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Nutrition Management of Cystic Fibrosis in the 21st Century

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Abstract

Despite significant advancements made in life expectancy over the past century, cystic fibrosis remains a life-threatening genetic disease that affects the gastrointestinal tract, and it has significant impact on the nutrition status of those with the disease. Nutrition management includes a high-calorie/high-fat diet, pancreatic enzyme replacement therapy, vitamin and mineral replacement, and enteral support as needed. As patients are living longer, clinicians may encounter patients with cystic fibrosis in obstetrician offices, endocrine clinics, or hospital settings, owing to lung transplantation or for treatment for distal intestinal obstruction syndrome. (*Nutr Clin Pract*. XXXX;xx:xx-xx)

Keywords

cystic fibrosis; pancreas; exocrine pancreas insufficiency; lung diseases; diabetes mellitus; nutrition therapy

Background

Cystic fibrosis (CF) is a life-shortening autosomal recessive genetic disorder that is the result of a defect in the CF transmembrane conductance regulator (CFTR) on chromosome 7.[1] This genetic defect results in defective transport of chloride across the cell membrane, leading to thick mucus secretions in the respiratory, digestive, and reproductive tracts. It also leads to excessive losses of sodium and chloride in sweat.

Manifestations of the disease often include frequent respiratory infections resulting in progressive scarring of lung tissue, impaired absorption resulting in suboptimal weight gain and growth, and impaired fertility.

Advancements in therapies have led to significant improvements in life expectancy over the past century. When CF was first recognized as a clinical entity in 1938 by Dorothy Andersen, most died in infancy from malnutrition.[2] Life expectancy now has reached mid- to late 30s owing to advancements in nutrition and respiratory treatments.

Among these advancements was the discovery of the CF gene in 1989. Since then, >1500 mutations of CFTR have been identified, which can cause various symptoms of ranging severity—from absence of the vas deferens (leading to infertility in males) to pancreatic insufficiency (PI) and progressive bronchiectasis.[3] About 50% of patients with CF carry 2 copies of the delta F508 mutation, and almost 90% of patients carry 1 copy of the mutation.[3] This mutation is associated with PI, particularly when a patient carries 2 copies of the gene. All 50 states now conduct newborn screening within the first 2–3 days of life, and the majority of cases of CF are now diagnosed within the first month of life.

Approximately 28,000 people with CF in the United States are part of the Cystic Fibrosis Foundation (CFF) patient registry; more than half are now adults.[4] There are 110 care centers across the United States that offer multidisciplinary specialty care to those affected with CF; team members include physicians, dietitians, social workers, nurses, and respiratory and/or physical therapists. Patients are followed quarterly, and routine care guidelines generally involve pulmonary function testing, measurement of weight and height/length, respiratory cultures, annual laboratory work, and at least annual assessments by multidisciplinary team members.[4]

In 2013, the first CFTR potentiator drug (VX-770, also known as ivacaftor) became available on the market to treat patients aged ≥6 years who carry the G551D mutation (approximately 4% of the CF population).[4,5] Ivacaftor has shown great promise in the CF community, leading to significant improvements in pulmonary function, weight, and CFTR activity as compared with placebo for those who carry the

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G551D mutation, and it offers much hope for other CFTR potentiator drugs currently being studied for more common mutations, such as delta F508.[4]

Nutrition and CF

Malnutrition was once thought of as an inevitable consequence of CF. Older pancreatic enzyme preparations were not enteric coated; as a result, much of the active enzyme was destroyed by gastric acid, leading to symptoms of steatorrhea whenever patients with CF consumed fat in their diet. A low-fat diet was recommended for many years as a way to control symptoms; however, severe malnutrition was a consequence of inadequate caloric intake, and poor growth was common. The evolution of enteric-coated enzymes in the 1970s and the results of a hallmark study in the 1980s—which showed that a high-fat diet led to improved nutrition status and longer survival—changed the nutrition management of CF.[6] Today, achieving and maintaining optimal nutrition status is viewed as a critical component of CF care. Indeed, research continues to support the important role of optimal nutrition status in improving clinical outcomes in CF. Yen et al showed an association between patients who had a greater weight at age 4 and greater height, better pulmonary function, fewer complications of CF, and better survival through age 18 years.[7] An analysis of the European CF patient registry indicated that CF patients with a lower body mass index (BMI) experience a sixfold-increased odds ratio of having severe lung disease as compared with patients with normal BMI.[8] As a result of more focus and attention toward improving nutrition outcomes in individuals with CF, improvements in weight and height percentiles have been noted over the past 3 decades; however, they have not yet achieved growth rates seen in healthy children without CF in the United States.[4]

Evidence-based nutrition goals based on age and sex for individuals with CF, based on U.S. CFF registry data analysis, are as follows[9]:

Birth–24 months: 50th-percentile weight/length (Centers for Disease Control and Prevention growth chart)
2–20 years: 50th-percentile BMI (Centers for Disease Control and Prevention growth chart)
≥*20 years:* women–BMI, 22; men–BMI, 23

Estimating energy needs can be complicated, and it is important to monitor weight gain to gauge response to nutrition interventions. Presence and degree of malabsorption (which can be difficult to quantify), sex, degree of pulmonary involvement, and secondary complications (eg, liver disease) can affect energy needs.[10,11] Ranges of 110%–200% of that of individuals without CF have been recommended by various sources.[9,12]

Infants with CF should receive human milk, similar to what is recommended for all healthy, full-term infants, to receive the benefits associated with breast milk feedings and possibly other benefits specific to infants with CF.[13] If human milk is not available, standard infant formula is an appropriate choice; enzyme replacement therapy is necessary for all infants with PI regardless of the type of feeding chosen.[13] Feedings, enzyme replacement therapy, and vitamin/mineral therapy should be managed by a CF center or in conjunction with a CF care team who will eventually be managing the infant if he or she is temporarily managed at an outside facility.

