diarrhea, no longer required? *J Pediatr Hematol Oncol*. 2014;35(6):486-489.
26. Shimamura A. Shwachman-Diamond syndrome. *Semin Hematol*. 2006;43(3):178-188.
27. Pichler J, Meyer R, Köglmeier J, Ancliff P, Shah N. Nutritional status in children with Shwachman-Diamond syndrome. *Pancreas*. 2015;44(4):590-595.
28. Ginzberg H, Shin J, Ellis L, et al. Shwachman syndrome: phenotypic manifestations of sibling sets and isolated cases in a large patient cohort are similar. *J Pediatr*. 1999;135(1):81-88.
29. Johanson A, Blizzard R. A syndrome of congenital aplasia of the alae nasi (beak-shaped appearance), deafness, hypothyroidism, dwarfism, absent permanent teeth, and malabsorption. *J Pediatr*. 1971;79(6):982-987.
30. Zenker M, Mayerle J, Lerch MM, et al. Deficiency of UBR1, a ubiquitin ligase of the N-end rule pathway, causes pancreatic dysfunction, malformations and mental retardation (Johanson-Blizzard syndrome). *Nat Genet*. 2005;37(12):1345-1350.
31. Sukalo M, Fiedler A, Guzman S, et al. Mutations in the human UBR1 gene and the associated phenotypic spectrum. *Hum Mutat*. 2014;35(5):521-531.
32. Zenker M, Mayerle J, Reis A, Lerch MM. Genetic basis and pancreatic biology of Johanson-Blizzard syndrome. *Endocrinol Metab Clin North Am*. 2006;35(2):243-253.
33. Falcon C, Howard T. Failure, an infant with Pearson syndrome: a rare cause of congenital sideroblastic anemia and bone marrow. *Blood*. 2017;129(19):2710.
34. Farruggia P, Di A, Rita C, et al. Pearson syndrome: a retrospective cohort study from the Marrow Failure Study Group of A. I. E. O. P. (Associazione Italiana Emato-Oncologia Pediatrica). *JIMD Rep*. 2016;26:37-43.
35. Drera B, Ferrari D, Cavalli P, Poggiani C. Case report. A case of neonatal Jeune syndrome expanding the phenotype. *Clin Case Reports Publ.* 2014;2(4):156-158.
36. Posovszky C. Congenital intestinal diarrhoeal diseases: a diagnostic and therapeutic challenge. *Best Pract Res Clin Gastroenterol*. 2016;30(2):187-211.
37. Abu-El-Haija M, Uc A, Werlin SL, et al. Nutritional considerations in pediatric pancreatitis: a position paper from the NASPHAN Pancreas Committee. *J Pediatr Gastroenterol Nutr*. 2018;67(1):131-143.
38. Wieczorek-Filipiak M, Drzymała-Czyz S, Szczepanik M, et al. Fecal fat concentration and excretion in the first 2 years of life: a cross-sectional study. *J Pediatr Gastroenterol Nutr*. 2019;68(2):285-289.
39. Giguere-rich C, Mathew A, Reid E, Autore K. Use of an in-line digestive cartridge with enteral nutrition improves the weight trajectory of 2 children with cystic fibrosis complicated by another medical diagnosis. *Nutr Clin Pract*. 2018;33(2):286-294.
40. Yen EH, Ms HQ, Borowitz D. Better nutritional status in early childhood is associated with improved clinical outcomes and survival in patients with cystic fibrosis. *J Pediatr*. 2013;162(3):530-535.e1.
41. Wilschanski M, Braegger CP, Colombo C, et al. Highlights of the ESPEN-ESPGHAN-ECFS guidelines on cystic fibrosis. *J Pediatr Gastroenterol Nutr*. 2016;63(6):671-675.
42. Walkowiak J, Nousia-Arvanitakis S, Henker J, Stern M, Sinaasappel M, Dodge JA. Indirect pancreatic function tests in children. *J Pediatr Gastroenterol Nutr*.2005;40(2):107-114.
43. Horvath K, Mehta D, Hill ID. Assessment of exocrine pancreatic function during endoscopy in children. *J Pediatr Gastroenterol Nutr*. 2019; 68(6):768-776.
44. Borowitz D, Baker RD, Stallings V. Consensus report on nutrition for pediatric patients with cystic fibrosis. *J Pediatr Gastroenterol Nutr*. 2002;35(3):246-259.
45. Woestenenk J, van der Ent C, Houwen R. Pancreatic enzyme replacement therapy and coefficient cystic fibrosis. *J Pediatr Gastroenterol Nutr*. 2015;61(3):355-360.