Once on solid foods, most individuals with CF are managed with a high-calorie diet, composed of a high-fat intake (35%–40% of energy needs) to help make it easier to meet the high-calorie demand.[14] In general, patients who take in adequate calories also consume adequate protein.[12] Healthy eating behaviors and positive meal-time environments should be encouraged from a young age, since problematic eating behaviors, such as picky and slow eating, have been described in the literature.[15] Promoting the use of high-calorie, high-fat additives to foods and beverages—such as oils/butter, cheese, nut butters, and avocado—can help meet high-energy demands without putting additional burden of increasing volume of food needing to be consumed by the patient.

Pancreatic Insufficiency

PI is the primary cause of malabsorption in individuals with CF; CFTR dysfunction at the apical surface of epithelial cells of pancreatic ducts results in ductal plugging, obstruction, and progressive damage to the pancreas.[16,17] Nutrient malabsorption does not occur until only 1%–2% of residual capacity of pancreatic enzyme secretion remains, known as PI.[16,17]

Pancreatic disease develops in utero as evidenced by the presence of PI in infancy.[16] However, some patients with CF are not diagnosed as having PI until they are toddlers and, in a few cases, not until they are adults. There are close associations between pancreatic phenotype—PI or pancreatic sufficient (PS)—and genotype, with mild CFTR mutations more likely to result in PS.[16,17] Eighty to ninety percent of patients with CF require pancreatic enzyme replacement therapy (PERT).[18]

Subjective symptoms of maldigestion secondary to PI can include frequent stooling, steatorrhea (large, oily, malodorous stools), excess flatus, abdominal bloating, abdominal pain, and yellow- or clay-colored stools that may or may not float but do often fall apart or are not formed at all.[16,19] Patients may have trouble gaining weight despite a voracious appetite. However, since these symptoms can mimic many other gastrointestinal disturbances, pancreatic function should always be confirmed using diagnostic tools.

Two noninvasive tests can confirm PI. The fecal elastase 1 test is a qualitative study that requires a small stool sample and is therefore easily obtained. Fecal elastase 1 is not affected by exogenous enzymes, so patients can be taking enzyme products at the time that the stool is collected for study.[19,20] Fecal elastase 1 values <200 μg/g show PI.[18] Loose, watery stools may result in a false positive, so it is important to repeat the test to confirm results, especially if the stools were loose at the time

Table 1. Pancreatic Enzyme Dosing and Administration Guidelines.[17]

Pancreatic Enzyme Dosing	Pancreatic Enzyme Administration
Based on lipase units/kg/meal	<4 y of age: begin with 1000 lipase units/kg/meal or 10,000 lipase units/kg/d divided into number of feedings/d
	>4 y of age: begin with 500 lipase/kg/meal
	Increase up to 2500 lipase units/kg/meal or 10,000 lipase units/kg/d. Use caution with doses above these levels.
	Half of meal dose given with snacks
Based on lipase units/g of fat eaten	Infant formula or breast milk: 2000–4000 lipase units/120 mL
	Solids and liquids: 500–4000 lipase units/g of fat eaten
	Mean of 1800 lipase units/g of fat eaten/d in divided doses. Use caution with doses >4000 lipase units/g of fat eaten
Enzyme administration guidelines	Enzyme capsules should be swallowed whole. For infants or children who cannot swallow pills, enzyme beads may mixed in a small amount of acidic food (pH ≤4.5) that does not require chewing (eg, applesauce)
	Enzymes are given before and/or during all meals and snacks, including milk and oral supplements

of testing.[19,20] A 72-hour fecal fat study can be used as a quantitative measure of absorption; since it is more cumbersome, it is generally used only to determine effectiveness of PERT.[19]

PI results in poor digestion and absorption of macronutrients (ie, fat, protein, and carbohydrate) and fat-soluble vitamins A, D, E, and K . The goal of treating PI is to optimize nutrient absorption, resulting in improved weight gain and growth, and to prevent nutrient deficiencies. Pancrelipase products consist of a mixture of porcine lipase, protease, and amylase. Most products are enteric-coated microspheres or microtablets contained within a gelatin capsule. The enteric coating protects the enzymes from gastric acid degradation, ideally being activated within the duodenum in an alkaline environment (pH >5.0–5.5).[19]

Enzymes can be dosed on the basis of a patient's weight and/or fat intake; see Table 1 for dosing and administration guidelines. Evaluating response to enzymes should be a routine part of the nutrition assessment, which includes monitoring for bulky, oily, light-colored stools; symptoms of gastrointestinal discomfort (including excessive flatus and/or abdominal pain); and weight gain in the context of caloric intake.[17] Many factors may contribute to suboptimal response, including lack of adherence, a "grazing" eating pattern (making enzyme dosing more difficult), and physiologic abnormalities such as hyperacidity of the small bowel or delayed gastric emptying.[17] Medications to decrease acid production, such as H2 antagonist or proton pump inhibitor, are often used as adjunctive therapy to alkalinize the proximal small intestine and increase enzyme efficacy.[17]

Table 2 contains current enzyme preparations on the market in the United States.

Adverse side effects of PERT are rare, but fibrosing colonopathy, resulting in colonic strictures, is associated with ingestion of large quantities of PERT (>6000 lipase units per kilogram per meal for >6 months).[18]

Vitamins and Minerals

Prior to the widespread use of newborn screening to diagnose CF, symptoms of overt vitamin and mineral deficiencies often were initial signs indicative of the CF diagnosis.[21,22] Fat-soluble vitamin deficiencies and zinc deficiency are often present at the time of diagnosis by newborn screening; therefore, initiation of vitamin and mineral supplementation at diagnosis is imperative, followed by testing of serum levels of fat-soluble vitamins (A, 25-hydroxy D, E) and prothrombin time or protein induced in vitamin K absence 3–4 months following initiation of therapy.[13,22,23] The CFF newborn care guidelines provide guidance for newborn care, including vitamin and mineral supplementation.[13]

Persons who have CF and PI are at risk for fat-soluble vitamin and certain mineral deficiencies despite appropriate use of PERT and therefore should receive specific daily vitamin supplementation. The supplementation is often above the upper limit as recommended by the dietary reference intakes of the National Academy of Sciences. There is evidence that pancreatic-sufficient persons require supplements of the fat-soluble vitamins.[24,25] With exception of newborns, vitamin levels are assessed at the time of diagnosis.[26] For established patients, it is recommended that assessment of fat-soluble vitamins and, as indicated, minerals be done annually and following any change (usually 3 months) to usual nutrition therapy prior to prescription of vitamin or mineral supplements.[26] Table 3 provides the recommended schedule of assessment.[26]

CF-specific vitamins contain fat- and water-soluble vitamins as well as zinc and reflect current vitamin research as it relates to CF. The content of these products is provided in Table 4. Vitamin D recommendations have been published by the CFF, and Table 5 document provide step-by-step vitamin D dosing recommendations.[27] To enhance absorption, it is recommended that fat-soluble vitamins be taken with PERT and a fat-containing food or drink.

Table 2. Food and Drug Administration–Approved Pancreatic Enzyme Brands.

	Units		
Enzyme	Lipase	Protease	Amylase
Creon (pancrelipase)[a]			
3000	3000	9500	15,000
6000	6000	19,000	30,000
12,000	12,000	38,000	60,000
24,000	24,000	76,000	120,000
36,000	36,000	114,000	180,000
Pancreaze (pancrelipase)[b]			
4200: MT4	4200	10,000	17,500
10,500: MT10	10,500	25,000	43,750
16,800: MT16	16,800	40,000	70,000
21,000: MT20	21,000	37,000	61,000
Pertzye (pancrelipase)[c]			
8000	8000	28,750	30,250
16,000	16,000	57,500	60,500
Ultresa (pancrelipase)[d]			
4000	4000	8000	8000
13,800	13,800	27,600	27,600
20,700	20,700	41,400	41,400
23,000	23,000	46,000	46,000
Viokace (pancrelipase)[e]			
10,400 (round)	10,400	39,150	39,150
20,880 (oval)	10,880	78,300	78,300
Zenpep (pancrelipase)[f]			
3000	3000	10,000	16,000
5000	5000	17,000	27,000
10,000	10,000	34,000	55,000
15,000	15,000	51,000	82,000
20,000	20,000	68,000	109,000
25,000	25,000	85,000	136,000
40,000	40,000	136,000	218,000

[a]Manufacturer: Abbvie Inc, http://www.creon.com.
[b]Manufacturer: Janssen Pharmaceuticals, http://www.pancreaze.net.
[c]Bicarbonate buffered. Manufacturer: Chiesi, http://www.pertzye.com.
[d]Manufacturer: Actavis Inc, http://www.ultresa.com.
[e]Nonenteric coated. Manufacturer: Actavis Inc, http://www.viokace.com.
[f]Manufacturer: Actavis Inc, http://www.zenpep.com.

The major minerals of concern in CF are sodium chloride and zinc. Individuals with CF lose excessive sodium chloride in their sweat; therefore, they require liberal amounts of salt in their diet to avoid salt depletion, particularly when they are sweating. For all full-term infants who have CF, the recommendation is 1/8 teaspoon of table salt daily, with an increase to 1/4 teaspoon at 6 months of age, if the infant is on the growth curve for weight. Premature infants or infants not on the growth curve for weight are dosed at 4 mEq/kg.[13] As the person with CF gets older and consumes a full diet, a liberal use of salt on food is recommended to meet sodium chloride needs. Those persons exposed to hot, humid conditions and those who are physically active require additional salt supplementation to avoid hyponatremic dehydration. One study recommends adding 1/8 salt to every 12 oz of standard sports drinks to stimulate thirst and drinking.[28]

CF-specific multivitamins contain zinc. Additional zinc at 1 mg/kg up to 25 mg for 6 months is recommended if zinc deficiency is suspected. Zinc deficiency should be considered in the breast-fed baby not receiving a dietary source of zinc (meat) at 6 months of age and not growing adequately, for all patients demonstrating an unexplained decline in growth parameters or appetite, and/or those with prolonged diarrhea or uncontrolled malabsorption and retinol deficiency refractory to retinol supplementation.

Nutrition Support in CF

Many factors contribute to poor appetite, intake, and nutrition status in CF, such as abdominal symptoms (ie, constipation, delayed gastric emptying, and/or abdominal pain), increased work of breathing, as well as a variety of psychosocial and socioeconomic factors.[29] According to the 2012 CF Patient Registry, 43.0% of CF patients use oral nutrition supplementation, while 11.4% require supplemental tube feeding.[4] Parenteral nutrition is rarely indicated in CF; it is mainly used only for patients who have persistent nonfunctioning bowel.

Nutrition interventions in patients with CF include behavioral approaches/interventions, oral supplementation, and enteral tube feedings.[30] Appetite stimulants are also commonly used.