46. Van De Vijver E, Desager ÃK, Mulberg AE, et al. Treatment of infants and toddlers with cystic malabsorption with pancrelipase MT. *J Pediatr Gastroenterol Nutr*. 2011;53(1):61-64.
47. Leeds JS, Oppong K, Sanders DS. The role of fecal elastase-1 in detecting exocrine pancreatic disease. *Nat Rev Gastroenterol Hepatol*. 2011;8(7):405-415.
48. van Dijk-van Aalst K, Van Den Driessche M, van Der Schoor S, et al. 13C mixed triglyceride breath test: a noninvasive method to assess lipase activity in children. *J Pediatr Gastroenterol Nutr*. 2001;32(5):579-585.
49. Balci NC, Smith A, Momtahen AJ, et al. MRI and S-MRCP findings in patients with suspected chronic pancreatitis: correlation with endoscopic pancreatic function testing (ePFT). *J Magn Reson Imaging*. 2010;31(3):601-606.
50. De La Iglesia-García D, Huang W, Szatmary P, et al. Efficacy of pancreatic enzyme replacement therapy in chronic pancreatitis: systematic review and meta-analysis. *Gut*. 2017;66(8):1474-1486.
51. Wooldridge JL, Heubi JE, Amaro-Galvez R, et al. EUR-1008 pancreatic enzyme replacement is safe and effective in patients with cystic fibrosis and pancreatic insufficiency. *J Cyst Fibros*. 2009;8(6):405-417.
52. Corey M, McLaughlin FJ, Williams M, Levison H. A comparison of survival, growth, and pulmonary function in patients with cystic fibrosis in Boston and Toronto. *J Clin Epidemiol*. 1988;41(6):583-591.
53. Schechter MS, Michel S, Liu S, et al. Relationship of initial pancreatic enzyme replacement therapy dose with weight gain in infants with cystic fibrosis. *J Pediatr Gastroenterol Nutr*. 2018;67(4):520-526.
54. Seiler CM, Izbicki J, Varga-Szabo L, et al. Randomised clinical trial: a 1-week, double-blind, placebo-controlled study of pancreatin 25 000 Ph. Eur. minimicrospheres (Creon 25000 MMS) for pancreatic exocrine insufficiency after pancreatic surgery, with a 1-year open-label extension. *Aliment Pharmacol Ther*. 2013;37(7):691-702.
55. Trapnell BC, Strausbaugh SD, Woo MS, et al. Efficacy and safety of PANCREAZE(R) for treatment of exocrine pancreatic insufficiency due to cystic fibrosis. *J Cyst Fibros*. 2011;10(5):350-356.
56. Gubergrits N, Malecka-Panas E, Lehman GA, et al. A 6-month, open-label clinical trial of pancrelipase delayed-release capsules (Creon) in patients with exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery. *Aliment Pharmacol Ther*. 2011;33(10):1152-1161.
57. Machogu E, Cao Y, Miller T, et al. Comparison of WHO and CDC growth charts in predicting pulmonary outcomes in cystic fibrosis. *J Pediatr Gastroenterol Nutr*. 2015 Mar;60(3):378-383.

58. Trapnell BC, Maguiness K, Graff GR, Boyd D, Beckmann K, Caras S. Efficacy and safety of Creon 24,000 in subjects with exocrine pancreatic insufficiency due to cystic fibrosis. *J Cyst Fibros*. 2009;8(6):370-377.
59. Cystic Fibrosis Foundation Patient Registry, 2017 Annual Data Report. Bethesda, Maryland. https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2017-Patient-Registry-Annual-Data-Report.pdf. Accessed March 18, 2019.
60. Cystic Fibrosis Foundation, Borowitz D, Robinson KA, et al. Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. *J Pediatr*. 2009;155(6 suppl):S73-S93.
61. Saxby N, Painter C, Kench A, King S, Crowder T, van der Haak N, the Australian and New Zealand Cystic Fibrosis Nutrition Guideline Authorship Group. In: Bell SC, ed. *Nutrition Guidelines for Cystic Fibrosis in Australia and New Zealand*. Thoracic Society of Australia and New Zealand, Sydney; 2017. https://www.thoracic.org.au/documents/item/1045. Accessed on March 18, 2019.
62. Borowitz D, Gelfond D, Maguiness K, Heubi JE, Ramsey B. Maximal daily dose of pancreatic enzyme replacement therapy in infants with cystic fibrosis: a reconsideration. *J Cyst Fibros*. 2013;12(6):784-785.