Comprehensive nutrition assessment is recommended at CF patient clinic visits, including review of changes to and overall appetite of the patient. When decreased appetite is determined to be the primary cause for decreased nutrition status and intake, appetite stimulants should be considered.[29] Four commonly used appetite stimulants used in pediatric and adult CF patients are megestrol acetate (Megace), cyproheptadine hydrochloride (Periactin), dronabinol (Marinol), and mirtazapine (Remeron).[29,31] Each of these 4 appetite stimulants have side effects, such as mild sedation or drowsiness, and some (eg, megestrol acetate) can cause adrenal suppression and hyperglycemia.[29,31] Appetite stimulants can be used prior to use of more invasive nutrition support, such as tube feedings, but choice of product should be made cautiously and according to each patient.

According to a recent Cochrane review, oral protein energy supplements do not result in improved nutrition status, and these supplements should not be thought of as an essential part of nutrition care in CF.[32] However, the CFF recommends oral calorie supplements but cautions that they should be used in addition to usual dietary intake.[9] In general, any high-calorie supplement can be used for oral calorie supplementation for individuals with CF as long as they take PERT; specialized products for individuals with malabsorption or diabetes are not necessary. Some of the enzyme companies offer programs that provide free supplements; accredited CF centers will have information for patients and families about these programs.

Table 3. Laboratory Monitoring of Nutritional Status.[8]

Nutrient	At diagnosis	How often to monitor		
		Annually	Other	Tests
Beta Carotene			At physician's discretion	Serum levels
Vitamin A	X[a]	x		Vitamin A (retinol)
Vitamin D	X[a]	x		25-OH-D
Vitamin E	X[a]	x		Alpha-tocopherol
Vitamin K	X[a]	x	Or if patient has hemoptysis or hematemesis; in patients with liver disease	PIVKA (preferably) or prothrombin time
Essential fatty acids				Triene:tetraene
Calcium/bone status			>age 8 years if risk factors are present	Calcium, phosphorus, ionized PTH, DEXA scan
Iron	x	x	Consider in-depth evaluation for patients with poor appetite	Hemoglobin, hematocrit
Zinc			Consider 6 month supplementation trial and follow growth	No acceptable measurement
Sodium			Consider checking if exposed to heat stress and becomes dehydrated	Serum sodium; spot urine sodium if total body sodium depletion suspected
Protein stores	x	x	Check in patients with nutritional failure or those at risk albumin	Albumin

FTT, failure to thrive; PIVKA, prothrombin induced by vitamin K absence; PTH, parathyroid hormone; DEXA, dual-energy xray absorptiometry. Adapted with permission from Borowitz D, Baker RD, Stallings V. Consensus report on nutrition for pediatric patients with cystic fibrosis. *J Pediatr Gastroenter Nutr*. 2002;35:246-259.

[a]Patients diagnosed by neonatal screening : see text for testing these patients or reference 13 for greater detail.

The CFF recommends enteral nutrition support for those with moderate to severe malnutrition, again in addition to usual dietary intake.[9] Enteral tube feeding is considered when dietary manipulation and oral supplements have failed.[33] The addition of enteral tube feeding has been associated with improved nutrition status, increased caloric intake, and delayed decline in pulmonary function.[33–35] Nasogastric and gastrostomy tube feedings are both well tolerated by CF patients and with few adverse side effects; however, most patients opt for gastrostomy tube feedings given the chronic need for nutrition support.[36] Individuals with CF and their caregivers, with guidance from CF care providers, must balance the potential benefits with the invasive nature of enteral feeding, the risks associated with it (eg, gastroesophageal reflux), and the costs associated with products and supplies.[35]

Special considerations for enteral tube feeding are PERT and glycemic control. There is no consensus for use of PERT during tube feedings. However, general recommendations include dosing PERT based on fat grams provided by the enteral feeding formulation.[18] PERT administration options include enzymes taken by mouth, bolused via nectar-thick acidic fluid, crushed to powder and added to enteral formula, or dissolved in a sodium bicarbonate solution and added to enteral formula.[18,36] Regarding glycemia, screening for CF-related diabetes (CFRD) by measuring mid- and immediate postfeeding plasma glucose levels is recommended for CF patients on continuous enteral feedings, at the time of gastrostomy feeding initiation and then monthly.[36] For patients who have CFRD or are diagnosed with CFRD after receiving tube feedings, insulin therapy should be used for management.[37]

CF-Related Diabetes

CFRD is the most common comorbidity associated with CF, and prevalence increases with age; up to 40%–50% of individuals with CF will have diabetes by the time that they are adults.[37-40] CFRD is associated with worse pulmonary function, lower BMI, and increased mortality.[37–42] In addition, patients with established CFRD are at equal risk of microvascular complications, such as retinopathy, nephropathy, neuropathy, and gastropathy, as are those with types 1 and 2 diabetes, particularly if fasting hyperglycemia is present.[43] In contrast to type 1 and type 2 diabetes, macrovascular disease does not appear to be a concern; there are no documented cases of deaths from atherosclerotic cardiac disease in patients with CFRD.[37]

CFRD is a distinct clinical entity but shares characteristics from type 1 and type 2 diabetes.[39,41,43,44] CFRD is mainly characterized by insulin insufficiency; however, patients also have fluctuating levels of insulin resistance related to chronic and acute infection, as well as intermittent use of steroids for some.[37,43,44] Many patients with CFRD do not have fasting hyperglycemia and have normal hemoglobin A1c levels at time

Table 4. CF-Specific Vitamin and Mineral Products Compared With Non-CF-Specific Products.[a]

Fat-Soluble Vitamins					
MVW Complete Formulation: Drops, Chewables, Softgels, D3000 Softgels[b]	AquADEKs: Drops, Chewables, Softgels	Vitamax: Drops, Chewables	ChoiceFul: Chewables, Softgels, Label Data	Libertas ABDEK: Drops, Chewables, Softgels	Poly-Vi-Sol: Drops, Centrum, Chewable, Tablet
Total vitamin A, IU (retinol and beta carotene)					
4627 / 0.5 mL; 75% as beta carotene	5,751 / 1 mL; 87% as beta carotene	3170 / 1 mL; 100% retinol palmitate	NP	4627 / 1 mL; 100% retinol palmitate	750 / 1 mL; 100% retinol palmitate
9254 / 1 mL; 75% as beta carotene	11,502 / 2 mL; 87% as beta carotene	6,340 / 2 mL; 100% retinol palmitate	NP	9254 / 2 mL; 100% retinol palmitate	1,500 / 2 mL; 100% retinol palmitate
16,000 / 1 chewable; 88% as beta carotene	18,167 / 2 chewables; 92% as beta carotene	5,000 / 1 chewable; 50% as beta carotene	13,000 / 1 chewable; 88% as beta carotene	16,000 / 1 chewable; 100% as beta carotene	3,500 / 1 chewable; 29% as beta carotene
32,000 / 2 softgels; 88% as beta carotene	36,334 / 2 softgels; 92% as beta carotene	NP	28,000 / 2 softgels; 88% as beta carotene	32,000 / 2 softgels; 88% as beta carotene	7,000 / 2 tablets; 29% as beta carotene
32,000 / 2 softgels (D3000); 88% as beta carotene	NP	NP	NP	NP	NP
Vitamin E, IU					
50 / 0.5 mL	50 / 1 mL[b]	50 / 1 mL	NP	50 / 1 mL	5 / 1 mL
100 / 1 mL	100 / 2 mL[b]	100 / 2 mL	NP	100 / 2 mL	10 / 2 mL
200 / 1 chewable	100 / 2 chewables[b]	200 / 1 chewable	180 / 1 chewable	200 / 1 chewable	30 / 1 chewable
400 / 2 softgels	300 / 2 softgels[b]	NP	340 / 2 softgels	400 / 2 softgels	60 / 2 tablets
400 / 2 softgels (D3000)	NP	NP	NP	NP	NP
Vitamin D, IU					
750 / 0.5 mL	600 / 1 mL	400 / 1 mL	NP	500 / 1 mL	400 / 1 mL
1500 / 1 mL	1200 / 2 mL	800 / 2 mL	NP	1000 / 2 mL	800 / 2 mL
1500/ 1 chewable	1200 / 2 chewables	400 / 1 chewable	800 / 1 chewable	1000 / 1 chewable	400 / 1 chewable
3000 / 2 softgels	2400 / 2 softgels	NP	2000 / 2 softgels	2000 / 2 softgels	800 / 2 tablets
6000 / 2 softgels (D3000)	NP	NP	NP	NP	NP
Vitamin K, mcg					
500 / 0.5 mL	400 / 1 mL	300 / 1 mL	NP	400 / 1 mL	0
1000 / 1 mL	800 / 2 mL	600 / 2 mL	NP	800 / 2 mL	0
1000 / 1 chewable	700 / 2 chewables	200 / 1 chewable	600 / 1 chewable	800 / 1 chewable	10 / 1 chewable
1600 / 2 softgels	1400 / 2 softgels	NP	1400 / 2 softgels	1600 / 2 softgels	50 / 2 tablets
1600 / 2 softgels (D3000)	NP	NP	NP	NP	NP

(continued)

Table 4. (continued)

Water-Soluble Vitamins and Zinc					
MVW Complete Formulation: Drops, Chewables, Softgels, D3000 Softgels	AquADEKs: Drops, Softgels	Vitamax: Drops, Chewables	ChoiceFul: Chewables, Softgels, Label Data	Libertas ABDEK: Drops, Chewables, Softgels	Poly-Vi-Sol: Drops, Centrum, Chewable, Tablet
			Thiamin B1, mg		
0.5 / 0.5 mL	0.6 / 1 mL	0.5 / 1 mL	NP	0.5 / 1 mL	0.5 / 1 mL
1 / 1 mL	1.2 / 2 mL	1 / 2 mL	NP	1 / 2 mL	1 / 2 mL
1.5 / 1 chewable	1.5 / 2 chewables	1.5 / 1 chewable	1.2 / 1 chewable	1.5 / 1 chewable	1.5 / 1 chewable
3 / 2 softgels or 2 softgels with D3000	3 / 2 softgels	NP	2 / 2 softgels	3 / 2 softgels	3 / 2 tablets
			Riboflavin B2, mg		
0.6 / 0.5 mL	0.6 / 1 mL	0.6 / 1 mL	NP	0.6 / 1 mL	0.6 / 1 mL
1.2 / 1 mL	1.2 / 2 mL	1.2 / 2 mL	NP	1.2 / 2 mL	1.2 / 2 mL
1.7 / 1 chewable	1.7 / 2 chewables	1.7 / 1 chewable	1.4 / 1 chewable	1.7 / 1 chewable	1.7 / 1 chewable
3.4 / 2 softgels or 2 softgels with D3000	3.4 / 2 softgels	NP	3 / 2 softgels	3.4 / 2 softgels	3.4 / 2 tablets
			Niacin, mg		
6 / 0.5 mL	6 / 1 mL	6 / 1 mL	NP	6 / 1 mL	8 / 1 mL
12 / 1 mL	12 / 2 mL	12 / 2 mL	NP	12 / 2 mL	16 / 2 mL
10 / 1 chewable	10 / 2 chewables	20 / 1 chewable	8 / 1 chewable	10 / 1 chewable	20 / 1 chewable
40 / 2 softgels or 2 softgels with D3000	20 / 2 softgels	NP	36 / 2 softgels	40 / 2 softgels	40 / 2 tablets
			Pyridoxine B6, mg		
0.6 / 0.5 mL	0.6 / 1 mL	0.6 / 1 mL	NP	0.6 1 mL	0.4 / 1 mL
1.2 / 1 mL	1.2 / 2 mL	1.2 / 2 mL	NP	1.2 / 2 mL	0.8 / 2 mL
1.9 / 1 chewable	1.9 / 2 chewables	2 / 1 chewable	1.5 / 1 chewable	1.9 / 1 chewable	2 / 1 chewable
3.8 / 2 softgels or 2 softgels with D3000	3.8 / 2 softgels	NP	3.8 / 2 softgels	3.8 / 2 softgels	4 / 2 tablets
			B12, mcg		
4 / 0.5 mL	0	4 / 1 mL	NP	4 / 1 mL	2 / 1 mL
8 / 1 mL	0	8 / 2 mL	NP	8 / 2 mL	4 / 2 mL
6 / 1 chewable	12 / 2 chewables	6 / 1 chewable	6 / 1 chewable	6 /1 chewable	6 / 1 chewable
12 / 2 softgels or 2 softgels with D3000	24 / 2 softgels	NP	10 / 2 softgels	12 / 2 softgels	12 /2 tablets
			Biotin, mcg		
15 / 0.5 mL	15 / 1 mL	15 / 1 mL	NP	15 / 1 mL	0
30 / 1 mL	30 / 2 mL	30 / 2 mL	NP	30 / 2 mL	0
100 / 1 chewable	100 / 2 chewables	300 / 1 chewable	80 / 1 chewable	100 / 1 chewable	45 / 1 chewable
200 / 2 softgels or 2 softgels with D3000	200 / 2 softgels	NP	160 / 2 softgels	200 / 2 softgels	60 / 2 tablets