63. Kalnins, D, Wilschanski M. Maintenance of nutritional status in patients with cystic fibrosis: new and emerging therapies. *Drug Des Devel Ther*. 2012;6:151-161.
64. Kunzelmann K, Schreiber R, Hadorn HB. Bicarbonate in cystic fibrosis. *J Cyst Fibros*. 2017;16(6):653-662.
65. Van Der Haak N, Boase J, Davidson G, et al. Preliminary report of the 13 C-mixed triglyceride breath test to assess timing of pancreatic enzyme replacement therapy in children with cystic fibrosis. *J Cyst Fibros*. 2016;15(5):669-674.
66. Konstan MW, Accurso FJ, Nasr SZ, Ahrens RC, Graff GR. Efficacy and safety of a unique enteric-coated bicarbonate-buffered pancreatic enzyme replacement therapy in children and adults with cystic fibrosis. *Clin Investig*. 2013;3(8):723-729.
67. Chamarthy LM, Reinstein LJ, Schnapf B, Good RA, Bahna SL. Desensitization to pancreatic enzyme intolerance in a child with cystic fibrosis. *Pediatrics*. 1998;102(1):e13.
68. Adler, J, Saif M. Pancrealipse-induced hypersensitivity reaction: case report and review of literature. *J Pancreas*. 2018;19(5):273-275.
69. van der Doef HP, Kokke FT, Beek FJ, Woestenenk JW, Froeling SP,Houwen RH. Constipation in pediatric cystic fibrosis patients: an underestimated medical condition. *J Cyst Fibros*. 2010;9(1): 59-63.
70. Borowitz DS, Grand RJ, Durie PR. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. Consensus Committee. *J Pediatr*. 1995;127(5):681-684.
71. FitzSimmons SC, Burkhart GA, Borowitz D, et al. High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. *N Engl J Med*. 1997;336(18):1283-1289.
72. Andersen D. Cystic fibrosis of the pancreas and its relation to celiac disease: a clinical and pathologic study. *Am J Dis Child*. 1938;56(2):344-399.
73. Rana M, Wong-See D, Katz T, et al. Fat-soluble vitamin deficiency in children and adolescents with cystic fibrosis. *J Clin Pathol*. 2014;67(7):605-608.
74. Siwamogsatham O, Dong W, Binongo JN, et al. Relationship between fat-soluble vitamin supplementation and blood concentrations in adolescent and adult patients with cystic fibrosis. *Nutr Clin Pract*. 2014;29(4):491-497.
75. Cystic Fibrosis Specific Multivitamins. https://www.cff.org/Life-With-CF/Daily-Life/Fitness-and-Nutrition/Nutrition/Getting-Your-Nutrients/Vitamin-Comparison-Chart-for-CF-Specific-Multivitamins.pdf%0A%0A. Accessed March 18, 2019.
76. Institute of Medicine. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. Washington, DC: The National Academies Press; 2001. https://doi.org/10.17226/10026. Accessed on March 18, 2019.
77. Institute of Medicine. *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids*. Washington, DC: The National Academies Press; 2000. https://doi.org/10.17226/9810. Accessed on March 18, 2019.
78. Institute of Medicine. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: The National Academies Press; 2011. https://doi.org/10.17226/13050. Accessed on March 18, 2019.
79. Tangpricha V, Kelly A, Stephenson A, et al. An update on the screening, diagnosis, management, and treatment of vitamin D deficiency in individuals with cystic fibrosis: evidence-based recommendations from the Cystic Fibrosis Foundation. *J Clin Endocrinol Metab*. 2012;97(4):1082-1093.
80. Duggan C, Colin AA, Agil A, Higgins L, Rifai N. Vitamin A status in acute exacerbations of cystic fibrosis. *Am J Clin Nutr*. 1996;64(4):635-639.
81. Carr SB, McBratney J. The role of vitamins in cystic fibrosis. *J R Soc Med*. 2000;93(suppl 38):14-19.
82. Rayner RJ, Tyrrell JC, Hiller EJ, et al. Night blindness and conjunctival xerosis caused by vitamin A deficiency in patients -with cystic fibrosis. *Arch Dis Child*. 1989;64(8):1151-116.
83. Bines JE, Truby HD, Armstrong DS, Carzino R, Grimwood K. Vitamin A and E deficiency and lung disease in infants with cystic fibrosis. *J Paediatr Child Health*. 2005;41(12):663-668.