(continued)

Table 4. (continued)

Water-Soluble Vitamins and Zinc (continued)					
MVW Complete Formulation: Drops, Chewables, Softgels, D3000 Softgels	AquADEKs: Drops, Softgels	Vitamax: Drops, Chewables	ChoiceFul: Chewables, Softgels, Label Data	Libertas ABDEK: Drops, Chewables, Softgels	Poly-Vi-Sol: Drops, Centrum, Chewable, Tablet
			Folic acid, mcg		
0	0	0	NP	0	0
0	0	0	NP	0	0
200 / 1 chewable	200 / 2 chewables	200 / 1 chewable	180 / 1 chewable	200 / 1 chewable	400 / 1 chewable
400 / softgels or 2 softgels with D3000	200/2 softgels	NP	360 / 2 softgels	400 / 2 softgels	800 / 2 tablets
			Ascorbic acid C, mg		
45 / 0.5 mL	45 / 1 mL	45 / 1 mL	NP	45 / 1 mL	35 / 1 mL
90 / 1 mL	90 / 2 mL	90 / 2 mL	NP	90 / 2 mL	70 / 2 mL
100 / 1 chewable	70 / 2 chewables	60 / 1 chewable	60 / 1 chewable	100 / 1 chewable	60 / 1 chewable
200 / 2 softgels or 2 softgels with D3000	150 / 2 softgels	NP	60 / 2 softgels	200 / 2 softgels	120 / 2 tablets
			Pantothenic acid, mg		
3 / 0.5 mL	3 / 1 mL	3 / 1 mL	NP	3 / 1 mL	0
6 / 1 mL	6 / 2 mL	6 / 2 mL	NP	6 / 2 mL	0
12 / 1 chewable	12 / 2 chewables	10 / 1 chewable	10 / 1 chewable	12 / 1 chewable	10 / 1 chewable
24 / 2 softgels or 2 softgels with D3000	24 / 2 softgels	NP	16 / 2 softgels	24 / 2 softgels	20 / 2 tablets
			Zinc, mg		
5 / 0.5 mL	5 / 1 mL	7.5 / 1 mL	NP	5 / 1 mL	0
10 / 1 mL	10 / 2 mL	15 / 2 mL	NP	10 / 2 mL	0
15 / 1 chewable	10 / 2 chewables	7.5 / 1 chewable	15 / chewable	15 / 1 chewable	15 / 1 chewable
20 / 2 softgels or 2 softgels with D3000	20 / 2 softgels	NP	30 / 2 softgels	30 / 2 softgels	22 / 2 tablets

NP, no equivalent product.

[a]The content of this table was confirmed as of May 2014. Created by Suzanne H. Michel, MPH, RD, LDN. AquADEKs is a registered trademark of Actavis. Vitamax is a registered trademark of Shear/Kershman Labs Inc. Poly-Vi-Sol is a registered trademark of Mead Johnson and Company. Centrum is a registered trademark of Wyeth Consumer Care. MVW Complete Formulation is a registered trademark of MVW Nutritionals Inc.

[b]Also contains mixed tocopherols.

Table 5. Vitamin D Intakes and Treatment Recommendations of Vitamin D Deficiency in Children and Adults With CF.[27]

Age	Routine Dosing: CF-Specific Vitamins, IU	Step 1: Dose Increases, IU	Step 2: Dose Titration Maximum, IU	Step 3
Birth–12 mo	400–500	800–1000	<2000	Refer
>12 mo–10 y	800–1000	1600–3000	<4000	Refer
>10 y–18 y	800–2000	1600–6000	<10,000	Refer
>18 y	800–2000	1600–6000	<10,000	Refer

CF, cystic fibrosis.

of diagnosis. Therefore, the U.S.-based CFF and the International Society of Pediatric and Adolescent Diabetes recommend annual screening for CFRD with an oral glucose tolerance test (OGTT; 1.75 g/kg of glucose; maximum, 75 g) starting at age 10. Hemoglobin A1c cannot be used alone as a screening mechanism, because it underestimates overall glycemic control and does not correlate well with OGTT results.[37,43] Individuals with CF can have increased red blood cell turnover, making hemoglobin A1c spuriously low in these patients.[45]

Ongoing diabetes self-management education from a multidisciplinary team of care providers familiar with CF as well as diabetes is recommended.[37,43] CFRD is an insulin-insufficient state, making treatment with insulin the treatment of choice.[37,43] Treatment with insulin, even at an early stage, can delay the decline in pulmonary function as well as improve BMI and overall nutrition status.[46] As with type 1 and type 2 diabetes, insulin treatment is individualized and meant to prevent large glycemic variability. An additional important treatment goal of insulin is to improve weight gain and BMI, both closely associated with pulmonary outcomes and mortality in individuals with CF. Generally, glycemic goals are similar to guidelines of the American Diabetes Association, including a target hemoglobin A1c <7%.[37]

Individuals with CFRD are not encouraged to make dramatic changes to their diet (Table 6).[37] Self-monitoring of blood glucose is encouraged at least 3 times daily, with quarterly A1c values measured for monitoring of CFRD.[37] In addition, annual screening for microvascular complications and annual lipid profile are recommended, after 5 years of diagnosis of CFRD.[37]

Pregnancy

More women who have CF are becoming pregnant and delivering babies. The majority of papers describing pregnancy by women who have CF are retrospective chart reviews. Edenborough and Morton provided a summary of the works and care recommendations.[47] On the whole, most women do well during and following pregnancy, and pregnancy does not affect survival; however, there is heightened concern for women with less-than-optimal weight and/or CFRD and/or poor lung function prior to conception. Optimal nutrition (weight and BMI), before and during pregnancy, is essential for the well-being of the woman and her infant. The involvement of a dietitian, knowledgeable about the special needs of individuals with CF, through the pregnancy process improves overall nutrition outcome.[48] Vitamin supplementation is based on serum levels of fat-soluble vitamins. Normal vitamin A levels were reported in pregnant women who have CF and take CF-specific multivitamins.[49] As shown in Table 2, the majority of vitamin A in the CF-specific multivitamins is in the form of beta-carotene, which is considered nontoxic. The CFF recommends blood glucose screening prior to pregnancy, for women who do not have CFRD and have not had a 2-hour OGTT in the previous 6 months. The test is repeated twice: during gestation weeks 12–16 and again during weeks 24–28. For women diagnosed with gestation diabetes, another 2-hour OGTT is recommended 6–12 weeks after delivery. Blood glucose levels are monitored per the CFF recommendations. The diet during pregnancy should contain sufficient calories to promote optimal weight gain; dietary restrictions are not appropriate to control blood sugars; and exogenous insulin is required if diabetes is present.[37]

Distal Intestinal Obstruction Syndrome

Patients with CF experience abdominal pain or discomfort regularly. Distal intestinal obstruction syndrome (DIOS) is a CF-specific complication that can cause significant abdominal pain, and it constitutes a medical emergency. While CF patients experience chronic and sometimes severe constipation, it is important to distinguish between DIOS and constipation.[50–52] DIOS is defined as an acute complete or incomplete fecal obstruction in the ileocecum.[50] Constipation, however, is defined as gradual fecal impaction of the total colon.[51] DIOS occurs primarily in patients with PI and is thought to be caused as a result of CFTR mutations resulting in accumulation of viscid fecal content.[53] Those who have had DIOS are at higher risk of subsequent episodes.

Complete DIOS includes complete intestinal obstruction with vomiting of bilious material and/or fecal loading in the right lower quadrant and with possible fluid levels in the small intestine on abdominal radiograph, fecal mass in the ileocecum, and abdominal pain with distention.[50] Incomplete or impending DIOS includes an ileocecal fecal mass and abdominal pain without complete obstruction and

Table 6. Dietary Recommendations for CFRD.

Nutrient	Type 1 and type 2 diabetes	CFRD
Calories	As needed for growth, maintenance, or reduction diets	1.2–1.5 times DRI for age; individualized based on weight gain and growth
Carbohydrate	Individualized. Monitor carbohydrates to achieve glycemic control; choose from fruits, vegetables, whole grains and fiber-containing foods, legumes, and low-fat milk. Sugar alcohols and nonnutritive sweeteners are safe within U.S. Food and Drug Administration–established consumption guidelines.	Individualized. Carbohydrates should be monitored to achieve glycemic control. Artificial sweeteners should be used sparingly due to lower calorie content.
Fat	Limit saturated fat to <7% of total calories; intake of trans fat should be minimized; limit dietary cholesterol to <200 mg/day. Consume two or more servings per week of fish high in n-3 polyunsaturated fatty acids.	No restriction on type of fat. High fat necessary for weight maintenance. Aim for 35–40% total calories.
Protein	15–20% of total calories; reduction to 0.8–1.0 g/kg with nephropathy	Approximately 1.5–2.0 times the DRI for age; no reduction for nephropathy
Sodium	<2,300 mg/day for blood pressure control	Liberal, high salt diet, especially in warm conditions and/or when exercising
Vitamins, minerals	No supplementation necessary unless deficiency noted	Routine supplementation with CF-specific multivitamins or a multivitamin and additional fat-soluble vitamins A, D, E, and K
Alcohol	If consumed, limit to a moderate amount; one drink per day for women and two or less drinks per day for men.	Consult with physician because of the higher prevalence of liver disease in CF and possible use of hepatotoxic drugs.
Special circumstances		
Gestational diabetes mellitus	Restricted calories/carbohydrate for weight and blood glucose control	No calorie or carbohydrate restriction; adequate calories for weight gain
Impaired Glucose Tolerance	Weight loss of 5–10% recommended; low-fat diet	No weight loss. Spread carbohydrates throughout the day; consume nutrient-dense beverages.