84. Christian P, West KP Jr. Interactions between zinc and vitamin A: an update. *Am J Clin Nutr*. 1998;68(2 suppl):435-441.
85. Navarro J, Desquilbet N. Depressed plasma vitamin A and retinol-binding protein in cystic fibrosis correlations with zinc deficiency. *Am J Clin Nutr*. 1981;34(7):1439.
86. Maqbool, A, Graham-Maar RC, Schall JI, Babette SZ, Stallings V. Vitamin A intake and elevated serum retinol levels. *J Cyst Fibros*. 2008;7(2):137-141.
87. Graham-Maar RC, Schall JI, Stettler N, Zemel BS, Stallings VA. Elevated vitamin A intake and serum retinol in preadolescent children with cystic fibrosis. *Am J Clin Nutr*. 2006;84(1):174-182.
88. Ho T, Gupta S, Brotherwood M, et al. Increased serum vitamin A and E levels after lung transplantation. *Transplantation*. 2011;92(5):601-606.
89. Stephenson A, Brotherwood M, Robert R, et al. Increased vitamin A and E levels in adult cystic fibrosis patients after lung transplantation. *Transplantation*. 2005;79(5):613-615.
90. Ferrer-Mayorga G, Larriba MJ, Crespo P, Muñoz A. Mechanisms of action of vitamin D in colon cancer. *J Steroid Biochem Mol Biol*. 2019;185:1-6.
91. Grossmann RE, Zughaier SM, Liu S, Lyles RH, Tangpricha V. Impact of vitamin D supplementation on markers of inflammation in adults with cystic fibrosis hospitalized for a pulmonary exacerbation. *Eur J Clin Nutr*. 2012;66(9):1072-1074.
92. Martineau AR, Jolliffe DA, Greenberg L, et al. Vitamin D supplementation to prevent acute respiratory infections: individual participant data meta-analysis. *Heal Technol Assess*. 2019;23(2):1-44.
93. Horwitt MK, Harvey CC, Dahm CH Jr., Searcy MT. Relationship nutritional, between tocopherol and serum lipid levels for determination of adequacy. *Ann N Y Acad Sci*. 1972;203:223-236.
94. Ford L, Farr J, Morris P, Berg J. The value of measuring serum cholesterol-adjusted vitamin E in routine practice. *Ann Clin Biochem*. 2006;43(Pt 2):130-134.
95. Sapiejka E, Krzyzanowska-Jankowska P, Wenska-Chyzy E, et al. Vitamin E status and its determinants in patients with cystic fibrosis. *Adv Med Sci*. 2018;63(2):341-346.

96. Farrell PM, Bieri JG, Fratantoni JF, Wood RE, di Sant'Agnese PA. The occurrence and effects of human vitamin E deficiency: a study in patients with cystic fibrosis. *J Clin Invest*. 1977;60(1):233-241.
97. Wilfond BS, Farrell PM, Laxova A, Mischler E. Severe hemolytic anemia associated with vitamin E deficiency in infants with cystic fibrosis. Implications for neonatal screening. *Clin Pediatr (Phila)*. 1994;33(1):2-7.
98. Koscik RL, Farrell PM, Kosorok MR, et al. Cognitive function of children with cystic fibrosis: deleterious effect of early malnutrition. *Pediatrics*. 2004;113(6):1549-1558.
99. Huang SH, Schall JI, Zemel BS, Stallings VA. Vitamin E status in children with cystic fibrosis and pancreatic insufficiency. *J Pediatr*. 2006;148(4):556-559.
100. Stigliano S, Waldthaler A, Martinez-moneo E, et al. Vitamins D and K as factors associated with osteopathy in chronic pancreatitis: a prospective multicentre study (P-BONE study). *Clin Transl Gastroenterol*. 2018;9(10):197. https://doi.org/10.1038/s41424-018-0066-8
101. Mosler K, von Kries R, Vermeer C, Saupe J, Schmitz T, Schuster A. Assessment of vitamin K deficiency in CF–how much sophistication is useful? *J Cyst Fibros*. 2003;2(2):91-96.
102. Dougherty KA, Schall JI, Stallings V. Suboptimal vitamin K status despite supplementation in children and young adults with cystic fibrosis. *Am J Clin Nutr*. 2010;92(3):660-667.
103. Torstenson OL, Humphrey GB, Edson JR, Warwick WJ. Cystic fibrosis presenting with severe hemorrhage due to vitamin K malabsorption: a report of three cases. *Pediatrics*. 1970;45(5):857-861.