DRI, daily recommended intake. Copyright 2010 American Diabetes Association, From Diabetes Care®, Vol. 33, 2010; 2697-2708 Table reprinted with permission from *The American Diabetes Association.*

vomiting.[50,51,53] The collection of fecal material in the lower right quadrant in DIOS, as well as fairly acute onset of symptoms, distinguishes DIOS from constipation, as abdominal radiographs in constipation indicate accumulation of fecal material throughout the colon.[53]

It is important to recognize and treat DIOS promptly to prevent need for surgical intervention.[53,54] Incomplete DIOS often will respond to oral rehydration with stool softeners such as polyethylene glycol.[53] Treatment for complete DIOS should aim to correct systemic dehydration, then to thin fecal content causing blockage with oral laxatives, polyethylene glycol lavage, or Gastrografin enema performed by an experienced radiologist.[50,53,54] Surgical intervention for complete DIOS is rarely needed with early aggressive treatment by a medical team familiar with the condition. Patients with CF are often encouraged to contact their CF clinical care team with symptoms of acute abdominal pain or discomfort. Recommended steps to prevent recurrent DIOS involves adherence to PERT, prevention of dehydration, and maintenance laxative therapy.[53]

Lung Transplant

While the life expectancy for individuals with CF continues to improve, respiratory failure continues to be the main cause of mortality for those afflicted with the disease. Lung transplantation offers those with end-stage lung disease a survival advantage and improved quality of life as compared with those who do not receive a transplant.

According to the CFF registry, >200 lung transplants were performed in individuals with CF in 2011, and about 2800 people with CF have received a lung transplant since 1990.[4] CF is the third major indication for lung transplantation, after emphysema and pulmonary fibrosis.[55] The majority of those transplanted receive a bilateral lung transplant; a small minority (<5%) require liver and lung transplantation.[56]

Survival rates for lung transplant recipients regardless of indication are lower when compared with most other solid organ transplants; however, when compared with individuals receiving lung transplants for other indications, median survival is slightly better in those with CF: 7.5 years for all recipients and 10.4 years for those who survive the first year.[55]

Malnutrition is commonly seen in individuals with CF who have end-stage lung disease. The cause of malnutrition is multifactorial and often includes elevated resting energy expenditure, poor appetite, and frequent pulmonary exacerbations. Mean resting energy expenditure was 132% predicted in pediatric patients awaiting lung transplantation (majority with CF).[57] In addition, delayed gastric emptying is a common complication of end-stage disease in CF.[58] Efforts should be made to improve or at least preserve nutrition status while patients wait for transplantation, as adult patients with CF who have a BMI <18.5 kg/m^2 have a significantly higher risk of posttransplant mortality than do such patients with a normal or higher BMI.[59,60] Additionally, depletion of fat-free mass was strongly associated with increased mortality while awaiting lung transplant and longer posttransplant intensive care unit stays.[61]

Patients who do not have known CFRD should be screened preoperatively by OGTT if they have not had CFRD screening in the 6 months prior to listing for transplant.[37] Patients benefit from anticipatory guidance regarding the increased likelihood of developing temporary hyperglycemia necessitating insulin therapy during the immediate posttransplant period. In addition, they need to continue routine monitoring for CFRD, even after transplant—either on an annual basis or earlier with symptoms such as unexplained weight loss if they have not developed diabetes.

For most patients with CF, significant improvements in weight gain and BMI are noted after they recover from the immediate posttransplant period.[62,63] There are no evidence-based guidelines to specify an optimal BMI for CF patients who are postlung transplant; the 2008 published guidelines with BMI goals of 23 for males and 22 for females are based on correlation to FEV_1 in pretransplant patients.[9] However, particularly since complications are quite common after transplant, it would seem prudent to recommend achieving and maintaining a normal BMI for age. Since energy expenditure may be lower and appetite significantly better, some patients may become overweight if they continue to follow the typical high-fat, high-calorie CF diet. Patients should be encouraged to return to their CF center for monitoring BMI trends, gastrointestinal symptoms/enzyme management, and secondary complications (eg, CFRD and gastrointestinal cancers), as well as for routine annual monitoring of fat-soluble vitamin levels. Increased vitamin A and E levels have been reported in CF patients after lung transplantation; hypervitaminosis A is particularly concerning, as toxicity can cause increased intracranial pressure, osteoporosis, and liver damage.[64] Standard CF vitamins may need to be discontinued since these products contain significant doses of vitamins A and E when compared with most general over-the-counter multivitamin products. Optimizing vitamin D levels may be particularly important in the posttransplant period, as low serum vitamin D levels are associated with increased rates of rejection and infection after lung transplantation.[65]

Summary

Significant strides have been made in the treatment and outcomes of CF. Clinicians play a critical role helping patients and their loved ones improve outcomes and quality of life with CF. As excitement builds for the potential to treat the disease at the cellular level, dedication to achieving and maintaining optimal nutrition status will help ensure that patients have the best chance at a long and relatively healthy life.

Statement of Authorship

Terri Schindler, Suzanne Michel, and Alexandra W. M. Wilson contributed to the conception/design of the work; drafted the manuscript; critically revised the manuscript; and agree to be fully accountable for ensuring the integrity and accuracy of the work. All authors read and approved the final manuscript.

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