104. Maqbool A, Schall JI, Garcia-Espana JF, Zemel BS, Strandvik B, Stallings VA. Serum linoleic acid status as a clinical indicator of essential fatty acid status in children with cystic fibrosis. *J Pediatr Gastroenterol Nutr*. 2008;47(5):635-644.
105. Zedek D, Morrell DS, Graham M, Goodman D, Groben P. Acrodermatitis enteropathica-like eruption and failure to thrive as presenting signs of cystic fibrosis. *J Am Acad Dermatol*. 2008;58(2 suppl):S5-S8.
106. Hoppe B, von Unruh GE, Blank G, et al. Absorptive hyperoxaluria leads to an increased risk for urolithiasis or nephrocalcinosis in cystic fibrosis. *Am J Kidney Dis*. 2005;46(3):440-445.
107. Schwarzenberg SJ, Hempstead SE, McDonald CM, et al. Enteral tube feeding for individuals with cystic fibrosis: Cystic Fibrosis Foundation evidence-informed guidelines. *J Cyst Fibros*. 2016;15(6):724-735.
108. Smyth RL, Rayner O. Oral calorie supplements for cystic fibrosis. *Cochrane Database Syst Rev*. 2014;(11):CD000406. https://doi.org/10.1002/14651858.CD000406.pub4.
109. Fink AK, Deena D, Ma RL, Marshall BC, Goss CH, Morgan WJ. Data that empower: the success and promise of CF patient registries. *Pediatr Pulmonol*. 2017;52(S48):S44-S51.
110. Sullivan JS, Mascarenhas MR. Nutrition: prevention and management of nutritional failure in cystic fibrosis. *J Cyst Fibros*. 2017;16(suppl 2):S87-S93.
111. McColley SA, Schechter MS, Morgan WJ, Pasta DJ, Craib ML, Konstan MW. Risk factors for mortality before age 18 years in cystic fibrosis. *Pediatr Pulmonol*. 2017;52(7):909-915.
112. Stallings VA, Stark LJ, Robinson KA, Feranchak AP, Quinton H, Clinical Practice Guidelines on Growth and Nutrition Subcommittee; Ad Hoc Working Group. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a system. *J Am Diet Assoc*. 2008;108(5):832-839.
113. Lahiri T, Hempstead SE, Brady C, et al. Clinical practice guidelines from the Cystic Fibrosis Foundation for preschoolers with cystic fibrosis. *Pediatrics*. 2016;137(4):e20151784.
114. Munck A, Boulkedid R, Weiss L, et al. Nutritional status in the first 2 years of life in cystic fibrosis diagnosed by newborn screening. *J Pediatr Gastroenterol Nutr*. 2018;67(1):123-130.
115. Declercq D, Van Meerhaeghe S, Marchand S, et al. The nutritional status in CF: being certain about the uncertainties. *Clin Nutr ESPEN*. 2019;29:15-21.
116. Zhang Z, Shoff SM, Lai HJ. Comparing the use of Centers for Disease Control and Prevention and World Health Organization Growth charts in children with cystic fibrosis through 2 years of age. *J Pediatr*. 2015;167(5):1089-1095.
117. Usatin D, Yen EH, McDonald C, Asfour F, Pohl J, Robson J. Differences between WHO AND CDC early growth measurements in the assessment of cystic fibrosis clinical outcomes. *J Cyst Fibros*. 2017;16(4):503-509.
118. Stevens J, Wyatt C, Brown P, Patel D, Grujic D, Freedman SD. Absorption and safety with sustained use of RELiZORB evaluation (ASSURE) study in patients with cystic fibrosis receiving enteral feeding. *J Pediatr Gastroenterol Nutr*. 2018;67(4):527-532.
119. Freedman S, Orenstein D, Black P, et al. Increased fat absorption from enteral formula through an in-line digestive cartridge in patients with cystic fibrosis. *J Pediatr Gastroenterol Nutr*. 2017;65(1):97-101.
120. Freedman S. Options for addressing exocrine pancreatic insufficiency in patients receiving enteral nutrition supplementation. *Am J Manag Care*. 2017;23(12 suppl):S220-S228.
121. Ferrie S, Graham C, Hoyle M. Pancreatic enzyme supplementation for patients receiving enteral feeds. *Nutr Clin Pr*. 2011;26(3):349-351.
122. Schwarzenberg SJ, Borowitz D; 20 gastroenterologists, 23 CF physicians 17 CF dietitians and 1 PharmD. Challenging barriers to an option for improved provision of enteral nutrition. *J Cyst Fibros*. 2019;18(4):447-449.